参考資料3－5

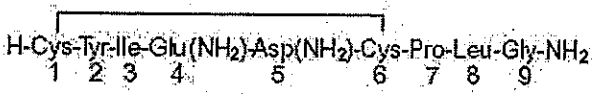
参考資料

1

OXYTOCIN - oxytocin injection
Baxter Healthcare Corporation

DESCRIPTION

Each mL of Oxytocin Injection sterile solution contains an oxytocic activity equivalent to 10 USP Posterior Pituitary Units, Chlorobutanol (a chloroform derivative), 0.5%, as a preservative, and acetic acid to adjust pH (3.0 to 5.0). Oxytocin is intended for IM or IV use. Oxytocin is a synthetic polypeptide; it occurs as a white powder and is soluble in water. It may be designated chemically as:



Oxytocin

CLINICAL PHARMACOLOGY

The pharmacologic and clinical properties of oxytocin are identical with those of naturally occurring oxytocin principle of the posterior lobe of pituitary. Oxytocin exerts a selective action on the smooth musculature of the uterus, particularly toward the end of pregnancy, during labor, and immediately following delivery. Oxytocin stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions, and raises the tone of the uterine musculature.
When given in appropriate doses during pregnancy, oxytocin is capable of eliciting graded increases in uterine motility from a moderate increase in the rate and force of spontaneous motor activity to sustained titanic contraction. The sensitivity of the uterus to oxytocic activity increases progressively throughout pregnancy until term when it is maximal.
Oxytocin is distributed throughout the extracellular fluid. Small amounts of this drug probably reach the fetal circulation. Oxytocin has a plasma half-life of about 3 to 5 minutes. Following parenteral administration, uterine response occurs within 3 to 5 minutes and persists for 2 to 3 hours. Its rapid removal from plasma is accomplished largely by the kidney and the liver. Only small amounts oxytocin are excreted in the urine unchanged.

INDICATIONS AND USAGE

IMPORTANT NOTICE
Oxytocin is indicated for the medical rather than the elective induction of labor. Available data and information are inadequate to define the benefits-to-risks considerations in the use of the drug product for elective induction. Elective induction of labor is defined as the initiation of labor for convenience in an individual with a term pregnancy who is free of medical indications.

Antepartum

Oxytocin is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable for reasons of fetal or maternal concern, in order to achieve early vaginal delivery. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, preeclampsia at or near term, when delivery is in the best interests of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) as adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum

Oxytocin is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

CONTRAINDICATIONS

Oxytocin is contraindicated in any of the following conditions:
- significant cephalopelvic disproportion;
- unfavorable fetal positions or presentations which are undeliverable without conversion prior to delivery, e.g., transverse lies;
- in obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention;
- in cases of fetal distress where delivery is not imminent;
- hypertonic uterine patterns;
- hypersensitivity to the drug.

Prolonged use in uterine inertia or severe toxemia is contraindicated.
Oxytocin should not be used in cases where vaginal delivery is not indicated, such as cord presentation or prolapse, total placenta previa, and vasa previa.

WARNINGS

Oxytocin, when given for induction or stimulation of labor, must be administered only by intravenous infusion (drip method) and with adequate medical supervision in a hospital.

PRECAUTIONS

General

1. All patients receiving intravenous infusions of oxytocin must be under continuous observation by trained personnel with a thorough knowledge of the drug and are qualified to identify complications. A physician qualified to manage any complications should be immediately available.

2. When properly administered, oxytocin should stimulate uterine contractions similar to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin.

3. Except in unusual circumstances, oxytocin should not be administered in the following conditions: prematurity, borderline cephalopelvic disproportion, previous major surgery on the cervix or uterus, including cesarean section, overdistention of the uterus, grand multiparity, or invasive cervical carcinoma. Because of the variability of the combinations of factors which may be present in the conditions listed above, the definition of "unusual circumstances" must be left to the judgment of the physician. The decision can only be made by carefully weighing the potential benefits which oxytocin can provide in a given case against the rare occurrence of hypertonicity or tetanic spasm with this drug.

4. Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, and fetal deaths and permanent CNS or brain damage of the infant due to various causes have been reported to be associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor.

5. Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

6. Oxytocin should be considered for use only in patients who have been carefully selected. Pelvic adequacy must be considered and maternal and fetal conditions thoroughly evaluated before use of the drug.

Drug Interactions

Severe hypertension has been reported when oxytocin was given three to four hours following prophylactic administration of a vasoconstrictor in conjunction with caudal-block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

Pregnancy

Pregnancy Category C.
There are no known indications for use of oxytocin in the first and second trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

Nonteratogenic Effects
See "**ADVERSE REACTIONS**" in the fetus or infant.

Labor and Delivery

See "**INDICATIONS AND USAGE**"

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxytocin is administered to a nursing woman.

ADVERSE REACTIONS

The following adverse reactions have been reported in the mother:

- Anaphylactic reaction
- Nausea
- Postpartum hemorrhage
- Vomiting
- Cardiac arrhythmia
- Premature ventricular contractions
- Fatal afibrinogenemia
- Pelvic hematoma

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.
The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.
Severe water intoxication with convulsions and coma has occurred, associated with a slow oxytocin infusion over a 24-hour period.
Maternal death due to oxytocin-induced water intoxication has been reported.
The following adverse reactions have been reported in the fetus or infant:
(Due to induced uterine motility)

- Bradycardia
- Premature ventricular contractions and other arrhythmias
- Permanent CNS or brain damage
- Fetal death

(Due to use of oxytocin in the mother)

- Low Apgar scores at five minutes
- Neonatal jaundice
- Neonatal retinal hemorrhage

OVERDOSAGE

Overdosage with oxytocin depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, utero-placental hypoperfusion, and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Dosage of oxytocin is determined by the uterine response. The following dosage information is based upon various regimens and indications in general use.

A. Induction or Stimulation of Labor
Intravenous infusion (drip method) is the only acceptable method of administration for the induction or stimulation of labor.

Accurate control of the rate of infusion flow is essential. An infusion pump or other such device and frequent monitoring of strength of contractions and fetal heart rate are necessary for the safe administration of oxytocin for the induction or stimulation of labor. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane.

1. An intravenous infusion of nonoxytocin-containing solution should be started. Physiologic electrolyte solution should be used except under unusual circumstances.

2. To prepare the usual solution for infusion, 1-mL Oxytocin Injection, 10 USP Units/mL is combined aseptically with 1,000 mL of nonhydrating diluent (physiologic electrolyte solution). The combined solution, rotated in the infusion bottle to ensure thorough mixing, containing 10 mU/mL. Add the container with dilute oxytocic solution to the system through use of a constant infusion pump or other such device, to control accurately the rate of infusion.

3. The initial dose should be no more than 1 to 2 mU/min. the dose may be gradually increased in increments of no more than 1 to 2 mU/min. until a contraction pattern has been established which is similar to normal labor.

4. The fetal heart rate, resting uterine tone, and the frequency, duration, and the force of contractions should be monitored.

5. The oxytocin infusion should be discontinued immediately in the event of uterine hyperactivity or fetal distress. Oxygen should be administered to the mother. The mother and the fetus must be evaluated by the responsible physician.

B. Control of Postpartum Uterine Bleeding

1. Intravenous Infusion (Drip Method):
   To control postpartum bleeding, 10 to 40 units of oxytocin may be added to 1,000 mL of a nonhydrating diluent (physiologic electrolyte solution) and run a rate necessary to control uterine atony.

2. Intramuscular Administration:
   1 mL (10 units) of oxytocin can be given after the delivery of the placenta.

C. Treatment of Incomplete or Inevitable Abortion

Intravenous infusion with physiologic saline solution, 500 mL, or 5% dextrose in physiologic saline solution to which 10 units of oxytocin have been added should be infused at a rate of 20 to 40 drops per minutes.

HOW SUPPLIED

Oxytocin Injection, USP (synthetic), 10 USP units per mL is packaged in single or multiple dose vial and supplied as follows:

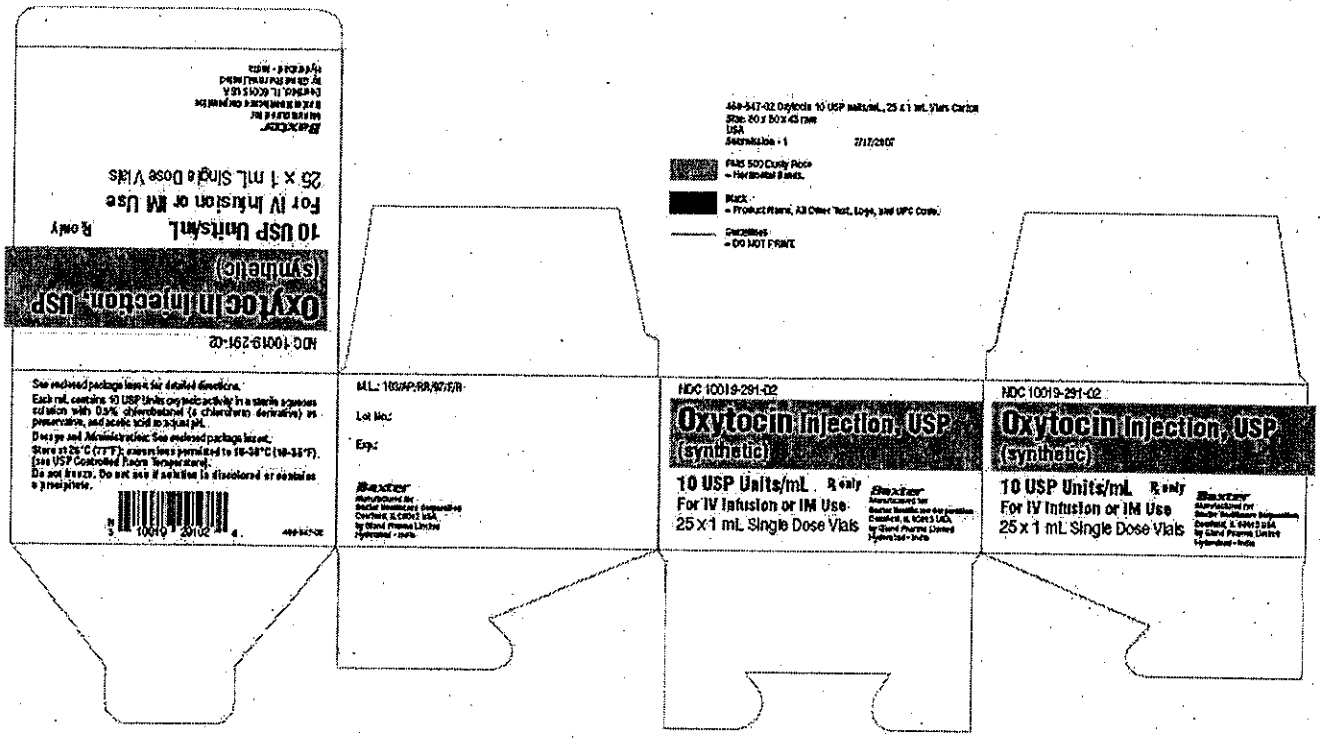
NDC	Vial Size	Fill Volume	Usage	Package size
10019-291-02	2 mL	1 mL	Single Dose Vial	25
10019-291-04	10 mL	10 mL	Multiple Dose Vial	25

Store at 25°C (77°F); excursions permitted to 15–30°C (59-86°F) [see USP Controlled Room Temperature].
Do not freeze.Do not use if solution is discolored or contains a precipitate.

Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
by Gland Pharma Limited
Hyderabad-India
For Product Inquiry 1 800 ANA DRUG (1-800-262-3784)
Revised: June 2006

PACKAGE LABEL - PRINCIPAL DISPLAY PANEL

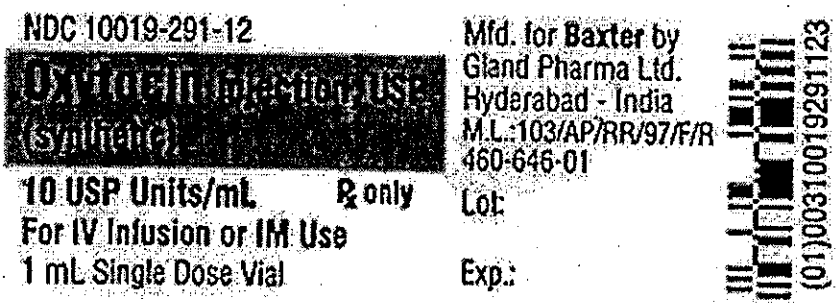
Carton Label



1mL Carton Label

NDC 10019-291-02
Oxytocin Injection, USP
(synthetic)
10 USP Units/mL
Rx only
For IV Infusion or IM Use
25 x 1 mL Single Dose Vials
Baxter
Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
by Gland Pharma Limited
Hyderabad - India

Container Label



1 mL Single Dose Vial

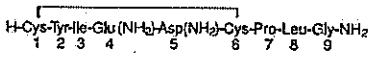
NDC 10019-291-12
Oxytocin Injection, USP
(synthetic)
10 USP Units/mL
Rx only
For IV Infusion or IM Use
1 mL Single Dose Vial

2

OXYTOCIN - oxytocin injection
JHP Pharmaceuticals, LLC

DESCRIPTION

Oxytocin injection, USP is a sterile, clear, colorless aqueous solution of synthetic oxytocin, for intravenous infusion or intramuscular injection. Oxytocin is a nonapeptide found in pituitary extracts from mammals. It is standardized to contain 10 units of oxytocic hormone/mL and contains 0.5% Chlorobutanol, a chloroform derivative as a preservative, with the pH adjusted with acetic acid. Oxytocin may contain up to 16% of total impurities. The hormone is prepared synthetically to avoid possible contamination with vasopressin (ADH) and other small polypeptides with biologic activity. Oxytocin has the empirical formula $C_{43}H_{66}N_{12}O_{12}S_2$ (molecular weight 1007.19). The structural formula is as follows:



CLINICAL PHARMACOLOGY

Uterine motility depends on the formation of the contractile protein actomyosin under the influence of the Ca^{2+} -dependent phosphorylating enzyme myosin light-chain kinase. Oxytocin promotes contractions by increasing the intracellular Ca^{2+}. Oxytocin has specific receptors in the myometrium and the receptor concentration increases greatly during pregnancy, reaching a maximum in early labor at term. The response to a given dose of oxytocin is very individualized and depends on the sensitivity of the uterus, which is determined by the oxytocin receptor concentration. However, the physician should be aware of the fact that oxytocin even in its pure form has inherent pressor and antidiuretic properties which may become manifest when large doses are administered. These properties are thought to be due to the fact that oxytocin and vasopressin differ in regard to only two of the eight amino acids (see PRECAUTIONS section).
Oxytocin is distributed throughout the extracellular fluid. Small amounts of the drug probably reach the fetal circulation. Oxytocin has a plasma half-life of about 1 to 6 minutes which is decreased in late pregnancy and during lactation. Following intravenous administration of oxytocin, uterine response occurs almost immediately and subsides within 1 hour. Following intramuscular injection of the drug, uterine response occurs within 3 to 5 minutes and persists for 2 to 3 hours. Its rapid removal from plasma is accomplished largely by the kidney and the liver. Only small amounts are excreted in urine unchanged.

INDICATIONS AND USAGE

IMPORTANT NOTICE

Elective induction of labor is defined as the initiation of labor in a pregnant individual who has no medical indications for induction. Since the available data are inadequate to evaluate the benefits-to-risks considerations, oxytocin injection is not indicated for elective induction of labor.

Antepartum
Oxytocin injection is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable for reasons of fetal or maternal concern, in order to achieve vaginal delivery. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, preeclampsia at or near term, when delivery is in the best interests of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) as adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum
Oxytocin injection is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

CONTRAINDICATIONS

Antepartum use of oxytocin injection is contraindicated in any of the following circumstances:

1. Where there is significant cephalopelvic disproportion;
2. In unfavorable fetal positions or presentations, such as transverse lies, which are undeliverable without conversion prior to delivery;
3. In obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention;
4. In fetal distress where delivery is not imminent;

5. Where adequate uterine activity fails to achieve satisfactory progress;

6. Where the uterus is already hyperactive or hypertonic;

7. In cases where vaginal delivery is contraindicated, such as invasive cervical carcinoma, active herpes genitalis, total placenta previa, vasa previa, and cord presentation or prolapse of the cord;

8. In patients with hypersensitivity to the drug.

WARNINGS

Oxytocin, when given for induction of labor or augmentation of uterine activity, should be administered only by the intravenous route and with adequate medical supervision in a hospital.

PRECAUTIONS

General

1. All patients receiving intravenous oxytocin must be under continuous observation by trained personnel who have a thorough knowledge of the drug and are qualified to identify complications. A physician qualified to manage any complications should be immediately available. Electronic fetal monitoring provides the best means for early detection of overdosage (see **OVERDOSAGE** section). However, it must be borne in mind that only intrauterine pressure recording can accurately measure the intrauterine pressure during contractions. A fetal scalp electrode provides a more dependable recording of the fetal heart rate than any external monitoring system.

2. When properly administered, oxytocin should stimulate uterine contractions comparable to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin. This fact must be considered by the physician in exercising his judgment regarding patient selection.

3. Except in unusual circumstances, oxytocin should not be administered in the following conditions: fetal distress, hydramnios, partial placenta previa, prematurity, borderline cephalopelvic disproportion, and any condition in which there is a predisposition for uterine rupture, such as previous major surgery on the cervix or uterus including cesarean section, overdistention of the uterus, grand multiparity, or past history of uterine sepsis or of traumatic delivery. Because of the variability of the combinations of factors which may be present in the conditions listed above, the definition of "unusual circumstances" must be left to the judgment of the physician. The decision can be made only by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

4. Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor.

5. Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

6. When oxytocin is used for induction or reinforcement of already existent labor, patients should be carefully selected. Pelvic adequacy must be considered and maternal and fetal conditions evaluated before use of the drug.

Drug Interactions

Severe hypertension has been reported when oxytocin was given three to four hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

Pregnancy

Teratogenic Effects
Animal reproduction studies have not been conducted with oxytocin. There are no known indications for use in the first trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

Nonteratogenic Effects
See ADVERSE REACTIONS in the fetus or neonate.

Labor and Delivery
See INDICATIONS AND USAGE section.

ADVERSE REACTIONS
The following adverse reactions have been reported in the mother:

Anaphylactic reaction	Premature ventricular contractions
Postpartum hemorrhage	Pelvic hematoma
Cardiac arrhythmia	Subarachnoid hemorrhage
Fatal afibrinogenemia	Hypertensive episodes
Nausea	Rupture of the uterus
Vomiting	

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.
The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.
Severe water intoxication with convulsions and coma has occurred, associated with a slow oxytocin infusion over a 24-hour period.
Maternal death due to oxytocin-induced water intoxication has been reported.
The following adverse reactions have been reported in the fetus or neonate:

Due to induced uterine motility:	Due to use of oxytocin in the mother:
Bradycardia	Low Apgar scores at five minutes
Premature ventricular contractions and other arrhythmias	Neonatal jaundice
Permanent CNS or brain damage	Neonatal retinal hemorrhage
Fetal death	
Neonatal seizures have been reported with the use of oxytocin.	

For medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact JHP at 1-866-923-2547 or MEDWATCH at 1-800-FDA-1088 (1-800-332-1088) or http://www.fda.gov/medwatch/.

OVERDOSAGE
Overdosage with oxytocin depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion, and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, perinatal hepatic necrosis or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The dosage of oxytocin is determined by the uterine response and must therefore be individualized and initiated at a very low level. The following dosage information is based upon various regimens and indications in general use.

A. Induction or Stimulation of Labor
Intravenous infusion (drip method) is the only acceptable method of parenteral administration of oxytocin injection for the induction or stimulation of labor. Accurate control of the rate of infusion is essential and is best accomplished by an infusion pump. It is convenient to piggyback the oxytocin infusion on a physiologic electrolyte solution, permitting the oxytocin infusion to be stopped abruptly without interrupting the electrolyte infusion. This is done in the following way.

1. **Preparation**

a. The standard solution for infusion of oxytocin injection is prepared by adding the contents of one 1-mL vial containing 10 units of oxytocin to 1000 mL of 0.9% aqueous sodium chloride or Ringer's lactate. The combined solution containing 10 milliunits (mU) of oxytocin/mL is rotated in the infusion bottle for thorough mixing.
b. Establish the infusion with a separate bottle of physiologic electrolyte solution not containing oxytocin.
c. Attach (piggyback) the oxytocin-containing bottle with the infusion pump to the infusion line as close to the infusion site as possible.

2. Administration

The initial dose should be 0.5–1 mU/min (equal to 3–6 mL of the dilute oxytocin solution per hour). At 30–60 minute intervals the dose should be gradually increased in increments of 1–2 mU/min until the desired contraction pattern has been established. Once the desired frequency of contractions has been reached and labor has progressed to 5–6 cm dilation, the dose may be reduced by similar increments.

Studies of the concentrations of oxytocin in the maternal plasma during oxytocin infusion have shown that infusion rates up to 6 mU/min give the same oxytocin levels that are found in spontaneous labor. At term, higher infusion rates should be given with great care, and rates exceeding 9–10 mU/min are rarely required. Before term, when the sensitivity of the uterus is lower because of a lower concentration of oxytocin receptors, a higher infusion rate may be required.

3. Monitoring

a. Electronically monitor the uterine activity and the fetal heart rate throughout the infusion of oxytocin. Attention should be given to tonus, amplitude and frequency of contractions, and to the fetal heart rate in relation to uterine contractions. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane (see **PRECAUTIONS** section).
b. Discontinue the infusion of oxytocin immediately in the event of uterine hyperactivity and/or fetal distress. Administer oxygen to the mother, who preferably should be put in a lateral position. The condition of mother and fetus should immediately be evaluated by the responsible physician and appropriate steps taken.

B. Control of Postpartum Uterine Bleeding

1. Intravenous infusion (drip method). If the patient has an intravenous infusion running, 10 to 40 units of oxytocin may be added to the bottle, depending on the amount of electrolyte or dextrose solution remaining (maximum 40 units to 1000 mL). Adjust the infusion rate to sustain uterine contraction and control uterine atony.

2. Intramuscular administration. (One mL) Ten (10) units of oxytocin injection can be given after the delivery of the placenta.

C. Treatment of Incomplete, Inevitable, or Elective Abortion

Intravenous infusion of 10 units of oxytocin injection added to 500 mL of a physiologic saline solution or 5% dextrose-in-water solution may help the uterus contract after a suction or sharp curettage for an incomplete, inevitable, or elective abortion. Subsequent to intra-amniotic injection of hypertonic saline, prostaglandins, urea, etc., for midtrimester elective abortion, the injection-to-abortion time may be shortened by infusion of oxytocin at the rate of 10 to 20 milliunits (20 to 40 drops) per minute. The total dose should not exceed 30 units in a 12-hour period due to the risk of water intoxication.

HOW SUPPLIED

Oxytocin Injection, USP, Synthetic is available as follows:
NDC 42023-140-25 Packages of twenty-five oversized 1-mL vials, each containing 10 units of oxytocin.
NDC 42023-141-01 A 10 mL multiple dose vial containing 10 units of oxytocin per mL (total = 100 units of oxytocin).
NDC 42023-141-25 Packages of twenty-five 10 mL multiple dose vials, each containing 10 units of oxytocin per mL (total = 100 units of oxytocin per vial).

STORAGE

Store between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)

REFERENCES

1. Seitchik J, Castillo M: Oxytocin augmentation of dysfunctional labor. I. Clinical data. *Am J Obstet Gynecol* 1982; 144:899–905.

2. Seitchik J, Castillo M: Oxytocin augmentation of dysfunctional labor. II. Multiparous patients. *Am J Obstet Gynecol* 1983; 145:777–780.

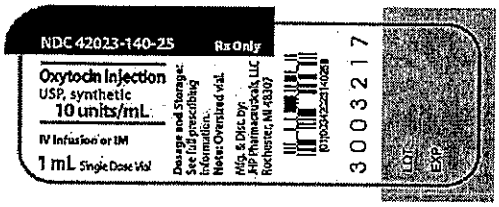
3. Fuchs A, Goeschen K, Husslein P, et al: Oxytocin and the initiation of human parturition. III. Plasma concentrations of oxytocin and 13, 14-dihydro-15-keto-prostaglandin F2a in spontaneous and oxytocin-induced labor at term. *Am J Obstet Gynecol* 1983; 145:497–502.

4. Seitchik J, Amico J, et al: Oxytocin augmentation of dysfunctional labor. IV. Oxytocin pharmacokinetics. *Am J Obstet Gynecol* 1984; 150:225–228.

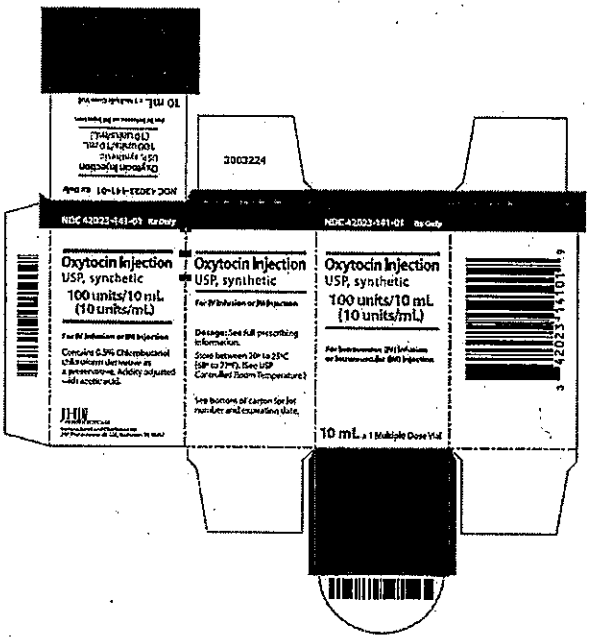
5. American College of Obstetricians and Gynecologists: ACOG Technical Bulletin Number 110—November 1987: Induction and augmentation of labor.

Rx Only.
Prescribing Information as of February 2012.
Manufactured and Distributed by: JHP Pharmaceuticals, LLC, Rochester, MI 48307
3003220

PRINCIPAL DISPLAY PANEL - 1 ML VIAL LABEL
NDC 42023-140-25
Oxytocin Injection
USP, synthetic
10 units/mL
IV Infusion or IM
1 mL Single Dose Vial



PRINCIPAL DISPLAY PANEL - 10 ML VIAL CARTON
NDC 42023-141-01
Rx Only
Oxytocin Injection
USP, synthetic
100 units/10 mL
(10 units/mL)
For Intravenous (IV) Infusion
or Intramuscular (IM) Injection
10 mL x 1 Multiple Dose Vial


3003224
NDC 42023-141-01 Rx Only
Oxytocin Injection
USP, synthetic
100 units/10 mL
(10 units/mL)
Oxytocin Injection
USP, synthetic
Oxytocin Injection
USP, synthetic
100 units/10 mL
(10 units/mL)
10 mL, a 1 Multiple Dose Vial

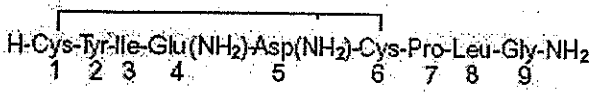
3

OXYTOCIN - oxytocin injection
West-ward Pharmaceutical Corp.

FOR INTRAVENOUS INFUSION OR INTRAMUSCULAR USE
Rx only

DESCRIPTION

Each mL of Oxytocin Injection sterile solution contains an oxytocic activity equivalent to 10 USP Posterior Pituitary Units, Chlorobutanol (a chloroform derivative), 0.5%, as a preservative, and acetic acid to adjust pH (3.0 to 5.0). Oxytocin is intended for IM or IV use. Oxytocin is a synthetic polypeptide; it occurs as a white powder and is soluble in water. It may be designated chemically as:



CLINICAL PHARMACOLOGY

The pharmacologic and clinical properties of oxytocin are identical with those of naturally occurring oxytocin principle of the posterior lobe of pituitary. Oxytocin exerts a selective action on the smooth musculature of the uterus, particularly toward the end of pregnancy, during labor, and immediately following delivery. Oxytocin stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions, and raises the tone of the uterine musculature.
When given in appropriate doses during pregnancy, oxytocin is capable of eliciting graded increases in uterine motility from a moderate increase in the rate and force of spontaneous motor activity to sustained titanic contraction. The sensitivity of the uterus to oxytocic activity increases progressively throughout pregnancy until term when it is maximal.
Oxytocin is distributed throughout the extracellular fluid. Small amounts of this drug probably reach the fetal circulation. Oxytocin has a plasma half-life of about 3 to 5 minutes. Following parenteral administration, uterine response occurs within 3 to 5 minutes and persists for 2 to 3 hours. Its rapid removal from plasma is accomplished largely by the kidney and the liver. Only small amounts oxytocin are excreted in the urine unchanged.

INDICATIONS AND USAGE

IMPORTANT NOTICE
Oxytocin is indicated for the medical rather than the elective induction of labor. Available data and information are inadequate to define the benefits-to-risks considerations in the use of the drug product for elective induction. Elective induction of labor is defined as the initiation of labor for convenience in an individual with a term pregnancy who is free of medical indications.

Antepartum
Oxytocin is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable for reasons of fetal or maternal concern, in order to achieve early vaginal delivery. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, preeclampsia at or near term, when delivery is in the best interests of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) as adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum
Oxytocin is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

CONTRAINDICATIONS

Oxytocin is contraindicated in any of the following conditions:
significant cephalopelvic disproportion;
unfavorable fetal positions or presentations which are undeliverable without conversion prior to delivery, e.g., transverse lies;
in obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention;
in cases of fetal distress where delivery is not imminent;
hypertonic uterine patterns;
hypersensitivity to the drug.
Prolonged use in uterine inertia or severe toxemia is contraindicated.
Oxytocin should not be used in cases where vaginal delivery is not indicated, such as cord presentation or prolapse, total placenta previa, and vasa previa.

WARNINGS

Oxytocin, when given for induction or stimulation of labor, must be administered only by intravenous infusion (drip method) and with adequate medical supervision in a hospital.

PRECAUTIONS

General

1. All patients receiving intravenous infusions of oxytocin must be under continuous observation by trained personnel with a thorough knowledge of the drug and are qualified to identify complications. A physician qualified to manage any complications should be immediately available.

2. When properly administered, oxytocin should stimulate uterine contractions similar to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin.

3. Except in unusual circumstances, oxytocin should not be administered in the following conditions: prematurity, borderline cephalopelvic disproportion, previous major surgery on the cervix or uterus, including cesarean section, overdistention of the uterus, grand multiparity, or invasive cervical carcinoma. Because of the variability of the combinations of factors which may be present in the conditions listed above, the definition of "unusual circumstances" must be left to the judgment of the physician. The decision can only be made by carefully weighing the potential benefits which oxytocin can provide in a given case against the rare occurrence of hypertonicity or tetanic spasm with this drug.

4. Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, and fetal deaths and permanent CNS or brain damage of the infant due to various causes have been reported to be associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor.

5. Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

6. Oxytocin should be considered for use only in patients who have been carefully selected. Pelvic adequacy must be considered and maternal and fetal conditions thoroughly evaluated before use of the drug.

Drug Interactions

Severe hypertension has been reported when oxytocin was given three to four hours following prophylactic administration of a vasoconstrictor in conjunction with caudal-block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

Pregnancy

PREGNANCY CATEGORY C.

There are no known indications for use of oxytocin in the first and second trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

NONTERATOGENIC EFFECTS

See **"ADVERSE REACTIONS"** in the fetus or infant.

Labor and Delivery

See **"INDICATIONS AND USAGE"**

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxytocin is administered to a nursing woman.

ADVERSE REACTIONS

The following adverse reactions have been reported in the mother:

Anaphylactic reaction	Nausea
Postpartum hemorrhage	Vomiting
Cardiac arrhythmia	Premature ventricular contractions
Fatal afibrinogenemia	Pelvic hematoma

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.
The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.
Severe water intoxication with convulsions and coma has occurred, associated with a slow oxytocin infusion over a 24-hour period.
Maternal death due to oxytocin-induced water intoxication has been reported.
The following adverse reactions have been reported in the fetus or infant:
(Due to induced uterine motility)
Bradycardia
Premature ventricular contractions and other arrhythmias
Permanent CNS or brain damage
Fetal death
(Due to use of oxytocin in the mother)
Low Apgar scores at five minutes
Neonatal jaundice
Neonatal retinal hemorrhage

OVERDOSAGE
Overdosage with oxytocin depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, utero-placental hypoperfusion, and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Dosage of oxytocin is determined by the uterine response. The following dosage information is based upon various regimens and indications in general use.

A. Induction or Stimulation of Labor
Intravenous infusion (drip method) is the only acceptable method of administration for the induction or stimulation of labor. Accurate control of the rate of infusion flow is essential. An infusion pump or other such device and frequent monitoring of strength of contractions and fetal heart rate are necessary for the safe administration of oxytocin for the induction or stimulation of labor. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane.

1. An intravenous infusion of nonoxytocin-containing solution should be started. Physiologic electrolyte solution should be used except under unusual circumstances.

2. To prepare the usual solution for infusion, 1-mL Oxytocin Injection, 10 USP Units/mL is combined aseptically with 1,000 mL of nonhydrating diluent (physiologic electrolyte solution). The combined solution, rotated in the infusion bottle to ensure thorough mixing, containing 10 mU/mL. Add the container with dilute oxytocic solution to the system through use of a constant infusion pump or other such device, to control accurately the rate of infusion.

3. The initial dose should be no more than 1 to 2 mU/min. the dose may be gradually increased in increments of no more than 1 to 2 mU/min. until a contraction pattern has been established which is similar to normal labor.

4. The fetal heart rate, resting uterine tone, and the frequency, duration, and the force of contractions should be monitored.

5. The oxytocin infusion should be discontinued immediately in the event of uterine hyperactivity or fetal distress. Oxygen should be administered to the mother. The mother and the fetus must be evaluated by the responsible physician.

B. Control of Postpartum Uterine Bleeding
1. Intravenous Infusion (Drip Method):
To control postpartum bleeding, 10 to 40 units of oxytocin may be added to 1,000 mL of a nonhydrating diluent (physiologic electrolyte solution) and run a rate necessary to control uterine atony.

2. Intramuscular Administration:
   1 mL (10 units) of oxytocin can be given after the delivery of the placenta.

C. Treatment of Incomplete or Inevitable Abortion
Intravenous infusion with physiologic saline solution, 500 mL, or 5% dextrose in physiologic saline solution to which 10 units of oxytocin have been added should be infused at a rate of 20 to 40 drops per minutes.

HOW SUPPLIED
Oxytocin Injection, USP (synthetic), 10 USP units per mL is packaged in single or multiple dose vial and supplied as follows:

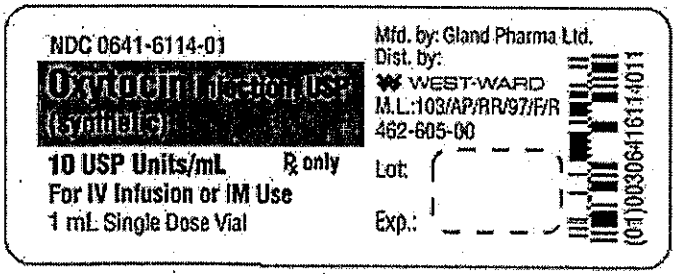
NDC	Vial Size	Fill Volume	Usage	Package size
0641-6114-25	2 mL	1 mL	Single Dose Vial	25
0641-6115-25	10 mL	10 mL	Multiple Dose Vial	25

Store at 25°C (77°F); excursions permitted to 15–30°C (59-86°F) [See USP Controlled Room Temperature].
Do not freeze. Do not use if solution is discolored or contains a precipitate.
To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceutcial Corp. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
For Product Inquiry call 1-877-845-0689.

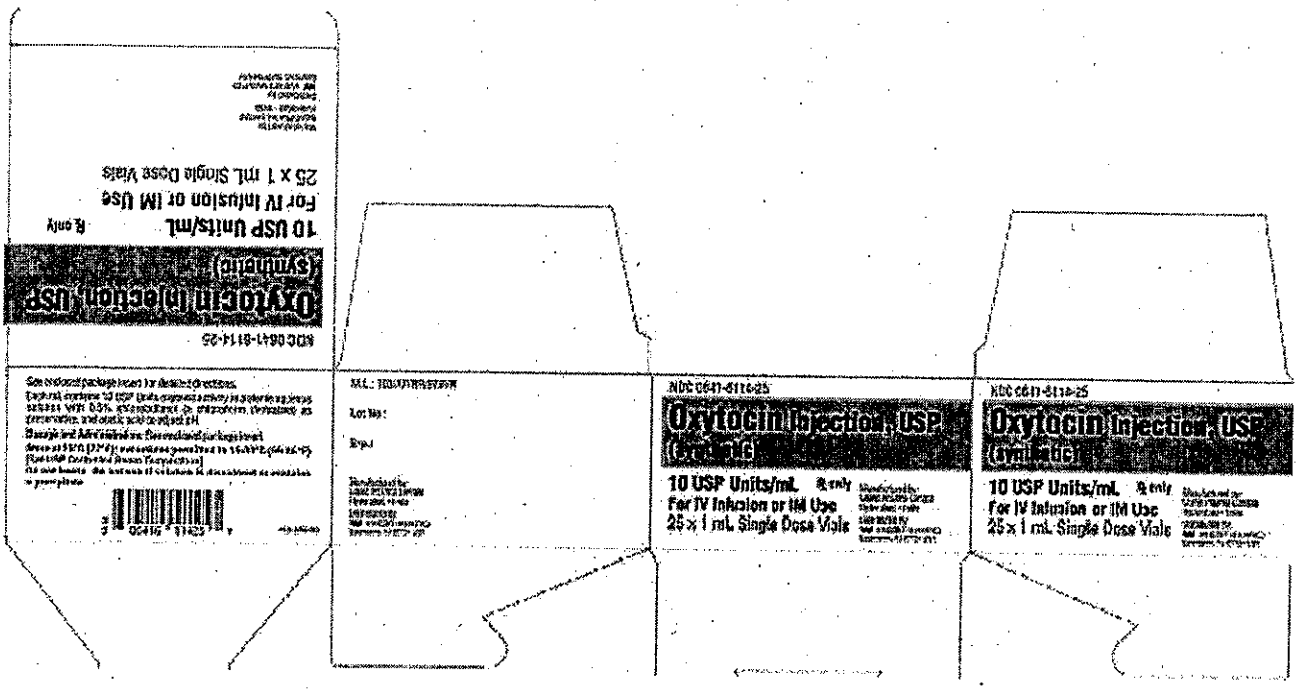
Manufactured by:
by Gland Pharma Limited
Hyderabad-India
Distributed by:

WEST-WARD
PHARMACEUTCIALS
Eatontown, NJ 07724 USA
Revised June 2011
462-604-00

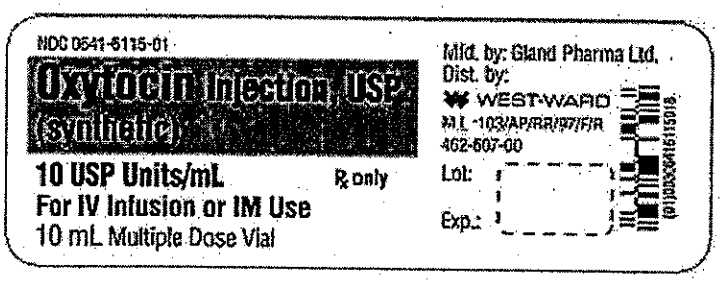
PRINCIPAL DISPLAY PANEL
Oxytocin Injection, USP (synthetic)
10 USP Units/mL
1 mL Single Dose Vial
NDC 0641-6114-01



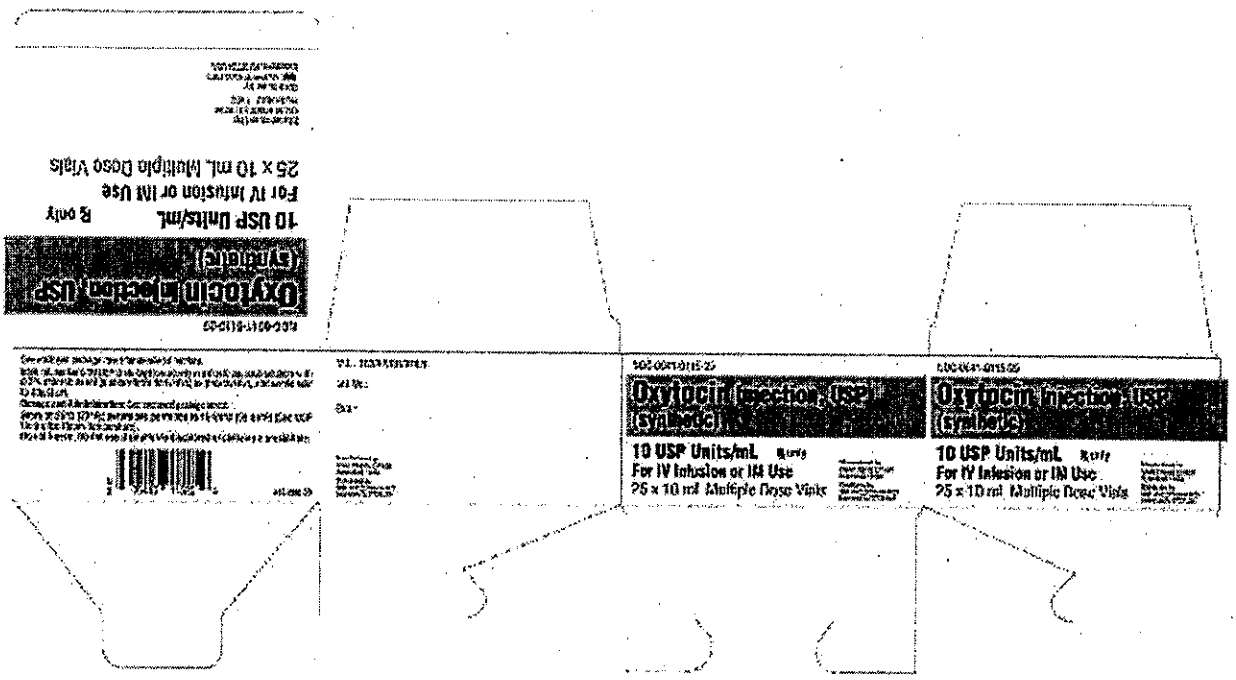
Oxytocin Injection, USP (synthetic)
10 USP Units/mL
25 x 1 mL Single Dose Vials
NDC 0641-6114-25



PRINCIPAL DISPLAY PANEL
Oxytocin Injection, USP (synthetic)
10 USP Units/mL
10 mL Multiple Dose Vial
NDC 0641-6115-01



Oxytocin Injection, USP (synthetic)
10 USP Units/mL
25 x 10 mL Multiple Dose Vials
NDC 0641-6115-25


10 USP Units/mL
For IV Infusion or IM Use
25 x 10 mL Multiple Dose Vials
10 USP Units/mL
For IV Infusion or IM Use
25 x 10 mL Multiple Dose Vials

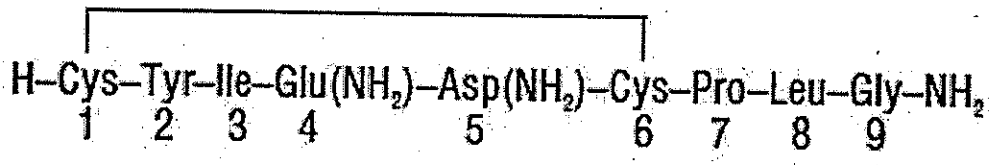
4

OXYTOCIN - oxytocin injection, solution
APP Pharmaceuticals, LLC

(SYNTHETIC)
FOR INTRAVENOUS INFUSION OR INTRAMUSCULAR USE

DESCRIPTION

Each mL of Oxytocin Injection, USP (synthetic), intended for intravenous infusion or intramuscular injection, possesses an oxytocic activity equivalent to 10 USP Oxytocin Units and contains chlorobutanol anhydrous (chloral derivative) 0.5%. This product may contain up to 12.5% decomposition products/impurities. Oxytocin injection (synthetic) is a sterile, clear, colorless solution of oxytocin in Water for Injection prepared by synthesis. Acetic acid may have been added for pH adjustment (pH 3.0-5.0). The structural formula is:



CLINICAL PHARMACOLOGY

Oxytocin injection (synthetic) acts on the smooth muscle of the uterus to stimulate contractions; response depends on the uterine threshold of excitability. It exerts a selective action on the smooth musculature of the uterus, particularly toward the end of pregnancy, during labor and immediately following delivery. Oxytocin stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions and raises the tone of the uterine musculature. Synthetic oxytocin does not possess the cardiovascular effects, such as elevation of blood pressure, as exhibited by vasopressin found in posterior pituitary injection.

INDICATIONS AND USAGE

IMPORTANT NOTICE:

Oxytocin Injection, USP (synthetic) is indicated for the medical rather than the elective induction of labor. Available data and information are inadequate to define the benefits to risks considerations in the use of the drug product for elective induction. Elective induction of labor is defined as the initiation of labor for convenience in an individual with a term pregnancy who is free of medical indications.

Antepartum

Oxytocin injection (synthetic) is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable, in order to achieve early vaginal delivery for fetal or maternal reasons. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, pre-eclampsia at or near term, when delivery is in the best interest of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum

Oxytocin injection (synthetic) is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

CONTRAINDICATIONS

Oxytocin injection (synthetic) is contraindicated in any of the following conditions:

- Significant cephalopelvic disproportion;
- Unfavorable fetal positions or presentations which are undeliverable without conversion prior to delivery, i.e., transverse lies;
- In obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention;
- In cases of fetal distress where delivery is not imminent;

- Prolonged use in uterine inertia or severe toxemia;
- Hypertonic uterine patterns;
- Patients with hypersensitivity to the drug;
- Induction or augmentation of labor in those cases where vaginal delivery is contraindicated, such as cord presentation or prolapse, total placenta previa, and vasa previa.

WARNINGS

Oxytocin injection (synthetic) when given for induction or stimulation of labor, must be administered only by the intravenous route and with adequate medical supervision in a hospital.

PRECAUTIONS

General

All patients receiving intravenous oxytocin must be under continuous observation by trained personnel with a thorough knowledge of the drug and qualified to identify complications. A physician qualified to manage any complications should be immediately available. When properly administered, oxytocin should stimulate uterine contractions similar to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin.

Except in unusual circumstances, oxytocin should not be administered in the following conditions: prematurity, borderline cephalopelvic disproportion, previous major surgery on the cervix or uterus including Caesarean section, overdistention of the uterus, grand multiparity or invasive cervical carcinoma. Because of the variability of the combinations of factors which may be present in the conditions above, the definition of "unusual circumstances" must be left to the judgement of the physician. The decision can only be made by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor and for augmentation in the first and second stages of labor.

Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

Drug Interactions

Severe hypertension has been reported when oxytocin was given three to four hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

Pregnancy Category C.

There are no known indications for use of oxytocin in the first and second trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

Nonteratogenic Effects—See **ADVERSE REACTIONS** in the fetus or infant.

Labor and Delivery—See **INDICATIONS AND USAGE.**

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxytocin is administered to a nursing woman.

ADVERSE REACTIONS

The following adverse reactions have been reported in the mother:

- Anaphylactic reaction
- Postpartum hemorrhage
- Cardiac arrhythmia

• Fatal afibrinogenemia

• Nausea

• Vomiting

• Premature ventricular contractions

• Pelvic hematoma

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction or rupture of the uterus.
The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.
Severe water intoxication with convulsions and coma has occurred, and is associated with a slow oxytocin infusion over a 24-hour period. Maternal death due to oxytocin-induced water intoxication has been reported.
The following adverse reactions have been reported in the fetus or infant:
Due to induced uterine mobility:
• Bradycardia

• Premature ventricular contractions and other arrhythmias

• Permanent CNS or brain damage

• Fetal death

Due to use of oxytocin in the mother:
• Neonatal retinal hemorrhage

• Low Apgar scores at five minutes

• Neonatal jaundice

OVERDOSAGE
Overdosage with oxytocin injection (synthetic) depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion and variable deceleration of fetal heart, fetal hypoxia, hypercapnia or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin, and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION
Dosage of oxytocin is determined by uterine response. The following dosage information is based upon the various regimens and indications in general use.

Induction or Stimulation of Labor
Intravenous infusion (drip method) is the only acceptable method of administration for the induction or stimulation of labor.
Accurate control of the rate of infusion flow is essential. An infusion pump or other such device and frequent monitoring of strength of contractions and fetal heart rate are necessary for the safe administration of oxytocin for the induction or stimulation of labor. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane.
An intravenous infusion of a non-oxytocin containing solution should be started. Physiologic electrolyte solutions should be used except under unusual circumstances.
To prepare the usual solution for intravenous infusion–one mL (10 units) is combined aseptically with 1,000 mL of a non-hydrating diluent.
The combined solution, rotated in the infusion bottle to insure thorough mixing, contains 10 mU/mL. Add the container with dilute oxytocic solution to the system through the use of a constant infusion pump or other such device to control accurately the rate of infusion.
The initial dose should be no more than 1 to 2 mU/min. The dose may be gradually increased in increments of no more than 1 to 2 mU/min., until a contraction pattern has been established which is similar to normal labor.
The fetal heart rate, resting uterine tone, and the frequency, duration, and force of contractions should be monitored.

The oxytocin infusion should be discontinued immediately in the event of uterine hyperactivity or fetal distress. Oxygen should be administered to the mother. The mother and fetus must be evaluated by the responsible physician.

Control of Postpartum Uterine Bleeding
Intravenous Infusion (Drip Method)—To control postpartum bleeding, 10 to 40 units of oxytocin may be added to 1,000 mL of a nonhydrating diluent and run at a rate necessary to control uterine atony.
Intramuscular Administration—1 mL (10 units) of oxytocin can be given after delivery of the placenta.

Treatment of Incomplete or Inevitable Abortion
Intravenous infusion with physiologic saline solution, 500 mL, or 5% dextrose in physiologic saline solution to which 10 units of oxytocin have been added should be infused at a rate of 20 to 40 drops/minute.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED
Oxytocin Injection, USP (synthetic) is supplied as follows:

Product No.	**NDC No.**	**Strength**	**Volume**
91201*	63323-012-01	10 USP Units/mL	1 mL fill in a 3 mL vial, packaged in trays of 25.
1210	63323-012-10	10 USP Units/mL	10 mL fill in a 10 mL multiple dose vial, packaged in trays of 25.
501230†	63323-012-30	10 USP Units/mL	30 mL fill in a 30 mL multiple dose vial, packaged in trays of 10.

*Packaged in a plastic vial.
†Vial stoppers do not contain natural rubber latex.
Discard unused portion.
Use only if solution is clear and seal intact.
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Do not permit to freeze.

APP
APP Pharmaceuticals, LLC
Schaumburg, IL 60173

45789F
Revised: December 2007

PACKAGE LABEL - PRINCIPAL DISPLAY - Oxytocin 10 mL Multiple Dose Vial Label
Oxytocin Injection, USP
(Synthetic)
10 USP Units/mL
For IV Infusion or IM Use
10 mL Multiple Dose Vial
Rx only

OXYTOCIN
INJECTION, USP (SYNTHETIC)

10 USP Units/mL

For IV Infusion or IM Use

10 mL Multiple Dose Vial

Rx only

Sterile

Each mL contains: Oxytocic activity equivalent to 10 USP Oxytocin Units; chlorobutanol anhydrous (chloral derivative) 0.5%; Water for Injection q.s. Acetic acid may have been added for pH adjustment.

Usual Dosage: See Insert.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not permit to freeze.

APP

APP Pharmaceuticals, LLC

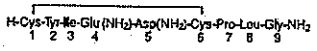
Schaumburg, IL 60173

5

PITOCIN - oxytocin injection
JHP Pharmaceuticals LLC

DESCRIPTION

Pitocin (oxytocin injection, USP) is a sterile, clear, colorless aqueous solution of synthetic oxytocin, for intravenous infusion or intramuscular injection. Pitocin is a nonapeptide found in pituitary extracts from mammals. It is standardized to contain 10 units of oxytocic hormone/mL and contains 0.5% Chlorobutanol, a chloroform derivative as a preservative, with the pH adjusted with acetic acid. Pitocin may contain up to 16% of total impurities. The hormone is prepared synthetically to avoid possible contamination with vasopressin (ADH) and other small polypeptides with biologic activity. Pitocin has the empirical formula $C_{43}H_{66}N_{12}O_{12}S_2$ (molecular weight 1007.19). The structural formula is as follows:



CLINICAL PHARMACOLOGY

Uterine motility depends on the formation of the contractile protein actomyosin under the influence of the Ca^{2+} dependent phosphorylating enzyme myosin light-chain kinase. Oxytocin promotes contractions by increasing the intracellular Ca^{2+}. Oxytocin has specific receptors in the myometrium and the receptor concentration increases greatly during pregnancy, reaching a maximum in early labor at term. The response to a given dose of oxytocin is very individualized and depends on the sensitivity of the uterus, which is determined by the oxytocin receptor concentration. However, the physician should be aware of the fact that oxytocin even in its pure form has inherent pressor and antidiuretic properties which may become manifest when large doses are administered. These properties are thought to be due to the fact that oxytocin and vasopressin differ in regard to only two of the eight amino acids (see PRECAUTIONS section).

Oxytocin is distributed throughout the extracellular fluid. Small amounts of the drug probably reach the fetal circulation. Oxytocin has a plasma half-life of about 1 to 6 minutes which is decreased in late pregnancy and during lactation. Following intravenous administration of oxytocin, uterine response occurs almost immediately and subsides within 1 hour. Following intramuscular injection of the drug, uterine response occurs within 3 to 5 minutes and persists for 2 to 3 hours. Its rapid removal from plasma is accomplished largely by the kidney and the liver. Only small amounts are excreted in urine unchanged.

INDICATIONS AND USAGE

IMPORTANT NOTICE

Elective induction of labor is defined as the initiation of labor in a pregnant individual who has no medical indications for induction. Since the available data are inadequate to evaluate the benefits-to-risks considerations, Pitocin is not indicated for elective induction of labor.

Antepartum

Pitocin is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable for reasons of fetal or maternal concern, in order to achieve vaginal delivery. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, preeclampsia at or near term, when delivery is in the best interests of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) as adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum

Pitocin is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

CONTRAINDICATIONS

Antepartum use of Pitocin is contraindicated in any of the following circumstances:

1. Where there is significant cephalopelvic disproportion;
2. In unfavorable fetal positions or presentations, such as transverse lies, which are undeliverable without conversion prior to delivery;
3. In obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention;
4. In fetal distress where delivery is not imminent;
5. Where adequate uterine activity fails to achieve satisfactory progress;

6. Where the uterus is already hyperactive or hypertonic;

7. In cases where vaginal delivery is contraindicated, such as invasive cervical carcinoma, active herpes genitalis, total placenta previa, vasa previa, and cord presentation or prolapse of the cord;

8. In patients with hypersensitivity to the drug.

WARNINGS

Pitocin, when given for induction of labor or augmentation of uterine activity, should be administered only by the intravenous route and with adequate medical supervision in a hospital.

PRECAUTIONS

General

1. All patients receiving intravenous oxytocin must be under continuous observation by trained personnel who have a thorough knowledge of the drug and are qualified to identify complications. A physician qualified to manage any complications should be immediately available. Electronic fetal monitoring provides the best means for early detection of overdosage (see **OVERDOSAGE** section). However, it must be borne in mind that only intrauterine pressure recording can accurately measure the intrauterine pressure during contractions. A fetal scalp electrode provides a more dependable recording of the fetal heart rate than any external monitoring system.

2. When properly administered, oxytocin should stimulate uterine contractions comparable to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin. This fact must be considered by the physician in exercising his judgment regarding patient selection.

3. Except in unusual circumstances, oxytocin should not be administered in the following conditions: fetal distress, hydramnios, partial placenta previa, prematurity, borderline cephalopelvic disproportion, and any condition in which there is a predisposition for uterine rupture, such as previous major surgery on the cervix or uterus including cesarean section, overdistention of the uterus, grand multiparity, or past history of uterine sepsis or of traumatic delivery. Because of the variability of the combinations of factors which may be present in the conditions listed above, the definition of "unusual circumstances" must be left to the judgment of the physician. The decision can be made only by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

4. Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor.

5. Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

6. When oxytocin is used for induction or reinforcement of already existent labor, patients should be carefully selected. Pelvic adequacy must be considered and maternal and fetal conditions evaluated before use of the drug.

Drug Interactions

Severe hypertension has been reported when oxytocin was given three to four hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

Pregnancy

Teratogenic Effects

Animal reproduction studies have not been conducted with oxytocin. There are no known indications for use in the first trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

Nonteratogenic Effects
See ADVERSE REACTIONS in the fetus or neonate.

Labor and Delivery
See INDICATIONS AND USAGE section.

ADVERSE REACTIONS
The following adverse reactions have been reported in the mother:

Anaphylactic reaction	Premature ventricular contractions
Postpartum hemorrhage	Pelvic hematoma
Cardiac arrhythmia	Subarachnoid hemorrhage
Fatal afibrinogenemia	Hypertensive episodes
Nausea	Rupture of the uterus
Vomiting	

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.
The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.
Severe water intoxication with convulsions and coma has occurred, associated with a slow oxytocin infusion over a 24-hour period.
Maternal death due to oxytocin-induced water intoxication has been reported.
The following adverse reactions have been reported in the fetus or neonate:

Due to induced uterine motility:	Due to use of oxytocin in the mother:
Bradycardia	Low Apgar scores at five minutes
Premature ventricular contractions and other arrhythmias	Neonatal jaundice
Permanent CNS or brain damage	Neonatal retinal hemorrhage
Fetal death	
Neonatal seizures have been reported with the use of Pitocin.	

For medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact JHP at 1-866-923-2547 or MEDWATCH at 1-800-FDA-1088 (1-800-332-1088) or http://www.fda.gov/medwatch/.

OVERDOSAGE
Overdosage with oxytocin depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion, and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, perinatal hepatic necrosis or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
The dosage of oxytocin is determined by the uterine response and must therefore be individualized and initiated at a very low level. The following dosage information is based upon various regimens and indications in general use.

A. Induction or Stimulation of Labor
Intravenous infusion (drip method) is the only acceptable method of parenteral administration of Pitocin for the induction or stimulation of labor. Accurate control of the rate of infusion is essential and is best accomplished by an infusion pump. It is convenient to piggyback the Pitocin infusion on a physiologic electrolyte solution, permitting the Pitocin infusion to be stopped abruptly without interrupting the electrolyte infusion. This is done in the following way.

1. **Preparation**

a. The standard solution for infusion of Pitocin is prepared by adding the contents of one 1-mL vial containing 10 units of oxytocin to 1000 mL of 0.9% aqueous sodium chloride or Ringer's lactate. The combined solution containing 10 milliunits (mU) of oxytocin/mL is rotated in the infusion bottle for thorough mixing.
b. Establish the infusion with a separate bottle of physiologic electrolyte solution not containing Pitocin.
c. Attach (piggyback) the Pitocin-containing bottle with the infusion pump to the infusion line as close to the infusion site as possible.

2. **Administration**

The initial dose should be 0.5–1 mU/min (equal to 3–6 mL of the dilute oxytocin solution per hour). At 30–60 minute intervals the dose should be gradually increased in increments of 1–2 mU/min until the desired contraction pattern has been established. Once the desired frequency of contractions has been reached and labor has progressed to 5–6 cm dilation, the dose may be reduced by similar increments.

Studies of the concentrations of oxytocin in the maternal plasma during Pitocin infusion have shown that infusion rates up to 6 mU/min give the same oxytocin levels that are found in spontaneous labor. At term, higher infusion rates should be given with great care, and rates exceeding 9–10 mU/min are rarely required. Before term, when the sensitivity of the uterus is lower because of a lower concentration of oxytocin receptors, a higher infusion rate may be required.

3. **Monitoring**

a. Electronically monitor the uterine activity and the fetal heart rate throughout the infusion of Pitocin. Attention should be given to tonus, amplitude and frequency of contractions, and to the fetal heart rate in relation to uterine contractions. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane (see **PRECAUTIONS** section).

b. Discontinue the infusion of Pitocin immediately in the event of uterine hyperactivity and/or fetal distress. Administer oxygen to the mother, who preferably should be put in a lateral position. The condition of mother and fetus should immediately be evaluated by the responsible physician and appropriate steps taken.

B. Control of Postpartum Uterine Bleeding

1. Intravenous infusion (drip method). If the patient has an intravenous infusion running, 10 to 40 units of oxytocin may be added to the bottle, depending on the amount of electrolyte or dextrose solution remaining (maximum 40 units to 1000 mL). Adjust the infusion rate to sustain uterine contraction and control uterine atony.

2. Intramuscular administration. (One mL) Ten (10) units of Pitocin can be given after the delivery of the placenta.

C. Treatment of Incomplete, Inevitable, or Elective Abortion

Intravenous infusion of 10 units of Pitocin added to 500 mL of a physiologic saline solution or 5% dextrose-in-water solution may help the uterus contract after a suction or sharp curettage for an incomplete, inevitable, or elective abortion.
Subsequent to intra-amniotic injection of hypertonic saline, prostaglandins, urea, etc., for midtrimester elective abortion, the injection-to-abortion time may be shortened by infusion of Pitocin at the rate of 10 to 20 milliunits (20 to 40 drops) per minute. The total dose should not exceed 30 units in a 12-hour period due to the risk of water intoxication.

HOW SUPPLIED

Pitocin (Oxytocin Injection, USP) Synthetic is available as follows:
NDC 42023-116-25 Packages of twenty-five oversized 1-mL vials, each containing 10 units of oxytocin.
NDC 42023-116-01 A 10 mL multiple-dose vial containing 10 units of oxytocin per mL (total = 100 units of oxytocin).
NDC 42023-116-02 Packages of twenty-five 10 mL multiple-dose vial, each containing 10 units of oxytocin per mL (total = 100 units of oxytocin per vial).

STORAGE

Store between 20° to 25°C (68° to 77°F). Excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]

REFERENCES

1. Seitchik J, Castillo M: Oxytocin augmentation of dysfunctional labor. I. Clinical data. Am J Obstet Gynecol 1982; 144:899–905.

2. Seitchik J, Castillo M: Oxytocin augmentation of dysfunctional labor. II. Multiparous patients. Am J Obstet Gynecol 1983; 145:777–780.

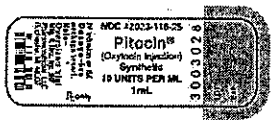
3. Fuchs A, Goeschen K, Husslein P, et al: Oxytocin and the initiation of human parturition. III. Plasma concentrations of oxytocin and 13, 14-dihydro-15-keto-prostaglandin F2a in spontaneous and oxytocin-induced labor at term. Am J Obstet Gynecol 1983; 145:497–502.

4. Seitchik J, Amico J, et al: Oxytocin augmentation of dysfunctional labor. IV. Oxytocin pharmacokinetics. Am J Obstet Gynecol 1984; 150:225–228.

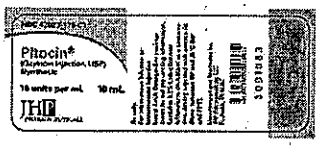
5. American College of Obstetricians and Gynecologists: ACOG Technical Bulletin Number 110—November 1987: Induction and augmentation of labor.

Rx only.
Prescribing Information as of February 2011.
Manufactured and Distributed by: JHP Pharmaceuticals, LLC, Rochester, MI 48307
3000791D

PRINCIPAL DISPLAY PANEL - 1ML LABEL
NDC 42023-116-25
Pitocin®
(Oxytocin Injection)
Synthetic
10 UNITS PER ML
1mL



PRINCIPAL DISPLAY PANEL - 10 ML LABEL
NDC 42023-116-01
Pitocin®
(Oxytocin Injection, USP)
Synthetic
10 units per mL
10 mL
JHP
PHARMACEUTICALS



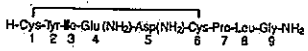
6

PITOCIN - oxytocin injection
JHP Pharmaceuticals LLC

Pharmacy Bulk Package – Not for Direct Infusion

DESCRIPTION

Pitocin (oxytocin injection, USP) is a sterile, clear, colorless aqueous solution of synthetic oxytocin, for intravenous infusion or intramuscular injection. Pitocin is a nonapeptide found in pituitary extracts from mammals. It is standardized to contain 10 units of oxytocic hormone/mL and contains 0.5% Chlorobutanol, a chloroform derivative as a preservative, with the pH adjusted with acetic acid. Pitocin may contain up to 16% of total impurities. The hormone is prepared synthetically to avoid possible contamination with vasopressin (ADH) and other small polypeptides with biologic activity. Pitocin has the empirical formula $C_{43}H_{66}N_{12}O_{12}S_2$ (molecular weight 1007.19). The structural formula is as follows:



CLINICAL PHARMACOLOGY

Uterine motility depends on the formation of the contractile protein actomyosin under the influence of the Ca^{2+}- dependent phosphorylating enzyme myosin light-chain kinase. Oxytocin promotes contractions by increasing the intracellular Ca^{2+}. Oxytocin has specific receptors in the myometrium and the receptor concentration increases greatly during pregnancy, reaching a maximum in early labor at term. The response to a given dose of oxytocin is very individualized and depends on the sensitivity of the uterus, which is determined by the oxytocin receptor concentration. However, the physician should be aware of the fact that oxytocin even in its pure form has inherent pressor and antidiuretic properties which may become manifest when large doses are administered. These properties are thought to be due to the fact that oxytocin and vasopressin differ in regard to only two of the eight amino acids (see PRECAUTIONS section).

Oxytocin is distributed throughout the extracellular fluid. Small amounts of the drug probably reach the fetal circulation. Oxytocin has a plasma half-life of about 1 to 6 minutes which is decreased in late pregnancy and during lactation. Following intravenous administration of oxytocin, uterine response occurs almost immediately and subsides within 1 hour. Following intramuscular injection of the drug, uterine response occurs within 3 to 5 minutes and persists for 2 to 3 hours. Its rapid removal from plasma is accomplished largely by the kidney and the liver. Only small amounts are excreted in urine unchanged.

INDICATIONS AND USAGE

IMPORTANT NOTICE

Elective induction of labor is defined as the initiation of labor in a pregnant individual who has no medical indications for induction. Since the available data are inadequate to evaluate the benefits-to-risks considerations, Pitocin is not indicated for elective induction of labor.

Antepartum

Pitocin is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable for reasons of fetal or maternal concern, in order to achieve vaginal delivery. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, preeclampsia at or near term, when delivery is in the best interests of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) as adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum

Pitocin is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

CONTRAINDICATIONS

Antepartum use of Pitocin is contraindicated in any of the following circumstances:

1. Where there is significant cephalopelvic disproportion;
2. In unfavorable fetal positions or presentations, such as transverse lies, which are undeliverable without conversion prior to delivery;
3. In obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention;
4. In fetal distress where delivery is not imminent;

5. Where adequate uterine activity fails to achieve satisfactory progress;

6. Where the uterus is already hyperactive or hypertonic;

7. In cases where vaginal delivery is contraindicated, such as invasive cervical carcinoma, active herpes genitalis, total placenta previa, vasa previa, and cord presentation or prolapse of the cord;

8. In patients with hypersensitivity to the drug.

WARNINGS

Pitocin, when given for induction of labor or augmentation of uterine activity, should be administered only by the intravenous route and with adequate medical supervision in a hospital.

PRECAUTIONS

General

1. All patients receiving intravenous oxytocin must be under continuous observation by trained personnel who have a thorough knowledge of the drug and are qualified to identify complications. A physician qualified to manage any complications should be immediately available. Electronic fetal monitoring provides the best means for early detection of overdosage (see **OVERDOSAGE** section). However, it must be borne in mind that only intrauterine pressure recording can accurately measure the intrauterine pressure during contractions. A fetal scalp electrode provides a more dependable recording of the fetal heart rate than any external monitoring system.

2. When properly administered, oxytocin should stimulate uterine contractions comparable to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin. This fact must be considered by the physician in exercising his judgment regarding patient selection.

3. Except in unusual circumstances, oxytocin should not be administered in the following conditions: fetal distress, hydramnios, partial placenta previa, prematurity, borderline cephalopelvic disproportion, and any condition in which there is a predisposition for uterine rupture, such as previous major surgery on the cervix or uterus including cesarean section, overdistention of the uterus, grand multiparity, or past history of uterine sepsis or of traumatic delivery. Because of the variability of the combinations of factors which may be present in the conditions listed above, the definition of "unusual circumstances" must be left to the judgment of the physician. The decision can be made only by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

4. Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor.

5. Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

6. When oxytocin is used for induction or reinforcement of already existent labor, patients should be carefully selected. Pelvic adequacy must be considered and maternal and fetal conditions evaluated before use of the drug.

Drug Interactions

Severe hypertension has been reported when oxytocin was given three to four hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

Pregnancy

Teratogenic Effects
Animal reproduction studies have not been conducted with oxytocin. There are no known indications for use in the first trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

Nonteratogenic Effects
See ADVERSE REACTIONS in the fetus or neonate.

Labor and Delivery
See INDICATIONS AND USAGE section.

ADVERSE REACTIONS
The following adverse reactions have been reported in the mother:

Anaphylactic reaction	Premature ventricular contractions
Postpartum hemorrhage	Pelvic hematoma
Cardiac arrhythmia	Subarachnoid hemorrhage
Fatal afibrinogenemia	Hypertensive episodes
Nausea	Rupture of the uterus
Vomiting	

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.
The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.
Severe water intoxication with convulsions and coma has occurred, associated with a slow oxytocin infusion over a 24-hour period.
Maternal death due to oxytocin-induced water intoxication has been reported.
The following adverse reactions have been reported in the fetus or neonate:

Due to induced uterine motility:	Due to use of oxytocin in the mother:
Bradycardia	Low Apgar scores at five minutes
Premature ventricular contractions and other arrhythmias	Neonatal jaundice
Permanent CNS or brain damage	Neonatal retinal hemorrhage
Fetal death	
Neonatal seizures have been reported with the use of Pitocin.	

For medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact JHP at 1-866-923-2547 or MEDWATCH at 1-800-FDA-1088 (1-800-332-1088) or http://www.fda.gov/medwatch/.

OVERDOSAGE
Overdosage with oxytocin depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion, and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, perinatal hepatic necrosis or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
The dosage of oxytocin is determined by the uterine response and must therefore be individualized and initiated at a very low level. The following dosage information is based upon various regimens and indications in general use.

A. Induction or Stimulation of Labor
Intravenous infusion (drip method) is the only acceptable method of parenteral administration of Pitocin for the induction or stimulation of labor. Accurate control of the rate of infusion is essential and is best accomplished by an infusion pump. It is convenient to piggyback the Pitocin infusion on a physiologic electrolyte solution, permitting the Pitocin infusion to be stopped abruptly without interrupting the electrolyte infusion. This is done in the following way.

1. **Preparation**

a. The standard solution for infusion of Pitocin is prepared by adding 1 mL (containing 10 units of oxytocin) to 1000 mL of 0.9% aqueous sodium chloride or Ringer's lactate. The combined solution containing 10 milliunits (mU) of oxytocin/mL is rotated in the infusion bottle for thorough mixing.
b. Establish the infusion with a separate bottle of physiologic electrolyte solution not containing Pitocin.
c. Attach (piggyback) the Pitocin-containing bottle with the infusion pump to the infusion line as close to the infusion site as possible.

2. **Administration**

The initial dose should be 0.5–1 mU/min (equal to 3–6 mL of the dilute oxytocin solution per hour). At 30–60 minute intervals the dose should be gradually increased in increments of 1–2 mU/min until the desired contraction pattern has been established. Once the desired frequency of contractions has been reached and labor has progressed to 5–6 cm dilation, the dose may be reduced by similar increments.

Studies of the concentrations of oxytocin in the maternal plasma during Pitocin infusion have shown that infusion rates up to 6 mU/min give the same oxytocin levels that are found in spontaneous labor. At term, higher infusion rates should be given with great care, and rates exceeding 9–10 mU/min are rarely required. Before term, when the sensitivity of the uterus is lower because of a lower concentration of oxytocin receptors, a higher infusion rate may be required.

3. **Monitoring**

a. Electronically monitor the uterine activity and the fetal heart rate throughout the infusion of Pitocin. Attention should be given to tonus, amplitude and frequency of contractions, and to the fetal heart rate in relation to uterine contractions. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane (see **PRECAUTIONS** section).
b. Discontinue the infusion of Pitocin immediately in the event of uterine hyperactivity and/or fetal distress. Administer oxygen to the mother, who preferably should be put in a lateral position. The condition of mother and fetus should immediately be evaluated by the responsible physician and appropriate steps taken.

B. Control of Postpartum Uterine Bleeding

1. Intravenous infusion (drip method). If the patient has an intravenous infusion running, 10 to 40 units of oxytocin may be added to the bottle, depending on the amount of electrolyte or dextrose solution remaining (maximum 40 units to 1000 mL). Adjust the infusion rate to sustain uterine contraction and control uterine atony.

2. Intramuscular administration. 1 mL (10 units) of Pitocin can be given after the delivery of the placenta.

C. Treatment of Incomplete, Inevitable, or Elective Abortion

Intravenous infusion of 10 units of Pitocin added to 500 mL of a physiologic saline solution or 5% dextrose-in-water solution may help the uterus contract after a suction or sharp curettage for an incomplete, inevitable, or elective abortion.
Subsequent to intra-amniotic injection of hypertonic saline, prostaglandins, urea, etc., for midtrimester elective abortion, the injection-to-abortion time may be shortened by infusion of Pitocin at the rate of 10 to 20 milliunits (20 to 40 drops) per minute. The total dose should not exceed 30 units in a 12-hour period due to the risk of water intoxication.

Directions for Dispensing

Pharmacy Bulk Package – Not for Direct Infusion
The pharmacy bulk package is for use in a pharmacy admixture service only in a suitable work area, such as a laminar flow hood. The closure should be penetrated only once utilizing an appropriate sterile transfer device, which allows measured distribution of the contents. The transfer device should be inserted into the Pharmacy Bulk Package using aseptic technique.

Contents should be used as soon as possible following initial closure puncture. Discard any unused portion within 24 hours of first entry. Following closure puncture, container should be maintained under labeled storage conditions between 20° to 25°C (68° to 77°F) under a laminar flow hood until contents are dispensed.

HOW SUPPLIED

Pitocin (Oxytocin Injection, USP) Synthetic is available as follows:
NDC 42023-130-06 Packages of six 50 mL Pharmacy Bulk Packages, each containing 10 units of oxytocin per mL (total = 500 units of oxytocin per vial).

STORAGE

Store between 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature.

REFERENCES

1. Seitchik J, Castillo M: Oxytocin augmentation of dysfunctional labor. I. Clinical data. Am J Obstet Gynecol 1982; 144:899–905.

2. Seitchik J, Castillo M: Oxytocin augmentation of dysfunctional labor. II. Multiparous patients. Am J Obstet Gynecol 1983; 145:777–780.

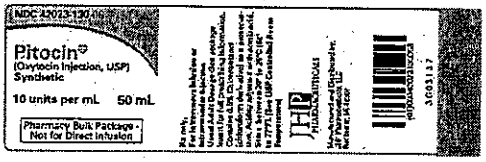
3. Fuchs A, Goeschen K, Husslein P, et al: Oxytocin and the initiation of human parturition. III. Plasma concentrations of oxytocin and 13, 14-dihydro-15-keto-prostaglandin F2a in spontaneous and oxytocin-induced labor at term. Am J Obstet Gynecol 1983; 145:497–502.

4. Seitchik J, Amico J, et al: Oxytocin augmentation of dysfunctional labor. IV. Oxytocin pharmacokinetics. Am J Obstet Gynecol 1984; 150:225–228.

5. American College of Obstetricians and Gynecologists: ACOG Technical Bulletin Number 110—November 1987: Induction and augmentation of labor.

Rx only.
Prescribing Information as of April 2012.
Manufactured and Distributed by: JHP Pharmaceuticals, LLC, Rochester, MI 48307

PRINCIPAL DISPLAY PANEL - 50 ML BOTTLE LABEL
NDC 42023-130-06
Pitocin®
(Oxytocin Injection, USP)
Synthetic
10 units per mL
50 mL
Pharmacy Bulk Package -
Not for Direct Infusion

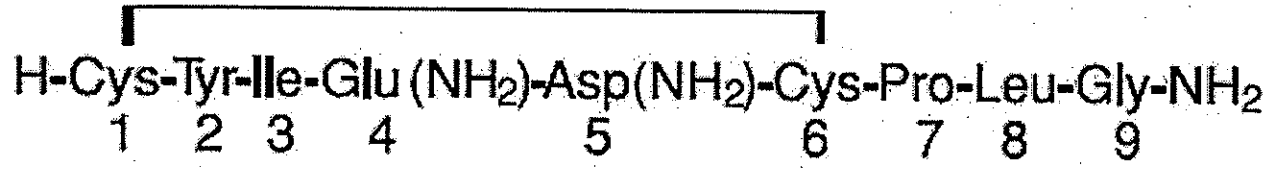


7

PITOCIN - oxytocin injection
Watson Laboratories, Inc.

DESCRIPTION

Oxytocin injection USP is a sterile, clear, colorless aqueous solution of synthetic oxytocin, for intravenous infusion or intramuscular injection. Oxytoxin is a nonapeptide found in pituitary extracts from mammals. It is standardized to contain 10 units of oxytocic hormone/mL and contains 0.5% Chlorobutanol, a chloroform derivative as a preservative, with the pH adjusted with acetic acid. Oxytocin may contain up to 16% of total impurities. The hormone is prepared synthetically to avoid possible contamination with vasopressin (ADH) and other small polypeptides with biologic activity. Oxytocin has the empirical formula $C_{43}H_{66}N_{12}O_{12}S_2$ (molecular weight 1007.19). The structural formula is as follows:



CLINICAL PHARMACOLOGY

Uterine motility depends on the formation of the contractile protein actomyosin under the influence of the Ca^{2+}-dependent phosphorylating enzyme myosin light-chain kinase. Oxytocin promotes contractions by increasing the intracellular Ca^{2+}. Oxytocin has specific receptors in the myometrium and the receptor concentration increases greatly during pregnancy, reaching a maximum in early labor at term. The response to a given dose of oxytocin is very individualized and depends on the sensitivity of the uterus, which is determined by the oxytocin receptor concentration. However, the physician should be aware of the fact that oxytocin even in its pure form has inherent pressor and antidiuretic properties which may become manifest when large doses are administered. These properties are thought to be due to the fact that oxytocin and vasopressin differ in regard to only two of the eight amino acids (see PRECAUTIONS section).

Oxytocin is distributed throughout the extracellular fluid. Small amounts of the drug probably reach the fetal circulation. Oxytocin has a plasma half-life of about 1 to 6 minutes which is decreased in late pregnancy and during lactation. Following intravenous administration of oxytocin, uterine response occurs almost immediately and subsides within 1 hour. Following intramuscular injection of the drug, uterine response occurs within 3 to 5 minutes and persists for 2 to 3 hours. Its rapid removal from plasma is accomplished largely by the kidney and the liver. Only small amounts are excreted in urine unchanged.

INDICATIONS AND USAGE

IMPORTANT NOTICE

Elective induction of labor is defined as the initiation of labor in a pregnant individual who has no medical indications for induction. Since the available data are inadequate to evaluate the benefits-to-risks considerations, oxytocin is not indicated for elective induction of labor.

Antepartum: Oxytocin is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable for reasons of fetal or maternal concern, in order to achieve vaginal delivery. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, preeclampsia at or near term, when delivery is in the best interests of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) as adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum: Oxytocin is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

CONTRAINDICATIONS

Antepartum use of oxytocin is contraindicated in any of the following circumstances:

1. Where there is significant cephalopelvic disproportion;
2. In unfavorable fetal positions or presentations, such as transverse lies, which are undeliverable without conversion prior to delivery;
3. In obstetrical emergencies where the benefit-torisk ratio for either the fetus or the mother favors surgical intervention;

4. In fetal distress where delivery is not imminent;

5. Where adequate uterine activity fails to achieve satisfactory progress;

6. Where the uterus is already hyperactive or hypertonic;

7. In cases where vaginal delivery is contraindicated, such as invasive cervical carcinoma, active herpes genitalis, total placenta previa, vasa previa, and cord presentation or prolapse of the cord;

8. In patients with hypersensitivity to the drug.

WARNINGS

Oxytocin, when given for induction of labor or augmentation of uterine activity, should be administered only by the intravenous route and with adequate medical supervision in a hospital.

PRECAUTIONS

General

1. All patients receiving intravenous oxytocin must be under continuous observation by trained personnel who have a thorough knowledge of the drug and are qualified to identify complications. A physician qualified to manage any complications should be immediately available. Electronic fetal monitoring provides the best means for early detection of overdosage (see OVERDOSAGE section). However, it must be borne in mind that only intrauterine pressure recording can accurately measure the intrauterine pressure during contractions. A fetal scalp electrode provides a more dependable recording of the fetal heart rate than any external monitoring system.

2. When properly administered, oxytocin should stimulate uterine contractions comparable to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin. This fact must be considered by the physician in exercising his judgment regarding patient selection.

3. Except in unusual circumstances, oxytocin should not be administered in the following conditions: fetal distress, hydramnios, partial placenta previa, prematurity, borderline cephalopelvic disproportion, and any condition in which there is a predisposition for uterine rupture, such as previous major surgery on the cervix or uterus including cesarean section, overdistention of the uterus, grand multiparity, or past history of uterine sepsis or of traumatic delivery. Because of the variability of the combinations of factors which may be present in the conditions listed above, the definition of "unusual circumstances" must be left to the judgment of the physician. The decision can be made only by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

4. Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor.

5. Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

6. When oxytocin is used for induction or reinforcement of already existent labor, patients should be carefully selected. Pelvic adequacy must be considered and maternal and fetal conditions evaluated before use of the drug.

Drug Interactions

Severe hypertension has been reported when oxytocin was given three to four hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

Pregnancy

Teratogenic Effects
Animal reproduction studies have not been conducted with oxytocin. There are no known indications for use in the first trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

Nonteratogenic Effects
See ADVERSE REACTIONS in the fetus or neonate.

Labor and Delivery
See INDICATIONS AND USAGE section.

ADVERSE REACTIONS
The following adverse reactions have been reported in the mother:

Anaphylactic reaction

Postpartum hemorrhage

Cardiac arrhythmia

Fatal afibrinogenemia

Oxytocin Injection USP

Nausea

Vomiting

Premature ventricular contractions

Pelvic hematoma

Subarachnoid hemorrhage

Hypertensive episodes

Rupture of the uterus

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.
The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.
Severe water intoxication with convulsions and coma has occurred, associated with a slow oxytocin infusion over a 24-hour period.
Maternal death due to oxytocininduced water intoxication has been reported.
The following adverse reactions have been reported in the fetus or neonate:

Due to induced uterine motility:

Bradycardia

Premature ventricular contractions and other arrhythmias

Permanent CNS or brain damage

Fetal death

Neonatal seizures have been reported with the use of oxytocin.

Due to use of oxytocin in the mother:

Low Apgar scores at five minutes

Neonatal jaundice

Neonatal retinal hemorrhage

OVERDOSAGE

Overdosage with oxytocin depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimula-tion with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion, and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, perinatal hepatic necrosis or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The dosage of oxytocin is determined by the uterine response and must therefore be individualized and initiated at a very low level. The following dosage information is based upon various regimens and indications in general use.

1. **Induction or Stimulation of Labor**

   Intravenous infusion (drip method) is the only acceptable method of parenteral administration of oxytocin for the induction or stimulation of labor. Accurate control of the rate of infusion is essential and is best accomplished by an infusion pump. It is convenient to piggyback the ocytocin infusion on a physiologic electrolyte solution, permitting the oxytocin infusion to be stopped abruptly without interrupting the electrolyte infusion. This is done in the following way.

1. **Preparation**

1. The standard solution for infusion of oxytocin is prepared by adding the contents of one 1-mL vial containing 10 units of oxytocin to 1000 mL of 0.9% aqueous sodium chloride or Ringer's lactate. The combined solution containing 10 milliunits (mU) of oxytocin/mL is rotated in the infusion bottle for thorough mixing.
2. Establish the infusion with a separate bottle of physiologic electrolyte solution not cotaining oxytocin.
3. Attach (piggyback) the oxytocin-containing bottle with the infusion pump to the infusion line as close to the infusion site as possible.

2. **Administration**

   The initial dose should be 0.5–1 mU/min (equal to 3–6 mL of the dilute oxytocin solution per hour). At 30–60 minute intervals the dose should be gradually increased in increments of 1–2 mU/min until the desired contraction pattern has been established. Once the desired frequency of contractions has been reached and labor has progressed to 5–6 cm dilation, the dose may be reduced by similar increments.

   Studies of the concentrations of oxytocin in the maternal plasma during oxytocin infusion have shown that infusion rates up to 6 mU/min give the same oxytocin levels that are found in spontaneous labor. At term, higher infusion rates should be given with great care, and rates exceeding 9–10 mU/min are rarely required. Before term, when the sensitivity of the uterus is lower because of a lower concentration of oxytocin receptors, a higher infusion rate may be required.

3. **Monitoring**

1. Electronically monitor the uterine activity and the fetal heart rate throughout the infusion of oxytocin. Attention should be given to tonus, amplitude and frequency of contractions, and to the fetal heart rate in relation to uterine contractions. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane (see PRECAUTIONS section).
2. Discontinue the infusion of oxytocin immediately in the event of uterine hyperactivity and/or fetal distress. Administer oxygen to the mother, who preferably should be put in a lateral position. The condition of mother and fetus should immediately be evaluated by the responsible physician and appropriate steps taken.

2. **Control of Postpartum Uterine Bleeding**

1. Intravenous infusion (drip method). If the patient has an intravenous infusion running, 10 to 40 units of oxytocin may be added to the bottle, depending on the amount of electrolyte or dextrose solution remaining (maximum 40 units to 1000 mL). Adjust the infusion rate to sustain uterine contraction and control uterine atony.
2. Intramuscular administration. (One mL) Ten (10) units of oxytocin can be given after the delivery of the placenta.

3. **Treatment of Incomplete, Inevitable, or Elective Abortion**

   Intravenous infusion of 10 units of oxytocin added to 500 mL of a physiologic saline solution or 5% dextrose-in-water solution may help the uterus contract after a suction or sharp curettagefor an incomplete, inevitable, or elective abortion. Subsequent to intra-amniotic injection of hypertonic saline, prostaglandins, urea, etc., for midtrimester elective abortion, the injection-toabortion time may be shortened by infusion of oxytocin at the rate of 10 to 20 milliunits (20 to 40 drops) per minute. The total dose should not exceed 30 units in a 12-hour period due to the risk of water intoxication.

HOW SUPPLIED

Oxytocin Injection USP Synthetic is available as follows:

NDC 0591-3553-69 Packages of twenty-five oversized 1-mL vials, each containing 10 units of oxytocin.

STORAGE

Store at 2°–8°C (36°–46°F). May be held at 15°–25°C (59°–77°F) for up to 30 days. Discard after holding at 15°–25°C (59°–77°F).

REFERENCES

1. Seitchik J, Castillo M: Oxytocin augmentation of dysfunctional labor. I. Clinical data. *Am J Obstet Gynecol* 1982; 144:899–905.
2. Seitchik J, Castillo M: Oxytocin augmentation of dysfunctional labor. II. Multiparous patients. *Am J Obstet Gynecol* 1983; 145:777–780.
3. Fuchs A, Goeschen K, Husslein P, et al: Oxytocin and the initiation of human parturition. III. Plasma concentrations of oxytocin and 13, 14-dihydro-15-keto-prostaglandin F2a in spontaneous and oxytocin-induced labor at term. *Am J Obstet Gynecol* 1983; 145:497–502.
4. Seitchik J, Amico J, et al: Oxytocin augmentation of dysfunctional labor. IV. Oxytocin pharmacokinetics. *Am J Obstet Gynecol* 1984; 150:225–228.
5. American College of Obstetricians and Gynecologists: ACOG Technical Bulletin Number 110—November 1987: Induction and augmentation of labor.

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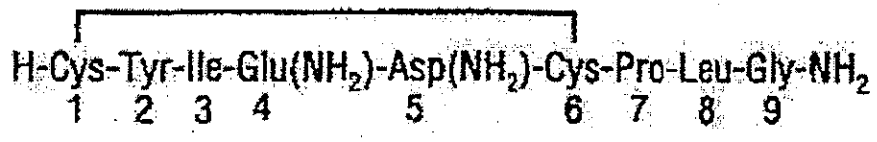
SYNTOCINON - oxytocin injection, solution
Sandoz Pharmaceuticals Corporation

Syntocinon®
(oxytocin) injection, USP
Caution: Federal law prohibits dispensing without prescription.

DESCRIPTION

Syntocinon® (oxytocin) is a synthetic, (1-6) cyclic nonapeptide. Chemically, oxytocin is designated as Glycinamide, L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl- L-leucyl-, cyclic (1-6)-disulfide.
The structural formula is:



$C_{43}H_{66}N_{12}O_{12}S_2$ Mol. wt. 1007.19

Syntocinon® (oxytocin) injection is provided as a sterile solution for intravenous or intramuscular administration. Each 1 mL of solution contains 10 USP or International Units of oxytocin and the following inactive ingredients:
acetic acid, NF, qs to ..... pH 4 ± 0.3
alcohol, USP..... 0.61 % by vol.
chlorobutanol, NF 0.5%
sodium acetate, USP ..... 1 mg
sodium chloride, USP ..... 0.017 mg
water for injection, USP, qs to ..... 1 mL

CLINICAL PHARMACOLOGY

The pharmacologic and clinical properties of Syntocinon® (oxytocin) are identical with the naturally occurring oxytocic principle of the posterior lobe of the pituitary. Syntocinon® (oxytocin) injection does not contain the amino acids characteristic of vasopressin, and therefore has fewer and less severe cardiovascular effects. Syntocinon® (oxytocin) exerts a selective action on the smooth musculature of the uterus, particularly toward the end of pregnancy, during labor and immediately following delivery. Oxytocin stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions, and raises the tone of the uterine musculature.

Syntocinon® (oxytocin), when given in appropriate doses during pregnancy, is capable of eliciting graded increases in uterine motility from a moderate increase in the rate and force of spontaneous motor activity to sustained tetanic contraction.

Syntocinon® (oxytocin) is promptly effective after parenteral administration. Following intramuscular injection, the myotonic effect on the uterus appears in 3-7 minutes, and persists for 30-60 minutes. With intravenous injection, the uterine effect appears within 1 minute and is of more brief duration.

INDICATIONS AND USAGE

Important Notice

Syntocinon® (oxytocin) injection is indicated for the medical rather than the elective induction of labor. Available data and information are inadequate to define the benefits to risk considerations in the use of the drug product for elective induction. Elective induction of labor is defined as the initiation of labor for convenience in an individual with a term pregnancy who is free of medical indications.

Antepartum

Syntocinon® (oxytocin) is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable, in order to achieve early vaginal delivery for fetal or maternal reasons. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, pre-eclampsia at or near term, when delivery is in the best interest of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) as adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In the second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum

Syntocinon® (oxytocin) injection is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

CONTRAINDICATIONS

Syntocinon® (oxytocin) injection is contraindicated in any of the following conditions: Significant cephalopelvic disproportion; unfavorable fetal positions or presentations which are undeliverable without conversion prior to delivery (transverse lies); i.e., in obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention; in cases of fetal distress where delivery is not imminent; prolonged use in uterine inertia or severe toxemia; hypertonic uterine patterns; patients with hypersensitivity to the drug; induction or augmentation of labor in those cases where vaginal delivery is contraindicated, such as cord presentation or prolapse, total placental previa, and vasa previa.

WARNINGS

Syntocinon® (oxytocin), when given for induction or stimulation of labor, must be administered only by the intravenous route and with adequate medical supervision in a hospital.

PRECAUTIONS

General

All patients receiving intravenous oxytocin must he under continuous observation by trained personnel with a thorough knowledge of the drug and qualified to identify complications. A physician qualified to manage any complications should be immediately available.

When properly administered, oxytocin should stimulate uterine contractions similar to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin.

Except in unusual circumstances, oxytocin should not be administered in the following conditions: prematurity, borderline cephalopelvic disproportion, previous major surgery on the cervix or uterus including cesarean section, over-distention of the uterus, grand multiparity, or invasive cervical carcinoma. Because of the variability of the combinations of factors which may be present in the conditions listed above, the definition of "unusual circumstances" must be left to the judgment of the physician. The decision can only be made by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor or for augmentation in the first and second stages of labor.

Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

Drug Interactions

Severe hypertension has been reported when oxytocin was given 3-4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

Pregnancy

Teratogenic Effects:

Animal reproduction studies have not been conducted with oxytocin. There are no known indications for use in the first trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

Nonteratogenic Effects:

See ADVERSE REACTIONS in the fetus or infant.

Labor and Delivery

See INDICATIONS AND USAGE.

Nursing Mothers

Syntocinon® (oxytocin) may be found in small quantities in mother's milk. If a patient requires the drug postpartum to control severe bleeding, she should not commence nursing until the day after Syntocinon® (oxytocin) has been discontinued.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The following adverse reactions have been reported in the mother: Anaphylactic reaction, Postpartum hemorrhage, Cardiac arrhythmia, Fatal afibrinogenemia, Nausea, Vomiting, Premature ventricular contractions, and Pelvic hematoma.
Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.
The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.
Severe water intoxication with convulsions and coma has occurred, associated with a slow oxytocin infusion over a 24-hour period. Maternal death due to oxytocin-induced water intoxication has been reported.
The following adverse reactions have been reported in the fetus or infant:
Due to induced uterine motility: Bradycardia, Premature ventricular contractions and other arrhythmias, Permanent CNS or brain damage, and Fetal death.
Due to use of oxytocin in the mother: Low Apgar scores at 5 minutes. Neonatal jaundice, and Neonatal retinal hemorrhage.

DRUG ABUSE AND DEPENDENCE

There is no evidence that Syntocinon® (oxytocin) has been abused or has provoked drug dependence.

OVERDOSAGE

Overdosage with oxytocin depends essentially on uterine hyperactivity, whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15-20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion, and variable deceleration of fetal heart, fetal hypoxia, hypercapnia, or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40-50 mL/minute) are infused for long periods. Treatment of water intoxication consists of discontinuation of oxytocin, restriction of fluid intake, diuresis, IV hypertonic saline solution, correction of electrolyte imbalance, control of convulsions with judicious use of a barbiturate, and special nursing care for the comatose patient.

DOSAGE AND ADMINISTRATION

Dosage of oxytocin is determined by uterine response. The following dosage information is based upon the various regimens and indications in general use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, wherever solution and container permit.

A. Induction of Stimulation of Labor

Intravenous infusion (drip method) is the only acceptable method of administration for the induction or stimulation of labor. Accurate control of the rate of infusion flow is essential. An infusion pump or other such device and frequent monitoring of strength of contractions and fetal heart rate are necessary for the safe administration of oxytocin for the induction or stimulation of labor. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocin stimulation of the uterine musculature will soon wane.

1. An intravenous infusion of non-oxytocin containing solution should be started. Physiologic electrolyte solution should be used except under unusual circumstances.

2. To prepare the usual solution for infusion, the contents of one 1-mL ampul are combined aseptically with 1,000 mL of non-hydrating diluent. The combined solution, rotated in the infusion bottle to insure thorough mixing, contains 10 mU/mL. Add the container with dilute oxytocin solution to the system through use of a constant infusion pump or other such device, to control accurately the rate of infusion.

3. The initial dose should be no more than 1-2 mU/minute. The dose may be gradually increased in increments of no more than 1-2 mU/minute, until a contraction pattern has been established which is similar to normal labor.

4. The fetal heart rate, resting uterine tone, and the frequency, duration, and force of contractions should be monitored.

5. The oxytocin infusion should be discontinued immediately in the event of uterine hyperactivity or fetal distress. Oxygen should be administered to the mother. The mother and the fetus must be evaluated by the responsible physician.

B. Control of Postpartum Uterine Bleeding

1. *Intravenous Infusion (Drip Method):* To control postpartum bleeding, 10-40 units of oxytocin may be added to 1,000 mL of a non-hydrating diluent and run at a rate necessary to control uterine atony.

2. *Intramuscular Administration*: 1 mL (10 units) of oxytocin can be given after delivery of the placenta.

C. Treatment of Incomplete or Inevitable Abortion

Intravenous infusion with physiologic saline solution, 500 mL, or 5% dextrose in physiologic saline solution to which 10 units of Syntocinon® (oxytocin) have been added should be infused at a rate of 20-40 drops/minute.

HOW SUPPLIED

Syntocinon® (oxytocin) injection, USP

Available as a 1 mL sterile ampul containing 10 USP or International Units of oxytocin. SandoPak® unit dose packages of 50 ampuls (NDC 0078-0060-04).

Store and dispense

Below 77°F (25°C); DO NOT FREEZE.

Sandoz Pharmaceuticals Corporation East Hanover, New Jersey 07936

REV: MAY 1996 30288904

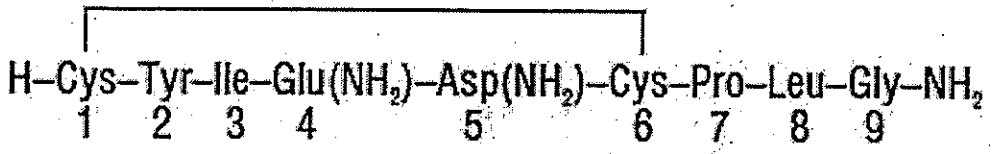
(9)

OXYTOCIN - oxytocin injection, solution
Fresenius Kabi USA, LLC

(SYNTHETIC)
FOR INTRAVENOUS INFUSION OR INTRAMUSCULAR USE

DESCRIPTION

Each mL of Oxytocin Injection, USP (synthetic), intended for intravenous infusion or intramuscular injection, possesses an oxytocic activity equivalent to 10 USP Oxytocin Units and contains chlorobutanol anhydrous (chloral derivative) 0.5%. This product may contain up to 12.5% decomposition products/impurities. Oxytocin injection (synthetic) is a sterile, clear, colorless solution of oxytocin in Water for Injection prepared by synthesis. Acetic acid may have been added for pH adjustment (pH 3.0-5.0). The structural formula is:



CLINICAL PHARMACOLOGY

Oxytocin injection (synthetic) acts on the smooth muscle of the uterus to stimulate contractions; response depends on the uterine threshold of excitability. It exerts a selective action on the smooth musculature of the uterus, particularly toward the end of pregnancy, during labor and immediately following delivery. Oxytocin stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions and raises the tone of the uterine musculature. Synthetic oxytocin does not possess the cardiovascular effects, such as elevation of blood pressure, as exhibited by vasopressin found in posterior pituitary injection.

INDICATIONS AND USAGE

IMPORTANT NOTICE:

Oxytocin Injection, USP (synthetic) is indicated for the medical rather than the elective induction of labor. Available data and information are inadequate to define the benefits to risks considerations in the use of the drug product for elective induction. Elective induction of labor is defined as the initiation of labor for convenience in an individual with a term pregnancy who is free of medical indications.

Antepartum

Oxytocin injection (synthetic) is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable, in order to achieve early vaginal delivery for fetal or maternal reasons. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, pre-eclampsia at or near term, when delivery is in the best interest of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum

Oxytocin injection (synthetic) is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

CONTRAINDICATIONS

Oxytocin injection (synthetic) is contraindicated in any of the following conditions:

- Significant cephalopelvic disproportion;
- Unfavorable fetal positions or presentations which are undeliverable without conversion prior to delivery, i.e., transverse lies;
- In obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention;
- In cases of fetal distress where delivery is not imminent;

- Prolonged use in uterine inertia or severe toxemia;
- Hypertonic uterine patterns;
- Patients with hypersensitivity to the drug;
- Induction or augmentation of labor in those cases where vaginal delivery is contraindicated, such as cord presentation or prolapse, total placenta previa, and vasa previa.

WARNINGS

Oxytocin injection (synthetic) when given for induction or stimulation of labor, must be administered only by the intravenous route and with adequate medical supervision in a hospital.

PRECAUTIONS

General

All patients receiving intravenous oxytocin must be under continuous observation by trained personnel with a thorough knowledge of the drug and qualified to identify complications. A physician qualified to manage any complications should be immediately available. When properly administered, oxytocin should stimulate uterine contractions similar to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin.

Except in unusual circumstances, oxytocin should not be administered in the following conditions: prematurity, borderline cephalopelvic disproportion, previous major surgery on the cervix or uterus including Caesarean section, overdistention of the uterus, grand multiparity or invasive cervical carcinoma. Because of the variability of the combinations of factors which may be present in the conditions above, the definition of "unusual circumstances" must be left to the judgement of the physician. The decision can only be made by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor and for augmentation in the first and second stages of labor.

Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

Drug Interactions

Severe hypertension has been reported when oxytocin was given three to four hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

Pregnancy Category C.

There are no known indications for use of oxytocin in the first and second trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

Nonteratogenic Effects—See **ADVERSE REACTIONS** in the fetus or infant.

Labor and Delivery—See **INDICATIONS AND USAGE.**

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxytocin is administered to a nursing woman.

ADVERSE REACTIONS

The following adverse reactions have been reported in the mother:

- Anaphylactic reaction
- Postpartum hemorrhage
- Cardiac arrhythmia

- Fatal afibrinogenemia
- Nausea
- Vomiting
- Premature ventricular contractions
- Pelvic hematoma

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction or rupture of the uterus.
The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.
Severe water intoxication with convulsions and coma has occurred, and is associated with a slow oxytocin infusion over a 24-hour period. Maternal death due to oxytocin-induced water intoxication has been reported.
The following adverse reactions have been reported in the fetus or infant:
Due to induced uterine mobility:
- Bradycardia
- Premature ventricular contractions and other arrhythmias
- Permanent CNS or brain damage
- Fetal death

Due to use of oxytocin in the mother:
- Neonatal retinal hemorrhage
- Low Apgar scores at five minutes
- Neonatal jaundice

OVERDOSAGE
Overdosage with oxytocin injection (synthetic) depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm H_2O or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion and variable deceleration of fetal heart, fetal hypoxia, hypercapnia or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin, and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION
Dosage of oxytocin is determined by uterine response. The following dosage information is based upon the various regimens and indications in general use.

Induction or Stimulation of Labor
Intravenous infusion (drip method) is the only acceptable method of administration for the induction or stimulation of labor. Accurate control of the rate of infusion flow is essential. An infusion pump or other such device and frequent monitoring of strength of contractions and fetal heart rate are necessary for the safe administration of oxytocin for the induction or stimulation of labor. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane.
An intravenous infusion of a non-oxytocin containing solution should be started. Physiologic electrolyte solutions should be used except under unusual circumstances.
To prepare the usual solution for intravenous infusion–one mL (10 units) is combined aseptically with 1,000 mL of a non-hydrating diluent.
The combined solution, rotated in the infusion bottle to insure thorough mixing, contains 10 mU/mL. Add the container with dilute oxytocic solution to the system through the use of a constant infusion pump or other such device to control accurately the rate of infusion.
The initial dose should be no more than 1 to 2 mU/min. The dose may be gradually increased in increments of no more than 1 to 2 mU/min., until a contraction pattern has been established which is similar to normal labor.
The fetal heart rate, resting uterine tone, and the frequency, duration, and force of contractions should be monitored.

The oxytocin infusion should be discontinued immediately in the event of uterine hyperactivity or fetal distress. Oxygen should be administered to the mother. The mother and fetus must be evaluated by the responsible physician.

Control of Postpartum Uterine Bleeding
Intravenous Infusion (Drip Method)—To control postpartum bleeding, 10 to 40 units of oxytocin may be added to 1,000 mL of a nonhydrating diluent and run at a rate necessary to control uterine atony.
Intramuscular Administration—1 mL (10 units) of oxytocin can be given after delivery of the placenta.

Treatment of Incomplete or Inevitable Abortion
Intravenous infusion with physiologic saline solution, 500 mL, or 5% dextrose in physiologic saline solution to which 10 units of oxytocin have been added should be infused at a rate of 20 to 40 drops/minute.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED
Oxytocin Injection, USP (synthetic) is supplied as follows:

Product No.	**NDC No.**	**Strength**	**Volume**
NP91201*	63323-012-01	10 USP Units/mL	1 mL fill in a 3 mL vial, packaged in trays of 25.

*Packaged in a plastic vial.
Discard unused portion.
Use only if solution is clear and seal intact.
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Do not permit to freeze.

NOVAPLUS®
Manufactured by:

APP
APP Pharmaceuticals, LLC
Schaumburg, IL 60173

451126A
Revised: January 2008

PACKAGE LABEL - PRINCIPAL DISPLAY - Oxytocin 1 mL Vial Label
Oxytocin Injection, USP
(Synthetic)
10 USP Units/mL
For IV Infusion or IM Use
1 mL
Rx only

(10)

NDC 63323-012-12
NP91201

OXYTOCIN
INJECTION, USP
(SYNTHETIC)
10 USP Units/mL

For IV Infusion or IM Use

1 mL Rx only

PACKAGE LABEL - PRINCIPAL DISPLAY - Oxytocin 1 mL Vial Tray Label
Oxytocin Injection, USP
(Synthetic)
10 USP Units/mL
For IV Infusion or IM Use
1 mL
Rx only

Sterile
Each mL contains:
Oxytocic activity equivalent to 10 USP Oxytocin Units;
chlorobutanol anhydrous (chloral derivative) 0.5%;
Water for Injection q.s.
Acetic acid may have been added for pH adjustment.
Usual Dosage: See Insert.
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not permit to freeze.
Use only if solution is clear and seal intact.

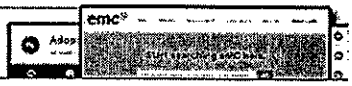
NDC 63323-012-12 NP91201

OXYTOCIN
INJECTION, USP
(SYNTHETIC)
10 USP Units/mL
For IV Infusion or IM Use
1 mL Rx only

Manufactured by:
APP Pharmaceuticals, LLC
Schaumburg, IL 60173

4281 4A

11



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ALLIAN

Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. Why?

Summary of Product Characteristics last updated on the eMC: 04

SPC **Syntocinon Ampoules 10 IU/ml**

Table of Contents

1. Name of the medicinal product

Go to top of the page

Syntocinon® 10 IU/ml Concentrate for solution for infusion

2. Qualitative and quantitative composition

Go to top of the page

Oxytocin.

Concentrate for solution for infusion (in 1 mL ampoule) containing 10 IU/mL.

Excipient(s) with known effect:

Ethanol 5.000mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Go to top of the page

Concentrate for solution for infusion.

A clear, colourless, sterile solution in 1ml clear glass ampoules.

4. Clinical particulars

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Antepartum

- Induction of labour for medical reasons, e.g.in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (pre-eclampsia)
- Stimulation of labour in hypotonic uterine inertia
- Early stages of pregnancy as adjunctive therapy for the management of incomplete, inevitable, or missed abortion.

Postpartum

- During caesarean section, but following delivery of the child
- Prevention and treatment of postpartum uterine atony and haemorrhage.

4.2 Posology and method of administration

Go to top of the page

Induction or enhancement of labour: Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Syntocinon should be administered as an intravenous (i.v.) drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU of Syntocinon be added to 500ml of a physiological electrolyte solution (such as sodium chloride 0.9%). For patients in whom infusion of sodium chloride must be avoided, 5% dextrose solution may be used as the diluent (see Section 4.4 "Special warnings and precautions for use"). To ensure even mixing, the bottle or bag must be turned upside down several times before use.

The initial infusion rate should be set at 1 to 4 milliunits/minute (2 to 8 drops/minute). It may be gradually increased at intervals not shorter than 20 minutes and increments of not more than 1-2 milliunits/minute, until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can often be achieved with an infusion of less than 10 milliunits/minute (20 drops/minute), and the recommended maximum rate is 20 milliunits/minute (40 drops/minute). In the unusual event that higher rates are required, as may occur in the management of foetal death *in utero* or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated Syntocinon solution, e.g., 10 IU in 500ml.

When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump.

The frequency, strength, and duration of contractions as well as the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity and/or foetal distress, the infusion must be discontinued immediately.

If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 IU, it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again from a rate of 1 to 4 milliunits/minute (see Section 4.3 "Contra-indications").

Incomplete, inevitable, or missed abortion: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), if necessary followed by i.v. infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) immediately after delivery.

Prevention of postpartum uterine haemorrhage: The usual dose is 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes) after delivery of the placenta. In women given Syntocinon for induction or enhancement of labour, the infusion should be continued at an increased rate during the third stage of labour and for the next few hours thereafter.

Treatment of postpartum uterine haemorrhage: 5 IU by i.v. infusion (5 IU diluted in physiological electrolyte solution and administered as an i.v. drip infusion or, preferably, by means of a variable-speed infusion pump over 5 minutes), followed in severe cases by i.v. infusion of a solution containing 5 to 20 IU of oxytocin in 500ml of an electrolyte-containing diluent, run at the rate necessary to control uterine atony.

Route of administration: Intravenous infusion.

Special populations

Renal impairment

No studies have been performed in renally impaired patients.

Hepatic impairment

No studies have been performed in hepatically impaired patients.

Paediatric population

No studies have been performed in paediatric patients.

Elderly population

No studies have been performed in elderly patients (65 years old and over).

4.3 Contraindications

Go to top of the page

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypertonic uterine contractions, mechanical obstruction to delivery, foetal distress.

Any condition in which, for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contra-indicated: e.g.:

- Significant cephalopelvic disproportion
- Foetal malpresentation
- Placenta praevia and vasa praevia
- Placental abruption
- Cord presentation or prolapse
- Overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy
- Polyhydramnios
- Grand multiparity
- In the presence of a uterine scar resulting from major surgery including classical caesarean section.

Syntocinon should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.

Syntocinon must not be administered within 6 hours after vaginal prostaglandins have been given (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use Go to top of the page

Syntocinon must only be administered as an i.v. infusion and never by i.v. bolus injection as it may cause an acute short-lasting hypotension accompanied with flushing and reflex tachycardia.

Induction of labour

The induction of labour by means of oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision.

Cardiovascular disorders

Syntocinon should be used with caution in patients who have a pre-disposition to myocardial ischaemia due to pre-existing cardiovascular disease (such as hypertrophic cardiomyopathy, valvular heart disease and/or ischaemic heart disease including coronary artery vasospasm), to avoid significant changes in blood pressure and heart rate in these patients.

QT Syndrome

Syntocinon should be given with caution to patients with known 'long QT syndrome' or related symptoms and to patients taking drugs that are known to prolong the QTc interval (see section 4.5 Interaction with other medicinal products and other forms of interaction).

When Syntocinon is given for induction and enhancement of labour:

•**Foetal distress and foetal death:** Administration of oxytocin at excessive doses results in uterine overstimulation which may cause foetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus. Careful monitoring of foetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual response.

• Particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.

•**Disseminated intravascular coagulation:** In rare circumstances, the pharmacological induction of labour using uterotonic agents, including oxytocin increases the risk of postpartum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent is linked to such risk. This risk is increased in particular if the woman has additional risk factors for DIC such as being 35 years of age or over, complications during pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other alternative drug should be used with care, and the practitioner should be alerted by signs of DIC.

Intrauterine death

In the case of foetal death *in utero*, and/or in the presence of meconium-stained amniotic fluid, tumultuous labour must be avoided, as it may cause amniotic fluid embolism.

Water intoxication

Because oxytocin possesses slight antidiuretic activity, its prolonged i.v. administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage, may cause water intoxication associated with hyponatraemia. The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia. To avoid these rare complications, the following precautions must be observed whenever high doses of oxytocin are administered over a long time: an electrolyte-containing diluent must be used (not dextrose); the volume of infused fluid should be kept low (by infusing oxytocin at a higher concentration than recommended for the induction or enhancement of labour at term); fluid intake by mouth must be restricted; a fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspected.

Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin (see section 5.2 Pharmacokinetics).

4.5 Interaction with other medicinal products and other forms of interaction Go to top of the page

Interaction resulting in a concomitant use not recommended

Prostaglandins and their analogues

Prostaglandins and its analogues facilitate contraction of the myometrium hence oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa (see section 4.3 Contraindications).

Drugs prolonging the QT interval

Oxytocin should be considered as potentially arrhythmogenic, particularly in patients with other risk factors for Torsades de Pointes such as drugs which prolong the QT interval or in patients with history of long QT syndrome (see section 4.4 Special warnings and precautions for use).

Interactions to be considered

Inhalation anaesthetics

Inhalation anaesthetics (e.g. cyclopropane, halothane, sevoflurane, desflurane) have a relaxing effect on the uterus and produce a notable inhibition of uterine tone and thereby, may diminish the uterotonic effect of oxytocin. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors/Sympathomimetics

Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, even those contained in local anaesthetics.

Caudal anaesthetics

When given during or after caudal block anaesthesia, oxytocin may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

4.6 Fertility, pregnancy and lactation Go to top of the page

Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated.

Oxytocin may be found in small quantities in mother's breast milk. However, oxytocin is not expected to cause harmful effects in the newborn because it passes into the alimentary tract where it undergoes rapid inactivation.

4.7 Effects on ability to drive and use machines Go to top of the page

Syntocinon can induce labour, therefore caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

4.8 Undesirable effects Go to top of the page

As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by i.v. infusion for the induction or enhancement of labour, administration at too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage or rupture of the uterus.

Rapid i.v. bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia (see section 4.4 Special warnings and precautions for use). These rapid haemodynamic changes may result in myocardial ischaemia, particularly in patients with pre-existing cardiovascular disease. Rapid i.v. bolus injection of oxytocin at doses amounting to several IU may also lead to QTc prolongation.

In rare circumstances the pharmacological induction of labour using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see section 4.4 Special warnings and precautions for use).

Water intoxication

Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see Section 4.4 "Special warnings and precautions for use"). The combined antidiuretic effect of oxytocin and the i.v. fluid administration may cause fluid overload leading to a haemodynamic form of acute pulmonary oedema without hyponatraemia (see section 4.4. Special warnings and precautions for use).

Symptoms of water intoxication include:

1. Headache, anorexia, nausea, vomiting and abdominal pain.

2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures.

3. Low blood electrolyte concentration.

Undesirable effects (Tables 1 and 2) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports; not known (cannot be estimated from the available data).The ADRs tabulated below are based on clinical trial results as well as postmarketing reports.

The adverse drug reactions derived from post-marketing experience with Syntocinon are via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions in mother

System organ class	Adverse drug reaction
Immune system disorders	Rare: Anaphylactoid reaction associated with dyspnoea, hypotension or Shock
Nervous system disorders	Common: Headache
Cardiac disorders	Common: Tachycardia, bradycardia Uncommon: Arrhythmia Not known: Myocardial ischaemia, QTc prolongation
Vascular disorders	Not known: Hypotension, haemorrhage
Gastrointestinal disorders	Common: Nausea, vomiting
Skin and subcutaneous tissue disorders	Rare: Rash
Pregnancy, puerperium and perinatal conditions	Not known: Uterine hypertonicity, tetanic contractions, rupture of the uterus
Metabolism and nutrition disorders	Not known: Water intoxication, maternal hyponatraemia
Respiratory, thoracic and mediastinal disorders	Not known: acute pulmonary oedema
General disorders and administration site conditions	Not known: Flushing
Blood and lymphatic system disorders	Not known: disseminated intravascular coagulation

Table 2 Adverse drug reactions in foetus/neonate

System organ class	Adverse drug reaction
Pregnancy, puerperium and perinatal conditions	Not known: foetal distress, asphyxia and death
Metabolism and nutrition disorders	Not known: Neonatal hyponatraemia

4.9 Overdose Go to top of the page

The fatal dose of Syntocinon has not been established. Syntocinon is subject to inactivation by proteolytic enzymes of the alimentary tract. Hence it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects". In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous i.v. administration of Syntocinon, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

5. Pharmacological properties Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page

Pharmacotherapeutic group: Posterior pituitary lobe hormones

ATC code: H01B B02

Mechanism of action

Oxytocin is a cyclic nonapeptide that is obtained by chemical synthesis. This synthetic form is identical to the natural hormone that is stored in the posterior pituitary and released into the systemic circulation in response to suckling and labour.

Oxytocin stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labour, and immediately postpartum. At these times, the oxytocin receptors in the myometrium are increased.

The oxytocin receptors are G-proteins coupled receptors. Activation of receptor by oxytocin triggers release of

calcium from intracellular stores and thus leads to myometrial contraction.

Oxytocin elicits rhythmic contractions in upper segment of uterus, similar in frequency, force and duration to those observed during labour.

Being synthetic, oxytocin in Syntocinon does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like antidiuretic activity.

Based on in vitro studies, prolonged exposure of oxytocin had been reported to cause desensitisation of oxytocin receptors probably due to down-regulation of oxytocin-binding sites, destabilisation of oxytocin receptors mRNA and internalisation of oxytocin receptors.

Plasma levels and onset/duration of effect

Intravenous infusion. When Syntocinon is given by continuous i.v. infusion at doses appropriate for induction or enhancement of labour, the uterine response sets in gradually and usually reaches a steady state within 20 to 40 minutes. The corresponding plasma levels of oxytocin are comparable to those measured during spontaneous first-stage labour. For example, oxytocin plasma levels in 10 pregnant women at term receiving a 4 milliunits per minute intravenous infusion were 2 to 5 microunits/mL. Upon discontinuation of the infusion, or following a substantial reduction in the infusion rate, e.g. in the event of overstimulation, uterine activity declines rapidly but may continue at an adequate lower level.

5.2 Pharmacokinetic properties Go to top of the page

Absorption

Plasma levels of oxytocin following intravenous infusion at 4 milliunits per minute in pregnant women at term were 2 to 5 microunits/mL.

Distribution

The steady-state volume of distribution determined in 6 healthy men after i.v. injection is 12.2 L or 0.17 L/kg. Plasma protein binding is negligible for oxytocin. It crosses the placenta in both directions. Oxytocin may be found in small quantities in mother's breast milk.

Biotransformation/Metabolism

Oxytocinase is a glycoprotein aminopeptidase that is produced during pregnancy and appears in the plasma. It is capable of degrading oxytocin. It is produced from both the mother and the foetus. Liver and kidney plays a major role in metabolising and clearing oxytocin from the plasma. Thus, liver, kidney and systemic circulation contribute to the biotransformation of oxytocin.

Elimination

Plasma half-life of oxytocin ranges from 3 to 20 min. The metabolites are excreted in urine whereas less than 1% of the oxytocin is excreted unchanged in urine. The metabolic clearance rate amounts to 20 mL/kg/ min in the pregnant woman.

Renal impairment

No studies have been performed in renally impaired patients. However, considering the excretion of oxytocin and its reduced urinary excretion because of anti-diuretic properties, the possible accumulation of oxytocin can result in prolonged action.

Hepatic impairment

No studies have been performed in hepatically impaired patients. Pharmacokinetic alteration in patients with impaired hepatic function is unlikely since metabolising enzyme, oxytocinase, is not confined to liver alone and the oxytocinase levels in placenta during the term has significantly increased. Therefore, biotransformation of oxytocin in impaired hepatic function may not result in substantial changes in metabolic clearance of oxytocin.

5.3 Preclinical safety data Go to top of the page

Pre-clinical data for oxytocin reveal no special hazard for humans based on conventional studies of single dose acute toxicity, genotoxicity, and mutagenicity.

6. Pharmaceutical particulars Go to top of the page

6.1 List of excipients Go to top of the page

Sodium acetate tri-hydrate, acetic acid, chlorobutanol, ethanol and water for injections.

6.2 Incompatibilities Go to top of the page

Syntocinon should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes. Syntocinon is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life Go to top of the page

Five years

6.4 Special precautions for storage Go to top of the page

Store between 2°C and 8°C. May be stored up to 30°C for 3 months, but must then be discarded.

6.5 Nature and contents of container Go to top of the page

Clear glass 1ml ampoules. Boxes of 5 ampoules.

6.6 Special precautions for disposal and other handling Go to top of the page

Snap ampoules: no file required.

Syntocinon is compatible with the following infusion fluids, but due attention should be paid to the advisability of using electrolyte fluids in individual patients: sodium/potassium chloride (103mmol Na^+ and 51mmol K^+), sodium bicarbonate 1.39%, sodium chloride 0.9%, sodium lactate 1.72%, dextrose 5%, laevulose 20%, macrodex 6%, rheomacrodex 10%, Ringer's solution.

7. Marketing authorisation holder Go to top of the page

Alliance Pharmaceuticals Ltd

Avonbridge House

Bath Road

Chippenham

Wiltshire

SN15 2BB

8. Marketing authorisation number(s) Go to top of the page

PL 16853/0020

9. Date of first authorisation/renewal of the authorisation Go to top of the page

25 June 1998

10. Date of revision of the text Go to top of the page

22 February 2013

11. Legal status Go to top of the page

POM

More information about this product

- Patient Information Leaflets (PILs):
  Syntocinon 5IU/ml and 10IU/ml
- Alternative format Patient Information Leaflets (X-PILs):
  Syntocinon 5IU/ml and 10IU/ml

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12

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ALLIANCE

Summary of Product Characteristics last updated on the eMC: 27/03/2007

Syntocinon Ampoules 5 IU/ml

1. Name of the medicinal product

Syntocinon® Ampoules 5 IU/ml

2. Qualitative and quantitative composition

Oxytocin PhEur 5 units in 1ml.

For excipients, see section 6.1.

3. Pharmaceutical form

A clear, colourless, sterile solution in 1ml clear glass ampoules.

4. Clinical particulars

4.1 Therapeutic indications

Induction of labour for medical reasons; stimulation of labour in hypotonic uterine inertia; during caesarean section, foll delivery of the child; prevention and treatment of postpartum uterine atony and haemorrhage.

Early stages of pregnancy as a adjunctive therapy for the management of incomplete, inevitable, or missed abortion.

4.2 Posology and method of administration

Induction or enhancement of labour: Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Syntocinon should be administered as an iv drip infusion or, preferably, by means of a variable-speed pump. For drip infusion it is recommended that 5 IU of Syntocinon be added to 500ml of a physiological electrolyte sol patients in whom infusion of sodium chloride must be avoided, 5% dextrose solution may be used as the diluent (see S "Special warnings and precautions for use"). To ensure even mixing, the bottle or bag must be turned upside down se times before use.

The initial infusion rate should be set at 1 to 4mU/min (2 to 8 drops/min). It may be gradually increased at intervals not than 20 min, until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can achieved with an infusion of less than 10mU/min (20 drops/min), and the recommended maximum rate is 20mU/min (4 drops/min). In the unusual event that higher rates are required, as may occur in the management of foetal death *in ute* induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use concentrated Syntocinon solution, e.g., 10 IU in 500ml.

When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the conce suitable for infusion within the recommended dosage range must be calculated according to the specifications of the p

The frequency, strength, and duration of contractions as well as the foetal heart rate must be carefully monitored throu infusion. Once an adequate level of uterine activity is attained, aiming for 3 to 4 contractions every 10 minutes, the infu can often be reduced. In the event of uterine hyperactivity and/or foetal distress, the infusion must be discontinued imn

If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again fi of 1 to 4mU/min (see Section 4.3 "Contra-indications").

Caesarean section: 5 IU by slow iv injection immediately after delivery.

Prevention of postpartum uterine haemorrhage: The usual dose is 5 IU slowly iv after delivery of the placenta. In w given Syntocinon for induction or enhancement of labour, the infusion should be continued at an increased rate during stage of labour and for the next few hours thereafter.

Treatment of postpartum uterine haemorrhage: 5 IU slowly iv, followed in severe cases by iv infusion of a solution c 5 to 20 IU of oxytocin in 500ml of a non-hydrating diluent, run at the rate necessary to control uterine atony.

Incomplete, inevitable, or missed abortion: 5 IU slowly iv, if necessary followed by iv infusion at a rate of 20 to 40m higher.

Children: Not applicable.

Elderly: Not applicable.

Route of administration: Intravenous infusion or intravenous injection.

4.3 Contraindications

Known hypersensitivity to oxytocin or to any of the excipients of Syntocinon. Hypertonic uterine contractions, mechanic obstruction to delivery, foetal distress. Any condition in which, for foetal or maternal reasons, spontaneous labour is ina and/or vaginal delivery is contra-indicated: e.g., significant cephalopelvic disproportion; foetal malpresentation; placent and vasa praevia; placental abruption; cord presentation or prolapse; overdistension or impaired resistance of the uter rupture as in multiple pregnancy; polyhydramnios; grand multiparity and in the presence of a uterine scar resulting fron surgery including classical caesarean section.

Syntocinon should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-ecla toxaemia or severe cardiovascular disorders.

4.4 Special warnings and precautions for use

The induction of labour by means of oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision. When given for induction ar enhancement of labour, Syntocinon must only be administered as an iv infusion and never by iv bolus injection. Admin oxytocin at excessive doses results in uterine overstimulation which may cause foetal distress, asphyxia and death, or to hypertonicity, titanic contractions or rupture of the uterus. Careful monitoring of foetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual respo

When Syntocinon is given for induction or enhancement of labour, particular caution is required in the presence of bor cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension c disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.

In rare circumstances, the pharmacological induction of labour using uterotonic agents increases the risk of post patun disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent is linked risk. This risk is increased in particular if the woman has additional risk factors for DIC such as being 35 years of age c complications during pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other alter should be used with care, and the practitioner should be alerted by signs of DIC.

In the case of foetal death *in utero*, and/or in the presence of meconium-stained amniotic fluid, tumultous labour must l avoided, as it may cause amniotic fluid embolism.

Because oxytocin possesses slight antidiuretic activity, its prolonged iv administration at high doses in conjunction with volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpar haemorrhage, may cause water intoxication associated with hyponatraemia. To avoid this rare complication, the follow precautions must be observed whenever high doses of oxytocin are administered over a long time: an electrolyte-cont diluent must be used (not dextrose); the volume of infused fluid should be kept low (by infusing oxytocin at a higher concentration than recommended for the induction or enhancement of labour at term); fluid intake by mouth must be re fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspecte

When Syntocinon is used for prevention or treatment of uterine haemorrhage, rapid iv injection should be avoided, as i cause an acute short-lasting drop in blood pressure accompanied with flushing and reflex tachycardia.

4.5 Interaction with other medicinal products and other forms of interaction

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that these drugs ar together. If used in sequence, the patient's uterine activity should be carefully monitored.

Some inhalation anaesthetics, e.g., cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and re oxytocic action. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

When given during or after caudal block anaesthesia, oxytocin may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this drug and chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when use indicated.

Oxytocin may be found in small quantities in mother's breast milk. However, oxytocin is not expected to cause harmful the newborn because it passes into the alimentary tract where it undergoes rapid inactivation.

4.7 Effects on ability to drive and use machines

Syntocinon can induce labour, therefore caution should be exercised when driving or operating machines. Women with contractions should not drive or use machines.

4.8 Undesirable effects

As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by iv infusion for the induction or enhancement of labour, administ too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage or rupture of the uterus.

Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high dose oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (: Section 4.4 "Special warnings and precautions for use"). Symptoms of water intoxication include:

1. Headache, anorexia, nausea, vomiting and abdominal pain.

2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures.

3. Low blood electrolyte concentration.

Rapid iv bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension aco with flushing and reflex tachycardia.

In rare circumstances the pharmacological induction of labour using uterotonic agents increases the risk of postpartum disseminated intravascular coagulation (see section 4.4 Special warnings and special precautions for use).

Oxytocin may occasionally cause nausea, vomiting, haemorrhage or cardiac arrhythmias. In a few cases, skin rashes anaphylactoid reactions associated with dyspnoea, hypotension, or shock have been reported.

Immune System disorders	
Rare:	Anaphylactoid reaction associated with dyspnoea, hypotension or shock
Nervous system disorders	
Common:	Headache
Cardiac disorders	
Common:	Tachycardia, bradycardia
Uncommon:	Arrhythmia
Gastrointestinal disorders	
Common:	Nausea, vomiting
Skin and subcutaneous tissue disorders	

Rare:	Rash

4.9 Overdose

The fatal dose of Syntocinon has not been established. Syntocinon is subject to inactivation by proteolytic enzymes of alimentary tract. Hence it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under Section 4.8 "Undesirable effects". In ad result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous iv administration of Syntocinon, the infusi be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restr intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur, by judicious diazepam. In the case of coma, a free airway should be maintained with routine measures normally employed in the n the unconscious patient.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The active principle of Syntocinon is a synthetic nonapeptide identical with oxytocin, a hormone released by the poster the pituitary. It exerts a stimulatory effect on the smooth musculature of the uterus, particularly towards the end of preg during labour, after delivery, and in the puerperium, i.e., at times when the number of specific oxytocin receptors in the myometrium is increased.

When given by low-dose iv infusion, Syntocinon elicits rhythmic uterine contractions that are indistinguishable in freque force, and duration from those observed during spontaneous labour. At higher infusion dosages, or when given by sing injection, the drug is capable of causing sustained uterine contractions.

Being synthetic, Syntocinon does not contain vasopressin, but even in its pure form oxytocin possesses some weak in vasopressin-like antidiuretic activity.

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid iv bolus consists of a transient direct relaxing effect on vascular smooth muscle, resulting in brief hypotension, flushing and refl tachycardia.

5.2 Pharmacokinetic properties

The plasma half-life of oxytocin is of the order of five minutes, hence the need for continuous iv infusion. Elimination is liver, kidney, functional mammary gland and oxytocinase.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sec the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium acetate tri-hydrate, acetic acid, chlorobutanol, ethanol and water for injections.

6.2 Incompatibilities

Syntocinon should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidl inactivated by oxytocin-inactivating enzymes. Syntocinon is incompatible with solutions containing sodium metabisulpl stabiliser.

6.3 Shelf life

Five years

6.4 Special precautions for storage

Store between 2° C and 8° C. May be stored up to 30° C for 3 months, but must then be discarded.

6.5 Nature and contents of container

Clear glass 1ml ampoules. Boxes of 5 ampoules.

6.6 Special precautions for disposal and other handling

Snap ampoules: no file required.

Syntocinon is compatible with the following infusion fluids, but due attention should be paid to the advisability of using fluids in individual patients: sodium/potassium chloride (103mmol Na^+ and 51mmol K^+), sodium bicarbonate 1.39%, sc chloride 0.9%, sodium lactate 1.72%, dextrose 5%, laevulose 20%, macrodex 6%, rheomacrodex 10%, Ringer's soluti

7. Marketing authorisation holder

Alliance Pharmaceuticals Ltd

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8. Marketing authorisation number(s)

PL 16853/0019

9. Date of first authorisation/renewal of the authorisation

25 June 1998

10. Date of revision of the text

February 2007

11. Legal status

POM

13

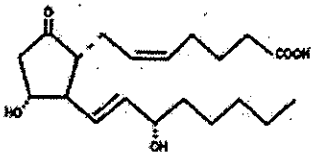
CERVIDIL - dinoprostone insert
Forest Laboratories, Inc.

Rev. 04/10 **Rx only** RMC 226

DESCRIPTION

Dinoprostone vaginal insert is a thin, flat, polymeric slab which is rectangular in shape with rounded corners contained within the pouch of an off-white knitted polyester retrieval system. Each slab is buff colored, semitransparent and contains 10 mg of dinoprostone in a hydrogel insert. An integral part of the knitted polyester retrieval system is a long tape designed to aid retrieval at the end of the dosing interval or earlier if clinically indicated. The finished product is a controlled release formulation which has been found to release dinoprostone *in vivo* at a rate of approximately 0.3 mg/hr.

The chemical name for dinoprostone (commonly known as prostaglandin E_2 or PGE_2) is 11α, 15S-dihydroxy-9-oxo-prosta-5Z,13E-dien-1-oic acid and the structural formula is represented below:



The molecular formula is $C_{20}H_{32}O_5$ and its molecular weight is 352.5. Dinoprostone occurs as a white to off-white crystalline powder. It has a melting point within the range of 65° to 69°C. Dinoprostone is soluble in ethanol and in 25% ethanol in water. Each insert contains 10 mg of dinoprostone in 241 mg of a cross-linked polyethylene oxide/urethane polymer which is a semi-opaque, beige colored, flat rectangular slab measuring 29 mm by 9.5 mm and 0.8 mm in thickness. The insert and its retrieval system, made of polyester yarn, are non-toxic and when placed in a moist environment, absorb water, swell, and release dinoprostone.

CLINICAL PHARMACOLOGY

Dinoprostone (PGE_2) is a naturally-occurring biomolecule. It is found in low concentrations in most tissues of the body and functions as a local hormone (1-3). As with any local hormone, it is very rapidly metabolized in the tissues of synthesis (the half-life estimated to be 2.5-5 minutes). The rate limiting step for inactivation is regulated by the enzyme 15-hydroxyprostaglandin dehydrogenase (PGDH) (1,4). Any PGE_2 that escapes local inactivation is rapidly cleared to the extent of 95% on the first pass through the pulmonary circulation (1,2).

In pregnancy, PGE_2 is secreted continuously by the fetal membranes and placenta and plays an important role in the final events leading to the initiation of labor (1,2). It is known that PGE_2 stimulates the production of $PGF_{2\alpha}$ which in turn sensitizes the myometrium to endogenous or exogenously administered oxytocin. Although PGE_2 is capable of initiating uterine contractions and may interact with oxytocin to increase uterine contractility, the available evidence indicates that, in the concentrations found during the early part of labor, PGE_2 plays an important role in cervical ripening without affecting uterine contractions (5-7). This distinction serves as the basis for considering cervical ripening and induction of labor, usually by the use of oxytocin (8-10), as two separate processes.

PGE_2 plays an important role in the complex set of biochemical and structural alterations involved in cervical ripening. Cervical ripening involves a marked relaxation of the cervical smooth muscle fibers of the uterine cervix which must be transformed from a rigid structure to a softened, yielding and dilated configuration to allow passage of the fetus through the birth canal (11-13). This process involves activation of the enzyme collagenase which is responsible for digestion of some of the structural collagen network of the cervix (1, 14). This is associated with a concomitant increase in the amount of hydrophilic glycosaminoglycan, hyaluronic acid and a decrease in dermatan sulfate (1). Failure of the cervix to undergo these natural physiologic changes, usually assessed by the method described by Bishop (15,16), prior to the onset of effective uterine contractions, results in an unfavourable outcome for successful vaginal delivery and may result in fetal compromise. It is estimated that in approximately 5% of pregnancies the cervix does not ripen normally (17). In an additional 10-11% of pregnancies, labor must be induced for medical or obstetric reasons prior to the time of cervical ripening (17).

The delivery rate of PGE_2 *in vivo* is about 0.3 mg/hour over a period of 12 hours. The controlled release of PGE_2 from the hydrogel insert is an attempt to provide sufficient quantities of PGE_2 to the local receptors to satisfy hormonal requirements. In the majority of patients, these local effects are manifested by changes in the consistency, dilatation and effacement of the cervix as measured by the Bishop score. Although some patients experience uterine hyperstimulation as a result of direct PGE_2- or $PGF_{2\alpha}$-, mediated sensitization of the myometrium to oxytocin, systemic effects of PGE_2 are rarely encountered. The insert is fitted with a biocompatible retrieval system which facilitates removal at the conclusion of therapy or in the event of an adverse reaction.

No correlation could be established between PGE_2 release and plasma concentrations of PGE_m. The relative contributions of endogenously and exogenously released PGE_2 to the plasma levels of the metabolite PGE_m could not be determined. Moreover, it is uncertain as to whether the measured concentrations of PGE_m reflect the natural progression of PGE_m concentrations in blood as birth

approaches or to what extent the measured concentrations following PGE_2 administration represent an increase over basal levels that might be measured in control patients.

INDICATIONS AND USAGE

Cervidil Vaginal Insert (dinoprostone, 10 mg) is indicated for the initiation and/or continuation of cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labor.

CONTRAINDICATIONS

Cervidil is contraindicated in:

* Patients with known hypersensitivity to prostaglandins.
* Patients in whom there is clinical suspicion or definite evidence of fetal distress where delivery is not imminent.
* Patients with unexplained vaginal bleeding during this pregnancy.
* Patients in whom there is evidence or strong suspicion of marked cephalopelvic disproportion.
* Patients in whom oxytocic drugs are contraindicated or when prolonged contraction of the uterus may be detrimental to fetal safety or uterine integrity, such as previous cesarean section or major uterine surgery (see **PRECAUTIONS** and **ADVERSE REACTIONS**).
* Patients already receiving intravenous oxytocic drugs.
* Multipara with 6 or more previous term pregnancies.

WARNINGS

For hospital use only

Cervidil should be administered only by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities. Women aged 30 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of postpartum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labor induction (See **ADVERSE REACTIONS**, Post-marketing surveillance). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum period.

The Clinician should be alert that use of dinoprostone may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

PRECAUTIONS

1. General Precautions: Since prostaglandins potentiate the effect of oxytocin, Cervidil must be removed before oxytocin administration is initiated and the patient's uterine activity carefully monitored for uterine hyperstimulation. If uterine hyperstimulation is encountered or if labor commences, the vaginal insert should be removed. Cervidil should also be removed prior to amniotomy.

Cervidil is contraindicated when prolonged contraction of the uterus may be detrimental to fetal safety and uterine integrity. Therefore, Cervidil should not be administered to patients with a history of previous cesarean section or uterine surgery given the potential risk for uterine rupture and associated obstetrical complications, including the need for hysterectomy and the occurrence of fetal or neonatal death.

Caution should be exercised in the administration of Cervidil for cervical ripening in patients with ruptured membranes, in cases of non-vertex or non-singleton presentation, and in patients with a history of previous uterine hypertony, glaucoma, or a history of childhood asthma, even though there have been no asthma attacks in adulthood.

Uterine activity, fetal status and the progression of cervical dilatation and effacement should be carefully monitored whenever the dinoprostone vaginal insert is in place. With any evidence of uterine hyperstimulation, sustained uterine contractions, fetal distress, or other fetal or maternal adverse reactions, the vaginal insert should be removed.

An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labor was induced by physiologic means, either with dinoprostone or oxytocin.

2. Drug Interactions: Cervidil may augment the activity of oxytocic agents and their concomitant use is not recommended. A dosing interval of at least 30 minutes is recommended for the sequential use of oxytocin following the removal of the dinoprostone vaginal insert. No other drug interactions have been identified.

3. Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity and fertility studies have not been conducted with Cervidil (dinoprostone) Vaginal Insert. No evidence of mutagenicity has been observed with prostaglandin E_2 in the Unscheduled DNA Synthesis Assay, the Micronucleus Test, or Ames Assay.

4. Pregnancy, Teratogenic Effects:
Pregnancy Category C.

Prostaglandin E_2 has produced an increase in skeletal anomalies in rats and rabbits. No effect would be expected clinically, when used as indicated, since Cervidil (dinoprostone) Vaginal Insert is administered after the period of organogenesis. Prostaglandin E_2 has been shown to be embryotoxic in rats and rabbits, and any dose that produces sustained increased uterine tone could put the embryo or fetus at risk.

5. Pediatric Use: The safety and efficacy of Cervidil has been established in women of a reproductive age and women who are pregnant. Although safety and efficacy has not been established in pediatric patients, safety and efficacy are expected to be the same for adolescents.

ADVERSE REACTIONS
Cervidil is well tolerated. In placebo-controlled trials in which 658 women were entered and 320 received active therapy (218 without retrieval system, 102 with retrieval system), the following events were reported.
Table 1 Total Cervidil – Treated Drug Related Adverse Events

	Controlled Studies[1]	
	Active	Placebo
Uterine hyperstimulation with fetal distress	2.8%	0.3%
Uterine hyperstimulation without fetal distress	4.7%	0%
Fetal Distress without uterine hyperstimulation	3.8%	1.2%
N	320	338
	STUDY 101-801[2]	
	Active	Placebo
Uterine hyperstimulation with fetal distress	2.9%	0%
Uterine hyperstimulation without fetal distress	2.0%	0%
Fetal Distress without uterine hyperstimulation	2.9%	1.0%
N	102	104

[1]Controlled Studies (with and without retrieval system)

[2]Controlled Study (with retrieval system)

Drug related fever, nausea, vomiting, diarrhea, and abdominal pain were noted in less than 1% of patients who received Cervidil.
In study 101-801 (with the retrieval system) cases of hyperstimulation reversed within 2 to 13 minutes of removal of the product. Tocolytics were required in one of the five cases.
In cases of fetal distress, when product removal was thought advisable there was a return to normal rhythm and no neonatal sequelae. Five minute Apgar scores were 7 or above in 98.2% (646/658) of studied neonates whose mothers received Cervidil. In a report of a 3 year pediatric follow-up study in 121 infants, 51 of whose mothers received Cervidil, there were no deleterious effects on physical examination or psychomotor evaluation (18).
Post-marketing surveillance:
Immune System Disorders: Hypersensitivity
Blood and lymphatic system disorders: Disseminated Intravascular Coagulation (See Warnings Section)
Reproductive system: Reports of uterine rupture have been reported in association with use of Cervidil some required a hysterectomy and some resulted in subsequent fetal or neonatal death.
Vascular Disorders: Hypotension
Pregnancy, Puerperium and Perinatal Conditions: Amniotic fluid embolism

DRUG ABUSE AND DEPENDENCE
No drug abuse or dependence has been seen with the use of Cervidil.

OVERDOSAGE

Cervidil is used as a single dosage in a single application. Overdosage is usually manifested by uterine hyperstimulation which may be accompanied by fetal distress, and is usually responsive to removal of the insert. Other treatment must be symptomatic since, to date, clinical experience with prostaglandin antagonists is insufficient.

The use of beta-adrenergic agents should be considered in the event of undesirable increased uterine activity.

DOSAGE AND ADMINISTRATION

The dosage of dinoprostone in the vaginal insert is 10 mg designed to be released at approximately 0.3 mg/hour over a 12 hour period. Cervidil should be removed upon onset of active labor or 12 hours after insertion.

Cervidil is supplied in an individually wrapped aluminium/polyethylene package with a "tear mark" on one side of the package. The package should only be opened by tearing the aluminium package along the tear mark. The package should never be opened with scissors or other sharp objects which may compromise or cut the knitted polyester pouch that serves as the retrieval system for the polymeric slab.

Cervidil must be kept frozen until use, and is administered by placing one unit transversely in the posterior fornix of the vagina immediately after removal from its foil package. The insertion of the vaginal insert does not require sterile conditions. The vaginal insert must not be used without its retrieval system. There is no need for previous warming of the product. A minimal amount of water-miscible lubricant may be used to assist insertion of Cervidil. Care should be taken not to permit excess contact or coating with the lubricant which could prevent optimal swelling and release of dinoprostone from the vaginal insert. Patients should remain in the recumbent position for 2 hours following insertion, but thereafter may be ambulatory. If the patient is ambulatory, care should be taken to ensure the vaginal insert remains in place. If uterine hyperstimulation is encountered or if labor commences, the vaginal insert should be removed. Cervidil should also be removed prior to amniotomy.

Upon removal of Cervidil, it is essential to ensure that the slab has been removed, as it will continue delivering the active ingredient. This is accomplished by visualizing the knitted polyester retrieval system and confirming that it contains the slab. In the rare instance that the slab is not contained within the polyester retrieval system, a vaginal exam should be performed to remove the slab.

HOW SUPPLIED

Cervidil (NDC 0456-4123-63) contains 10 mg dinoprostone. The product is wound and enclosed in an aluminium/polyethylene pack. Store in a freezer: between -20°C and -10°C (-4°F and 14°F). Cervidil is packed in foil and is stable when stored in a freezer for a period of three years. Vaginal inserts exposed to high humidity will absorb moisture from the air and thereby alter the release characteristics of dinoprostone. Once used, the vaginal insert should be discarded.

CLINICAL STUDIES

Table 2 Efficacy of Cervidil in Double Blind Studies

		Primip/Nullip		Multip		
Parameter	**Study #**	**Cervidil**	**Placebo**	**Cervidil**	**Placebo**	**P-Value**
Treatment Success*	101-103 (N=81)	65%	28%	87%	29%	<0.001
	101-003 (N=371)	68%	24%	77%	24%	<0.001
	101-801 (N=206)	72%	48%	55%	41%	0.003
Time to Delivery (hours) Average Median	101-103 (N=81)	33.7 25.7	48.6 34.5	14.0 12.3	28.6 24.6	0.001
Average Median	101-801 (N=206)	31.1 25.5	51.8 37.2	52.3 20.8	45.9 27.4	<0.001
Time to Onset of Labor (hrs) Average Median	101-103 (N=81)	19.9 12.0	39.4 19.2	6.8 6.9	22.4 18.3	<0.001

*Treatment success was defined as Bishop score increase at 12 hours of≥ 3, vaginal delivery within 12 hours or Bishop score at 12 hours≥ 6. These studies were not designed with the power to show differences in cesarean section rates between Cervidil and placebo groups and none were noted.

REFERENCES

1. Physiology of Labor In: Williams Obstetrics. Eds. Pritchard, J. A., MacDonald, P. C., and Gant, N.F. Appleton-Century-Crofts, Conn, Pp 295-321, (1985).

2. Rall, T. W. and Schliefer, L. S. Oxytocin, prostaglandin, ergot alkaloids, and other drugs; tocolytics agents, In: The Pharmacological Basis of Therapeutics. Eds. Gilman, A.G., Goodman, L.S., Rall, T.W., and Murad, F. MacMillan, Publ. Co., New York, Pp. 926-945, (1985).

3. Casey, M.L. and MacDonald, P.C. The initiation of labor in women: Regulation of phospholipid and arachidonic acid metabolism and of prostaglandin production. Semin. Perinat. 10:270-275, (1986).

4. Casey, M.L., MacDonald, P.C. and Mitchell, M.D. Stimulation of Prostaglandin E_2 production in amnion cells in culture by a substance(s) in human fetal urine. Biochem. Biophys. Res. Comm. 114:1056, (1983).

5. Olson, C.M., Lye, S.J., Skinner, K. and Challis, J.R.G. Prostanoid concentrations in maternal/fetal plasma and amniotic fluid and intrauterine tissue prostanoid output in relation to myometrial contractility during the onset of Endocrinology, 116: 389-397, (1985).

6. Ledger, W.L., Ellwood, D.A., and Taylor, M.J. Cervical softening in late pregnant sheep by infusion of Prostaglandin E_2 into cervical artery. J. Reprod. Fert. 69, 511-515, (1983).

7. Olson, D.M., Lye, S.J., Skinner, K. and Challis, J.R.G. Early changes in prostaglandin concentrations in ovine maternal and fetal plasma, amniotic fluid and from dispersed cells of intrauterine tissues before the onset of ACTH-induced pre-term labor. J. Reprod. Fert., 71: 45-55, (1984).

8. Caldero-Garcia, R. and Posiero, J. Oxytocin and the contractility of the human uterus, Ann, N. Y. Acad. Sci. 75:813, (1959).

9. Posiero, J. and Noriega-Guerra, L. Dose-response relationships in uterine effects of oxytocin infusion. Oxytocin. Eds., Caldero-Garcia, R. and Heller, J. Pergamon Press, New York, (1961).

10. Cibils, L. Enhancement of induction of labor. In: Risks in the Practice of Modern Obstetrics. Aldjem, S. Ed. Mosby Publishing, St. Louis, (1972).

11. Bryman, I., Lindblom, B., and Norstrom, A. Extreme sensitivity of cervical musculature to prostaglandin E_2 in early pregnancy. Lancet, 2:1471, (1982).

12. Thiery, M. Induction of labor with prostaglandins. In: Human Parturition. Eds. Keirse, M.J.N.C., Anderson, A.B.M., and Gravenhorst, J.B. Martinus Nijhoff Publ., Boston, 155-164, (1979).

13. Thiery, M. and Amy, J.J. Induction of labor with prostaglandins. In:Advances in Prostaglandin Research. Prostaglandin and Reproduction, Karim, S.M.M., Ed., MTP, Lancaster, Pp. 149-228, (1975).

14. MacLennan, A.H., Katz, M., and Creasey, R. The morphologic characteristics of cervical ripening induced by the hormones relaxin and prostaglandin F_2 in a rabbit model. Am. J. Obstet. Gynecol, 152:910696, (1985).

15. Bishop, E. Elective induction of labor. Obstet & Gynecol, 5: 519-527, (1955).

16. Bishop, E. Pelvic scoring for elective induction. Obstet & Gynecol. 24: 266-268, (1969).

17. Thiery, M. Preinduction cervical ripening. In: Obstetrics and Gynecology Annual, Vol. 12, Ed. Wynn, R. M. Appleton-Century-Crofts, New York, Pp. 103-146, (1983).

18. MacKenzie, I.; Information on File: Controlled Therapeutics (Scotland).

19. De Abajo FJ et al. Labor induction with dinoprostone or oxytocin and postpartum disseminated intravascular coagulation: a hospital-based case-control study. Am J Obs Gynecol, 2004, 191: 1637-1643.

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Controlled Therapeutics
East Kilbride, Scotland, G74 5PB
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PRINCIPAL DISPLAY PANEL
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CERVIDIL®
DINOPROSTONE 10 mg
vaginal insert
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DINOPROSTONE 10 mg
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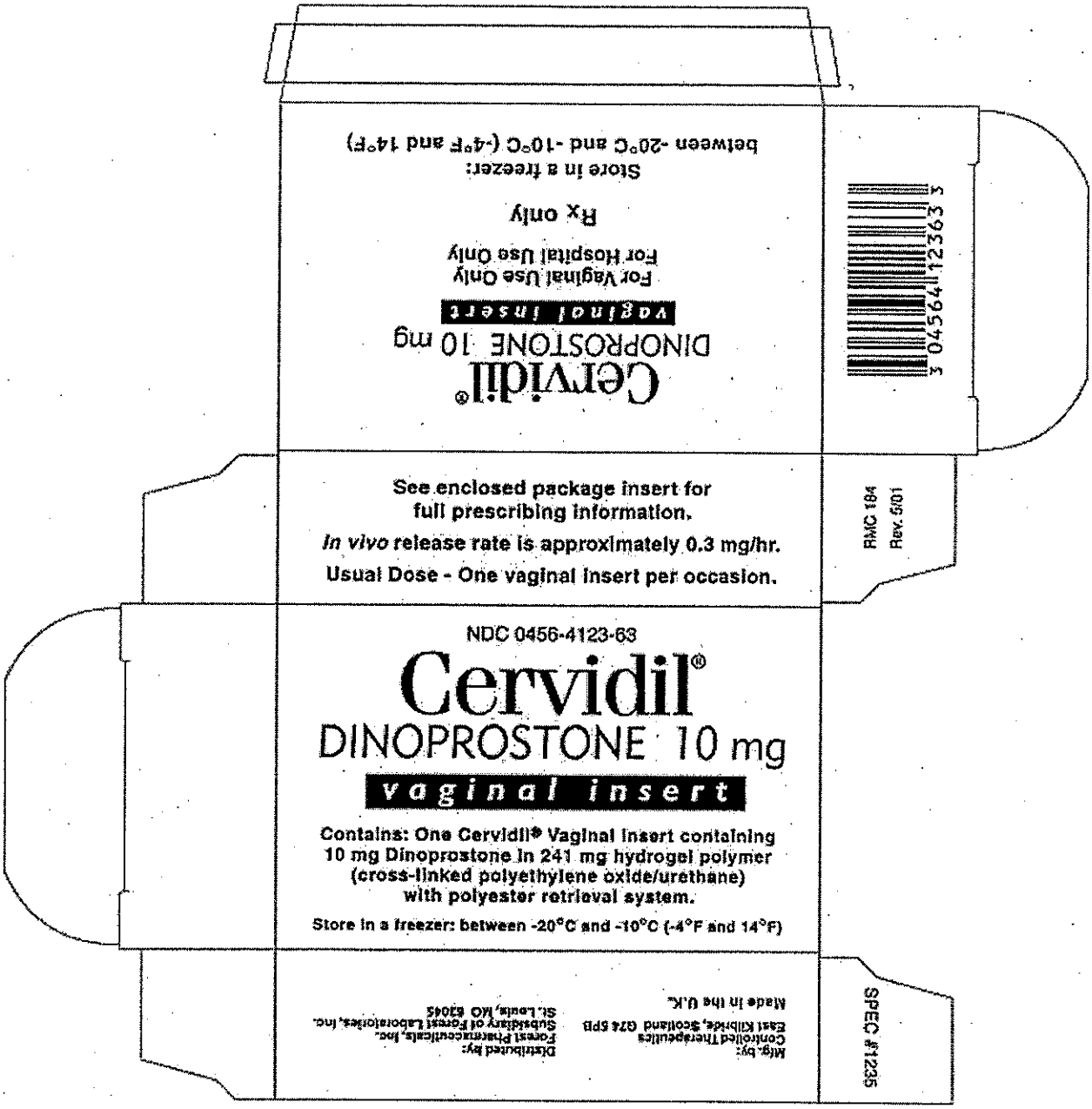
Contains: One Cervidil® Vaginal Insert containing
10 mg Dinoprostone in 241 mg hydrogel polymer
(cross-linked polyethylene oxide/urethane)
With polyester retrieval system.
Store in freezer: between -20C and -10C (-4F and 14F)



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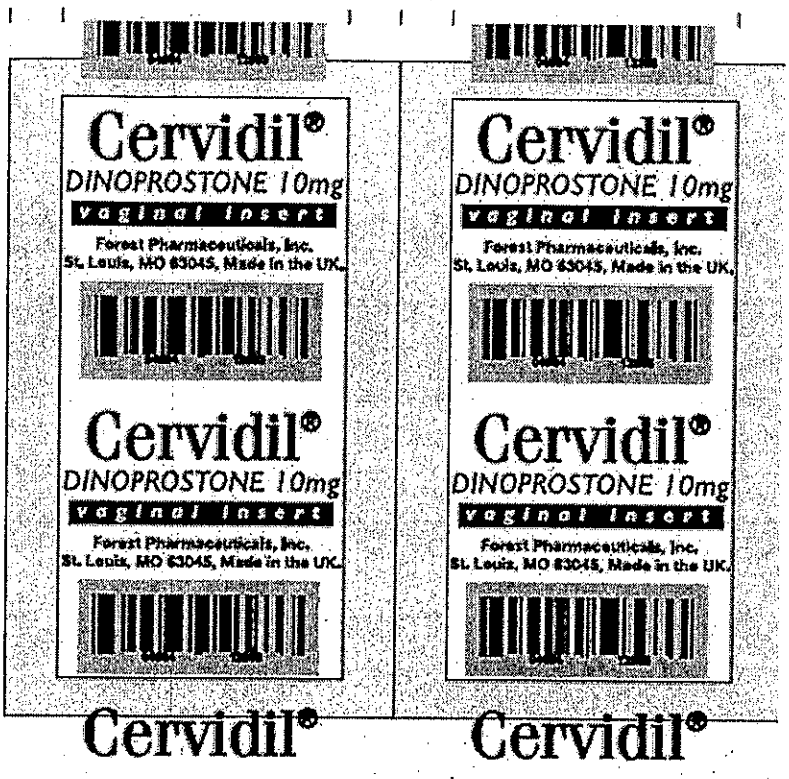
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(14)

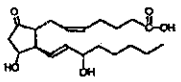
PREPIDIL - dinoprostone gel
Pharmacia and Upjohn Company

For Endocervical Use

DESCRIPTION

PREPIDIL Gel contains dinoprostone as the naturally occurring form of prostaglandin E_2 (PGE_2) and is designated chemically as (5Z, 11a, 13E, 15S)-11,15-Dihydroxy-9-oxo-prosta-5,13-dien-1-oic acid. The molecular formula is $C_{20}H_{32}O_5$ and the molecular weight is 352.5. Dinoprostone occurs as a white to off-white crystalline powder with a melting point within the range of 65° to 69°C. It is soluble in ethanol, in 25% ethanol in water, and in water to the extent of 130 mg/100 mL. The active constituent of PREPIDIL Gel is dinoprostone 0.5 mg/3 g (2.5 mL gel); other constituents are colloidal silicon dioxide NF (240 mg/3 g) and triacetin USP (2760 mg/3 g).

The structural formula is represented below:



CLINICAL PHARMACOLOGY

PREPIDIL Gel (dinoprostone) administered endocervically may stimulate the myometrium of the gravid uterus to contract in a manner similar to contractions seen in the term uterus during labor. Whether or not this action results from a direct effect of dinoprostone on the myometrium has not been determined. Dinoprostone is also capable of stimulating smooth muscle of the gastrointestinal tract in humans. This activity may be responsible for the vomiting and/or diarrhea that is occasionally seen when dinoprostone is used for preinduction cervical ripening.

In laboratory animals, and also in humans, large doses of dinoprostone can lower blood pressure, probably as a result of its effect on smooth muscle of the vascular system. With the doses of dinoprostone used for cervical ripening this effect has not been seen.

In laboratory animals, and also in humans, dinoprostone can elevate body temperature; however, with the dosing used for cervical ripening this effect has not been seen.

In addition to an oxytocic effect, there is evidence suggesting that this agent has a local cervical effect in initiating softening, effacement, and dilation. These changes, referred to as cervical ripening, occur spontaneously as the normal pregnancy progresses toward term and allow evacuation of uterine contents by decreasing cervical resistance at the same time that myometrial activity increases. While not completely understood, biochemical changes within the cervix during natural cervical ripening are similar to those following PGE_2-induced ripening. Further, it has been shown that these changes can take place independent of myometrial activity; however, it is quite likely that PGE_2 administered endocervically produces effacement and softening by combined contraction-inducing and cervical-ripening properties. There is evidence to suggest that the changes that take place within the cervix are due to collagen degradation resulting from collagenase secretion as a response, at least in part, to PGE_2.

Using an unvalidated assay, the following information was determined. When PREPIDIL Gel was administered endocervically to women undergoing preinduction ripening, results from measurement of plasma levels of the metabolite 13,14-dihydro-15-keto-PGE_2 (DHK-PGE_2) showed that PGE_2 was relatively rapidly absorbed and the T_{max} was 0.5 to 0.75 hours. Plasma mean C_{max} for gel-treated subjects was 433 ± 51 pg/mL versus 137 ± 24 pg/mL for untreated controls. In those subjects in which a clinical response was observed, mean C_{max} was 484 ± 57 pg/mL versus 213 ± 69 pg/mL in nonresponders and 219 ± 92 pg/mL in control subjects who had positive clinical progression toward normal labor. These elevated levels in gel-treated subjects appear to be largely a result of absorption of PGE_2 from the gel rather than from endogenous sources.

PGE_2 is completely metabolized in humans. PGE_2 is extensively metabolized in the lungs, and the resulting metabolites are further metabolized in the liver and kidney. The major route of elimination of the products of PGE_2 metabolism is the kidneys.

INDICATIONS AND USAGE

PREPIDIL Gel is indicated for ripening an unfavorable cervix in pregnant women at or near term with a medical or obstetrical need for labor induction.

CONTRAINDICATIONS

Endocervically administered PREPIDIL Gel is not recommended for the following:

a. Patients in whom oxytocic drugs are generally contraindicated or where prolonged contractions of the uterus are considered inappropriate, such as:

- cases with a history of cesarean section or major uterine surgery
- cases in which cephalopelvic disproportion is present
- cases in which there is a history of difficult labor and/or traumatic delivery
- grand multiparae with six or more previous term pregnancies cases with non-vertex presentation
- cases with hyperactive or hypertonic uterine patterns

- cases of fetal distress where delivery is not imminent
- in obstetric emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention

b. Patients with hypersensitivity to prostaglandins or constituents of the gel.

c. Patients with placenta previa or unexplained vaginal bleeding during this pregnancy.

d. Patients for whom vaginal delivery is not indicated, such as vasa previa or active herpes genitalia.

WARNINGS

FOR HOSPITAL USE ONLY

Dinoprostone, as with other potent oxytocic agents, should be used only with strict adherence to recommended dosages. Dinoprostone should be administered by physicians in a hospital that can provide immediate intensive care and acute surgical facilities.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labor induction (see **ADVERSE REACTIONS, Post-marketing surveillance**). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

The Clinician should be alert that the intracervical placement of dinoprostone gel may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

PRECAUTIONS

1. General Precautions

During use, uterine activity, fetal status, and character of the cervix (dilation and effacement) should be carefully monitored either by auscultation or electronic fetal monitoring to detect possible evidence of undesired responses, e.g., hypertonus, sustained uterine contractility, or fetal distress. In cases where there is a history of hypertonic uterine contractility or tetanic uterine contractions, it is recommended that uterine activity and the state of the fetus should be continuously monitored. The possibility of uterine rupture should be borne in mind when high-tone myometrial contractions are sustained. Feto-pelvic relationships should be carefully evaluated before use of PREPIDIL Gel (see CONTRAINDICATIONS).

Caution should be exercised in administration of PREPIDIL Gel in patients with:

- asthma or history of asthma

- glaucoma or raised intraocular pressure

Caution should be taken so as not to administer PREPIDIL Gel above the level of the internal os. Careful vaginal examination will reveal the degree of effacement which will regulate the size of the shielded endocervical catheter to be used. That is, the 20 mm endocervical catheter should be used if no effacement is present, and the 10 mm catheter should be used if the cervix is 50% effaced. Placement of PREPIDIL Gel into the extra-amniotic space has been associated with uterine hyperstimulation.

As PREPIDIL Gel is extensively metabolized in the lung, liver, and kidney, and the major route of elimination is the kidney, PREPIDIL Gel should be used with caution in patients with renal and hepatic dysfunction.

2. Patients With Ruptured Membranes

Caution should be exercised in the administration of PREPIDIL Gel in patients with ruptured membranes. The safety of use of PREPIDIL Gel in these patients has not been determined.

3. Drug Interactions

PREPIDIL Gel may augment the activity of other oxytocic agents and their concomitant use is not recommended. For the sequential use of oxytocin following PREPIDIL Gel administration, a dosing interval of 6–12 hours is recommended.

4. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic bioassay studies have not been conducted in animals with PREPIDIL Gel due to the limited indications for use and short duration of administration. No evidence of mutagenicity was observed in the Micronucleus Test or Ames Assay.

5. Pregnancy

Teratogenic Effects

PREGNANCY CATEGORY C

Prostaglandin E_2 produced an increase in skeletal anomalies in rats and rabbits. No effect would be expected clinically, when used as indicated, since PREPIDIL Gel is administered after the period of organogenesis. PREPIDIL Gel has been shown to be embryotoxic

in rats and rabbits, and any dose that produces sustained increased uterine tone could put the embryo or fetus at risk. See statements under General Precautions.

6. Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

PREPIDIL Gel is generally well-tolerated. In controlled trials, in which 1731 women were entered, the following events were reported at an occurrence of ≥ 1%:

Adverse Reaction	PGE_2 (N = 884)	Control* (N = 847)
Maternal	N (%)	N (%)
Uterine contractile abnormality	58 (6.6)	34 (4.0)
Any gastrointestinal effect	50 (5.7)	22 (2.6)
Back pain	27 (3.1)	0 (0)
Warm feeling in vagina	13 (1.5)	0 (0)
Fever	12 (1.4)	10 (1.2)
Fetal		
Any fetal heart rate abnormality	150 (17.0)	123 (14.5)
Bradycardia	36 (4.1)	26 (3.1)
Deceleration		
Late	25 (2.8)	18 (2.1)
Variable	38 (4.3)	29 (3.4)
Unspecified	19 (2.1)	19 (2.2)

*placebo gel or no treatment

In addition, in other trials amnionitis and intrauterine fetal sepsis have been associated with extra-amniotic intrauterine administration of PGE_2. Uterine rupture has been reported in association with the use of PREPIDIL Gel intracervically. Additional events reported in the literature, associated by the authors with the use of PREPIDIL Gel, included premature rupture of membranes, fetal depression (1 min Apgar < 7), and fetal acidosis (umbilical artery pH < 7.15).

Post-marketing surveillance

Blood and lymphatic system disorders
An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labor was induced by pharmacological means, either with dinoprostone or oxytocin (see section **WARNINGS**). The frequency of this adverse event, however, appears to be rare (<1 per 1,000 labors).

DRUG ABUSE AND DEPENDENCE

No drug abuse or drug dependence has been seen with the use of PREPIDIL Gel.

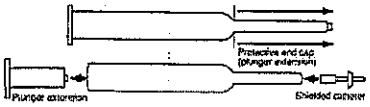
OVERDOSAGE

Overdosage with PREPIDIL Gel may be expressed by uterine hypercontractility and uterine hypertonus. Because of the transient nature of PGE_2-induced myometrial hyperstimulation, nonspecific, conservative management was found to be effective in the vast majority of the cases; i.e., maternal position change and administration of oxygen to the mother. β-adrenergic drugs may be used as a treatment of hyperstimulation following the administration of PGE_2 for cervical ripening.

DOSAGE AND ADMINISTRATION

NOTE: USE CAUTION IN HANDLING THIS PRODUCT TO PREVENT CONTACT WITH SKIN. WASH HANDS THOROUGHLY WITH SOAP AND WATER AFTER ADMINISTRATION.
PREPIDIL Gel should be brought to room temperature (59° to 86°F; 15° to 30°C) just prior to administration. Do not force the warming process by using a water bath or other source of external heat (eg, microwave oven).
To prepare the product for use remove the protective end cap (to serve as plunger extension) and insert the protective end cap into the plunger stopper assembly in the barrel of syringe. Choose the appropriate length shielded catheter (10 mm or 20 mm) and aseptically remove the sterile shielded catheter from the package. Careful vaginal examination will reveal the degree of effacement which will regulate the size of the shielded endocervical catheter to be used. That is, the 20 mm endocervical catheter should be used if no effacement is present, and the 10 mm catheter should be used if the cervix is 50% effaced. Firmly attach the catheter hub to the

syringe tip as evidenced by a distinct click. Fill the catheter with sterile gel by pushing the plunger assembly to expel air from the catheter prior to administration to the patient. Proper assembly of the dosing apparatus is shown below.



To properly administer the product, the patient should be in a dorsal position with the cervix visualized using a speculum. Using sterile technique, introduce the gel with the catheter provided into the cervical canal just below the level of the internal os. Administer the contents of the syringe by gentle expulsion and then remove the catheter. The gel is easily extrudable from the syringe. Use the contents of one syringe for one patient only. No attempt should be made to administer the small amount of gel remaining in the catheter. The syringe, catheter, and any unused package contents should be discarded after use. Following administration of PREPIDIL Gel, the patient should remain in the supine position for at least 15–30 minutes to minimize leakage from the cervical canal. If the desired response is obtained from PREPIDIL Gel, the recommended interval before giving intravenous oxytocin is 6–12 hours. If there is no cervical/uterine response to the initial dose of PREPIDIL Gel, repeat dosing may be given. The recommended repeat dose is 0.5 mg dinoprostone with a dosing interval of 6 hours. The need for additional dosing and the interval must be determined by the attending physician based on the course of clinical events. The maximum recommended cumulative dose for a 24-hour period is 1.5 mg of dinoprostone (7.5 mL PREPIDIL Gel).

HOW SUPPLIED

PREPIDIL Gel is available as a sterile semitranslucent viscous preparation for endocervical application: 0.5 mg PGE_2 per 3.0 g (2.5 mL) in syringe. In addition, each package contains two shielded catheters (10 mm and 20 mm tip) enclosed in sterile envelopes. The contents are not guaranteed sterile if envelopes are not intact.

Each 3 gram syringe applicator contains:

dinoprostone, 0.5 mg; colloidal silicon dioxide, 240 mg; triacetin, 2760 mg.

5 × 3 gram syringes NDC 0009-3359-02

PREPIDIL Gel needs to be stored under continuous refrigeration (36° to 46°F; 2° to 8°C).

Rx only

Manufactured by
Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

July 2008

LAB-0062-4.0

PRINCIPAL DISPLAY PANEL - PACKAGE LABEL

NDC 0009-3359-02

Contains 5 of NDC 0009-3359-01

5–3 gram syringes

Rx only

Prepidil® Gel

dinoprostone cervical gel

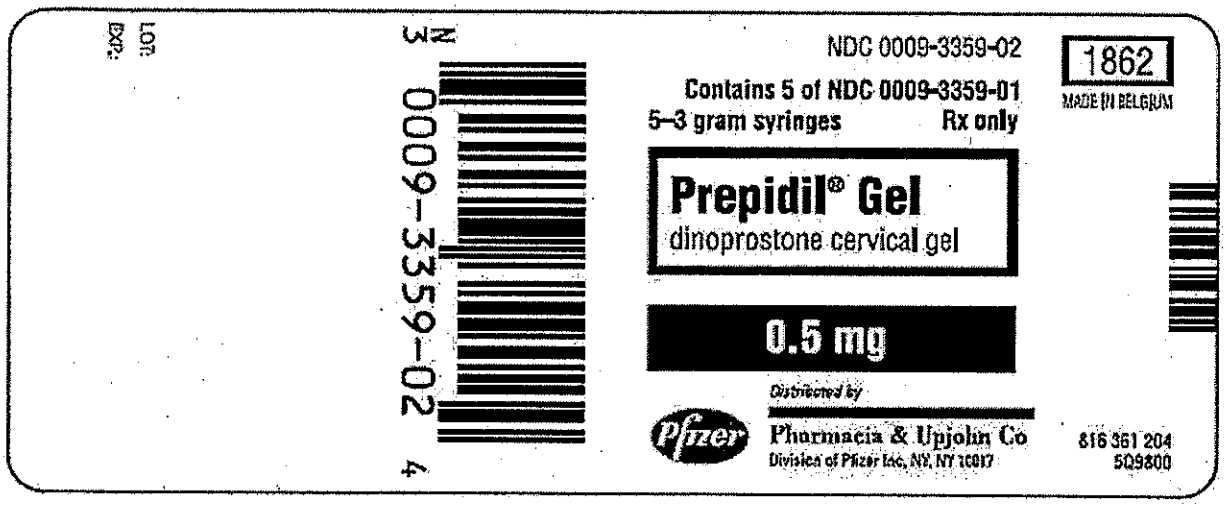
0.5 mg

Pfizer

Distributed by

Pharmacia & Upjohn Co

Division of Pfizer Inc, NY, NY 10017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Prepidil® Gel
dinoprostone cervical gel
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Distributed by
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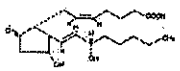
PROSTIN E2 - dinoprostone suppository
Pharmacia and UpJohn Company

DESCRIPTION

PROSTIN E2 Vaginal Suppository, an oxytocic, contains dinoprostone as the naturally occurring prostaglandin E2 (PGE2).
Its chemical name is (5Z,11α,13E,15S)-11,15-Dihydroxy-9-oxo-prosta-5,13-dien-1-oic acid and the structural formula is represented below:



The molecular formula is $C_{20}H_{32}O_5$. The molecular weight of dinoprostone is 352.5. Dinoprostone occurs as a white crystalline powder. It has a melting point within the range of 64° to 71°C. Dinoprostone is soluble in ethanol and in 25% ethanol in water. It is soluble in water to the extent of 130 mg/100 mL.
Each suppository contains 20 mg of dinoprostone in a mixture of glycerides of fatty acids.

CLINICAL PHARMACOLOGY

PROSTIN E2 Vaginal Suppository administered intravaginally stimulates the myometrium of the gravid uterus to contract in a manner that is similar to the contractions seen in the term uterus during labor. Whether or not this action results from a direct effect of dinoprostone on the myometrium has not been determined with certainty at this time. Nonetheless, the myometrial contractions induced by the vaginal administration of dinoprostone are sufficient to produce evacuation of the products of conception from the uterus in the majority of cases.
Dinoprostone is also capable of stimulating the smooth muscle of the gastrointestinal tract of man. This activity may be responsible for the vomiting and/or diarrhea that is not uncommon when dinoprostone is used to terminate pregnancy.
In laboratory animals, and also in man, large doses of dinoprostone can lower blood pressure, probably as a consequence of its effect on the smooth muscle of the vascular system. With the doses of dinoprostone used for terminating pregnancy this effect has not been clinically significant. In laboratory animals, and also in man, dinoprostone can elevate body temperature. With the clinical doses of dinoprostone used for the termination of pregnancy some patients do exhibit temperature increases.

INDICATIONS AND USAGE

1. PROSTIN E2 Vaginal Suppository is indicated for the termination of pregnancy from the 12th through the 20th gestational week as calculated from the first day of the last normal menstrual period.

2. PROSTIN E2 is also indicated for evacuation of the uterine contents in the management of missed abortion or intrauterine fetal death up to 28 weeks of gestational age as calculated from the first day of the last normal menstrual period.

3. PROSTIN E2 is indicated in the management of nonmetastatic gestational trophoblastic disease (benign hydatidiform mole).

CONTRAINDICATIONS

1. Hypersensitivity to dinoprostone

2. Acute pelvic inflammatory disease

3. Patients with active cardiac, pulmonary, renal, or hepatic disease

WARNINGS

Dinoprostone, as with other potent oxytocic agents, should be used only with strict adherence to recommended dosages. Dinoprostone should be used by medically trained personnel in a hospital which can provide immediate intensive care and acute surgical facilities.

Dinoprostone does not appear to directly affect the fetoplacental unit. Therefore, the possibility does exist that the previable fetus aborted by dinoprostone could exhibit transient life signs. Dinoprostone is not indicated if the fetus in utero has reached the stage of viability. Dinoprostone should not be considered a feticidal agent.
Evidence from animal studies has suggested that certain prostaglandins may have some teratogenic potential. Therefore, any failed pregnancy termination with dinoprostone should be completed by some other means.
PROSTIN E2 Vaginal Suppository should not be used for extemporaneous preparation of any other dosage form.
Neither the PROSTIN E2 Vaginal Suppository, as dispensed nor any extemporaneous formulation made from the PROSTIN E2 Vaginal Suppository should be used for cervical ripening or other indication in the patient with term pregnancy.

PRECAUTIONS

1. General precautions

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series can induce proliferation of bone. Such effects have also been noted in newborn infants who have received prostaglandin E1 during prolonged treatment. There is no evidence that short term administration of PROSTIN E2 Vaginal Suppository can cause similar bone effects.

As in spontaneous abortion, where the process is sometimes incomplete, abortion induced by PROSTIN E2 may sometimes be incomplete. In such cases, other measures should be taken to assure complete abortion.

In patients with a history of asthma, hypo-or hypertension, cardiovascular disease, renal disease, hepatic disease, anemia, jaundice, diabetes or history of epilepsy, dinoprostone should be used with caution.

Dinoprostone administered by the vaginal route should be used with caution in the presence of cervicitis, infected endocervical lesions, or acute vaginitis.

As with any oxytocic agent, dinoprostone should be used with caution in patients with compromised (scarred) uteri.

Dinoprostone vaginal therapy is associated with transient pyrexia that may be due to its effect on hypothalamic thermoregulation. In the patients studied, temperature elevations in excess of 2°F (1.1°C) were observed in approximately one-half of the patients on the recommended dosage regimen. In all cases, temperature returned to normal on discontinuation of therapy. Differentiation of post-abortion endometritis from drug-induced temperature elevations is difficult, but with increasing clinical exposure and experience with PGE2 vaginal therapy the distinctions become more obviously apparent and are summarized below:

Endometritis pyrexia	PGE2 induced pyrexia
a. **Time of onset:** Typically, on third post-abortional day (38°C or higher).	Within 15–45 minutes of suppository administration.
b. **Duration:** Untreated pyrexia and infection continue and may give rise to other infective pelvic pathology.	Elevations revert to pretreatment levels within 2–6 hours after discontinuation of therapy or removal of suppository from vagina without any other treatment.
c. **Retention:** Products of conception are often retained in the cervical os or uterine cavity.	Elevation occurs irrespective of any retained tissue.
d. **Histology:** Endometrium shows evidence of inflammatory lymphocytic infiltration with areas of necrotic hemorrhagic tissue.	Although the endometrial stroma may be edematous and vascular, there is relative absence of inflammatory reaction.
e. **The uterus:** Often remains boggy and soft with tenderness over the fundus, and pain on moving the cervix, on bimanual examination.	Normal uterine involution not tender.
f. **Discharge:** Often associated foul-smelling lochia and leukorrhea.	Lochia normal.
g. **Cervical culture** The culture of pathological organisms from the cervix or uterine cavity after abortion does not, of itself, warrant the diagnosis of septic abortion in the absence of clinical evidence of sepsis. It is not uncommon to culture pathogens from cases of recent abortion *not* clinically infected. Persistent positive culture with clear clinical signs of infection are significant in the differential diagnosis.	
h. **Blood count** Leukocytosis and differential white cell counts are not of major clinical importance in distinguishing between the two conditions, since total WBC's may be increased as a result of infection and transient leukocytosis may also be drug induced.	

In the absence of clinical or bacteriological evidence of intrauterine infection, supportive therapy for drug induced fevers includes the forcing of fluids. As all PGE2-induced fevers have been found to be transient or self-limiting, it is doubtful if any simple empirical measures for temperature reduction are indicated.

2. Laboratory tests

When a pregnancy diagnosed as missed abortion is electively interrupted with intravaginal administration of dinoprostone, confirmation of intrauterine fetal death should be obtained in respect to a *negative pregnancy test* for chorionic gonadotropic activity (U.C.G. test or equivalent). When a pregnancy with late fetal intrauterine death is interrupted with intravaginal administration of dinoprostone, confirmation of intrauterine fetal death should be obtained prior to treatment.

3. Drug interactions

PROSTIN E2 may augment the activity of other oxytocic drugs. Concomitant use with other oxytocic agents is not recommended.

4. Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenic bioassay studies have not been conducted in animals with PROSTIN E2 due to the limited indications for use and short duration of administration. No evidence of mutagenicity was observed in the Micronucleus Test or Ames Assay.

5. Pregnancy

Teratogenic Effects: Pregnancy Category C
Animal studies do not indicate that PROSTIN E2 is teratogenic, however, it has been shown to be embryotoxic in rats and rabbits and any dose which produces increased uterine tone could put the embryo or fetus at risk. See WARNINGS section.

6. Pediatric use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
The most frequent adverse reactions observed with the use of dinoprostone for abortion are related to its contractile effect on smooth muscle.
In the patients studied, approximately two-thirds experienced vomiting, one-half temperature elevations, two-fifths diarrhea, one-third some nausea, one-tenth headache, and one-tenth shivering and chills.
In addition, approximately one-tenth of the patients studied exhibited transient diastolic blood pressure decreases of greater than 20 mmHg.
Two cases of myocardial infarction following the use of dinoprostone have been reported in patients with a history of cardiovascular disease.
It is not known whether these events were related to the administration of dinoprostone.
Adverse effects in decreasing order of their frequency, observed with the use of dinoprostone, not all of which are clearly drug related include:

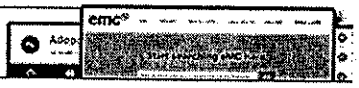
Vomiting	Nocturnal leg cramps
Diarrhea	Uterine rupture
Nausea	Breast tenderness
Fever	Blurred vision
Headache	Coughing
Chills or shivering	Rash
Backache	Myalgia
Joint inflammation or pain new or exacerbated	Stiff neck
Flushing or hot flashes	Dehydration
Dizziness	Tremor
Arthralgia	Paresthesia
Vaginal pain	Hearing impairment
Chest pain	Urine retention
Dyspnea	Pharyngitis
Endometritis	Laryngitis
Syncope or fainting sensation	Diaphoresis
Vaginitis or vulvitis	Eye pain
Weakness	Wheezing
Muscular cramp or pain	Cardiac arrhythmia
Tightness in chest	Skin discoloration
	Vaginismus
	Tension

DOSAGE AND ADMINISTRATION
STORE IN A FREEZER NOT ABOVE -20°C (-4°F) BUT BRING TO ROOM TEMPERATURE JUST PRIOR TO USE. REMOVE FOIL BEFORE USE.
A suppository containing 20 mg of dinoprostone should be inserted high into the vagina. The patient should remain in the supine position for ten minutes following insertion.
Additional intravaginal administration of each subsequent suppository should be at 3- to 5-hour intervals until abortion occurs. Within the above recommended intervals administration time should be determined by abortifacient progress, uterine contractility response, and by patient tolerance. Continuous administration of the drug for more than 2 days is not recommended.

HOW SUPPLIED
PROSTIN E2 Vaginal Suppositories are available in foil strips of 5 individually sealed suppositories, NDC 0009-0827-03. Each suppository contains 20 mg of dinoprostone in a mixture of glycerides of fatty acids.
STORE IN A FREEZER NOT ABOVE -20°C (-4°F).

Rx only

16



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FERRI
PHARMACEU

Summary of Product Characteristics last updated on the eMC: 25

SPC **Propess 10mg vaginal delivery system**

Table of Contents

Document Links

More information about this product

View all medicines from this company

Print this page

View document history

Legal Categories

› POM – Prescription Only Medicine

Active Ingredients/Gen

› dinoprostone

1. Name of the medicinal product

Go to top of the page

PROPESS 10mg vaginal delivery system

2. Qualitative and quantitative composition

Go to top of the page

Each vaginal delivery system consists of a non-biodegradable polymeric drug delivery device containing 10mg dinoprostone (Prostaglandin E_2) dispersed throughout its matrix.

For a full list of excipients, see 6.1

3. Pharmaceutical form

Go to top of the page

Vaginal delivery system

PROPESS is presented as a thin, flat semi-opaque polymeric vaginal delivery system which is rectangular in shape with radiused corners contained within a knitted polyester retrieval system.

4. Clinical particulars

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Initiation of cervical ripening in patients, at term (from 38th week of gestation).

4.2 Posology and method of administration Go to top of the page

One vaginal delivery system is administered high into the posterior vaginal fornix.

If there has been insufficient cervical ripening in 24 hours, the vaginal delivery system should be removed.

A dosing interval of at least 30 minutes is recommended for the sequential use of oxytocin following the removal of the vaginal delivery system.

Administration

PROPESS should be removed from the freezer in direct connection with the insertion.

The vaginal delivery system should be inserted high into the posterior vaginal fornix using only small amounts of water soluble lubricants to aid insertion. After the vaginal delivery system has been inserted, the withdrawal tape may be cut with scissors always ensuring there is sufficient tape outside the vagina to allow removal. No attempt should be made to tuck the end of the tape into the vagina as this may make retrieval more difficult.

The patient should be recumbent for 20 minutes to 30 minutes after insertion. As dinoprostone will be released continuously over a period of 24 hours, it is important to monitor uterine contractions and fetal condition at frequent regular intervals.

Removal

The vaginal delivery system can be removed quickly and easily by gentle traction on the retrieval tape.

It is necessary to remove the vaginal delivery system to terminate drug administration when cervical ripening is judged to be complete or for any of the reasons listed below.

1. Onset of labour. For the purposes of induction of labour with PROPESS, the onset of labour is defined as the presence of regular painful uterine contractions occurring every 3 minutes irrespective of any cervical change. There are two important points to note:

(i) Once regular, painful contractions have been established with PROPESS they will not reduce in frequency or intensity as long as PROPESS remains *in situ* because dinoprostone is still being administered.

(ii) Patients, particularly multigravidae, may develop regular painful contractions without any apparent cervical change. Effacement and dilatation of the cervix may not occur until uterine activity is established. Because of this, once regular painful uterine activity is established with PROPESS *in situ*, the vaginal delivery system should be removed irrespective of cervical state to avoid the risk of uterine hyperstimulation.

2. Spontaneous rupture of the membranes or amniotomy.

3. Any suggestion of uterine hyperstimulation or hypertonic uterine contractions.

4. Evidence of fetal distress.

5. Evidence of maternal systemic adverse dinoprostone effects such as nausea, vomiting, hypotension or tachycardia.

6. At least 30 minutes prior to starting an intravenous infusion of oxytocin.

The opening on one side of the retrieval device is present only to allow the manufacturer to enclose the vaginal delivery system into the retrieval device during manufacture. The vaginal delivery system should NEVER be removed from the retrieval device.

On removal of the product from the vagina, the vaginal delivery system will have swollen to 2-3 times its original size and be pliable.

4.3 Contraindications Go to top of the page

PROPESS should not be used or left in place:

1. When labour has started.

2. When oxytocic drugs are being given.

3. When strong prolonged uterine contractions would be inappropriate such as in patients:

a. who have had previous major uterine surgery, e.g. caesarean section, myomectomy etc (see sections 4.4 and 4.8)

b. with cephalopelvic disproportion

c. with fetal malpresentation

d. with suspicion or evidence of fetal distress

e. who have had more than three full term deliveries

f. previous surgery or rupture of the cervix

4. When there is current pelvic inflammatory disease, unless adequate prior treatment has been instituted.

5. When there is hypersensitivity to dinoprostone or to any of the excipients.

6. When there is placenta previa or unexplained vaginal bleeding during the current pregnancy.

4.4 Special warnings and precautions for use Go to top of the page

The condition of the cervix should be assessed carefully before PROPESS is used. After insertion, uterine activity and fetal condition must be monitored regularly. PROPESS must only be used if facilities for continuous fetal and uterine monitoring are available. If there is any suggestion of maternal or fetal complications or if adverse effects occur, the vaginal delivery system should be removed from the vagina.

The experience of PROPESS in patients with ruptured membranes is limited. Therefore, PROPESS should be used with caution in those patients. Since the release of dinoprostone from the insert can be affected in the presence of amniotic fluid, special attention should be given to uterine activity and fetal condition.

PROPESS should be used with caution in patients with a previous history of uterine hypertony, glaucoma or asthma.

Medication with non-steroidal anti-inflammatory drugs, including acetylsalicylic acid, should be stopped before administration of dinoprostone.

If uterine contractions are prolonged or excessive, there is possibility of uterine hypertonus or rupture and the vaginal delivery system should be removed immediately.

Uterine rupture has been reported in association with the use of PROPESS, mainly in patients with contra-indicated conditions (see section 4.3). Therefore, PROPESS should not be administered to patients with a history of previous caesarean section or uterine surgery given the potential risk for uterine rupture and associated obstetrical complications.

PROPESS should be used with caution when there is a multiple pregnancy. No studies in multiple pregnancy have been performed.

A second dose of PROPESS is not recommended, as the effects of a second dose have not been studied.

The use of the product in patients with diseases which could affect the metabolism or excretion of dinoprostone, e.g. lung, liver or renal disease, has not been specifically studied. The use of the product in such patients is not recommended.

Women aged 35 and over, women with complications during pregnancy, such as gestational diabetes, arterial hypertension and hypothyroidism, and women at gestational age above 40 weeks have a higher post-partum risk for developing disseminated intravascular coagulation (DIC). These factors may additionally enhance the risk of disseminated intravascular coagulation in women with pharmacologically induced labour (see section 4.8). Therefore, dinoprostone and oxytocin should be used with caution in these women. In the immediate post-partum phase the physician should look out carefully for early signs of a developing DIC (e.g fibrinolysis).

4.5 Interaction with other medicinal products and other forms of interaction

Go to top of the page

Prostaglandins potentiate the uterotonic effect of oxytocic drugs. Therefore, PROPESS should not be used concurrently with the use of oxytocic drugs.

4.6 Pregnancy and lactation

Go to top of the page

The product is for the initiation of cervical ripening in pregnant patients at term only where labour induction is indicated.

PROPESS is not indicated for use during early or other phases of pregnancy or during lactation.

4.7 Effects on ability to drive and use machines

Go to top of the page

Not relevant.

4.8 Undesirable effects

Go to top of the page

The occasional effects seen have been those normally associated with intravaginal dinoprostone administration.

CTG changes and unspecified fetal distress have been reported during and after administration of intravaginal dinoprostone. Increased uterine activity with hypertonic contractions with or without fetal distress has been reported. There is a much greater risk of hyperstimulation if the dinoprostone source is not removed before administration of oxytocin because prostaglandins are known to potentiate the uterotonic effects of oxytocic drugs.

Frequency	MedDRA System Organ Class	Adverse Events (MedDRA Preferred Term)
Common (>1/100, <1/10)	Pregnancy, puerperium and perinatal conditions	Abnormal labour affecting fetus Fetal heart rate disorder Fetal distress syndrome Uterine hypertonus
Uncommon (>1/1,000, <1/100)	Gastro-intestinal disorders	Nausea, vomiting, diarrhoea
Rare (>1/10,000, <1/1,000)	Blood and lymphatic system disorders Pregnancy, puerperium and	Disseminated intravascular coagulation

	perinatal conditions	Uterine rupture
Very rare (<1/10,000) including isolated reports	Immune system disorders Reproductive system and breast disorders	Anaphylactic reaction Genital oedema

In the pivotal efficacy study, five (4.9%) of 102 patients had hyperstimulation. Of these, three cases were associated with fetal distress. Of the five cases, uterine hypertonus was resolved in four after removal of the insert.

In post-marketing experience reports, uterine rupture has been reported rarely in association with the use of PROPESS (see sections 4.3 and 4.4).

An increased risk of post-partum disseminated intravascular coagulation has been reported in patients whose labour was induced by pharmacological means, either with dinoprostone or oxytocin (see section 4.4).

PGE_2 is known to be responsible for the patency of the ductus arteriosus in pregnancy but there have been no reports of "blue babies" in the neonatal period after the use of PROPESS.

4.9 Overdose Go to top of the page

Overdosage or hypersensitivity may lead to hyperstimulation of the uterine muscle or fetal distress. The PROPESS vaginal delivery system should be removed immediately and the patient should be managed in accordance with local protocol.

5. Pharmacological properties Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page

Pharmacotherapeutic group: oxytocics, ATC-code: G02AD02

Prostaglandin E_2 (PGE_2) is a naturally occurring compound found in low concentrations in most tissues of the body. It functions as a local hormone.

Prostaglandin E_2 plays an important role in the complex set of biochemical and structural alterations involved in cervical ripening. Cervical ripening involves a marked relaxation of the cervical smooth muscle fibres of the uterine cervix which must be transformed from a rigid structure to a soft, dilated configuration to allow passage of the fetus through the birth canal. This process involves activation of the enzyme collagenase which is responsible for the breakdown of the collagen.

Local administration of dinoprostone to the cervix results in cervical ripening which then induces the subsequent events which complete labour.

5.2 Pharmacokinetic properties Go to top of the page

PGE_2 is rapidly metabolised primarily in the tissue of synthesis. Any which escapes local inactivation is rapidly cleared from the circulation with a half-life generally estimated as 1-3 minutes.

No correlation could be established between PGE_2 release and plasma concentrations of its metabolite, PGE_m. The relative contributions of endogenously and exogenously released PGE_2 to the plasma levels of the metabolite PGE_m could not be determined.

The reservoir of 10mg dinoprostone serves to maintain a controlled and constant release. The release rate is approximately 0.3mg per hour over 24 hours in women with intact membranes whereas release is higher and more variable in women with premature rupture of membranes. PROPESS releases dinoprostone to the cervical tissue continuously at a rate which allows cervical ripening to progress until complete, and with the facility to remove the dinoprostone source when the clinician decides that cervical ripening is complete or labour has started, at which point no further dinoprostone is required.

5.3 Preclinical safety data Go to top of the page

Preclinical studies have demonstrated that dinoprostone is a locally acting substance which is rapidly inactivated and thus it has no significant systemic toxicity.

The hydrogel and polyester polymers are inert compounds with good local tolerability.

Reproduction toxicity, genotoxic or carcinogenic effects of the polymers have not been investigated but systemic exposure is negligible.

6. Pharmaceutical particulars Go to top of the page

6.1 List of excipients Go to top of the page

Crosslinked polyethylene glycol (hydrogel)

Polyester yarn

6.2 Incompatibilities Go to top of the page

Not applicable

6.3 Shelf life Go to top of the page

3 Years

6.4 Special precautions for storage Go to top of the page

Store in a freezer. Store in the original container in order to protect from moisture.

6.5 Nature and contents of container Go to top of the page

PROPESS vaginal delivery systems are presented in individual, sealed aluminium/polyethylene laminate sachets in packs of 5 vaginal delivery systems.

6.6 Special precautions for disposal and other handling Go to top of the page

PROPESS should be removed from the freezer in direct connection with the insertion.

After usage, the whole product should be disposed of as clinical waste.

7. Marketing authorisation holder Go to top of the page

Ferring Pharmaceuticals Ltd.

Drayton Hall

Church Road

West Drayton

UB7 7PS (UK)

8. Marketing authorisation number(s) Go to top of the page

PL 03194/0084

9. Date of first authorisation/renewal of the authorisation Go to top of the page

15th February 2001

10. Date of revision of the text Go to top of the page

October 2011

More information about this product

- Patient Information Leaflets (PILs):
  Propess 10mg vaginal delivery system

Link to this document from your website: http://www.medicines.org.uk/emc/medicine/16898/SPC/

Return to the top of the page

Home | Contact us | Useful links | Accessibility | Legal and privacy policy | Glossary | Site map

17

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PHARMA

Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. Why?

Summary of Product Characteristics last updated on the eMC: 23

SPC **Prostin E2 Sterile Solution 10 mg/ml Intravenous**

Table of Contents

Document Links

More information about this product

View all medicines from this company

Print this page

View document history

Legal Categories

› POM – Prescription Only Medicine

Active Ingredients/Gen

› dinoprostone

1. Name of the medicinal product

Go to top of the page

Prostin E2 Sterile Solution 10 mg/ml

2. Qualitative and quantitative composition

Go to top of the page

Each ml contains 10 mg dinoprostone.

3. Pharmaceutical form

Go to top of the page

Colourless, sterile solution, which after appropriate dilution is intended for intravenous administration to human beings.

4. Clinical particulars

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Oxytocic agent. Therapeutic termination of pregnancy, missed abortion and hydatidiform mole by the intravenous route.

4.2 Posology and method of administration

Go to top of the page

Adults: Ampoule contents must be diluted before use and full instructions on method of dilution and dosage are given on the package insert which should be consulted prior to initiation of therapy. The following is a guide to dosage:

Dilute with normal saline or 5% dextrose according to the package insert to produce a 5 micrograms/ml solution. The 5 micrograms/ml solution is infused at 2.5 micrograms/minute for 30 minutes and then maintained or increased to 5 micrograms/minute. The rate should be maintained for at least 4 hours before increasing further.

Elderly: Not applicable

Children: Not applicable

4.3 Contraindications Go to top of the page

Prostin E2 Sterile Solution should not be used where the patient is sensitive to prostaglandins.

Prostin E2 Sterile Solution 10 mg/ml is not recommended in the following circumstances:

1. For patients in whom oxytocic drugs are generally contra-indicated or where prolonged contractions of the uterus are considered inappropriate such as:

Cases with a history of Caesarean section or major uterine surgery;

Cases where there is evidence of a potential for obstructed labour.

2. In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatment has been instituted.

3. Patients with active cardiac, pulmonary, renal or hepatic disease.

4.4 Special warnings and precautions for use Go to top of the page

This product is only available to hospitals and clinics with specialised obstetric units and should only be used where 24-hour resident medical cover is provided

Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

It is advised that Prostin E2 Sterile Solution should not be administered by the intramyometrial route since there have been reports of a possible association between this route of administration and cardiac arrest in severely ill patients.

Caution should be exercised in the administration of Prostin E2 Sterile Solution in patients with:

(i) asthma or a history of asthma;

(ii) epilepsy or a history of epilepsy;

(iii) glaucoma or raised intra-ocular pressure;

(iv) compromised cardiovascular, hepatic, or renal function;

(v) hypertension.

As with any oxytocic agent, Prostin E2 Sterile Solution should be used with caution in patients with compromised (scarred) uteri.

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series can induce proliferation of bone. Such effects have also been noted in newborn infants who received prostaglandin E_1 during prolonged treatment. There is no evidence that short-term administration of prostaglandin E_2 can cause similar bone effects.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labour induction (see section 4.8 Undesirable Effects). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

4.5 Interaction with other medicinal products and other forms of interaction Go to top of the page

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that these drugs are used together. If used in sequence, the patient's uterine activity should be carefully monitored.

4.6 Pregnancy and lactation Go to top of the page

Prostin E2 Sterile Solution 10 mg/ml is only used during pregnancy for therapeutic termination of pregnancy, missed abortion and hydatidiform mole. There has been some evidence in animals of a low order of teratogenic activity, therefore, if abortion does not occur or is suspected to be incomplete as a result of prostaglandin therapy, (as in spontaneous abortion, where the process is sometimes incomplete), the appropriate treatment for complete evacuation of the pregnant uterus should be instituted in all instances.

Prostaglandins are excreted in breast milk. This is not expected to be a hazard given the circumstances in which the product is used.

4.7 Effects on ability to drive and use machines Go to top of the page

Not applicable.

Go to top of the page

4.8 Undesirable effects

Cardiac disorders: Cardiac arrest

Vascular disorders: Hypertension

Gastrointestinal disorders: Diarrhoea, nausea, vomiting

General disorders and administration site conditions: Fever, local tissue irritation / erythema (injection site), temporary pyrexia, local infections

Immune system disorders: Hypersensitivity reactions such as anaphylactoid reactions and anaphylactic reactions including anaphylactic shock

Investigations: Elevated WBC

Musculoskeletal and connective tissue disorders: Back pain

Nervous system disorders: Transient vasovagal symptoms (flushing, shivering, headache, dizziness)

Pregnancy and puerperium conditions

Maternal-related conditions: Uterine hypertonus, uterine rupture, abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Blood and lymphatic system disorders: An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labour was induced by pharmacological means, either with dinoprostone or oxytocin (see **section 4.4 Special Warnings and Special Precautions for Use**). The frequency of this adverse event, however, appears to be rare (<1 per 1,000 labours).

4.9 Overdose Go to top of the page

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. During use, uterine activity and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, e.g. hypertonus or sustained uterine contractions. Because of the transient nature of PGE2-induced myometrial hyperstimulation, non-specific, conservative management should be used (rate of infusion should be decreased or discontinued, maternal position change and administration of oxygen). If conservative management is not effective, a tocolytic agent may be used in appropriate patients as a treatment of hyperstimulation following administration of PGE2 or appropriate measures should be considered.

5. Pharmacological properties Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page

Dinoprostone is a prostaglandin of the E series with actions on smooth muscle. It induces contraction of uterine muscle at any stage of pregnancy.

5.2 Pharmacokinetic properties Go to top of the page

5.2a General characteristics of active substance

Dinoprostone is rapidly metabolised in the body. Intravenous administration results in very rapid distribution and metabolism, with only 3% of unchanged drug remaining in the blood after 15 minutes. At least nine prostaglandin E_2 metabolites have been identified in human blood and urine.

5.2b Characteristics in patients

No special characteristics. See "Special warnings and special precautions for use" for further information.

5.3 Preclinical safety data Go to top of the page

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars Go to top of the page

6.1 List of excipients Go to top of the page

Dehydrated alcohol.

6.2 Incompatibilities Go to top of the page

None known.

6.3 Shelf life Go to top of the page

24 months.

6.4 Special precautions for storage Go to top of the page

Store in a refrigerator at 4°C. Once diluted, the diluted solution should be stored in a refrigerator at 4°C and used within 24 hours.

6.5 Nature and contents of container Go to top of the page

Ph. Eur. Type I glass ampoule, containing 0.5 ml sterile solution, packed in a carton.

6.6 Special precautions for disposal and other handling Go to top of the page

Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

7. Marketing authorisation holder Go to top of the page

Pharmacia Limited

Ramsgate Road

Sandwich

Kent

CT13 9NJ

UK

8. Marketing authorisation number(s) Go to top of the page

PL 0032/0021R

9. Date of first authorisation/renewal of the authorisation Go to top of the page

27 June 1986/17 November 1998

10. Date of revision of the text Go to top of the page

March 2011

11 Dosimetry Go to top of the page

IF APPLICABLE

12 Instructions for preparation of radiopharmaceuticals Go to top of the page

IF APPLICABLE

PR2_0

More information about this product

- Patient Information Leaflets (PILs):
  Prostin E2 Sterile Solution 10 mg/ml Intravenous
  Prostin E2 Sterile Solution 10mg/ml Extra-Amniotic
- Medicine Guides:
  Prostin E2

Link to this document from your website: http://www.medicines.org.uk/emc/medicine/9666/SPC/

Return to the top of the page

Home | Contact us | Useful links | Accessibility | Legal and privacy policy | Glossary | Site map

18

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Summary of Prc

SPC Prostin E2 Sterile Solution 10mg/ml Extra-Amniotic

Table of Contents

Go to to

1. Name of the medicinal product

Prostin E2 Sterile Solution 10 mg/ml.

2. Qualitative and quantitative composition Go to tc

Each ml contains 10 mg dinoprostone.

3. Pharmaceutical form Go to tc

Colourless, sterile solution, which after appropriate dilution is intended for extra-amniotic administration to beings.

4. Clinical particulars Go to tc

4.1 Therapeutic indications Go to tc

Oxytocic agent. The therapeutic termination of pregnancy, by the extra-amniotic route.

4.2 Posology and method of administration Go to tc

Adults: Ampoule contents must be diluted before use and full instructions on method of dilution and dosag on the package insert which should be consulted prior to initiation of therapy. The following is a guide to d

Dilute with the 50 ml of diluent provided according to the package insert to produce a 100 micrograms/ml The 100 micrograms/ml solution is instilled via a 12-14 French gauge Foley catheter. Initial instillation is 1 dependent on uterine response, 1 or 2 ml usually at two hour intervals.

Elderly: Not applicable

Children: Not applicable

4.3 Contraindications Go to tc

Prostin E2 Sterile Solution should not be used where the patient is sensitive to prostaglandins.

Prostin E2 Sterile Solution 10 mg/ml is not recommended in the following circumstances:

1. For patients in whom oxytocic drugs are generally contra-indicated or where prolonged contractions o uterus are considered inappropriate such as:

   Cases with a history of Caesarean section or major uterine surgery;

   Cases where there is evidence of a potential for obstructed labour;

2. In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatr been instituted.

3. In patients with cervicitis or vaginal infections.

4. Patients with active cardiac, pulmonary, renal or hepatic disease.

4.4 Special warnings and precautions for use Go to tc

This product is only available to hospitals and clinics with specialised obstetric units and should only be u: 24-hour resident medical cover is provided.

Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and w administration.

It is advised that Prostin E2 Sterile Solution should not be administered by the intramyometrial route since been reports of a possible association between this route of administration and cardiac arrest in severely i

Caution should be exercised in the administration of Prostin E2 Sterile Solution to patients with:

(i) asthma or a history of asthma;

(ii) epilepsy or a history of epilepsy;

(iii) glaucoma or raised intra-ocular pressure;

(iv) compromised cardiovascular, hepatic, or renal function;

(v) Hypertension.

As with any oxytocic agent, Prostin E2 Sterile Solution should be used with caution in patients with compr (scarred) uteri.

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series proliferation of bone. Such effects have also been noted in newborn infants who received prostaglandin E prolonged treatment. There is no evidence that short-term administration of prostaglandin E_2 can cause si effects.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational a weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation addition, these factors may further increase the risk associated with labour induction (see section 4.8 Und Effects). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures sl applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

4.5 Interaction with other medicinal products and other forms of interaction Go to tc

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that th are used together. If used in sequence, the patient's uterine activity should be carefully monitored.

4.6 Pregnancy and lactation Go to tc

Pregnancy Code D

Prostin E2 Sterile Solution 10 mg/ml is only used during pregnancy for therapeutic termination of pregnan has been some evidence in animals of a low order of teratogenic activity, therefore, if abortion does not oc suspected to be incomplete as a result of prostaglandin therapy, (as in spontaneous abortion, where the p sometimes incomplete), the appropriate treatment for complete evacuation of the pregnant uterus should instituted in all instances.

Prostaglandins are excreted in breast milk. This is not expected to be a hazard given the circumstances ir product is used.

4.7 Effects on ability to drive and use machines Go to tc

Not applicable

4.8 Undesirable effects Go to tc

Cardiac disorders: Cardiac arrest

Vascular disorders: Hypertension

Gastrointestinal disorders: Diarrhoea, nausea, vomiting

General disorders and administration site conditions: Fever, local tissue irritation / erythema (injection site temporary pyrexia, local infections

Immune system disorders: Hypersensitivity reactions such as anaphylactoid reactions and anaphylactic re including anaphylactic shock

Investigations: Elevated WBC

Musculoskeletal and connective tissue disorders: Back pain

Nervous system disorders: Transient vasovagal symptoms (flushing, shivering, headache, dizziness)

Pregnancy and puerperium conditions

Maternal-related conditions: Uterine hypertonus, uterine rupture, abruptio placenta, pulmonary amniotic fl embolism, rapid cervical dilatation

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Blood and lymphatic system disorders: An increased risk of post-partum disseminated intravascular coagu been described in patients whose labour was induced by pharmacological means, either with dinoproston oxytocin (see **section 4.4 Special Warnings and Special Precautions for Use**). The frequency of this a event, however, appears to be rare (<1 per 1,000 labours).

4.9 Overdose Go to tc

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. During use, uterine a the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired e.g. hypertonus or sustained uterine contractions. Because of the transient nature of PGE2-induced myon hyperstimulation, non-specific, conservative management should be used (rate of infusion should be decr discontinued, maternal position change and administration of oxygen). If conservative management is not tocolytic agent may be used in appropriate patients as a treatment of hyperstimulation following administr PGE2 or appropriate measures should be considered.

5. Pharmacological properties Go to tc

5.1 Pharmacodynamic properties Go to tc

Dinoprostone is a prostaglandin of the E series with actions on smooth muscle. It induces contraction of u muscle at any stage of pregnancy.

5.2 Pharmacokinetic properties Go to tc

General characteristics of active substance

Dinoprostone is rapidly metabolised in the body. Intravenous administration results in very rapid distributic metabolism, with only 3% of unchanged drug remaining in the blood after 15 minutes. At least nine prosta metabolites have been identified in human blood and urine.

Characteristics in Patients

No special characteristics. See "Special Warnings and Precautions for use" for further information.

5.3 Preclinical safety data Go to tc

In mice and rats, the oral LD_{50} values were >500mg/kg and 141-513 mg/kg respectively.

Three month oral administration to rats resulted in significantly heavier stomach weights for treated compa untreated rats, which effect was reversible on treatment cessation. Treated rats had a dose related acanth squamous glandular junction and thickened glandular gastric mucosal epithelium. No significant alteration recognized in routine evaluation of the stemebrae and the femur.

A fourteen day oral toxicity study in dogs showed a maximum tolerated dose of 6-20 mg/kg/day. All treate microscopic evidence of increased fundic and pyloric mucus. The fundic and pyloric mucosa were thicken a cobblestone appearance and had an increased gastric mucus in both 20 mg/kg/day treated dogs and th mg/kg/day male dog. These were the only gross and microscopic drug related changes observed.

Satisfactory results were obtained in intravenous and intramuscular tolerability tests performed in dog and

Teratogenic effects were observed in rats injected subcutaneously with 0.5 mg/animal. No teratogenic eff seen in the rabbit at dosage levels of up to 1.5 mg/kg day.

No evidence of mutagenicity was obtained using the Ames Assay, the DNA Damage/Alkaline Elution Ass micronucleus test.

6. Pharmaceutical particulars

Go to tc

6.1 List of excipients

Go to tc

Dehydrated alcohol BP

6.2 Incompatibilities

Go to tc

None known.

6.3 Shelf life

Go to tc

24 months.

6.4 Special precautions for storage

Go to tc

Store in a refrigerator at 4° C. The product after dilution should be stored in a refrigerator at 4° C and sh kept for more than 48 hours.

6.5 Nature and contents of container

Go to tc

Ph. Eur. Type I glass ampoule, containing 0.5 ml sterile solution, packed in a carton, together with a vial c diluent.

6.6 Special precautions for disposal and other handling

Go to tc

Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and w administration.

Administrative data

Go to tc

7. Marketing authorisation holder

Go to tc

Pharmacia Limited

Ramsgate Road

Sandwich

Kent

UK

CT13 9NJ

8. Marketing authorisation number(s) Go to tc

PL 0032/0026R

9. Date of first authorisation/renewal of the authorisation Go to tc

1 July 1991 / 18 March 1997

10. Date of revision of the text Go to tc

March 2011

PR2_0

website: http://www.medicines.org.uk/emc/medicine/9571/SPC/

Document Links

More information about this product

View all medicines from this company

Print this page

View document history

Legal Categories

- POM – Prescription Only Medicine

Active Ingredients/Generics

- dinoprostone

Return to the top of the page

19

Pharmacia Limited
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Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. **Why?**

Summary of Product Characteristics last updated on the eMC: 23/03/2011

Prostin E2 Sterile Solution 1mg/ml Intravenous

1. Name of the medicinal product

Prostin E2 Sterile Solution 1 mg/ml.

2. Qualitative and quantitative composition

Each ml contains 1 mg dinoprostone.

3. Pharmaceutical form

Colourless, sterile solution, which after appropriate dilution is intended for intravenous administration to human beings.

4. Clinical particulars

4.1 Therapeutic indications

The induction of labour by the intravenous route.

4.2 Posology and method of administration

Adults: Ampoule contents must be diluted before use and full instructions on method of dilution and dosage are given i package insert which should be consulted prior to initiation of therapy. The following is a guide to dosage:

Dilute with normal saline or 5% dextrose according to the package insert to produce a 1.5 micrograms/ml solution. The micrograms/ml solution is infused at 0.25 micrograms/minute for 30 minutes and then maintained or increased. Cases death *in utero* may require higher doses. An initial rate of 0.5 micrograms/minute may be used with stepwise increases intervals of not less than one hour.

Elderly: Not applicable

Children: Not applicable

4.3 Contraindications

Prostin E2 Sterile Solution should not be used where the patient is sensitive to prostaglandins.

Prostin E2 Sterile Solution 1 mg/ml is not recommended in the following circumstances:

1. For patients in whom oxytocic drugs are generally contra-indicated or where prolonged contractions of the uterus ar considered inappropriate such as:

Cases with a history of Caesarean section or major uterine surgery;

Cases where there is cephalopelvic disproportion;

Cases in which fetal malpresentation is present;

Cases where there is clinical suspicion or definite evidence of pre-existing fetal distress;

Cases in which there is a history of difficult labour and/or traumatic delivery;

Grand multiparae with over five previous term pregnancies.

2. In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatment has been

3. In patients where there is clinical suspicion or definite evidence of placenta praevia or unexplained vaginal bleeding pregnancy.

4. Patients with active cardiac, pulmonary, renal or hepatic disease.

4.4 Special warnings and precautions for use

This product is only available to hospitals and clinics with specialised obstetric units and should only be use 24-hour resident medical cover is provided

Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

It is advised that Prostin E2 Sterile Solution should not be administered by the intramyometrial route since there have l reports of a possible association between this route of administration and cardiac arrest in severely ill patients.

Caution should be exercised in the administration of Prostin E2 Sterile Solution 1 mg/ml for the induction of labour in p with:

(i) asthma or a history of asthma;

(ii) epilepsy or a history of epilepsy;

(iii) glaucoma or raised intra-ocular pressure;

(iv) compromised cardiovascular, hepatic, or renal function;

(v) hypertension.

As with any oxytocic agent, Prostin E2 Sterile Solution should be used with caution in patients with compromised (scar

In labour induction, cephalopelvic relationships should be carefully evaluated before use of Prostin E2 Sterile Solution. use, uterine activity, fetal status and the progression of cervical dilation should be carefully monitored to detect possibl of undesired responses, e.g. hypertonus, sustained uterine contractions, or fetal distress. In cases where there is a kn history of hypertonic uterine contractility or tetanic uterine contractions, it is recommended that uterine activity and the the fetus (where applicable) should be continuously monitored throughout labour. The possibility of uterine rupture sho borne in mind where high-tone uterine contractions are sustained.

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series can induce p of bone. Such effects have also been noted in newborn infants who received prostaglandin E_1 during prolonged treatm is no evidence that short-term administration of prostaglandin E_2 can cause similar bone effects.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational age over 40 w been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factor further increase the risk associated with labour induction (see section 4.8 Undesirable Effects). Therefore, in these wo of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evol fibrinolysis in the immediate post-partum phase.

4.5 Interaction with other medicinal products and other forms of interaction

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that these drugs a together. If used in sequence, the patient's uterine activity should be carefully monitored.

4.6 Pregnancy and lactation

Prostin E2 Sterile Solution 1 mg/ml is only used during pregnancy, to induce labour.

Prostaglandins are excreted in breast milk. This is not expected to be a hazard given the circumstances in which the p used.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Cardiac disorders: Cardiac arrest

Vascular disorders: Hypertension

Gastrointestinal disorders: Diarrhoea, nausea, vomiting

General disorders and administration site conditions: Fever, local tissue irritation / erythema (injection site)

Immune system disorders: Hypersensitivity reactions such as anaphylactoid reactions and anaphylactic reactions inclu anaphylactic shock

Investigations: Elevated WBC

Musculoskeletal and connective tissue disorders: Back pain

Nervous system disorders: Transient vasovagal symptoms (flushing, shivering, headache, dizziness)

Pregnancy, Puerperium and Perinatal conditions:

Maternal-related conditions: Uterine hypertonus, uterine rupture, abruptio placenta, pulmonary amniotic fluid embolism cervical dilatation

Foetus-related conditions: Uterine hypercontractility with/without fetal bradycardia fetal distress/altered fetal heart rate

Neonatal conditions: Neonatal distress, neonatal death, stillbirths, low Apgar score

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Blood and lymphatic system disorders: An increased risk of post-partum disseminated intravascular coagulation has b described in patients whose labour was induced by pharmacological means, either with dinoprostone or oxytocin (see **4.4 Special Warnings and Special Precautions for Use**). The frequency of this adverse event, however, appears to (<1 per 1,000 labours).

4.9 Overdose

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. During use, uterine activity, fetal s the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, hypertonus, sustained uterine contractions, or fetal distress. Because of the transient nature of PGE2-induced myomet hyperstimulation, non-specific, conservative management was found to be effective in the vast majority of cases: i.e. r position change and administration of oxygen to the mother. If conservative management is not effective, ß-adrenergic may be used as a treatment of hyperstimulation following administration of PGE2 for cervical ripening, in appropriate p

5. Pharmacological properties

5.1 Pharmacodynamic properties

Dinoprostone is a prostaglandin of the E series with actions on smooth muscle. It induces contraction of uterine muscl stage of pregnancy.

5.2 Pharmacokinetic properties

5.2 a General characteristics of active substance

Dinoprostone is rapidly metabolised in the body. Intravenous administration results in very rapid distribution and metab with only 3% of unchanged drug remaining in the blood after 15 minutes. At least nine prostaglandin E_2 metabolites ha identified in human blood and urine.

5.2 b Characteristics in patients

No special characteristics. See "Special warnings and special precautions for use" for further information.

5.3 Preclinical safety data

There are no pre-clinical data of relevance which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients
Dehydrated alcohol

6.2 Incompatibilities
None known

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store in a refrigerator at 4° C. The product after dilution should be stored in a refrigerator at 4° C and should not be k more than 24 hours.

6.5 Nature and contents of container
Ph. Eur. Type I glass ampoule, containing 0.75 ml sterile solution, packed in a carton.

6.6 Special precautions for disposal and other handling
Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

7. Marketing authorisation holder
Pharmacia Limited

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UK

8. Marketing authorisation number(s)
PL 0032/0020R

9. Date of first authorisation/renewal of the authorisation
27 June 1986/17 November 1998

10. Date of revision of the text
March 2011

11 Dosimetry

IF APPLICABLE

12 Instructions for preparation of radiopharmaceuticals

IF APPLICABLE

PR2_0

20

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PHARMA

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Summary of Product Characteristics last updated on the eMC: 22

SPC **Prostin E2 Vaginal Gel 1mg, 2mg**

Table of Contents

Document Links

More information about this product

View all medicines from this company

Print this page

View document history

Legal Categories

› POM – Prescription Only Medicine

Active Ingredients/Gen

› dinoprostone

1. Name of the medicinal product

Go to top of the page

Prostin E2 Vaginal Gel 1 mg

Prostin E2 Vaginal Gel 2 mg

2. Qualitative and quantitative composition

Go to top of the page

Each 3 g gel (2.5 ml) contains 1 mg dinoprostone.

Each 3 g gel (2.5 ml) contains 2 mg dinoprostone.

3. Pharmaceutical form

Go to top of the page

Translucent, thixotropic gel.

4. Clinical particulars

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Oxytocic. Prostin E2 Vaginal Gel is indicated for the induction of labour, when there are no fetal or maternal contra-indications.

4.2 Posology and method of administration

Adults: In primigravida patients with unfavourable induction features (Bishop score of 4 or less), an initial dose of 2 mg should be administered vaginally. In other patients an initial dose of 1 mg should be administered vaginally.

In both groups of patients, a second dose of 1 mg or 2 mg may be administered after 6 hours as follows:

1 mg should be used where uterine activity is insufficient for satisfactory progress of labour.

2 mg may be used where response to the initial dose has been minimal.

Maximum dose 4 mg in unfavourable primigravida patients or 3 mg in other patients (see "Precautions").

The gel should be inserted high into the posterior fornix avoiding administration into the cervical canal. The patient should be instructed to remain recumbent for at least 30 minutes.

Elderly: Not applicable

Children: Not applicable

4.3 Contraindications Go to top of the page

Prostin E2 Vaginal Gel should not be used where the patient is sensitive to prostaglandins or other constituents of the gel.

Prostin E2 Vaginal Gel is not recommended in the following circumstances:

1. For patients in whom oxytocic drugs are generally contra-indicated or where prolonged contractions of the uterus are considered inappropriate such as:

Cases with a history of Caesarean section or major uterine surgery;

Cases where there is cephalopelvic disproportion;

Cases in which fetal malpresentation is present;

Cases where there is clinical suspicion or definite evidence of pre-existing fetal distress;

Cases in which there is a history of difficult labour and/or traumatic delivery;

Grand multiparae with over five previous term pregnancies.

2. Patients with ruptured membranes.

3. In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatment has been instituted.

4. In patients where there is clinical suspicion or definite evidence of placenta praevia or unexplained vaginal bleeding during this pregnancy.

5. Patients with active cardiac, pulmonary, renal or hepatic disease.

4.4 Special warnings and precautions for use Go to top of the page

This product is only available to hospitals and clinics with specialised obstetric units and should only be used where 24-hour resident medical cover is provided.

Use the total contents of the syringe for one patient only. Discard after use. Use caution in handling the product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

Prostin E2 Vaginal Gel and Prostin E2 Vaginal Tablets are not bioequivalent.

Caution should be exercised in the administration of Prostin E2 Vaginal Gel for the induction of labour in patients with:

(i) asthma or a history of asthma;

(ii) epilepsy or a history of epilepsy;

(iii) glaucoma or raised intra-ocular pressure;

(iv) compromised cardiovascular, hepatic, or renal function;

(v) hypertension.

As with any oxytocic agent, Prostin E2 Vaginal Gel should be used with caution in patients with compromised (scarred) uteri.

In labour induction, cephalopelvic relationships should be carefully evaluated before use of Prostin E2 Vaginal Gel. During use, uterine activity, fetal status and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, e.g. hypertonus, sustained uterine contractions, or fetal distress.

In cases where there is a known history of hypertonic uterine contractility or tetanic uterine contractions, it is recommended that uterine activity and the state of the fetus (where applicable) should be continuously monitored throughout labour. The possibility of uterine rupture should be borne in mind where high-tone uterine contractions are sustained.

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series can induce proliferation of bone. Such effects have also been noted in newborn infants who received prostaglandin E_1 during prolonged treatment. There is no evidence that short-term administration of prostaglandin E_2 can cause similar bone effects.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labour induction (see section 4.8 Undesirable Effects). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

4.5 Interaction with other medicinal products and other forms of interaction Go to top of the page

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that these drugs are used together. If used in sequence, the patient's uterine activity should be carefully monitored.

4.6 Pregnancy and lactation Go to top of the page

Pregnancy Code A

Prostin E2 Vaginal Gel is only used during pregnancy, to induce labour.

Prostaglandins are excreted in breast milk. This is not expected to be a hazard given the circumstances in which the product is used.

4.7 Effects on ability to drive and use machines Go to top of the page

Not applicable.

4.8 Undesirable effects Go to top of the page

Cardiac disorders: Cardiac arrest

Vascular disorders: Hypertension

Gastrointestinal disorders: Diarrhoea, nausea, vomiting

General disorders and administration site conditions: Fever

Immune system disorders: Hypersensitivity reactions such as anaphylactoid reactions and anaphylactic reactions including anaphylactic shock

Musculoskeletal and connective tissue disorders: Back pain

Pregnancy Puerperium and Perinatal conditions:

Maternal-related conditions: Uterine hypertonus, uterine rupture, abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation

Foetus-related conditions: Uterine hypercontractility with/without fetal bradycardia fetal distress/altered fetal heart rate (FHR)

Neonatal conditions: Neonatal distress, neonatal death, stillbirths, low Apgar score

Reproductive system and breast disorders: Warm feeling in vagina, irritation, pain

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Skin and subcutaneous tissue disorders: Rash

Blood and lymphatic system disorders: An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labour was induced by pharmacological means, either with dinoprostone or oxytocin (see **section 4.4 Special Warnings and Special Precautions for Use**). The frequency of this adverse event, however, appears to be rare (<1 per 1,000 labours)

4.9 Overdose Go to top of the page

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. During use, uterine activity, fetal status and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, e.g. hypertonus, sustained uterine contractions, or fetal distress. Because of the transient nature of PGE2-induced myometrial hyperstimulation, non-specific, conservative management was found to be effective in the vast majority of cases: i.e. maternal position change and administration of oxygen to the mother. If conservative management is not effective, ß-adrenergic drugs may be used as a treatment of hyperstimulation following administration of PGE2 for cervical ripening, in appropriate patients.

5. Pharmacological properties Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page.

Dinoprostone is a prostaglandin of the E series which induces myometrial contractions and promotes cervical ripening.

5.2 Pharmacokinetic properties Go to top of the page

General characteristics of active substance

When given vaginally, PGE_2 is rapidly absorbed. Plasma levels of 15-keto PGE_2 equivalents peak at 1.5 hours after administration of a 5 mg dose. *In vitro* work indicates that PGE_2 is 73% bound to human plasma albumin. It is rapidly

metabolised in the lungs, kidneys, spleen and liver, with a single pass of the circulatory system converting 90% of an injected PGE_2 dose to metabolites.

Characteristics in patients

No special characteristics. See "Special warnings and special precautions for use" for further information.

5.3 Preclinical safety data Go to top of the page

There are no pre-clinical data of relevance which are additional to those already included in other sections of the SPC.

6. Pharmaceutical particulars Go to top of the page

6.1 List of excipients Go to top of the page

Triacetin and colloidal silicon dioxide.

6.2 Incompatibilities Go to top of the page

None known.

6.3 Shelf life Go to top of the page

Prostin E2 Vaginal Gel has a shelf-life of 24 months when stored in a refrigerator at 2-8°C.

6.4 Special precautions for storage Go to top of the page

Store in a refrigerator at 2-8°C.

6.5 Nature and contents of container Go to top of the page

Polyethylene syringe containing 3 g or 2.5 ml of gel.

6.6 Special precautions for disposal and other handling Go to top of the page

Use the total contents of the syringe for one patient only. Discard after use. Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

7. Marketing authorisation holder Go to top of the page

Pharmacia Limited

Ramsgate Road

Sandwich

Kent

CT13 9NJ

UK

8. Marketing authorisation number(s) Go to top of the page

Prostin E2 Vaginal Gel 1 mg PL 0032/0123

Prostin E2 Vaginal Gel 2 mg PL 0032/0124

9. Date of first authorisation/renewal of the authorisation Go to top of the page

30 April 1986/17 November 1998

10. Date of revision of the text Go to top of the page

March 2011

11 Dosimetry Go to top of the page

IF APPLICABLE

12 Instructions for preparation of radiopharmaceuticals Go to top of the page

IF APPLICABLE

21
Conti

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PHARMA

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Summary of Product Characteristics last updated on the eMC: 23

SPC **Prostin E2 Vaginal Tablets**

Table of Contents

Document Links

More information about this product

View all medicines from this company

Print this page

View document history

Legal Categories

› POM – Prescription Only Medicine

Active Ingredients/Gen

› dinoprostone

1. Name of the medicinal product

Go to top of the page

Prostin E2 Vaginal Tablets 3mg

2. Qualitative and quantitative composition

Go to top of the page

Dinoprostone HSE 3 mg

3. Pharmaceutical form

Go to top of the page

Tablet for vaginal administration

4. Clinical particulars

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Oxytocic. Prostin E2 Vaginal Tablets 3mg are indicated for the induction of labour, especially in patients with favourable induction features, when there are no fetal or maternal contra-indications.

4.2 Posology and method of administration

Go to top of the page

Method of administration: Vaginal tablets are administered by insertion high into the posterior fornix.

One tablet to be inserted high into the posterior fornix. A second tablet may be inserted after six to eight hours if labour is not established. Maximum dose 6 mg.

Children: Not applicable

Elderly: Not applicable

4.3 Contraindications Go to top of the page

Prostin E2 Vaginal Tablets should not be used where the patient is sensitive to prostaglandins or other constituents of the tablet.

Prostin E2 Vaginal Tablets are not recommended in the following circumstances:

1. For patients in whom oxytocic drugs are generally contra-indicated or where prolonged contractions of the uterus are considered inappropriate such as:

- Cases with a history of Caesarean section or major uterine surgery;
- Cases where there is cephalopelvic disproportion;
- Cases in which fetal malpresentation is present;
- Cases where there is clinical suspicion or definite evidence of pre-existing fetal distress;
- Cases in which there is a history of difficult labour and/or traumatic delivery;
- Grand multiparae with over five previous term pregnancies.

2. Patients with ruptured membranes.

3. In patients with a past history of, or existing, pelvic inflammatory disease, unless adequate prior treatment has been instituted.

4. In patients where there is clinical suspicion or definite evidence of placenta praevia or unexplained vaginal bleeding during this pregnancy.

5. Patients with active cardiac, pulmonary, renal or hepatic disease.

4.4 Special warnings and precautions for use Go to top of the page

This product is only available to hospitals and clinics with specialised obstetric units and should only be used where 24-hour resident medical cover is provided.

Use caution in handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after administration.

Caution should be exercised in the administration of Prostin E2 Vaginal Tablets for the induction of labour in patients with:

(i) asthma or a history of asthma;

(ii) epilepsy or a history of epilepsy;

(iii) glaucoma or raised intra-ocular pressure;

(iv) compromised cardiovascular, hepatic, or renal function;

(v) hypertension.

As with any oxytocic agent, Prostin E2 Vaginal Tablets should be used with caution in patients with compromised (scarred) uteri.

In labour induction, cephalopelvic relationships should be carefully evaluated before use of Prostin E2 Vaginal Tablets. During use, uterine activity, fetal status and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, e.g. hypertonus, sustained uterine contractions, or fetal distress.

In cases where there is a known history of hypertonic uterine contractility or tetanic uterine contractions, it is recommended that uterine activity and the state of the fetus (where applicable) should be continuously monitored throughout labour. The possibility of uterine rupture should be borne in mind where high-tone uterine contractions are sustained.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labour induction (see section 4.8 Undesirable Effects). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

4.5 Interaction with other medicinal products and other forms of interaction Go to top of the page

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that these drugs are used together. If used in sequence, the patient's uterine activity should be carefully monitored.

4.6 Pregnancy and lactation Go to top of the page

Prostin E2 Vaginal Tablets are only used during pregnancy, to induce labour.

Prostaglandins are excreted in breast milk. This is not expected to be a hazard given the circumstances in which the product is used.

4.7 Effects on ability to drive and use machines Go to top of the page

Not applicable.

4.8 Undesirable effects Go to top of the page

Cardiac disorders: Cardiac arrest

Vascular disorders: Hypertension

Gastrointestinal disorders: Diarrhoea, nausea, vomiting

General disorders and administration site conditions: Fever

Immune system disorders: Hypersensitivity reactions such as anaphylactoid reactions and anaphylactic reactions including anaphylactic shock.

Musculoskeletal and connective tissue disorders: Back pain

Pregnancy, Puerperium and Perinatal conditions:

Maternal-related conditions: Uterine hypertonus, uterine rupture, abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation

Foetus-related conditions: Uterine hypercontractility with/without fetal bradycardia fetal distress/altered fetal heart rate (FHR)

Neonatal conditions: Neonatal distress, neonatal death, stillbirths, low Apgar score

Reproductive system and breast disorders: Warm feeling in vagina, irritation, pain

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Skin and subcutaneous tissue disorders: Rash

Blood and lymphatic system disorders: An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labour was induced by pharmacological means, either with dinoprostone or oxytocin (see **section 4.4 Special Warnings and Special Precautions for Use**). The frequency of this adverse event, however, appears to be rare (<1 per 1,000 labours).

4.9 Overdose Go to top of the page

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. During use, uterine activity, fetal status and the progression of cervical dilation should be carefully monitored to detect possible evidence of undesired responses, e.g. hypertonus, sustained uterine contractions, or fetal distress. Because of the transient nature of PGE2-induced myometrial hyperstimulation, non-specific, conservative management was found to be effective in the vast majority of cases: i.e. maternal position change and administration of oxygen to the mother. If conservative management is not effective, ß-adrenergic drugs may be used as a treatment of hyperstimulation following administration of PGE2 for cervical ripening, in appropriate patients.

5. Pharmacological properties Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page

Dinoprostone is a prostaglandin of the E series with actions on smooth muscle; the endogenous substance is termed prostaglandin E2 (PGE_2). It induces contraction of uterine muscle at any stage of pregnancy and is reported to act predominantly as a vasodilator on blood vessels and as a bronchodilator on bronchial muscle. It is postulated that vaginal absorption of PGE_2 stimulates endogenous PGE_2 and $PGF_{2\alpha}$ production, similar to that which is seen in spontaneous labour.

5.2 Pharmacokinetic properties Go to top of the page

Following insertion of the tablet, PGE_2 absorption (as measured by the presence of PGE_2 metabolites) increases to reach a peak at about 40 minutes. PGE_2 is rapidly metabolised to 13, 14-dihydro, 15-keto PGE_2 which is converted to 13, 14-dihydro, 15-keto PGA_2 which binds covalently to albumen.

There has been found to be inter-patient variability regarding systemic absorption of PGE_2. This can be attributed to different conditions of the vaginal mucosa between patients.

5.3 Preclinical safety data Go to top of the page

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series can induce proliferation of bone. Such effects have also been noted in newborn infants who received prostaglandin E_1 during prolonged treatment. There is no evidence that short-term administration of prostaglandin E_2 can cause similar bone effects.

Go to top of the page

6. Pharmaceutical particulars

6.1 List of excipients

Go to top of the page

Lactose

Microcrystalline Cellulose

Colloidal Silicon Dioxide

Maize Starch

Magnesium Stearate

6.2 Incompatibilities

Go to top of the page

None known

6.3 Shelf life

Go to top of the page

24 months.

6.4 Special precautions for storage

Go to top of the page

Store in a refrigerator.

Where the tablets are pack in a bottle, the tablets should be used within one month of opening the bottle.

6.5 Nature and contents of container

Go to top of the page

Amber glass bottle with screw cap and tac seal. Each bottle contains a desiccant capsule and 4 tablets.

Aluminium foil strip of 4 tablets, each box containing 4 or 8 tablets.

6.6 Special precautions for disposal and other handling

Go to top of the page

Wash hands thoroughly with soap and water after administration.

7. Marketing authorisation holder

Go to top of the page

Pharmacia Limited

Ramsgate Road

Sandwich

Kent

CT13 9NJ

UK

8. Marketing authorisation number(s)

Go to top of the page

PL 0032/0074

9. Date of first authorisation/renewal of the authorisation

Go to top of the page

15 March 1982/15 March 1998

10. Date of revision of the text

Go to top of the page

March 2011

Legal category

Go to top of the page

POM

PR2_0

More information about this product

- Patient Information Leaflets (PILs):
  Prostin E2 Vaginal Tablets

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産婦人科診療ガイドライン

産科編2011

編集・監修
日本産科婦人科学会／日本産婦人科医会

Guideline
for Obstetrical Practice
in Japan 2011

産婦人科
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社団法人 日本産科婦人科学会
社団法人 日本産婦人科医会

CQ311 常位胎盤早期剝離（早剝）の診断・管理は？

Answer

1. 妊娠高血圧症候群，早剝既往，切迫早産（前期破水），外傷（交通事故など）は早剝危険因子であるので注意する．(B)
2. 妊娠後半期に切迫早産様症状（性器出血，子宮収縮，下腹部痛）と同時に異常胎児心拍パターンを認めた時は早剝を疑い以下の検査を行う．
   ・超音波検査（B）
   ・血液検査（血小板，アンチトロンビン活性［以前のアンチトロンビンIII活性］，FDPあるいはD-dimer，フィブリノゲン，AST，LDHなど）(B)
3. 腹部外傷では軽症であっても早剝を起こすことがあるので注意する．特に，子宮収縮を伴う場合，早剝発症率は上昇するので，胎児心拍数モニタリングによる継続的な監視を行う．(C)
4. 早剝と診断した場合，母児の状況を考慮し，原則，急速遂娩を図る．(A)
5. 母体にDICを認める場合は可及的速やかにDIC治療を開始する．(A)
6. 早剝による胎児死亡と診断した場合，DIC評価・治療を行いながら，施設のDIC対応能力や患者の状態等を考慮し，以下のいずれかの方法を採用する．(B)
   ・オキシトシン等を用いた積極的経腟分娩促進
   ・緊急帝王切開
7. 早剝を疑う血腫が観察されても胎児心拍数異常，子宮収縮，血腫増大傾向，凝固系異常出現・増悪のいずれもない場合，週数によっては妊娠継続も考慮する．(C)

▷解　説

常位胎盤早期剝離（早剝）は，単胎で1,000分娩あたり，5.9件，双胎で12.2件に発生し[1]，その周産期死亡率は，全体の周産期死亡率に対し10倍以上高い（8.2/1,000 vs 119/1,000）[2]．また，早剝は，しばしば母体死亡の原因ともなる．本邦の1991年から1992年に起こった母体死亡230例のうち，その原因について詳しく調査できた197例の検討では，その13例（6.6%）が，早剝かつDIC・出血性ショックによる死亡であった[3]．これは早剝が極めてDICを合併しやすいことを示している．因みに同報告のなかで前置胎盤による死亡は7例（4例は癒着胎盤合併）であった．

早剝は，前回早剝既往のある妊婦で10倍[4]，母体の妊娠中期のAFP高値を示す妊婦で10倍[5]，慢性高血圧で3.2倍[4]，妊娠24週の子宮動脈血流波形にnotchがみられる症例で4.5倍多く[6]，また，妊娠初期に出血があった症例[7]や胎児発育不全[8]や妊娠高血圧症候群に多いことが報告されている．さらに，早剝は，子宮内感染例では，9.7倍起こりやすく，前期破水でも48時間未満で2.4倍であるところが，48時間以上経過すると9.9倍に発症リスクが上昇するなど，早剝と切迫早産（前期破水，絨毛膜羊膜炎）との関連も指摘されている[9]．その他のリスクファクターとして，喫煙，麻薬，外傷などがある[10]．

出血と下腹痛が，早剝の代表的な臨床症状であり，子宮筋の過緊張，触診上の子宮板状硬などが起こるとされるが，無症状の早剝も存在する．剝離部が後壁の場合には，腰痛となることもある．早剝の重

（表 1） 早剝関連 DIC 診断スコア（産科 DIC スコア[11] より抜粋）

Ⅰ. 基礎疾患	点数
a. 常位胎盤早期剝離	
・子宮硬直，児死亡	5
・子宮硬直，児生存	4
・エコーあるいは CTG 所見で診断	4
Ⅱ. 臨床症状	
a. 急性腎不全	
・無尿（～ 5mL/ 時間）	4
・乏尿（5.1 ～ 20mL/ 時間）	3
d. 出血傾向	
・肉眼的血尿，メレナ，紫斑，あるいは皮膚，粘膜，歯肉，注射部位からの出血	4
e. ショック症状	
・以下，それぞれに 1 点（例えば 2 つあれば 2 点） 脈拍数≧ 100/ 分，収縮期血圧≦ 90mmHg，冷汗，蒼白	
Ⅲ. 検査所見	
以下，それぞれに 1 点（例えば 3 つあれば 3 点） 血清 FDP ≧ 10μg/mL，血小板数≦ 10 万/μL， フィブリノゲン≦ 150mg/dL， プロトロンビン時間≧ 15 秒またはヘパプラスチンテスト≦ 50%， 赤沈≦ 4mm/15 分または赤沈≦ 15mm/時間， 出血時間≧ 5 分	

注：基礎疾患，臨床症状，検査所見の総合点数が 8 点以上で DIC としての治療を開始できる．
例えば，エコーで早剝が疑われ（4 点），乏尿（3 点）と冷汗（1 点）があれば，血液検査結果を待たなくとも DIC 治療を開始できる．

症度は，胎児予後の観点からは胎盤剝離面積に相関し，50% 以上の胎盤剝離が起こると子宮内胎児死亡が高率に起こる[8]．母体予後の観点からは止血・凝固能異常（DIC）の程度が問題となる．より，早期に DIC 診断を行うために産科 DIC スコアが考案されている（表 1）．この特徴は血液検査結果を待たずに DIC としての治療を開始できることにある．

診断は，性器出血や腹痛を訴えた患者に早剝を疑うことから始まる[10]．早剝は切迫早産と同様な症状（性器出血，子宮収縮，あるいは下腹部痛）で始まることがあり，異常胎児心拍数パターンが観察された場合には早剝である可能性が高くなる．徐脈と基線細変動の消失は胎盤剝離面積と相関するとの成績も報告されている[11]．予後改善の観点から速やかな診断が要求されており，超音波検査，胎児心拍数モニタリング，血液検査（血小板，アンチトロンビン（以前のアンチトロンビン III）活性，FDP，D-dimer，フィブリノゲン，AST，LDH など）の 3 者を可能な施設にあっては同時進行的に行う．早剝では FDP 高値（D-dimer 高値），フィブリノゲン低値を伴いやすいので，これらの異常は診断の助けとなるとともに DIC の重症度判定に有用である．早剝の鑑別診断時に HELLP 症候群が発見されることもあるので血小板数，アンチトロンビン活性，AST，LDH にも注意する．超音波検査では，出血部は検査が早期に行われた場合，胎盤に比べ高輝度から等輝度にみえ，1 週間以内に低輝度になる．後方視的な検討で，超音波による早剝診断は，感度 24%，特異度 96%，陽性的中率 88%，陰性的中率 53% と報告されており，超音波で早剝所見を認めた場合の的中率は高いが，超音波所見がなくても早剝を否定できない[12]．胎児心拍数モニタリングで，繰り返す遅発・変動一過性徐脈や，基線細変動の減少，徐脈，sinusoidal pattern が認められれば早剝の可能性は高くなり[10]，診断はともかく児救命の観点から急速遂娩が必要になる．

早剝は，腹部の鈍的な外傷によって発症することがあり，外傷の直後に顕在化する場合と数時間おい

て診断される場合がある．早剥は，腹部の重症な鈍的外傷の 40%，また，子宮に圧力がかかるような軽い外傷でも 3% に起こると報告されており，外傷後には，早剥を念頭に入れた管理が必要になる[14]．早剥の診断には，超音波検査と胎児心拍数モニタリングが用いられるが，特に遅れて発症するタイプの早剥を診断するためには，胎児心拍数モニタリングが有用である．受傷後の胎児心拍数モニタリングをどの位の時間行うかについては，前方視的な検討の報告はなく一定の方向性は示されていない．受傷後，4 時間観察し，胎児心拍数モニタリングが正常で，10 分に 1 回未満の子宮収縮しかない症例では早剥は起こらないとの報告がある[15][16]．しかし，10 分に 1 回以上の子宮収縮があった妊婦では 20% に早剥が起こっており[15]，子宮収縮などの臨床症状のある妊婦においては継続的な監視が必要である．ACOG Educational Bulletin[18]にも腹部外傷後の胎児心拍数モニタリングの継続時間について 4 時間継続すべきという見解[15][17]と 2〜6 時間との見解[19]が併記されている．しかしながら，2〜6 時間経過し，子宮収縮や胎児心拍数モニタリング上の NRFS 所見，性器出血，子宮の圧痛，破水などがみられない場合には，胎児心拍数モニタリングを中止しても良いと考えられる．現実的には，腹部外傷で早剥の危険があると判断した場合，最低 2 時間は胎児心拍数モニタリングを行うことが勧められる．

早剥の治療であるが，急速遂娩が原則である．胎児徐脈を伴った臨床的に明らかな早剥単胎妊娠 33 例の検討では分娩までの時間が短いと児の無障害生存機会の上昇が示唆されている[20]．しかしながら，母体 DIC が高度で，既に出血による hypovolemia が疑われる場合には，帝王切開そのものが母体生命を危険に曝す可能性がある．このような場合には，アンチトロンビン製剤 3,000 単位，新鮮凍結血漿，ならびに RCC 等を投与する母体 DIC 治療と母体状態安定化策を優先するか，あるいはこれら治療を急速遂娩と並行して行うことが勧められる．また，このような状況では高次医療施設との連携が必要となることもある．日本産科婦人科学会周産期委員会調べ[21]によれば早剥の 22%（124/556）に輸血が行われ，子宮内胎児死亡（IUFD）合併例では非合併例に比し高頻度に輸血が行われていた（50%［58/115］vs 15%［66/441］）．

早剥により既に児が死亡している場合，母体状態安定化策後の積極的な経腟分娩促進方針と急速遂娩方針とを比較した検討では，母体合併症頻度に差がなかったとされる[20]．また，死亡胎児ならびに剝離した胎盤の子宮内残留が母体 DIC 改善を妨げるとのエビデンスは存在しない[22]．さらに，胎児死亡時，発症から分娩までの時間より，適切な補液や輸血を行っていたかどうかが母体予後にとって重要とされている[22]．これらのことから，米国や英国では，早剥による胎児死亡を発見した場合，大量の出血があり，多量の輸血によってさえ十分に補いきれない場合以外では，人工破膜やオキシトシンを併用した積極的な経腟分娩が推奨されている[22][23]．本邦においても経腟分娩方針の方が優れていることを示唆する報告がある[24][25]．野田ら[24]は 1996〜2001 年の 6 年間に扱った早剥胎児死亡症例 15 例すべてに経腟分娩方針で臨み，それ以前の帝王切開方針症例 7 例と比較し，経腟分娩方針で良好な結果を得たと報告している．しかしながら，「本邦では伝統的・経験的に母体合併症軽減を目的として急速遂娩を行ってきた」こと，ならびに「死亡胎児の早期娩出が母体 DIC からの早期離脱に寄与する可能性」を否定できないことを勘案し，本ガイドラインでは Answer 6（DIC の評価・治療を行いながらの積極的経腟分娩もしくは帝王切開）を勧めた．積極的経腟分娩においては，周期的な子宮収縮が発来していない状況ではオキシトシンによる陣痛促進を通常用量から行う．オキシトシンの使用によってトロンボプラスチンの母体循環への流入増加，凝固因子の消費促進，羊水塞栓症の発症増加を証明するエビデンスはない[22]．また，人工破膜にも分娩に促進的な効果が期待される．しかし，人工破膜には子宮内圧を低下させトロンボプラスチンや活性化凝固因子の母体循環への流入低減，子宮収縮による剝離部位での出血量低減に効果が期待されているが，その効果についても証明されていない[22]．また，胎児が未成熟の場合，人工破膜しない方がスムースな頸管開大に繋がりやすいとの指摘もある[22]．

早剝では，胎盤床脱落膜内の出血により，子宮・胎盤のうっ血が起こり，その出血，組織変性・壊死が子宮漿膜面にまで及び Couvelaire 兆候を示すことがある．このような症例では，胎児胎盤娩出後に子宮収縮が不良となりやすく，十分な子宮収縮薬の投与や子宮双手圧迫などが必要になる．その際，子宮収縮促進を目的とした子宮筋層内プロスタグランジン F_2・局注は極力これを行わない(CQ404 参照)．もし，緊急避難的に行う場合には高血圧，不整脈，ショック等の出現に十分に注意する．これらによっても子宮収縮が不良で，出血が続く場合には母体救命のために子宮摘出も考慮される．

早剝の中には胎児 well-being と母体健康が障害されない一群が存在し，それらでは妊娠継続が可能であることが示唆されている[26][27]．このことは，「出血」を主訴とする比較的早期に起こった胎児 well-being を障害しない軽度の早剝患者では，母体・胎児の健康について十分モニターしながら妊娠継続する選択肢があることを示唆している．しかし，これら患者群でも 21% には分娩前に輸血が必要であったと報告されており[27]，止血・凝固能の推移について十分な監視が必要である．

文 献

1) Ananth CV, Smulian JC, Demissie K, et al.: Placental abruption among singleton and twin births in the United States: risk factor profiles. Am J Epidemiol 2001; 153: 771—778 (II)
2) Ananth CV, Wilcox AJ: Placental abruption and perinatal mortality in the United States. Am J Epidemiol 2001; 153: 332—337 (II)
3) 武田佳彦：厚生省心身障害研究：妊産婦死亡の防止に関する研究．平成８年度研究報告書，1996 (II)
4) Ananth CV, Savitz DA, Williams MA: Placental abruption and its association with hypertension and prolonged rupture of membranes: a methodologic review and meta-analysis. Obstet Gynecol 1996; 88: 309—318 (I)
5) Katz VL, Chescheir NC, Cefalo RC: Unexplained elevations of maternal serum alphafetoprotein. Obstet Gynecol Surv 1990; 45: 719—726 (II)
6) Harrington K, Cooper D, Lees C, et al.: Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abruption or delivery of a small-for-gestational-age baby. Ultrasound Obstet Gynecol 1996; 7: 182—188 (II)
7) Ananth CV, Oyelese Y, Prasad V, et al.: Evidence of placental abruption as a chronic process: associations with vaginal bleeding early in pregnancy and placental lesions. Eur J Obstet Gynecol Reprod Biol 2006; 128: 15—21 (II)
8) Ananth CV, Berkowitz GS, Savitz DA, et al.: Placental abruption and adverse perinatal outcomes. JAMA 1999; 282: 1646—1651 (II)
9) Ananth CV, Oyelese Y, Srinivas N, et al.: Preterm premature rupture of membranes, intrauterine infection, and oligohydramnios: risk factors for placental abruption. Obstet Gynecol 2004; 104: 71—77 (II)
10) Oyelese Y, Ananth CV: Placental abruption. Obstet Gynecol 2006; 108: 1005—1016 (Review)
11) 真木正博，寺尾俊彦，池ノ上克：産科 DIC スコア．産婦治療 1985；50：119—124 (III)
12) Usui R, Matsubara S, Ohkuchi A, et al.: Fetal heart rate pattern reflecting the severity of the placental abruption. Arch Gynecol Obstet 2008; 277: 249—253 (II)
13) Glantz C, Purnell L: Clinical utility of sonography in the diagnosis and treatment of placental abruption. J Ultrasound Med 2002; 21: 837—840 (II)
14) Brown HL: Trauma in pregnancy. Obstet Gynecol 2009; 114: 147—160 (Review)

15) Pearlman MD, Tintinalli JE, Lorenz RP: A prospective controlled study of outcome after trauma during pregnancy. Am J Obstet Gynecol 1990; 162: 1502—1510 (II)
16) Dahmus MA, Sibai BM. Blunt abdominal trauma: are there predictive factors for abruption placentae or maternal-fetal distress? Am J Obstet Gynecol 1993; 169: 1054—1059 (II)
17) Pearlman MD, Tintinalli JE, Lorenz RP: Blunt trauma during pregnancy. New Engl J Med 1990; 323: 1609—1613 (Review)
18) ACOG Educational Bulletin. Number 251, September 1998. Obstetric aspects of trauma management. Int J Gynaecol Obstet. 1999 Jan; 64 (1): 87—94 (Committee Report)
19) ACOG Guideline for Perinatal Care 6th Ed. October 2007. Chapter 6. Obstetric and Medical Complications. http://www.acog.org/publications/guidelinesForPerinatalCare/ (Committee Report)
20) Kayani SI, Walkinshaw SA, Preston C: Pregnancy outcome in severe placental abruption. Br J Obstet Gynaecol 2003; 110: 679—683 (III)
21) 日本産科婦人科学会周産期委員会報告 (水上尚典, 久保隆彦, 竹田 省他). 早剥, HELLP 症候群, ならびに子癇に関して. 日産婦誌 2009;61:1539—1567 (III)
22) Placental Abruption. Williams Obstetrics, 23rd edition, McGraw-Hill Co, 2010, 761—769 (Text book)
23) Chamberlain G, Steer P: Obstetric emergencies. BMJ 1999; 318: 1342—1345 (III)
24) 野田清史, 森 巍：児死亡例の分娩方針. 臨床婦人科産科 2005；59：194—197 (II)
25) 光田信明, 天満久美子：常位胎盤早期剥離による子宮内胎児死亡に溶血性尿毒症症候群を発症し, 経腟分娩, 子宮動脈塞栓術, 血漿交換, 人工透析にて腎機能・子宮温存し得た症例. 臨床婦人科産科 2005；59：140—143 (III)
26) Bond AL, Edersheim TG, Curry L, et al.: Expectant management of abruptio placentae before 35 weeks gestation. Am J Perinatol 1989; 6: 121—123 (II)
27) Towers CV, Pircon RA, Heppard M: Is tocolysis safe in the management of third-trimester bleeding? Am J Obstet Gynecol 1999; 180: 1572—1578 (II)

CQ315 子癇の予防と対応については？

Answer

1. 妊婦が分娩のために入院した時には血圧測定と尿中蛋白半定量検査を行う.(B)
2. 妊娠高血圧症候群妊婦，蛋白尿陽性妊婦，ならびに入院時に高血圧を示した妊婦においては，陣痛発来後は定期的に血圧を測定する.(B)
3. 分娩中に頭痛，視覚異常，あるいは上腹部痛等を訴えた場合には血圧を測定する.(B)
4. 分娩時に高血圧重症（収縮期≧160mmHg あるいは拡張期≧110mmHg）が確認されたら $MgSO_4$ を使用する，あるいは $MgSO_4$ と降圧剤を併用する(特に急激な血圧上昇を認める場合)．降圧目標は高血圧軽症レベル（140～159/90～109 mmHg）とする（CQ312, 表 1 参照).(C)
5. 痙攣が確認された場合には以下のすべてを行う.(B)
   - 血圧測定
   - ジアゼパム（5～10mg 静注）あるいは $MgSO_4$（4g，10 分で静注）投与
   - 痙攣発作終了後には気道を確保して，酸素投与
   - 痙攣再発予防のために $MgSO_4$ の 24 時間持続静注開始（1～2g/時間）
6. 意識低下(痙攣を含む)が認められた場合には，子癇とみなして治療を開始するが，HELLP 症候群，脳内出血，脳梗塞などを除外するために以下の検査を行う．また，ヒステリー，てんかん，低血糖発作，過呼吸発作，あるいは局麻剤中毒(無痛分娩時など）も鑑別診断として考慮する.
   1）麻痺等検出のための理学所見(呼びかけへの応答，四肢筋力の状態や病的反射の有無，瞳孔の左右差など）検査（B)
   2）血液検査（血小板数を含む血算，アンチトロンビン活性，AST，ALT，LDH，FDP あるいは D-dimer，動脈血ガス分析)(B)
   3）必要と判断された場合には CT/MRI 検査（B)
7. 母体の状態安定化後には胎児 well-being に留意し，児の早期娩出をはかる.(B)

▷解　説

危険因子

子癇の危険因子を表 1 に示す．子癇の頻度は先進諸国では 2,000～3,700 例に 1 例と推定される[1)~3)]．子癇は，高血圧が軽度である妊婦や，高血圧が認められてなかった妊婦にも起こる．子癇発症前 1 週以内に行われた定期健診時に高血圧を示した患者は子癇患者の 48%（101/214）で[1)]，蛋白尿のみを示していた患者も 7.5%（16/214)～10%（32/325）存在する[1)2)]．分娩子癇の 25～30% は発症前に高血圧，蛋白尿いずれも認められない[2)3)]．本邦 54 例の検討では，子癇発作に先行して高血圧が確認されていた症例は 44% であった[4)]．子癇では子癇発作後（直前？）には高血圧を示すが，発症前

（表1） 子癇の危険因子

10代妊娠，初産婦，双胎，子癇既往
妊娠蛋白尿
妊娠高血圧症候群
HELLP症候群

には高血圧を示さない患者が30～50%存在し，それら患者でも蛋白尿は示していることが多い．前方視的立場（子癇リスクの評価・予知という立場）に立った場合，蛋白尿のみを示した患者（妊娠高血圧症候群の範疇には含まれないが）もハイリスク群であることに注意する（子癇は妊娠高血圧症候群妊婦に起こるが，しばしば高血圧は分娩中，分娩後に発症し，妊娠高血圧症候群の診断は産褥12週に行われる後方視的診断名である）．

分娩子癇は子癇の約40%を占めるが，それらには以下の特徴がある．本邦の1施設10例の分娩子癇（9例が初産婦）の検討[5]では，6例には定期健診で高血圧が認められなかった（蛋白尿はこの6例に認められていた）が，入院時あるいは陣痛発来時には高血圧が認められ，高血圧の程度が陣痛とともに悪化し，子癇発作を起こした．いわゆる先進国での分娩子癇は妊娠高血圧腎症の期間（蛋白尿と高血圧をともに示す期間）が短いのが特徴である．そこで，分娩のための入院時には全例において血圧測定と尿中蛋白半定量検査を勧めた（B）．また，妊娠高血圧症候群はもとより，蛋白尿のみ，あるいは入院時に初めて高血圧を示した妊婦においても，陣痛発来後の定期的血圧測定を勧めた．しかし，これら検査の励行が子癇・脳内出血回避あるいは予後改善につながるかについては知られていない．

初産婦は子癇の危険因子である[3)～5)]．スウェーデンで起こった子癇80例の80%が初産婦（スウェーデンでは初産婦の分娩は全分娩の41%）であった[3)]．本邦2004年の子癇54例の調査[4)]では89%が初産婦（初産婦の分娩は約47%）であった．すなわち初産婦は経産婦に比し，6～9倍子癇に罹患しやすい．また，子癇患者の平均年齢は低く[3)4)]，20代での頻度を1.0とすると10代では3.2，30～34歳では0.83，35～39歳では1.08，40歳以降では1.07であった[4)]．英国においても10代妊娠での頻度は他の年代の3.0倍であった[2)]．すなわち，10代妊娠は子癇の危険因子である．子癇既往妊婦の約25%は次回，妊娠高血圧腎症になり，約2%が子癇を再発する[6)]．本邦で当初，子癇と診断された79例において，25例はHELLP症候群も合併していた[4)]．この25例中，6例は脳内出血を合併していたため（脳内出血は子癇に含まれない）子癇73例のHELLP症候群合併率は26%（19/73）であった[4)]．また，同報告[4)]のなかで双胎は単胎に比し，子癇に4.8倍，HELLP症候群に16.0倍罹患しやすいことが指摘された．したがって，HELLP症候群ならびに双胎妊娠も危険因子である．定期的なHELLP症候群検出のための血液検査（血小板数，アンチトロンビン活性，GOT/LDH）は子癇発症前の児娩出の時期決定に寄与する可能性がある．

子癇発症前に頭痛，視覚異常（かすんで見える，チラチラする），上腹部痛等の訴えが60～75%の患者に認められる[6)]ので，これらは子癇発作出現の予測・診断に有用である．したがって，妊婦が頭痛，視覚異常，あるいは上腹部痛を訴えた場合，ただちに血圧を測定する（上腹部痛についてはCQ311参照）．しかし，このような血圧測定が子癇予防につながる否かについては知られていない．

予防

妊娠高血圧や妊娠高血圧腎症患者の入院管理が子癇予防につながるかどうかについてはランダム化比較試験が行われておらず不明である．また降圧薬による血圧調節の子癇予防効果も判明していない[6)]．$MgSO_4$については子癇予防効果が確認されている[6)]．重症妊娠高血圧腎症患者を対象とした比較試験では，$MgSO_4$群投与により子癇は減少した（0.6% vs 2.0%；RR，0.39［95%信頼限界0.28～

0.55])[6].

対応

以下の記述はランダム化比較試験によりその有効性が確認された対処法ではないが，研究者の多くが勧める方法である．速やかに痙攣を抑制するためにジアゼパム 5～10mg のワンショット静注あるいは $MgSO_4$（4～6g を 10～15 分かけて静注[7]）を投与する．子癇の再発予防には $MgSO_4$ がジアゼパム（発作時に 10mg 静注，その後 40mg/500mL 生理食塩水，24 時間かけて持続静注）より優れている[8]が，初回痙攣を速やかに抑制するにはジアゼパムのほうが優れているという意見[9]がある．痙攣重積中のバイトブロックの使用に関しては，賛否両論あり，今回はその使用を求めなかった．引き続いて子癇の再発予防のために $MgSO_4$ を 24 時間程度（1～2g/時間）持続静注する．口腔内を十分吸引し誤嚥を防止しつつ酸素投与を行う．血圧を測定し，高血圧が認められた場合にはヒドララジンあるいはニカルジピンを投与する（投与法に関しては CQ312 参照）（脳内出血の場合，二次性の高血圧が認められる場合があることに注意）．陣痛発作時には血圧は高めに測定されるので，その点に注意する．また高頻度に HELLP 症候群（7.1%[2]），26%（19/73）[4]）や凝固障害（8.6%[2]）を合併するので，血液検査（血小板を含む血算，アンチトロンビン活性，GOT，GPT，LDH，FDP あるいは D-dimer）を行う．子癇発作後は高頻度に母体アシドーシスが認められる[5]ので血液ガス分析も行う．脳内出血では神経症状を示すことが多いので理学所見を参考とする．四肢筋力の左右差，四肢の麻痺・硬直，瞳孔の左右差，舌変位等，脳内出血が疑われる所見がある場合には，状態安定化後，速やかに画像診断（CT/MRI など）を行う．子癇発作後には胎児機能不全が起こりやすいので胎児 well-being に十分留意し，母体の状態安定化後には適切な方法（子宮口開大度により緊急帝王切開あるいは経腟分娩）により児の早期娩出をはかる．胎児徐脈が繰り返し出現する場合には常位胎盤早期剥離合併も考慮する．なお，日本妊娠高血圧学会よりガイドライン[7]が刊行されたので，それらも参考にする．

予後

子癇による死亡は稀である．英国 1992 年の調査では母体死亡率は 1.8%（7/382）[2]であったが 2005 年調査では 0%（0/214）[1]，スウェーデン 1991～1992 年では 0%（0/80）であった．本邦の調査[4]でも，母体死亡率は 0.0%（0/73）であった．しかし，脳内出血 6 例（当初，子癇と診断されたが）の母体死亡率は 67%(4/6)であった[4]．同報告[4]の中で解析された HELLP 症候群 131 例中，脳内出血合併例は 4.6%（6/131）であった．同様な症例報告が認められ[10]，HELLP 症候群では脳内出血を起こしやすく，脳内出血例は子癇と診断されやすく，また死亡率が高いのが特徴である．このように子癇と診断される症例の中に脳内出血例が含まれるので，十分注意する必要があり，脳内出血を診断・否定するために CT 検査は有用である．また，脳血管障害による妊婦死亡の未然防止は困難と判断される場合が多い[11]．英国 1992 年当時，脳内出血・脳梗塞は子癇と当初診断された症例の 1.8%（7/382）[2]を占めており，また母集団となる妊娠分娩は 774,436 であった[2]ことから，子癇と見誤れるような脳内出血・脳梗塞出現頻度はおよそ 10 万分娩に 1 例程度と推測される．すなわち，本邦では年間約 10 例程度の子癇と見誤れるような脳内出血・脳梗塞が起こっていると推測される．

子癇の母体死亡は稀であるものの，重篤な合併症（心停止，ARDS，DIC，肺水腫，腎不全，敗血症，一過性皮質盲等）が数 10% に起こるので，子癇発作後には厳重な管理が必要である．

病因

子癇患者の特徴的な MRI 所見は，皮質下白質と灰白質に接する部分の浮腫や梗塞の所見である[12]．しかし，脳浮腫が子癇の原因，あるいは結果なのかについては知られていない．子癇の病態として forced dilatation theory と vasospasm theory の 2 つが考えられている．前者では，脳血管障害に加えて血圧の上昇により脳血液関門が破綻する事で脳血圧の自己調節能が喪失した結果，脳血管が拡張し，血流

過剰となり，血管性脳浮腫が引き起こされるとするものである．後者は，急激に脳血圧が上昇することにより脳血管の過剰収縮（over regulation）が起こり，血管攣縮に引き続く脳虚血による脳浮腫（cytotoxic edema）が引き起こされるとするものである．重症妊娠高血圧腎症例を対象とした前方視的検討では，MRI で脳浮腫が確認された 9 例中 6 例で子癇発作が起こり，脳浮腫が確認されなかった 44 症例は子癇発作を起こさなかった[13][14]．脳浮腫と関連があったパラメータは，拡張期血圧≧110mmHg，HELLP 症候群，血清クレアチニン値≧0.8mg/dL，ヘマトクリット値≧36% であった[13][14]．HELLP 症候群では血管透過性亢進による血液濃縮（循環血漿量減少）が示唆されており，血清クレアチニン高値，ヘマトクリット高値はいずれも血液濃縮（循環血漿量減少）を示唆する所見である．これら結果は子癇に先行する脳浮腫が血管透過性亢進と関連がある事象であり，子癇患者における循環血漿量減少の存在を示唆している．

鑑別疾患

意識消失を来す疾患の中に，てんかん，脳内出血，脳梗塞，低血糖などの内分泌代謝疾患，過呼吸発作などがある．無痛分娩時の局所麻酔薬中毒も鑑別疾患の 1 つである[15]．

文 献

1) Knight M on behalf of UKOSS: Eclamlpsia in the United Kingdom 2005. Br J Obstet Gynaecol DOI:10.1111/j. 1471-0528. 2007. 01423.x (II)
2) Douglas KA, Redman CWG: Eclampsia in the United Kingdom. Br Med J 1994; 309: 1395—1400 (II)
3) Kullberg G, Lindeberg S, Hanson U: Eclampsia in Sweden. Hypertens Preg 2002; 21: 13—21 (II)
4) 日本産科婦人科学会周産期委員会報告（水上尚典，久保隆彦，竹田省他）．早剥，HELLP 症候群，ならびに子癇に関して．日産婦誌　2009；61：1539—1567（III）
5) Minakami H, Izumi A, Takahashi T, 他：Current presentation of eclampsia. 日本産婦人科・新生児血液学会誌　1992；2：1—5（III）
6) Sibai BM: Diagnosis, prevention, and management of eclampsia. Am J Obstet Gynecol 2005; 105: 402—410 (III)
7) CQ4 子癇の管理は？．日本妊娠高血圧学会編，妊娠高血圧症候群（PIH）管理ガイドライン 2009，東京；メジカルビュー，2009；70—71（Guideline）
8) The Eclampsia Trial Collaborative Group: Which anticonvulsant for women with eclampsia? Evidence from the collaborative eclampsia trial. Lancet 1995; 345: 1455—1463 (I)
9) Fox R, Draycott T: Prefer diazepam for initial control of pre-eclampsic fits. BMJ 1995; 31.1: 1433 (III)
10) Hirashima C, Ohkuchi A, Matsubara S, et al.: Hydrocephalus after intraventricular hemorrhage ineclamptic woman with HELLP syndrome. Hypertens Pregnancy 2006; 25: 255—257 (III)
11) Preventability of pregnancy-related deaths. Results of a sate-wide review. Obstet Gynecol 2005; 106: 1228—1234 (III)
12) Thomas SV: Neurological aspect of eclampsia. J Neurological Science 1998; 155: 37—43 (III)
13) Matsuda H, Sakaguchi K, Shibasaki T, et al.: Cerebral edema on MRI in severe preeclamptic women developing eclampsia. J Perinat Med 2005; 33: 199—205 (III)
14) 松田秀雄，川上裕一，芝崎智子，他：子癇の診断．周産期医学　2007：37：1151—1154（III）

15) Yoshida M, Matsuda H, Fukuda I, et al.: Sudden cardiac arrest during cesarean section due to epidural anaesthesia using ropivacaine: a case report. Arch Gyneccol Obstet 2008; 277: 91—94 (III)

CQ401 分娩室または分娩室近くに準備しておく薬品・物品は？

Answer

1．表 1 ならびに表 2 に示されるような薬品・物品を装備する

（表 1） 推奨レベル別母体用分娩室装備品

	(A)	(B)	(C)
医療機器	分娩監視装置 聴診器 血圧計 体温計 酸素吸入装置 吸引器 パルスオキシメーター 酸素マスク アンビューバッグ バイトブロック 心電図モニター 精密輸液装置※ 分娩用吸引器または鉗子	喉頭鏡 自動血圧計 超音波断層装置	AED（自動体外式除細動器）
医薬品	子宮収縮薬 ・オキシトシン ・ジノプロスト ・メチルエルゴメトリン 昇圧薬 ・塩酸ドパミン ・エピネフリン 血漿増量薬 ・ヒドロキシエチルデンプン 各種輸液用製剤 局所麻酔薬	マグネシウム製剤 降圧薬 ・塩酸ヒドララジン ・塩酸ニカルジピン 抗不安薬 ・ジアゼパム ステロイド剤	蛋白分解酵素阻害剤 ・ウリナスタチン ・メシル酸ガベキサート アンチトロンビン製剤
物品	膀胱内留置カテーテル 尿測袋 膣・子宮充填用ガーゼ 乾電池	気管挿管チューブ	経鼻挿管チューブ

※精密輸液装置；医科点数表の解釈（平成 18 年 4 月版）第 6 部：注射：通則 4：精密持続点滴注射は，自動輸液ポンプを用いて 1 時間に 30mL 以下の速度で体内（皮下を含む）または注射回路に薬剤を注入すること，とされ，輸液ポンプ・シリンジポンプの区別はない

（表 2） 推奨レベル別新生児用分娩室装備品

	(A)	(B)	(C)
医療機器	インファントウォーマー 聴診器 酸素吸入装置 バッグ＆マスク装置 （90 ～ 100％濃度酸素供給が可能な装置が望ましい）	新生児用喉頭鏡	精密輸液装置
医薬品	エピネフリン 生理食塩水		
物品		新生児用気管内挿管チューブ 胃管チューブ	

▷解　説

本稿の目的は分娩中，分娩後に起こりうる母体ならびに新生児の緊急事態に対して，速やかに対処(緊急帝王切開を除く)するために，必要な薬品や物品を示すことにある．分娩中は妊娠中に比し，胎児 well-being 悪化が起こりやすいので胎児 well-being をモニターできる分娩監視装置をただちに利用できる状態にしておく．超音波装置は子宮内の解剖学的異変（常位胎盤早期剝離・胎盤遺残・子宮破裂・子宮内反症など）を迅速に診断するのに有用なので分娩室に常備することが望ましい．

分娩直後に新生児蘇生が必要になることがある．新生児蘇生に必要な物品としては，新生児用聴診器，バッグ＆マスク，インファントウォーマー，喉頭鏡，気管内挿管チューブ，酸素，吸引器，新生児用心電図モニター，酸素飽和度モニター等が挙げられる[1]．しかし，正常に経過すると判断された分娩の多くが新生児科医の立ち会いなしに行われている現状を考慮すると，これら新生児蘇生用器具すべてを全分娩施設が常備することは現状では求められていないが，万一に備え，整備に努めるのが望ましい．挿管しなくても，正しいバッグ＆マスクで 90% 以上の児は蘇生できるとする報告もある[1][2]．

本邦における母体死亡原因統計[3]から，分娩時に起こる母体生命を脅かす母体緊急状態は，頻度的に出血性ショック；2）高血圧緊急症（脳内出血，子癇，高度高血圧），3）呼吸不全（肺血栓塞栓症，羊水塞栓症）である．これらの場合いずれもバイタルサインの経時的モニターが重要であり，自動血圧計，心電図モニター，酸素飽和度モニターはそれらに有用である．

出血性ショック（血圧の低下）は頻脈を伴うのが特徴である．分娩後，中等度の出血であっても，頻脈を伴う症例はプレショック状態の可能性を考え注意が必要である．脳血流を保つための骨盤高位はショック時の体位として勧められる．クッションなどを利用して下半身を高位にすることもできる．出血原因として弛緩出血は頻度も高いので，子宮収縮薬(オキシトシン：アトニン®，オキシトシン F®等，マレイン酸メチルエルゴメトリン：メテルギン®，メテナリン®，パルタン M®等)，膣・子宮ガーゼ（滅菌ガーゼ）は常備しておく．速やかに静脈路を確保し，輸液を行う．血漿増量薬（ヒドロキシエチルデンプン：ヘスパンダー®，サリンヘス®等)を常備しておくと緊急時に便利である．ショックが持続するようであればステロイド剤(ソルコーテフ®，サクシゾン®，水溶性ハイドロコートン®等)，昇圧薬(塩酸ドパミン：カコージン®，イノバン®，カタボン®，エピネフリン：ボスミン®等)，蛋白分解酵素阻害剤(ウリナスタチン：ミラクリッド®など　メシル酸ガベキサート：FOY®，リナレス®など　メシル酸ナファモスタット：フサン®，コアヒビター®など)の投与も考慮されるので準備しておくことが望ましい．また，ショック時には尿量減少が観察される．カテーテル膀胱内留置と尿測袋は水分出納把握に有用である．

肺血栓塞栓症や羊水塞栓症時には動脈血酸素化障害・ショック・DIC が短時間内に出現してくる．これらの頻度は極めて低い(肺血栓塞栓症，羊水塞栓症はそれぞれ 1 万分娩に 1 以下，すなわち万が一以下）が，迅速な気道確保と酸素投与が救命に奏効する可能性がある．酸素飽和度モニターは動脈血酸素化障害の迅速診断に有用である．酸素，ステロイド，昇圧剤投与が考慮され，迅速な高次施設との連携診療が求められる．バイトブロック，アンビュバック，喉頭鏡，気管挿管チューブ，吸引器等がそれらに必要な物品であるがこれらすべてを全分娩施設で常備すべきかについてはそれらの頻度を考慮し，否定的な意見もあるが，合併症妊娠を多数扱うような施設では常備が望ましい．

脳内出血時には瞳孔の左右不同が観察される場合があるのでペンライトを用いてその有無について判定する．脳内出血時には高血圧が認められることが多いが高血圧が出血に先行する場合と出血後の二次性高血圧として認められる場合があり，高血圧と脳内出血の因果関係については慎重な判断が必要である．また，分娩時脳内出血の頻度は約 10 万分の 1 と推定されておりその発症率は極めて低いため分娩時の頻回の血圧測定が脳内出血頻度減少に寄与するか否かについては知られていない．

その他，大出血時には血中アンチトロンビン活性が低下している場合が多く，そのような場合，アンチトロンビン製剤（ノイアート®，アンスロビンP®，献血ノンスロン®等）による補充が考慮される．また，分娩時に高血圧が観察された場合，子癇や脳内出血予防のためにマグネシウム製剤($MgSO_4$：マグネゾール®等)，抗不安薬（ジアゼパム：セルシン®，ホリゾン®等），降圧剤（塩酸ヒドララジン：アプレゾリン®，ヒドラプレス®等，塩酸ニカルジピン：ペルジピン®，ニコデール®など)の投与も考慮される．しかし，これらの投与により，子癇や脳出血を完全に防止できるわけではない．

本稿はAmerican Heart Association (AHA) の妊婦蘇生に対するガイドライン，American Society of Anesthesiologistsの産科麻酔ガイドライン，American Academy of Pediatrics・AHAの新生児蘇生ガイドラインを参考にした[4)5)]．

文 献

1) Neonatal Resuscitation Guidelines: 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation: IV. 2005; 112: 188—195 (Guideline)
2) 田村正徳，監訳．AAP/AHA新生児蘇生テキストブック．東京：医学書院，2006;1－26—1－7
3) 国民衛生の動向（厚生労働省編）2004
4) Cardiac Arrest Associated With Pregnancy, 2005. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation: X. 8 2005; 112: 150—153
5) Practice Guidelines for Obstetric Anesthesia. Anesthesiology 2007; 106: 843—863

子宮収縮薬による
陣痛誘発・陣痛促進に際しての
留意点
改訂2011年版

平成23年4月

社団法人日本産科婦人科学会

社団法人日本産婦人科医会

本書（子宮収縮薬による陣痛誘発・陣痛促進に際しての留意点：改訂2011年版）は，その作成を委嘱された産婦人科診療ガイドライン産科編委員会が原案を作成し，産婦人科診療ガイドライン産科編評価委員会，日本産科婦人科学会周産期委員会，日本産婦人科医会医療安全・紛争対策委員会，ならびにガイドライン産科編コンセンサスミーティングでの審議，日本産科婦人科学会と日本産婦人科医会の承認を経て出版された．

以下，ガイドライン産科編委員会委員名，同評価委員会委員名，日本産科婦人科学会周産期委員会委員名，日本産婦人科医会医療安全・紛争対策委員会委員名（2010年4月1日現在）を記す

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子宮収縮薬による陣痛誘発・陣痛促進に際しての留意点：改訂2011年版

本書中の下線部は「留意点2006」と大きく変更された部分と追記された部分を示します．

1．改訂の趣旨

日本産科婦人科学会と日本産婦人科医会は，2006年７月に「子宮収縮薬による陣痛誘発・陣痛促進に際しての留意点」（以下，「留意点2006」）を発刊した．子宮収縮薬が，診療現場において共通の認識に基づいて適切に使用されることを目的とした発刊であった．その後2008年４月に「産婦人科診療ガイドライン―産科編2008」（日本産科婦人科学会と日本産婦人科医会共同監修）が発刊された．「留意点2006」は発刊後５年経過し，また「留意点2006」と「ガイドライン」中の子宮収縮薬に関する記述の統一化が望まれるようになったため，本書「子宮収縮薬による陣痛誘発・陣痛促進に際しての留意点：改訂2011年版」発刊の運びとなった．これに伴い，「留意点2006」中の記述は失効する．

本書全文は「産婦人科診療ガイドライン―産科編2011」巻末に収載され，「産婦人科診療ガイドライン―産科編2011」は子宮収縮薬を使用する場合，本書の順守を求めている（CQ404, CQ405, CQ409, CQ412, 推奨レベルA）．本書の作成は「産婦人科診療ガイドライン―産科編2011」と同等以上の幾重もの審議・検討を経てなされている．したがって，本書は「産婦人科診療ガイドライン―産科編2011」の一部である．このような観点から今後，本書の単独発刊は行われず，今後の子宮収縮薬使用法に関する見直し作業は「産婦人科診療ガイドライン―産科編」の改訂時に同時に行われる．2014年４月以降に子宮収縮薬を使用する場合には2014年４月発刊予定「産婦人科診療ガイドライン―産科編2014」中に新たに追加される予定の「CQ：子宮収縮薬を使用する場合には？」を参考にすることになる．

本書中の「CQ」は「産婦人科診療ガイドライン―産科編2011」中のCQである．

2．子宮収縮薬（オキシトシン，プロスタグランジン$F_{2\alpha}$[$PGF_{2\alpha}$]，プロスタグランジンE_2[PGE_2]）使用のための適応，使用のための条件，ならびに禁忌

1）子宮収縮薬適応（表1）

経腟分娩の条件を満たしていて，表１のような場合（CQ404, 405, 409, 412参照）．

表1．陣痛誘発もしくは促進の適応となりうる場合
（下線は付してないが2006年版より変更あり）

医学的適応		
	胎児側の因子	1. 児救命等のために新生児治療を必要とする場合 2. 絨毛膜羊膜炎 3. 過期妊娠またはその予防 4. 糖尿病合併妊娠 5. 胎児発育不全 6. 巨大児が予想される場合 7. 子宮内胎児死亡 8. その他，児早期娩出が必要と判断された場合
	母体側の因子	1. 微弱陣痛 2. 前期破水 3. 妊娠高血圧症候群 4. 墜落分娩予防 5. 妊娠継続が母体の危険を招くおそれがある場合
非医学的適応		1. 妊産婦側の希望等（CQ405参照）

2）子宮収縮薬使用（陣痛誘発・陣痛促進）のための条件

①子宮収縮薬使用のためのインフォームドコンセントが得られていること．

②子宮収縮薬投与開始前から分娩監視装置が装着されていること．

PGE_2経口錠も同様とする．

③子宮収縮薬静脈内投与時，精密持続点滴装置（輸液ポンプ等）が利用できること．
④事前に頸管熟化について評価すること．頸管が極端に未熟な場合は，他の方法により頸管熟化を図った後に子宮収縮薬を使用する（CQ412参照）．
ラミナリアあるいはプラステロン硫酸ナトリウム（マイリス®，レボスパ®，アイリストーマ®等）と子宮収縮薬同時併用は行わない．
⑤母児の状態が比較的良好であり，子宮収縮薬使用中は母児の状態の適切なモニターが可能であること．子宮内胎児死亡の場合にも子宮収縮の状態が適切にモニターされること（過強陣痛予防のため）．
⑥オキシトシンあるいは PG $F_{2\alpha}$ を使用する場合は PGE_2 最終投与時点から１時間以上経ていること．
⑦PGE_2 を使用する場合はオキシトシンあるいは PG $F_{2\alpha}$ 最終投与時点から１時間以上経ていること．
⑧メトロイリンテル挿入時点から１時間以上経ていること．

3）子宮収縮薬使用の禁忌（表2，下線は付してないが2006年版より大きく変更されている）
表２に禁忌となる例および慎重投与例を示す．

表2．子宮収縮薬（オキシトシン，$PGF_{2\alpha}$，PGE_2）の禁忌と慎重投与

子宮収縮薬	禁忌	慎重投与
三薬剤共通	1. 当該薬剤に過敏症 2. 帝王切開既往２回以上† 3. 子宮体部に切開を加えた帝王切開既往（古典的帝切，T字切開，底部切開など）† 4. 子宮筋全層もしくはそれに近い子宮切開†（子宮鏡下筋腫核出術含む）† 5. 他の子宮収縮薬との同時使用 6. プラステロン硫酸（マイリス®，レボスパ®等）との併用† 7. メトロイリンテル挿入後１時間以内† 8. 吸湿性頸管拡張材（ラミナリア等）との同時使用† 9. 前置胎盤 10. 児頭骨盤不均衡が明らかな場合 11. 骨盤狭窄 12. 横位† 13. 常位胎盤早期剝離（胎児生存時）¶ 14. 重度胎児機能不全（CQ411, Answer 2の場合）† 15. 過強陣痛†	1. 児頭骨盤不均衡が疑われる場合† 2. 多胎妊婦
オキシトシン	1. PGE_2 最終投与から１時間以内†	1. 異常胎児心拍数図出現（CQ411参照） 2. 妊娠高血圧症候群 3. 胎位胎勢異常による難産 4. 心・腎・血管障害 5. 帝王切開既往回数１回 6. 禁忌にあるもの以外の子宮切開† 7. 常位胎盤早期剝離（胎児死亡時）¶
$PGF_{2\alpha}$	1. PGE_2 最終投与から１時間以内† 2. 帝王切開既往（単回も）・子宮切開既往‡ 3. 気管支喘息・その既往 4. 緑内障‡ 5. 骨盤位等の胎位異常	1. 異常胎児心拍数図出現（CQ411参照）† 2. 高血圧 3. 心疾患 4. 急性骨盤腔内感染症・その既往 5. 常位胎盤早期剝離（胎児死亡時）¶
PGE_2	1. 子宮収縮薬静注終了後１時間以内† 2. 帝王切開既往（単回も）・子宮切開既往† 3. 異常胎児心拍数図（CQ411参照）出現† 4. 常位胎盤早期剝離（胎児死亡時でも）¶ 5. 骨盤位等の胎位異常	1. 緑内障 2. 喘息

注：ここに記載されている禁忌あるいは慎重投与の対象は主に胎児が生存している場合を想定している．したがって，常位胎盤早期剝離¶で示したように胎児死亡時には異なった基準が考慮され，禁忌対象への子宮収縮薬使用が

あり得る．しかし，このような場合にも子宮収縮薬使用のための条件や使用法は順守する．
†本書で特に追加したもの；‡ジノプロストトロメタミン（プロナルゴン F®）添付文書による；¶常位胎盤早期剥離はオキシトシンならびに $PGF_{2\alpha}$ 添付文書では原則禁忌で PGE_2 添付文書では禁忌となっている．本書では胎児生存時にはいずれの子宮収縮薬も禁忌，胎児死亡時にはオキシトシンならびに $PGF_{2\alpha}$ は慎重投与（CQ311参照），PGE_2 は胎児死亡時であっても禁忌とした；胎児機能不全はオキシトシンならびにジノプロスト（プロスタルモン F®）添付文書では原則禁忌，ジノプロストトロメタミン（プロナルゴン F®）ならびに PGE_2 添付文書では禁忌となっている．本書は重度胎児機能不全（CQ411, Answer 2）の場合はいずれの子宮収縮薬においても禁忌とした．また，異常胎児心拍数図（CQ411参照）出現時は PGE_2 は禁忌，オキシトシンならびに $PGF_{2\alpha}$ は慎重投与とした（CQ408参照）；経産婦はいずれの子宮収縮薬添付文書でも慎重投与となっているが，本書はいずれの子宮収縮薬の慎重投与対象からも外した；オキシトシン添付文書では高年初産婦と軟産道強靭が慎重投与となっているが，本書は慎重投与対象から両者を外した；$PGF_{2\alpha}$ はジノプロストトロメタミン（プロナルゴン F®）添付文書では多胎，急性骨盤腔内感染症・その既往，ならびに多産婦が禁忌となっているが，本書は前2者については慎重投与とし，後者については慎重投与対象からも外した；子宮収縮薬の「メトロイリンテル挿入後1時間以内」の使用，「PGE_2 最終内服から1時間以内」の静脈内投与，「プラステロン硫酸（マイリス®，レボスパ®等）との併用」，ならびに「吸湿性頸管拡張材（ラミナリア等）との同時使用」に関しては CQ412を参照．このように禁忌対象が増加したので，子宮収縮薬投与の際には本表参照を勧める．帝王切開既往経腟分娩時には CQ403参照．

3. 子宮収縮薬使用中に行うこと

①母体バイタルサイン（血圧と脈拍数）のチェック

血圧と脈拍数を原則1時間ごとにチェックする（CQ404参照）．子宮収縮が増強すると血圧が上昇する場合がある．また定期的に内診し頸管の変化を把握する．

②子宮収縮と胎児心拍の連続的モニター

分娩監視装置を用いて子宮収縮と胎児心拍を連続的モニターする．

PGE_2 経口錠を使用している場合にも同様とする．トイレ歩行時など，医師が必要と認めた場合に一時的に外すことは可能である（CQ410参照）．

③投与量が基準範囲内であることの確認（表4参照）

④増量間隔が適切（最終増量から30分以上経ている）であることの確認

⑤胎児 well-being の確認

CQ410（分娩監視法），CQ 411（胎児心拍数図読み方・対応）を参考にする．

⑥異常胎児心拍数パターン出現時の適切な対応

CQ 411（胎児心拍数図読み方・対応）を参考に胎児心拍数パターンの正常・異常の判断を行い，異常と判断した場合には CQ411を参考に適切に対応する．また，子宮収縮薬投与中断の必要性について検討する（CQ408参照）．必要と判断された場合には CQ408を参考に胎児蘇生を試みる．

4. インフォームドコンセント

子宮収縮薬を使用する必要性（適応），手技・方法，予想される効果，主な有害事象（表3を参考にする），ならびに緊急時の対応などについて，事前に説明し同意を得る．その際，文書での同意が望ましい．

表3．子宮収縮薬との関連が示唆される主な有害事象

重大な有害事象	①ショック ②過強陣痛，子宮破裂，頸管裂傷，微弱陣痛，弛緩出血 ③胎児機能不全	
その他の有害事象	過敏症	過敏症状
	新生児	新生児黄疸
	循環器	不整脈，静脈注射後の一過性血圧上昇・下降
	消化器	悪心・嘔吐
	その他	水中毒症状

注：子宮収縮薬と羊水塞栓症の因果関係については否定的である（Clark SL, Hankins GDV, Dudley DA, et al. Amniotic fluid embolism : analysis of the national registry. Am J Obstet Gynecol 1995 ; 172 : 1158–1169）

5. 診療録への記録

文書によるインフォームドコンセントを得た場合には，診療録に添付しておく．口頭で同意を得た場合にはその旨を診療録に記載する．母体の血圧と脈拍数，内診所見，子宮収縮，胎児心拍の所見は診療録に記載する．分娩監視装置記録紙は保存する．

6. 子宮収縮薬の使用法（表4）

表4に則して使用する．静脈内投与時にはオキシトシン，$PGF_{2\alpha}$ いずれにおいても精密持続点滴装置（輸液ポンプ等）を使用し，希釈液は5％糖液あるいは生理食塩水を用いる．増量についてはオキシトシン，$PGF_{2\alpha}$ いずれにおいても30分以上の間隔をあけた後，必要と判断された場合のみ実施する．希釈倍数（使用する希釈液のオキシトシンあるいは $PGF_{2\alpha}$ 濃度）に関しては独自に設定してもよい．

表4．子宮収縮薬の使用法

1．オキシトシン：精密持続点滴装置（輸液ポンプ等）を用いる

オキシトシン	開始時投与量	維持量	安全限界
	1～2ミリ単位/分	5～15ミリ単位/分	20ミリ単位/分
5単位を5%糖液あるいは生理食塩水500mLに溶解（10ミリ単位/mL）	6～12mL/時間	30～90mL/時間	120mL/時間

増量：30分以上経てから時間当たりの輸液量を6～12mL（1～2ミリ単位/分）増やす

注意点：PGE_2錠内服後のオキシトシン点滴静注は最終内服時から1時間以上経た後に開始し，過強陣痛に注意する（CQ412参照）．

2．$PGF_{2\alpha}$：精密持続点滴装置（輸液ポンプ等）を用いる

$PGF_{2\alpha}$	開始時投与量	維持量	安全限界
	1.5～3.0μg/分	6～15μg/分	25μg/分
3,000μgを5%糖液あるいは生理食塩水500mL/に溶解（6μg/mL）	15～30mL/時間	60～150mL/時間	250mL/時間

増量：30分以上経てから時間当たりの輸液量を15～30mL（1.5～3.0μg/分）増やす

注意点：PGE_2錠内服後の $PGF_{2\alpha}$ 点滴静注は最終内服時から1時間以上経た後に開始し，過強陣痛に注意する（CQ412参照）．

気管支喘息，緑内障，骨盤位ならびに帝王切開・子宮切開既往には $PGF_{2\alpha}$ を使用しない．

3．PGE_2錠（経口）の使用法

PGE_2	1回1錠，次回服用には1時間以上あける 1日最大で6錠まで

注意点：他の子宮収縮薬同様に投与開始前から分娩監視装置を装着し，投与中は原則連続的モニターを行う．帝王切開・子宮切開既往ならびに骨盤位には PGE_2 を使用しない．子宮収縮薬静脈投与終了後1時間以内は使用しない．

また，異常胎児心拍パターンを確認したら投与中止とする．

(1) オキシトシン

オキシトシンは自然陣痛に近い子宮収縮が得られる．しかし感受性に個人差や妊娠週数による差が認められる．投与開始5分ほどで効果が現れるが，開始後早期に過強陣痛が出現しやすいため30分ほどは子宮収縮，胎児心拍数に十分注意する．「PGE_2錠内服」後の「オキシトシン点滴静注」は最終内服時から1時間以上経た後に開始し，過強陣痛に注意する（CQ412参照）．

表5. オキシトシンの有害事象

①ショック ②過強陣痛，子宮破裂，頸管裂傷，微弱陣痛，弛緩出血 ③胎児機能不全	
過敏症	過敏症状
新生児	新生児黄疸
循環器	不整脈，静脈注射後の一過性血圧上昇・下降
消化器	悪心・嘔吐
その他	水中毒症状

(2) $PGF_{2\alpha}$

$PGF_{2\alpha}$による妊娠末期の子宮収縮は，オキシトシンによる収縮が投与開始初期から規則的収縮が来るのに対し，周期性が不明瞭な内圧20mmHg，持続１分～1分30秒に及ぶ長いゆるやかな収縮がみられるのが特徴的である．

帝王切開・子宮切開既往には用いない(CQ403参照)．「PGE_2錠内服」後の「$PGF_{2\alpha}$点滴静注」は最終内服時から１時間以上経た後に開始し，過強陣痛に注意する(CQ412参照)．

分娩後の子宮収縮促進を目的とした$PGF_{2\alpha}$の子宮筋層内局注は，原則行わない（CQ404参照)．

開始時投与量（2006年版では0.1μg/kg/分)，増量のための間隔（2006年版では15～30分ごと)，ならびに増量分（2006年版では1.5μg/分）が変更になっていることに注意する．これらは主に，ジノプロストトロメタミン（既に販売が中止されている）の添付文書（日本医薬品集　医療薬2008年版，発行所じほう）に基づく変更である．増量間隔の変更はオキシトシンの増量間隔(30分以上)と一致させたものであり，ヒヤリ・ハット報告中で最も多い与薬エラー回避を目的としたヒューマンエラー防止策の一環である．なお，低濃度液（例えば，2,000μg/500mL）や高濃度液を使用することも可能だが，開始時投与速度（1.5～3.0μg/分)，増量の速度(30分以上あけて1.5～3.0μg/分)，最大投与速度(25μg/分)については順守する．すなわち，いずれの濃度液を使用しても開始速度は1.5～3.0μg/分，増量は30分以上あけて1.5～3.0μg/分，最大投与速度は25μg/分とする．

表6. $PGF_{2\alpha}$の有害事象

重大な副作用	①過強陣痛，子宮破裂，頸管裂傷 ②胎児機能不全（羊水混濁，徐脈，頻脈） ③心室細動，呼吸困難，喘鳴	
その他の副作用	循環器	心悸亢進，顔面紅潮，血圧上昇・下降，頻脈，胸内苦悶，不整脈
	過敏症	発疹など
	消化器	嘔気・嘔吐，腹痛，下痢，腹部膨満感・鼓腸
	注射部	血管痛，静脈炎，発赤
	その他	発汗，しびれ感，冷感，口渇，頭痛，発熱

(3) PG E_2経口錠

本剤は経口投与という簡便さはあるが，点滴投与と異なり調節性が低いため，一律に投与すると過強陣痛となることがある．投与は入院して行い，投与開始前に分娩監視装置を装着し投与中は分娩監視装置を用いて子宮収縮ならびに胎児心拍数を原則として連続的にモニターする．帝王切開・子宮切開既往には用いない（CQ403参照)．異常胎児心拍パターンを確認した場合には投与中止とする．

表7. PGE_2経口錠の有害事象

重大な副作用	①過強陣痛，子宮破裂，頸管裂傷 ②胎児機能不全（羊水混濁，徐脈，頻脈） ③心室細動，呼吸困難，喘鳴	
その他の副作用	消化器	嘔気・嘔吐，下痢
	循環器	顔面紅潮，血圧上昇，血圧下降
	その他	頭痛，頭重，めまい

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Induction of Labor

More than 22% of all gravid women undergo induction of labor in the United States, and the overall rate of induction of labor in the United States has more than doubled since 1990 to 225 per 1,000 live births in 2006 (1). The goal of induction of labor is to achieve vaginal delivery by stimulating uterine contractions before the spontaneous onset of labor. Generally, induction of labor has merit as a therapeutic option when the benefits of expeditious delivery outweigh the risks of continuing the pregnancy. The benefits of labor induction must be weighed against the potential maternal and fetal risks associated with this procedure (2). The purpose of this document is to review current methods for cervical ripening and induction of labor and to summarize the effectiveness of these approaches based on appropriately conducted outcomes-based research. These practice guidelines classify the indications for and contraindications to induction of labor, describe the various agents used for cervical ripening, cite methods used to induce labor, and outline the requirements for the safe clinical use of the various methods of inducing labor.

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics with the assistance of Mildred Ramirez, MD, and Susan Ramin, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

WOMEN'S HEALTH CARE PHYSICIANS

Background

In 1948, Theobald and associates described their use of the posterior pituitary extract, oxytocin, by intravenous drip for labor induction (3). Five years later, oxytocin was the first polypeptide hormone synthesized by du Vigneaud and associates (4). This synthetic polypeptide hormone has since been used to stimulate uterine contractions. Other methods used for induction of labor include membrane stripping, amniotomy, nipple stimulation, and administration of prostaglandin E analogues.

Cervical Ripening

The goal of cervical ripening is to facilitate the process of cervical softening, thinning, and dilating with resultant reduction in the rate of failed induction and

Clinical Considerations and Recommendations

▶ *What are the indications and contraindications to induction of labor?*

Indications for induction of labor are not absolute but should take into account maternal and fetal conditions, gestational age, cervical status, and other factors. Following are examples of maternal or fetal conditions that may be indications for induction of labor:

- Abruptio placentae
- Chorioamnionitis
- Fetal demise
- Gestational hypertension
- Preeclampsia, eclampsia
- Premature rupture of membranes
- Postterm pregnancy
- Maternal medical conditions (eg, diabetes mellitus, renal disease, chronic pulmonary disease, chronic hypertension, antiphospholipid syndrome)
- Fetal compromise (eg, severe fetal growth restriction, isoimmunization, oligohydramnios)

Labor also may be induced for logistic reasons, for example, risk of rapid labor, distance from hospital, or psychosocial indications. In such circumstances, at least one of the gestational age criteria in the box should be met, or fetal lung maturity should be established. A mature fetal lung test result before 39 weeks of gestation, in the absence of appropriate clinical circumstances, is not an indication for delivery.

The individual patient and clinical situation should be considered in determining when induction of labor is contraindicated. Generally, the contraindications to labor induction are the same as those for spontaneous labor and vaginal delivery. They include, but are not limited to, the following situations:

- Vasa previa or complete placenta previa
- Transverse fetal lie
- Umbilical cord prolapse
- Previous classical cesarean delivery
- Active genital herpes infection
- Previous myomectomy entering the endometrial cavity

▶ *What criteria should be met before the cervix is ripened or labor is induced?*

Assessment of gestational age and consideration of any potential risks to the mother or fetus are of paramount importance for appropriate evaluation and counseling before initiating cervical ripening or labor induction. The patient should be counseled regarding the indications for induction, the agents and methods of labor stimulation, and the possible need for repeat induction or cesarean delivery. Although prospective studies are limited in evaluating the benefits of elective induction of labor, nulliparous women undergoing induction of labor with unfavorable cervices should be counseled about a twofold increased risk of cesarean delivery (33, 34, 35). In addition, labor progression differs significantly for women with an elective induction of labor compared with women who have spontaneous onset of labor (36). Allowing at least 12–18 hours of latent labor before diagnosing a failed induction may reduce the risk of cesarean delivery (37, 38).

Confirmation of Term Gestation

- Ultrasound measurement at less than 20 weeks of gestation supports gestational age of 39 weeks or greater.
- Fetal heart tones have been documented as present for 30 weeks by Doppler ultrasonography.
- It has been 36 weeks since a positive serum or urine human chorionic gonadotropin pregnancy test result.

Additional requirements for cervical ripening and induction of labor include assessment of the cervix, pelvis, fetal size, and presentation. Monitoring FHR and uterine contractions is recommended as for any high-risk patient in active labor. Although trained nursing personnel can monitor labor induction, a physician capable of performing a cesarean delivery should be readily available.

▶ *What is the relative effectiveness of available methods for cervical ripening in reducing the duration of labor?*

A systematic review found that in patients with an unfavorable cervix, Foley catheter placement before oxytocin induction significantly reduced the duration of labor (21). This review also concluded that catheter placement resulted in a reduced risk of cesarean delivery. When the Foley catheter was compared with PGE_2 gel, the majority of the studies have found no difference in duration of induction to delivery or cesarean delivery rate. The use of prostaglandins is associated with an increased risk of tachysystole with or without FHR changes when compared with the Foley catheter (21). The use of different size Foley catheters, insufflation volumes, as well as dif-

ferent misoprostol protocols, yields inconsistent results to determine induction to delivery times, cesarean delivery rate, and risk of meconium passage (18, 21). The addition of oxytocin along with the use of the Foley catheter does not appear to shorten the time of delivery in a randomized controlled trial (39).

Studies examining extraamniotic saline infused through the Foley catheter compared with use of the Foley catheter with concurrent oxytocin administration report conflicting results on the time from induction to delivery (19, 40, 41). Differences in methodology could explain the opposing findings. The Foley catheter is a reasonable and effective alternative for cervical ripening and inducing labor.

Intracervical or intravaginal PGE_2 (dinoprostone) commonly is used and is superior to placebo or no therapy in promoting cervical ripening (42). Several prospective randomized clinical trials and two meta-analyses have demonstrated that PGE_1 (misoprostol) is an effective method for cervical ripening (43–48). Misoprostol administered intravaginally has been reported to be either superior to or as efficacious as dinoprostone gel (48–51). Vaginal misoprostol has been associated with less use of epidural analgesia, more vaginal deliveries within 24 hours, and more uterine tachysystole with or without FHR changes compared with dinoprostone and oxytocin (48). In contrast, misoprostol compared with oxytocin for cervical ripening resulted in longer intervals to active labor and delivery in a randomized controlled trial (52). It is difficult, however, to compare the results of studies on misoprostol because of differences in endpoints, including Bishop score, duration of labor, total oxytocin use, successful induction, and cesarean delivery rate. Pharmacologic methods for cervical ripening do not decrease the likelihood of cesarean delivery.

▶ *How should prostaglandins be administered?*

One quarter of an unscored 100-mcg tablet (ie, approximately 25 mcg) of misoprostol should be considered as the initial dose for cervical ripening and labor induction. The frequency of administration should not be more than every 3–6 hours. In addition, oxytocin should not be administered less than 4 hours after the last misoprostol dose. Misoprostol in higher doses (50 mcg every 6 hours) may be appropriate in some situations, although higher doses are associated with an increased risk of complications, including uterine tachysystole with FHR decelerations.

If there is inadequate cervical change with minimal uterine activity after one dose of intracervical dinoprostone, a second dose may be given 6–12 hours later. The manufacturers recommend a maximum cumulative dose of 1.5 mg of dinoprostone (three doses or 7.5 mL of gel) within a 24-hour period. A minimum safe time interval between prostaglandin administration and initiation of oxytocin has not been determined. According to the manufacturers' guidelines, after use of 1.5 mg of dinoprostone in the cervix or 2.5 mg in the vagina, oxytocin induction should be delayed for 6–12 hours because the effect of prostaglandins may be heightened with oxytocin. After use of dinoprostone in sustained-release form, delaying oxytocin induction for 30–60 minutes after removal is sufficient. Limited data are available on the use of buccal or sublingual misoprostol for cervical ripening or induction of labor, and these methods are not recommended for clinical use until further studies support their safety (53).

▶ *What are the potential complications with each method of cervical ripening, and how are they managed?*

Tachysystole with or without FHR changes is more common with vaginal misoprostol compared with vaginal prostaglandin E_2, intracervical prostaglandin E_2, and oxytocin (48). Tachysystole (defined in some studies as greater than 5 uterine contractions in 10 minutes in consecutive 10-minute intervals) and tachysystole with associated FHR decelerations are increased with a 50-mcg or greater dose of misoprostol (43, 47, 48, 54). There seems to be a trend toward lower rates of uterine tachysystole with FHR changes with lower dosages of misoprostol (25 mcg every 6 hours versus every 3 hours) (48).

The use of misoprostol in women with prior cesarean delivery or major uterine surgery has been associated with an increase in uterine rupture and, therefore, should be avoided in the third trimester (55, 56). An increase in meconium-stained amniotic fluid also has been reported with misoprostol use (47, 48). Although misoprostol appears to be safe and effective in inducing labor in women with unfavorable cervices, further studies are needed to determine the optimal route, dosage, timing interval, and pharmacokinetics of misoprostol. Moreover, data are needed on the management of complications related to misoprostol use and when it should be discontinued. If uterine tachysystole and a Category III FHR tracing (defined as either a sinusoidal pattern or an absent baseline FHR variability and any of the following: recurrent late decelerations, recurrent variable decelerations, or bradycardia) occurs with misoprostol use and there is no response to routine corrective measures (maternal repositioning and supplemental oxygen administration), cesarean delivery should be considered (32). Subcutaneous terbutaline also can be used in an attempt to correct the Category III FHR tracing or uterine tachysystole.

The intracervical PGE_2 gel (0.5 mg) has a 1% rate of uterine tachysystole with associated FHR changes while the intravaginal PGE_2 gel (2–5 mg) or vaginal insert is associated with a 5% rate (42, 57, 58). Uterine tachysystole typically begins within 1 hour after the gel or insert is placed but may occur up to 9 1/2 hours after the vaginal insert has been placed (57–59).

Removing the PGE_2 vaginal insert usually will help reverse the effect of uterine tachysystole. Irrigation of the cervix and vagina is not beneficial. Maternal side effects from the use of low-dose PGE_2 (fever, vomiting, and diarrhea) are quite uncommon (60). Prophylactic antiemetics, antipyretics, and antidiarrheal agents usually are not needed. The manufacturers recommend that caution be exercised when using PGE_2 in patients with glaucoma, severe hepatic or renal dysfunction, or asthma. However, PGE_2 is a bronchodilator, and there are no reports of bronchoconstriction or significant blood pressure changes after the administration of the low-dose gel.

Increased maternal and neonatal infections have been reported in connection with the use of *Laminaria japonicum* and hygroscopic dilators when compared with the PGE_2 analogues (7, 13, 20). The Foley catheter can cause significant vaginal bleeding in women with a low-lying placenta (21). Other reported complications include rupture of membranes, febrile morbidity, and displacement of the presenting part (61).

▶ *What are the recommended guidelines for fetal surveillance after prostaglandin use?*

The prostaglandin preparations should be administered where uterine activity and the FHR can be monitored continuously for an initial observation period. Further monitoring can be governed by individual indications for induction and fetal status.

The patient should remain recumbent for at least 30 minutes. The FHR and uterine activity should be monitored continuously for a period of 30 minutes to 2 hours after administration of the PGE_2 gel (62). Uterine contractions usually are evident in the first hour and exhibit peak activity in the first 4 hours (62, 63). The FHR monitoring should be continued if regular uterine contractions persist; maternal vital signs also should be recorded.

▶ *Are cervical ripening methods appropriate in an outpatient setting?*

Limited information is available on the safety of outpatient management of induction of labor. In a randomized, double-blind, controlled trial comparing 2 mg of intravaginal PGE_2 gel with placebo for 5 consecutive days as an outpatient procedure, it was noted that PGE_2 gel was effective and safe for initiation of labor in women at term with a Bishop score of 6 or less (64). No significant differences in adverse outcomes were noted in another randomized trial of 300 women at term comparing the use of controlled-release PGE_2 in an outpatient versus inpatient setting (65). Larger controlled studies are needed to establish an effective and safe dose and vehicle for PGE_2 before use on an outpatient basis can be recommended. However, outpatient use may be appropriate in carefully selected patients. Mechanical methods may be particularly appropriate in the outpatient setting. A randomized trial comparing the Foley catheter in an outpatient versus inpatient setting for preinduction cervical ripening demonstrated similar efficacy and safety with a reduction of hospital stay of 9.6 hours (66).

▶ *What are the potential complications of various methods of induction?*

The side effects of oxytocin use are principally dose related; uterine tachysystole and Category II or III FHR tracings are the most common side effects. Uterine tachysystole may result in abruptio placentae or uterine rupture. Uterine rupture secondary to oxytocin use is rare even in parous women (67). Water intoxication can occur with high concentrations of oxytocin infused with large quantities of hypotonic solutions, but is rare in doses used for labor induction.

Misoprostol appears to be safe and beneficial for inducing labor in a woman with an unfavorable cervix. Although the exact incidence of uterine tachysystole with or without FHR changes is unknown and the criteria used to define this complication are not always clear in the various reports, there are reports of uterine tachysystole with or without FHR changes occurring more frequently in women given misoprostol compared with women given PGE_2 (43, 45, 48, 68). There does not appear to be a significant increase in adverse fetal outcomes from tachysystole without associated FHR decelerations (68, 69). The occurrence of complications does appear to be dose-dependent (10, 48). Clinical trials have shown that at an equivalent dosage, the vaginal route produces greater clinical efficacy than the oral route (53). Oral misoprostol administration is associated with fewer abnormal FHR patterns and episodes of uterine tachy-systole with associated FHR changes when compared with vaginal administration (70, 71).

The potential risks associated with amniotomy include prolapse of the umbilical cord, chorioamnionitis, significant umbilical cord compression, and rupture of vasa previa. The physician should palpate for an umbilical cord and avoid dislodging the fetal head. The FHR

should be assessed before and immediately after amniotomy. Amniotomy for induction of labor may be contraindicated in women known to have HIV infection because duration of ruptured membranes has been identified as an independent risk factor for vertical transmission of HIV infection (29).

Stripping the amniotic membranes is associated with bleeding from undiagnosed placenta previa or low-lying placenta, and accidental amniotomy. Bilateral breast stimulation has been associated with uterine tachysystole with associated FHR decelerations. In a systematic review, breast stimulation was associated with an increased trend in perinatal death (31). Until safety issues are studied further, this practice is not recommended in an unmonitored setting.

▶ *When oxytocin is used for induction of labor, what dosage should be used and what precautions should be taken?*

Any of the low- or high-dose oxytocin regimens outlined in Table 2 are appropriate for labor induction (72–78). Low-dose regimens and less frequent increases in dose are associated with decreased uterine tachysystole with associated FHR changes (70). High-dose regimens and more frequent dose increases are associated with shorter labor and less frequent cases of chorioamnionitis and cesarean delivery for dystocia, but increased rates of uterine tachysystole with associated FHR changes (74, 79).

Each hospital's obstetrics and gynecology department should develop guidelines for the preparation and administration of oxytocin. Synthetic oxytocin generally is diluted 10 units in 1,000 mL of an isotonic solution for an oxytocin concentration of 10 mU/mL. Oxytocin should be administered by infusion using a pump that allows precise control of the flow rate and permits accurate minute-to-minute control. Bolus administration of oxytocin can be avoided by piggybacking the infusion into the main intravenous line near the venipuncture site.

A numeric value for the maximum dose of oxytocin has not been established. The FHR and uterine contractions should be monitored closely. Oxytocin should be administered by trained personnel who are familiar with its effects.

Table 2. Labor Stimulation with Oxytocin: Examples of Low- and High-Dose Oxytocin

Regimen	Starting Dose	Incremental Increase (mU/min)	Dosage Interval (min)
Low-Dose	0.5–2	1–2	15–40
High-Dose	6	3–6*	15–40

*The incremental increase is reduced to 3 mU/min in presence of hyperstimulation and reduced to 1 mU/min with recurrent hyperstimulation.

Data from Hauth JC, Hankins GD, Gilstrap LC 3rd, Strickland DM, Vance P. Uterine contraction pressures with oxytocin induction/augmentation. Obstet Gynecol 1986;68:305–9; Satin AJ, Leveno KJ, Sherman ML, Brewster DS, Cunningham FG. High- versus low-dose oxytocin for labor stimulation. Obstet Gynecol 1992;80:111–6; Crane JM, Young DC. Meta-analysis of low-dose versus high-dose oxytocin for labour induction. J SOGC 1998;20:1215–23; Cummiskey KC, Dawood MY. Induction of labor with pulsatile oxytocin. Am J Obstet Gynecol 1990;163:1868–74; Blakemore KJ, Qin NG, Petrie RH, Paine LL. A prospective comparison of hourly and quarter-hourly oxytocin dose increase intervals for the induction of labor at term. Obstet Gynecol 1990;75:757–61; Mercer B, Pilgrim P, Sibai B. Labor induction with continuous low-dose oxytocin infusion: a randomized trial. Obstet Gynecol 1991;77:659–63; *and* Muller PR, Stubbs TM, Laurent SL. A prospective randomized clinical trial comparing two oxytocin induction protocols. Am J Obstet Gynecol 1992;167:373–80; discussion 380–1.

▶ *How should complications associated with oxytocin use be managed?*

If uterine tachysystole with Category III FHR tracings occur, prompt evaluation is required and intravenous infusion of oxytocin should be decreased or discontinued to correct the pattern (32). Additional measures may include turning the woman on her side and administering oxygen or more intravenous fluid. If uterine tachysystole persists, use of terbutaline or other tocolytics may be considered. Hypotension may occur following a rapid intravenous injection of oxytocin; therefore, it is imperative that a dilute oxytocin infusion be used even in the immediate puerperium.

▶ *Are there special considerations that apply for induction in a woman with ruptured membranes?*

The largest randomized study to date found that oxytocin induction reduced the time interval between premature rupture of membranes and delivery as well as the frequencies of chorioamnionitis, postpartum febrile morbidity, and neonatal antibiotic treatments, without increasing cesarean deliveries or neonatal infections (80). These data suggest that for women with premature rupture of membranes at term, labor should be induced at the time of presentation, generally with oxytocin infusion, to reduce the risk of chorioamnionitis. An adequate time for the latent phase of labor to progress should be allowed.

The same precautions should be exercised when prostaglandins are used for induction of labor with ruptured membranes as for intact membranes. Intravaginal PGE_2 for induction of labor in women with premature rupture of membranes appears to be safe and effective (81). In a randomized study of labor induction in women with premature rupture of membranes at term, only one dose of intravaginal misoprostol was necessary for successful labor induction in 86% of the patients (67). There is no evidence that use of either of these prostag-

landins increases the risk of infection in women with ruptured membranes (67, 81). There is insufficient evidence to guide the physician on use of mechanical dilators in women with ruptured membranes.

A meta-analysis that included 6,814 women with premature rupture of membranes at term compared induction of labor with prostaglandins or oxytocin to expectant management (82). A significant reduction in the risk of women developing chorioamnionitis or endometritis and a reduced number of neonates requiring admission to the neonatal intensive care unit was noted in the women who underwent induction of labor compared with expectant management (82).

▶ *What methods can be used for induction of labor with intrauterine fetal demise in the late second or third trimester?*

The method and timing of delivery after a fetal death depends on the gestational age at which the death occurred, on the maternal history of a previous uterine scar, and maternal preference. Although most patients will desire prompt delivery, the timing of delivery is not critical; coagulopathies are associated with prolonged fetal retention and are uncommon. In the second trimester, dilation and evacuation can be offered if an experienced health care provider is available, although patients should be counseled that dilation and evacuation may limit efficacy of autopsy for the detection of macroscopic fetal abnormalities.

Labor induction is appropriate at later gestational ages, if second-trimester dilation and evacuation is unavailable, or based on patient preference. Much of the data for management of fetal demise has been extrapolated from randomized trials of management of second trimester pregnancy termination. Available evidence from randomized trials supports the use of vaginal misoprostol as a medical treatment to terminate nonviable pregnancies before 24 weeks of gestation (83). Based on limited data, the use of misoprostol between 24 to 28 weeks of gestation also appears to be safe and effective (84, 85). Before 28 weeks of gestation, vaginal misoprostol appears to be the most efficient method of labor induction, regardless of cervical Bishop score (84, 86), although high-dose oxytocin infusion also is an acceptable choice (87, 88). Typical dosages for misoprostol use are 200–400 mcg vaginally every 4–12 hours. After 28 weeks of gestation, induction of labor should be managed according to usual obstetric protocols. Cesarean delivery for fetal demise should be reserved for unusual circumstances because it is associated with potential maternal morbidity without any fetal benefit.

Several studies have evaluated the use of misoprostol at a dosage of 400 mcg every 6 hours in women with a stillbirth up to 28 weeks of gestation and a prior uterine scar (85, 89). There does not appear to be an increase in complications in those women. Further research is required to assess effectiveness and safety, optimal route of administration, and dose.

In patients after 28 weeks of gestation, cervical ripening with a transcervical Foley catheter has been associated with uterine rupture rates comparable to spontaneous labor (90) and this may be a helpful adjunct in patients with an unfavorable cervical assessment. Therefore, in patients with a prior low transverse cesarean delivery, trial of labor remains a favorable option. There are limited data to guide clinical practice in a patient with a prior classical cesarean delivery, and the delivery plan should be individualized.

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- Prostaglandin E analogues are effective for cervical ripening and inducing labor.
- Low- or high-dose oxytocin regimens are appropriate for women in whom induction of labor is indicated (Table 2).
- Before 28 weeks of gestation, vaginal misoprostol appears to be the most efficient method of labor induction regardless of Bishop score, although high-dose oxytocin infusion also is an acceptable choice.
- Approximately 25 mcg of misoprostol should be considered as the initial dose for cervical ripening and labor induction. The frequency of administration should not be more than every 3–6 hours.
- Intravaginal PGE_2 for induction of labor in women with premature rupture of membranes appears to be safe and effective.
- The use of misoprostol in women with prior cesarean delivery or major uterine surgery has been associated with an increase in uterine rupture and, therefore, should be avoided in the third trimester.
- The Foley catheter is a reasonable and effective alternative for cervical ripening and inducing labor.

調査結果報告書

平成22年5月21日
独立行政法人医薬品医療機器総合機構

I. 品目の概要

［一　般　名］　別添1のとおり
［販　売　名］　別添1のとおり
［承認取得者］　別添1のとおり
［効能・効果］　別添1のとおり
［用法・用量］　別添1のとおり
［備　　考］　特になし
［調査担当部］　安全第二部

II. 検討の背景

「医薬品等の安全性に係る調査依頼について」（平成21年12月25日付薬食安発第1225第2号）にて、陣痛促進剤の使用上の注意の妥当性に関する調査の依頼を受けたため、医薬品医療機器総合機構安全第二部（以下「機構」）は、陣痛促進剤について、製造販売業者から機構あてに報告された副作用報告状況や関連学会のガイドライン等について調査を行い、現行の安全対策の妥当性及び更なる安全対策の要否について検討を行った。国内では、陣痛促進剤として、オキシトシン注射剤、ジノプロスト注射剤、ジノプロストン経口剤が承認されている。また、子宮頸管熟化剤であるプラステロン硫酸ナトリウム注射剤及び腟剤に関して、陣痛促進剤と併用される場合の安全対策についても検討を行った。なお、プラステロン硫酸ナトリウム腟剤については、すでに販売が終了されており、平成22年3月末で経過措置期間が終了している。

なお、平成20年11月5日付けで陣痛促進剤による被害を考える会より「陣痛促進剤及び子宮頸管熟化剤の添付文書改訂の要望」が提出されている。

III. 機構における調査

1. 使用上の注意に未記載の重篤な副作用の追記の必要性について

陣痛促進剤の現行の添付文書においては、「警告」の項に、陣痛促進剤の使用にあたっては、過強陣痛や強直性子宮収縮により、胎児仮死、子宮破裂、頸管裂傷、羊水塞栓症等が起こることがあるため、陣痛促進剤の適応を慎重に判断することや、分娩監視装置を用いて十分に監視すること、他の陣痛促進剤との同時併用は行わないことの注意喚起がなされている。機構は、平成16年4月から平成21年11月までに報告された陣痛促進剤の副作用

報告を精査し、現行の添付文書の使用上の注意に未記載の重篤な副作用のうち、複数件集積があった、出血性脳血管障害（脳内出血及びくも膜下出血）、常位胎盤早期剥離及び子癇について、陣痛促進剤使用との因果関係を評価し、使用上の注意へ追記する必要性を検討した。

1)　出血性脳血管障害について

陣痛促進剤（オキシトシン、ジノプロスト（以下、PGF2α）、ジノプロストン（以下、PGE2））による出血性脳血管障害については、現在の添付文書において注意喚起がなされていない状況である。

分娩時の出血性脳血管障害の発症に関して、産婦人科診療ガイドライン産科編 2008（日本産科婦人科学会、日本産婦人科医会編）では、分娩時に起こる母体生命を脅かす母体緊急状態のうち 2 番目に頻度の高いものとして、脳内出血を含む高血圧緊急症が挙げられている。なお、分娩時脳内出血の頻度は約 10 万分の 1 と推定されている。また、海外では、妊娠中から産後 6 週間までの脳内出血の発生率は 7.1/10 万人年であり、同年代の非妊娠女性の 5.0/10 万人年に比べ高いとの報告（Neurology 67:424-429.2006）や、妊娠中から産後 2 週間までの脳内出血の発生率は 4.6/10 万分娩であるとの報告（Stroke 26:930-936.1995）がなされている。なお、出血性脳血管障害はくも膜下出血と脳内出血に分類されるが、厚生労働省より発表されている心疾患－脳血管疾患死亡統計の概況によると、本邦の 50 歳未満の女性のくも膜下出血、脳内出血による死亡率は人口 10 万人年あたりそれぞれ 5.9、3.8 である。

○機構における調査内容

①　欧米の添付文書の状況

海外の添付文書における出血性脳血管障害に関する注意喚起について、米国では、オキシトシン添付文書に、オキシトシン使用と関連するものとしてくも膜下出血等による母体死亡の報告がある旨が記載されているが、その記載根拠については明らかではなかった。また、英国では、現行の添付文書において出血性脳血管障害に関する注意喚起はなされていない。

②　文献等の調査

国際的に標準的な産科の教科書である「Williams OBSTERICS」（22nd edition, 2005. McGraw-Hill）によれば、妊娠中のくも膜下出血の原因の 80%が脳動脈瘤破裂であり、脳血管奇形が原因となることが多いと記載されていた。その他の原因としては脳動静脈奇形破裂や凝固障害、血管障害、静脈血栓症、感染、麻薬乱用、腫瘍、外傷が挙げられている。また、「High risk Pregnancy: Management Options.」（3rd edition, 2005. SAUNDERS）においても、妊娠中のくも膜下出血の主な原因として動脈瘤破裂や脳動静脈奇形が挙げられており、その他の原因としてもやもや病や硬膜静脈洞血栓、真菌性動脈瘤、絨毛癌、血管炎、脳腫瘍、血液凝固異常が挙げられているが、いずれの教科書においても、陣痛促進剤の使用は

妊娠中のくも膜下出血のリスク要因として記載されていない。

さらに、陣痛促進剤による出血性脳血管障害のリスク増大について、国内外の論文報告等を調査した。医学中央雑誌の検索で国内の論文報告を調査したところ、オキシトシンについては、1 件の論文が検出されたが、症例報告であり、当該症例はオキシトシン使用により出血性脳血管障害を来したものではなかった。PGF2α、PGE2 については、医学中央雑誌の検索で検出された報告はなかった。

また、PubMed の検索で国内外の論文報告を調査したところ、オキシトシンについて 8 件、PGF2α については 1 件の論文が検出されたが、陣痛促進剤の使用と出血性脳血管障害の因果関係について検討した論文ではなかった。なお、PGE2 については、検出された報告はなかった。

Martindale 及び DRUGDEX （MICROMEDEX）のデータベースを用いて出血性脳血管障害に関連する情報の検索を行ったところ、オキシトシンについては、DRUGDEX において、くも膜下出血に関する報告が 1 件記載されていた。当該文献は症例報告であり、陣痛誘発のためにオキシトシンを使用後、くも膜下出血を来した症例であったが、動脈瘤のあった患者であることから、機構は、本剤との因果関係は不明と評価した。当該文献中でも、オキシトシンとくも膜下出血の因果関係について検討されていなかった。PGF2α、PGE2 については、該当する記載はなかった。

③　副作用報告の因果関係評価

調査対象副作用報告は、それぞれの医薬品の販売開始後から、平成 21 年 11 月までに報告され、出血性脳血管障害に該当する副作用報告とした。オキシトシン、PGF2α、PGE2 の調査対象となる国内症例は、それぞれ 0 件、4 件、1 件（合計 5 例）であった。機構は、因果関係を評価した結果、いずれの副作用報告についても、患者の既往歴や陣痛促進剤の投与量及び投与間隔、副作用発現時の患者の状態や剖検に関する情報等の情報不足により因果関係評価が困難な症例、妊娠高血圧症候群を合併していた症例、脳内出血のリスクとなる脳動脈奇形を合併していた症例などであることから、医薬品と出血性脳血管障害の因果関係は不明と評価した。海外症例については、調査対象となる症例はなかった。

また、「日本の母体死亡　妊産婦死亡症例集」（株）三宝社、1998 年）に、陣痛促進剤を使用した症例における出血性脳血管障害の事例が 4 例紹介されている。この 4 症例についても確認したが、患者の既往歴や陣痛促進剤の投与量及び投与速度、剖検に関する情報等が記載されておらず、因果関係が評価できるだけの情報が不足していた。

④　陣痛促進剤による血圧上昇に起因した脳内出血の発現の可能性について

一般的に知られている脳内出血の危険因子の一つとして高血圧が挙げられることから、陣痛促進剤による血圧上昇に起因した脳内出血の発現の可能性について調査した。

PGE2、PGF2α 及びオキシトシンの血圧上昇作用に対する影響について、まず、文献調査により抽出された関連文献や製造販売業者より提出された社内資料を精査した結果、PGF2α 投与の対象が健康成人、妊婦のいずれの場合においても、PGF2α 投与により血圧が上昇す

るとの報告と、変化がないとの報告があり、臨床的に PGF2α が血圧に及ぼす影響については明確でなかった。また、PGE2 については、健康成人に投与した場合、PGE2 投与により血圧が低下するとの報告があった。また、オキシトシンについては、妊婦にオキシトシンを投与した際、血圧が低下するとの報告があった。

次に、陣痛促進剤による血圧上昇と脳内出血との関連について文献調査を行ったが、陣痛促進剤使用による血圧上昇の結果、脳内出血が起こることを示唆するような報告はなかった。

2) 常位胎盤早期剥離について

陣痛促進剤（オキシトシン、PGF2α、PGE2）による常位胎盤早期剥離については、現在の添付文書において注意喚起がなされていない状況である。産婦人科診療ガイドライン 2008（前出）によると、常位胎盤早期剥離は、単胎で 1000 分娩あたり 5.9 件、双胎で 12.2 件に発生するとされており、その危険因子として、妊娠高血圧症候群、常位胎盤早期剥離の既往、子宮内感染、切迫早産（前期破水、絨毛膜羊膜炎）、外傷などが挙げられている。

○機構における調査内容

① 欧米の添付文書の状況

英国では、PGF2α の添付文書において、undesirable effect として常位胎盤早期剥離が記載されているが、その記載根拠については明らかではなかった。また、米国の添付文書においては、常位胎盤早期剥離に関する注意喚起はなされていない。

② 文献等の調査

「Williams OBSTERICS」（前出）では、常位胎盤早期剥離の主な原因は不明とされており、これまでの疫学調査から、常位胎盤早期剥離の発現と関連する症状として、年齢や経産回数、子癇前症、慢性高血圧、前期破水、多胎妊娠、羊水過多、喫煙、血栓症、コカインの使用、常位胎盤早期剥離の既往、子宮平滑筋腫が挙げられている。また、「High risk Pregnancy: Management Options.」（前出）では、常位胎盤早期剥離について、少数例では子宮への直接的な外傷のように原因が明らかな場合もあるものの、多くの場合その原因は不明であるとされており、危険因子としては、常位胎盤早期剥離の既往、年齢、経産回数、喫煙歴、羊水過多や多胎妊娠の患者における破水後の急激な子宮内圧の低下、児頭外回転術、胎盤の異常（周郭胎盤など）、腹部外傷、α-フェトプロテインの増加などが挙げられている。「妊産婦と新生児の薬の使い方」（(株) 南山堂、1986 年）には、過強陣痛の合併症として常位胎盤早期剥離が起こる可能性があると記載されているが、国内のガイドラインや国際的に標準となる教科書「Williams OBSTERICS」（前出）や「High risk Pregnancy: Management Options.」（前出）において、過強陣痛が常位胎盤早期剥離のリスクである旨の記載はなかった。

さらに、陣痛促進剤による常位胎盤早期剥離のリスク増大について、国内外の論文報告を

調査した。医学中央雑誌の検索で国内の論文報告を調査したところ、オキシトシン、PGF2α、PGE2 について、検出された報告はなかった。

また、PubMed の検索で海外の論文報告を調査したところ、オキシトシンについては 6 件、PGE2 については 1 件の論文が検出された。そのうちオキシトシンに関する 1 件は、オキシトシン使用後に常位胎盤早期剥離が発現した症例の報告（Am. J. Obstet. Gynecol. 125:276.1976）であったが、常位胎盤早期剥離の既往のある患者であったことなどから、医薬品と常位胎盤早期剥離の因果関係は不明と評価した。また、PGE2 に関する 1 件は、PGE2 ペッサリー（国内では未承認）を腟内投与した後、常位胎盤早期剥離が発現した症例の報告（West Engl. Med. J. 105:114-115.1990）であり、報告医が PGE2 との因果関係を疑った論文であったが、本症例については、患者背景に関する情報等、医薬品と常位胎盤早期剥離の因果関係を評価できるだけの情報が不足していた。その他の論文については、陣痛促進剤の使用と常位胎盤早期剥離の因果関係について検討した論文ではなかった。なお、PGF2α については、検出された報告はなかった。

Martindale 及び DRUGDEX （MICROMEDEX）のデータベースを用いて常位胎盤早期剥離に関連する情報の検索を行ったところ、PGF2α、PGE2、オキシトシンについて該当する記載はなかった。

③　副作用報告の因果関係評価

調査対象副作用報告は、それぞれの医薬品の販売開始後から、平成 21 年 11 月までに報告され、常位胎盤早期剥離に該当する副作用報告とした。オキシトシン、PGF2α、PGE2 の調査対象報告は、それぞれ 3 件、1 件、4 件（合計 6 例）であった。因果関係を評価した結果、いずれの副作用報告についても、患者の既往歴や陣痛促進剤投与中の患者の状態に関する情報不足により因果関係評価が困難な症例や、偶発的な可能性も考えられる症例であることから、機構は医薬品と常位胎盤早期剥離の因果関係は不明と評価した。

また、「分娩事故判例分析」（医療問題弁護団・分娩事故判例研究会、2008 年）に、陣痛促進剤を使用した症例における常位胎盤早期剥離の事例が 2 例紹介されている。この 2 症例についても確認したが、患者の既往歴や陣痛促進剤の投与量及び投与速度、陣痛促進剤投与中の患者の状態に関する情報が記載されておらず、因果関係が評価できるだけの情報が不足していた。

国内の常位胎盤早期剥離の副作用報告においては、6 例中 1 例で過強陣痛後に常位胎盤早期剥離が起こった症例であったが、機構は、当該症例では陣痛促進剤による過強陣痛と常位胎盤早期剥離の因果関係は不明と評価した。

海外症例については、PGE2 であるジノプロストンベータデクスの報告が 2 件あったが、2 件とも陣痛促進剤使用時の経過の情報がなく、因果関係評価は困難であった。なお、ジノプロストンベータデクスは国内では平成 21 年 4 月 16 日に承認整理されており、また、これら症例で使用されていた腟剤は国内未承認である。

3)　子癇について

陣痛促進剤（オキシトシン、PGF2α、PGE2）による子癇については、現在の添付文書において注意喚起がなされていない状況である。

妊娠高血圧症候群管理ガイドライン 2009（日本妊娠高血圧学会編）によると、子癇は妊娠高血圧症候群の妊婦に起こるが、うち 18～36%が分娩時に発症するとされている。また、「High risk Pregnancy: Management Options.」（前出）では、子癇の発症頻度は 1/1600 分娩であると記載されている。

○機構における調査内容

①　欧米の添付文書の状況

英国、米国においては、現在の添付文書において子癇に関する注意喚起はなされていない。

②　文献等の調査

陣痛促進剤による子癇のリスク増大について、国内外の論文報告等を調査した。医学中央雑誌の検索で国内の論文報告を調査したところ、オキシトシンについては、3 件の該当論文が検出された。うち 1 例は症例報告であり、オキシトシン使用後に子癇を発症した症例であったが、その因果関係については不明であり、当該文献中にも陣痛促進剤と子癇の関連を示唆する記載はなかった。また、PubMed の検索で海外の論文報告を調査したところ、オキシトシンについては 38 件、PGE2 については 7 件、PGF2α については 16 件の論文が検出されたが、陣痛促進剤の使用と子癇の因果関係について検討した論文ではなかった。

Martindale 及び DRUGDEX （MICROMEDEX）のデータベースを用いて子癇に関連する情報の検索を行ったところ、PGF2α、PGE2、オキシトシンについて該当する記載はなかった。

③　副作用報告の因果関係評価

調査対象副作用報告は、それぞれの医薬品の販売開始後から、平成 21 年 11 月までに報告され、子癇に該当する副作用報告とした。オキシトシン、PGF2α、PGE2 の調査対象報告は、それぞれ 2 件、0 件、0 件（合計 2 例）であった。機構は、因果関係を評価した結果、いずれの副作用報告についても、陣痛促進剤投与前から妊娠高血圧症候群（妊娠中毒症）の悪化が見られていた症例や、本剤投与時の血圧等の情報が不足しており因果関係評価が困難である症例であることから、医薬品と子癇の因果関係は不明と評価した。

海外症例については、調査対象副作用報告はなかった。

4)　調査結果

以上の結果を踏まえ、機構は次のように考える。陣痛促進剤の使用上の注意に未記載である、上記の重篤な副作用については、その発現と陣痛促進剤使用の因果関係は不明であり、重大な副作用として添付文書に追記する根拠には乏しいと判断した。一方、分娩進行中には、陣痛促進剤使用の有無にかかわらず、脳内出血、くも膜下出血や常位胎盤早期剥離、

子癇のみならず、既に陣痛促進剤による副作用として記載されている子宮破裂、羊水塞栓等も含め、重篤な転帰をたどることもある事象が発現する可能性がある。このような緊急状態（子宮破裂、羊水塞栓、脳内出血、くも膜下出血、常位胎盤早期剥離、子癇、分娩時大量出血等）において、早期診断と迅速な治療が母体の周産期予後を左右することを考慮すると、分娩進行中に十分な患者観察が行われることは重要と考える。機構は、「重要な基本的注意」の項に、陣痛促進剤の使用の有無に関わらず、分娩時には母児の生命を脅かす緊急状態が起こることがあるため、陣痛促進剤を用いた陣痛誘発、陣痛促進、分娩促進にあたっては、分娩監視装置を用いた分娩監視に加え、定期的にバイタルサインのモニターを行うなど、患者の状態を十分に観察する必要がある旨を追記することが妥当であると判断した。

専門協議において、調査対象とした個々の症例に関して議論を行ったところ、いずれの症例も薬剤との因果関係は否定的あるいは情報不足のため判定不能との意見が多数であり、協議の結果、国内外の文献等を含め、現在得られている情報からは、陣痛促進剤と出血性脳血管障害、常位胎盤早期剥離及び子癇との因果関係は明確でなく、添付文書に追記する必要性は低いとの結論に達した。また、重篤な緊急状態が起こることがあるため、患者の状態を十分に観察すべき旨を添付文書に追記する必要があるとの機構の判断は、専門委員より妥当と評価された。さらに、専門協議において、出血性脳血管障害等と陣痛促進剤の因果関係を検討するためには、陣痛促進剤を使用しなかった症例との比較検討が必須であるとの意見、また、妊娠・分娩時の脳出血の発現頻度は非常に低いため、そのリスク要因の特定を行うためには国内全体の情報を集約する必要があり、関連学会の事業や公的研究等でも引き続き検討されることが重要であるとの意見が出された。

機構は、陣痛促進剤の使用と出血性脳血管障害、常位胎盤早期剥離、子癇との関連性については、専門協議における議論も踏まえ、今後も同様の症例や研究等の新たな情報の集積に注目する必要があるものの、現段階においては、重大な副作用としての新たな注意喚起は不要であると判断した。また、陣痛促進剤の使用の有無にかかわらず重篤な緊急状態が起こることがあるため、患者の状態を十分に観察すべき旨を添付文書に追記することが妥当であると判断した。

2. オキシトシン増量間隔の再検討について

1) 国内におけるこれまでの経緯

オキシトシンの添付文書において、平成 19 年 4 月、「用法・用量に関連する使用上の注意」の「分娩誘発、微弱陣痛の治療の目的で使用する場合」の項に記載されている点滴速度を上げる際の時間間隔について、40 分以上経過を観察しつつ増量する旨の注意喚起が、30 分以上経過を観察しつつ増量する旨の記載に改訂されている。

改訂の背景は次のとおりである。平成 18 年 6 月に日本産科婦人科学会及び日本産婦人科

医会により「子宮収縮薬による陣痛誘発・陣痛促進に際しての留意点」（以下「留意点」）が取りまとめられ、平成 18 年 6 月 20 日付薬食案発第 0620001 号厚生労働省医薬食品局安全対策課長通知により、関係業者に対し、周知が図られた。これに伴い、「留意点」とオキシトシンの添付文書との不整合を検討し、「留意点」では「30～40 分ごとに 1～2 ミリ単位／分増量」とされていること、英国産婦人科学会（Royal College of Obstetricians and Gynaecologist、以下 RCOG）による分娩誘発に関するガイドライン（RCOG Evidence-based Clinical Guidelines No. 9, 2001）では「increase at intervals of 30 minutes or more」、米国産婦人科学会（American College of Obstetricians and Gynecologists、以下 ACOG）による分娩誘発に関するガイドライン（ACOG practice bulletin No. 10, 1999）では、より子宮過刺激の少ない Low dose として、開始用量の違いにより「dosage intervals: 15minutes」もしくは「dosage intervals: 30－40 minutes」と記載されていることから、日本の添付文書もこれらとの整合を図る必要があるとし、オキシトシンの添付文書が前述のとおり改訂されたものである。

この改訂において、オキシトシンの点滴速度を上げる際の時間間隔を「30 分以上」と記載としたことの妥当性について、現時点までに得られている情報に基づき検討することとした。

2) 機構における調査内容及び調査結果

① 副作用報告の評価

平成 16 年 4 月から平成 21 年 11 月までのオキシトシンの副作用報告 33 症例のうち、30 分から 40 分の間隔で増量している症例は 6 例であった。この 6 症例について、増量までの間隔と副作用発現について因果関係を評価した結果、機構は、これら症例は分娩の進行の過程で偶発的に有害事象が発現したと思われる症例や、分娩の監視が不十分であったことが原因と思われる症例であり、いずれも、増量までの間隔が短かったことにより作用が発現したと考えられる症例ではないと評価した。

② 欧米における状況

現在の米国のガイドライン（ACOG practice bulletin No. 109, 2009）には、陣痛誘発にオキシトシンを用いる際の投与方法について、前述の ACOG practice bulletin No. 10 と同様の記載がなされている。また、英国のガイドライン（National Institute for Health and Clinical Excellence Clinical Guideline No. 70, 2008）には、オキシトシンを用いた陣痛誘発について詳細な記載はなかった。

米国の現在の添付文書には、点滴速度を上げる際の時間間隔に関する注意喚起として、「30－60 分の間隔で徐々に増量する」旨が記載されている。また、英国の添付文書には、「徐々に増量し、20 分より短い間隔で増量しない」旨が記載されている。

以上の調査結果に加え、現在のオキシトシンの添付文書では、「30 分以上十分に観察し、

陣痛の状況に応じて増減する」旨の注意喚起が記載されており、これは時間間隔30分ですぐに増量することを促す内容ではないことや、欧米のガイドラインや添付文書の記載から逸脱した内容ではないことなどから、機構は、「30分以上」の記載を変更する必要性は低いと判断した。

以上の機構の判断は、専門委員より妥当と評価された。また、専門協議において以下の意見が示された。

- ガイドライン等の記載からも医学的に40分以上の間隔を置く必要があるとは考えられない。患者の状態を十分に観察して増量の必要性を判断することが徹底されるのであれば、「40 分」ではなく「30 分」ごとに患者の状態を確認し増量の要否を判断することを原則としたほうが、増量までの時間に関するヒューマンエラーを防ぐことが期待でき、より確実に患者観察や投与速度の確認がなされるのではないか。
- 陣痛促進剤の増量に必要以上に時間をかけることは、総合的に陣痛誘発にかかる時間が増え、妊婦に体力的時間的に負担がかかることになり、望ましいことではない。
- 30分から40分の間に増量し副作用が起こった症例については、増量間隔が短すぎたために副作用が発現したと考えられる症例はないが、かなり短い間隔で大幅な増量をしたことが問題と思われる症例も散見された。改めて現行の添付文書の注意喚起の遵守が徹底されること及び十分な観察が行われることが重要である。

機構は、以上の専門委員の意見を踏まえ、オキシトシンの増量間隔については、「30分以上」の記載を変更する必要性はなく、現行の添付文書の注意喚起が徹底され、十分な観察が行われることが重要であると判断した。

3. インフォームドコンセントについて

産婦人科診療ガイドライン産科編 2008（前出）では、陣痛誘発にあたってインフォームドコンセントを行うことが強く推奨されている。また、前述の「留意点」でも、「陣痛促進剤の実際の使用にあたっては、その時点で適切と考えられる使用法を行ったとしても異常に遭遇する可能性があるという医療側、患者側双方の共通した認識が必要であり、陣痛促進剤を使用する必要性（適応）と手技・方法並びに使用により予想される効果並びに副作用の危険、さらに緊急時の対応などについて、分娩誘発を実施する前に、必ず文書による説明を行い、同意を得ておく。」と述べられている。

機構は、分娩誘発や陣痛促進のための陣痛促進剤の使用に関しては、患者がその必要性と危険性を十分に理解した上で使用されることが必要であり、ガイドラインや「留意点」でインフォームドコンセントの重要性が強調されていることも考慮すると、添付文書においても同様の注意喚起は必要と考える。したがって、各薬剤の添付文書の「警告」の項に、分娩誘発や陣痛促進のためにこれら薬剤を使用する際は、陣痛促進剤を用いた陣痛誘発・陣痛促進・分娩促進の必要性及びリスクについて十分に説明し、同意を得た上で使用する

旨の注意喚起を追記することが妥当であると判断した。

以上の機構の判断は、専門委員より妥当と評価された。専門協議において、インフォームドコンセントの必要性はガイドラインや「留意点」に既に記載されているため、ほとんどの施設で実施されているとの意見、インフォームドコンセントの際には陣痛促進剤のリスクのみでなく、陣痛誘発・陣痛促進・分娩促進を行う医学的な必要性が十分説明される必要があるとの意見が示された。機構は、専門協議の議論を踏まえ、添付文書にインフォームドコンセントの必要性を追記することが妥当と判断した。

4. 陣痛促進剤の投与速度変更及び投与中止の目安となる陣痛周期の時間の記載の要否について

オキシトシン、PGF2α の添付文書において、投与速度を変更するあるいは投与を中止する場合の目安となる陣痛の周期や陣痛持続時間は記載されていない。機構は、そのことにより安全対策上の問題があるか否かについて、検討した。

産婦人科診療ガイドライン産科編 2008（前出）においては、陣痛促進薬使用にあたって、原則として分娩監視装置による子宮収縮・胎児心拍数を連続的に記録することが強く推奨されている。また、「留意点」（前出）においても、陣痛促進薬使用時における子宮収縮の評価について、分娩監視装置を用いて原則として連続的にモニターする必要があることが記載されている。しかしながら、いずれにおいても、目標とする陣痛間隔や陣痛持続時間に関する具体的な記載はない。

本件に関して、機構は以下のように考える。ガイドライン等の勧奨状況を踏まえると、患者の分娩進行に有効な陣痛であるかどうかは陣痛周期や陣痛持続時間のみにより判断されるものではなく、患者個々の状態、分娩の進行状況及び陣痛の強さと併せて陣痛促進剤の投与速度の変更及び投与継続の要否が判断されるべきものと考える。したがって、陣痛周期や陣痛持続時間のみでなく患者の状態及び分娩の進行状況を十分に観察したうえで投与を継続すべきか否かを検討する必要があり、陣痛促進剤の投与速度変更や投与中止の目安として、一律に陣痛周期の時間を定めることは適切でないと考える。

以上の機構の判断は、専門委員より妥当と評価された。また、専門委員より以下の意見が示された。

- 陣痛間隔が短くても陣痛が弱く分娩が進行しないこともあるため、陣痛間隔のみで投与速度変更や投与中止の判断することは適切でなく、添付文書に具体的な陣痛間隔の時間を記載することも困難である。
- 投与速度の変更や投与中止の判断には、陣痛間隔や陣痛の強さ、内診所見も含めた分娩の進行状況の適切な監視が重要である。
- 陣痛間隔だけで一律に投与中止を規制すると、本来もう少し促進すれば経腟分娩できたような産婦が、分娩に至らずに帝王切開となってしまう例が多くなると予想され、

患者にとっては不要な帝王切開を受けてしまうデメリットが生じる。

以上の専門協議における議論を踏まえ、機構は以下のように考える。

陣痛促進剤の投与に際しては、陣痛の進行状況、母体及び胎児の状態の十分な観察のうえで投与の継続や投与速度の変更を検討することが重要であり、投与速度変更や投与中止の目安として、一律に陣痛間隔の時間を定め添付文書に記載することは適切ではないと判断した。

5. 子宮頸管熟化剤と陣痛促進剤の併用の際の投与間隔について

1) 国内におけるこれまでの経緯

子宮頸管熟化剤のプラステロン硫酸ナトリウムと陣痛促進剤の併用について、プラステロン硫酸ナトリウム、陣痛促進剤それぞれの添付文書に「同時投与は避ける」旨の記載がされている。この記載に関して、併用の際は子宮頸管熟化剤使用後に陣痛促進剤を使用する際の投与間隔は記載されていないが、機構は、そのことにより安全対策上の問題があるか否かについて、検討することとした。

2) 機構における調査内容及び調査結果

平成16年4月から平成21年11月までに報告された、プラステロン硫酸ナトリウムと陣痛促進剤を併用している副作用報告 6 例について、各々の薬剤の使用時期について確認したところ、陣痛促進剤使用後に子宮頸管熟化剤を使用し、その後再度陣痛促進剤を使用している症例や、子宮頸管熟化剤と陣痛促進剤を同時投与している症例であった。陣痛促進剤の添付文書には、「ビショップスコア等により頸管の熟化を確認した後、陣痛促進剤を投与することが望ましい」旨が既に記載されており、上記の症例については、この注意事項が遵守されておらず、使用方法が必ずしも適切でなかったと考えられる。

本件に関して、機構は以下のように考える。子宮頸管熟化剤と陣痛促進剤の併用に関しては、頸管の熟化の進行には個人差があることから、現時点では投与間隔を一律に記載する必要性は低く、頸管の熟化の程度を確認した上で投与を判断することが徹底される必要があり、現行の添付文書における注意喚起の内容が遵守されることが重要であると考える。

以上の機構の判断は、専門委員より妥当と評価された。

6. 精密持続点滴装置の使用について

専門協議において、PGF2α及びオキシトシンの添付文書において、点滴静注による投与に関しては輸液ポンプ等の精密持続点滴装置を使用することが望ましい旨の記載がなされているが、患者の体動などにより投与速度が変化し過量投与となるリスクを防ぐために、精密持続点滴装置を用いた投与を必須とするよう添付文書の変更が必要であるとの意見が出された。専門協議において、現在ではほとんどの施設で精密持続点滴装置の使用は常識的に行われ、その必要性や重要性が広く認識されていることも考慮すると、添付文書にお

いても、精密持続点滴装置の使用が必須である旨を記載すべきであるとの意見で一致した。

機構は、専門協議の議論を踏まえ、PGF2α 及びオキシトシンの添付文書における警告欄の「精密持続点滴装置を用いて投与することが望ましい」との記載を、「精密持続点滴装置を用いて投与すること」に変更するとともに、用法・用量に関連する使用上の注意においても同様の内容を記載することが妥当と判断した。

7. その他

専門委員より、PGF2α の点滴静注の希釈に用いる輸液の量及び種類に関して、現行の用法・用量の記載では患者の状態によっては適切な投与が出来ない場合があるとの指摘があった。

現在の点滴静注の用法・用量は、本剤 1mL を 5%ブドウ糖注射液または糖液を加えて 500mL に希釈し、0.1μg/kg/分で投与するとされているが、機構が国内で使用されている診療マニュアルや教科書、ガイドライン及び「留意点」を確認したところ、承認用法・用量のとおり記載されているものはなく、2~5 アンプル（2000～5000μg）を 500ml の 5%ブドウ糖液で希釈するよう記載されているものが多い状況であり、ガイドライン及び「留意点」における記載は平成 21 年 4 月末に経過措置期間が終了となったジノプロストトロメタミン注射剤の用法・用量における希釈方法と同様の内容であった。

専門協議において以下の意見が示された。

- ジノプロストの承認用法・用量どおりに投与すると、過量の水分負荷となる場合も懸念されることから、診療実態では、ガイドラインや「留意点」の記載内容に沿って、2～3 アンプルを 500mL に希釈して用いていることが多い。また、絶食下の陣痛誘発や糖尿病患者における陣痛誘発においては、患者の状態に応じ 5%ブドウ糖液以外の輸液で希釈して用いるほうが適切な場合も想定される。
- 投与にあたり重要なことは、適切な投与速度で正確に投与することであり、精密持続点滴装置を用いて投与速度（濃度）が遵守されるのであれば、輸液の種類や希釈濃度は一律に規定する必要は低い。

機構は、専門協議の議論を踏まえ、PGF2α の用法・用量の希釈については、患者の状態に合わせた投与が可能となるような内容へ変更するよう、今後検討する必要があると考える。

IV. 総合評価

陣痛促進剤に関して、機構は、以下のとおり添付文書の使用上の注意を改訂することが適切であると判断した。

調査対象医薬品一覧

別添 1

一般名	販売名	承認取得者	効能・効果	用法・用量
オキシトシン	①アトニン-O 注 1 単位/5 単位 ②オキシトシン注射液 5 単位「F」	①あすか製薬株式会社 ②富士製薬工業株式会社	子宮収縮の誘発，促進並びに子宮出血の治療の目的で，次の場合に使用する． 分娩誘発，微弱陣痛，弛緩出血，胎盤娩出前後，子宮復古不全，帝王切開術（胎児の娩出後），流産，人工妊娠中絶	オキシトシンとして，通常 5～10 単位を 5%ブドウ糖注射液（500mL）等に混和し，点滴速度を 1～2 ミリ単位/分から開始し，陣痛発来状況及び胎児心拍等を観察しながら適宜増減する．なお，点滴速度は 20 ミリ単位/分を超えないようにすること．
ジノプロスト	①プロスタルモン・F 注射液 1000/2000 ②プロスタグランジン F2α 注射液「科研」1000	①小野薬品工業株式会社 ②科研製薬株式会社	I. 静脈内注射投与 1.妊娠末期における陣痛誘発・陣痛促進・分娩促進 2.下記における腸管蠕動亢進 ●胃腸管の手術における術後腸管麻痺の回復遷延の場合 ●麻痺性イレウスにおいて他の保存的治療で効果が認められない場合 II. 卵膜外投与 治療的流産	通常 1～2mL（ジノプロストとして 1000～2000μg）を静脈内に点滴又は持続注入する。 (1)点滴静注 本剤 1mL に 5%ブドウ糖注射液又は糖液を加えて 500mL に希釈し、通常ジノプロストとして 0.1μg/kg/分の割合で点滴静注する。 (2) インフュージョン・ポンプによる静注（持続注入） 本剤 1mL に生理食塩液を加えて 50mL に希釈し、通常ジノプロストとして 0.1μg/kg/分（0.05μg～0.15μg/kg/分）の割合で静注する。 (3) 症状により適宜増減する。
ジノプロストン	プロスタグランジン E2 錠 0.5mg「科研」	科研製薬株式会社	妊娠末期における陣痛誘発並びに陣痛促進	1. 通常 1 回 1 錠を 1 時間毎に 6 回、1 日総量 6 錠（ジノプロストンとして 3mg）を 1 クールとし、経口投与する。 2. 体重、症状及び経過に応じ適宜増減する。 3. 本剤の投与開始後、陣痛誘発、分娩進行効果を認めたとき、本剤の投与を中止する。 4. 1 日総量ジノプロストンとして 1 クール 3mg （6 錠）を投与し、効果の認められない場合は本剤の投与を中止し、翌日あるいは以降に投与を再開する。

【改訂案】　オキシトシン

現　　行	改 訂 案
■ 警 告 本剤を分娩誘発，微弱陣痛の治療の目的で使用するにあたって 過強陣痛や強直性子宮収縮により，胎児仮死，子宮破裂，頸管裂傷，羊水塞栓等が起こることがあり，母体あるいは児が重篤な転帰に至った症例が報告されているので，本剤の投与にあたっては以下の事項を遵守し慎重に行うこと． 1）患者及び胎児の状態を十分観察して，本剤の有益性及び危険性を考慮した上で，慎重に適応を判断すること．特に子宮破裂，頸管裂傷等は経産婦，帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので，注意すること． 2）（省略） 3）本剤の感受性は個人差が大きく，少量でも過強陣痛になる症例も報告されているので，ごく少量からの点滴より開始し，陣痛の状況により徐々に増減すること．また，精密持続点滴装置を用いて投与することが~~望ましい~~． 4）（省略） 本剤の使用にあたっては，添付文書を熟読すること．	■ 警 告 本剤を分娩誘発，微弱陣痛の治療の目的で使用するにあたって 過強陣痛や強直性子宮収縮により，胎児仮死，子宮破裂，頸管裂傷，羊水塞栓等が起こることがあり，母体あるいは児が重篤な転帰に至った症例が報告されているので，本剤の投与にあたっては以下の事項を遵守し慎重に行うこと． 1）母体及び胎児の状態を十分観察して，本剤の有益性及び危険性を考慮した上で，慎重に適応を判断すること．特に子宮破裂，頸管裂傷等は経産婦，帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので，注意すること． 2）（省略） 3）本剤の感受性は個人差が大きく，少量でも過強陣痛になる症例も報告されているので，ごく少量からの点滴より開始し，陣痛の状況により徐々に増減すること．また，精密持続点滴装置を用いて投与すること． 4）（省略） 5）患者に本剤を用いた分娩誘発、微弱陣痛の治療の必要性及び危険性を十分説明し、同意を得てから本剤を使用すること。 本剤の使用にあたっては，添付文書を熟読すること．
用法及び用量に関連する使用上の注意 1．（省略） 2．分娩誘発，微弱陣痛の治療の目的で使用する場合は，以下の点に留意すること． (1)（省略） (2)（省略）	用法及び用量に関連する使用上の注意 1．（省略） 2．分娩誘発，微弱陣痛の治療の目的で使用する場合は，以下の点に留意すること． (1)（省略） (2)（省略） (3) 本剤を投与する際は、精密持続点滴装置を用いて投与すること．
2．重要な基本的注意 （省略）	2．重要な基本的注意 3）薬剤の使用の有無によらず、分娩時には母体の生命を脅かす緊急状態（子宮破裂、羊水塞栓、脳内出血、くも膜下出血、常位胎盤早期剥離、子癇、分娩時大量出血等）が起こることがあるため、本剤を用いた分娩誘発、微弱陣痛の治療にあたっては、分娩監視装置を用いた分娩監視に加えて、定期的にバイタルサインのモニターを行うなど、患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。

【改訂案】　ジノプロスト

現　　行	改　訂　案
■ 警　告 本剤を妊娠末期における陣痛誘発、陣痛促進、分娩促進の目的で使用するにあたって 過強陣痛や強直性子宮収縮により、胎児仮死、子宮破裂、頸管裂傷、羊水塞栓等が起こることがあり、母体あるいは児が重篤な転帰に至った症例が報告されているので、本剤の投与にあたっては以下の事項を遵守し慎重に行うこと。 1．~~患者および~~胎児の状態を十分観察して、本剤の有益性および危険性を考慮した上で、慎重に適応を判断すること。特に子宮破裂、頸管裂傷等は経産婦、帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので、注意すること。 2．（省略） 3．本剤の感受性は個人差が大きく、少量でも過強陣痛になる症例も報告されているので、ごく少量からの点滴より開始し、陣痛の状況により徐々に増減すること。また、精密持続点滴装置を用いて投与することが~~望ましい~~。（「用法及び用量」の項参照） 4．（省略） 本剤の使用にあたっては、添付文書を熟読すること。	■ 警　告 本剤を妊娠末期における陣痛誘発、陣痛促進、分娩促進の目的で使用するにあたって 過強陣痛や強直性子宮収縮により、胎児仮死、子宮破裂、頸管裂傷、羊水塞栓等が起こることがあり、母体あるいは児が重篤な転帰に至った症例が報告されているので、本剤の投与にあたっては以下の事項を遵守し慎重に行うこと。 1．母体及び胎児の状態を十分観察して、本剤の有益性及び危険性を考慮した上で、慎重に適応を判断すること。特に子宮破裂、頸管裂傷等は経産婦、帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので、注意すること。 2．（省略） 3．本剤の感受性は個人差が大きく、少量でも過強陣痛になる症例も報告されているので、ごく少量からの点滴より開始し、陣痛の状況により徐々に増減すること。また、精密持続点滴装置を用いて投与すること。（「用法及び用量」、「用法及び用量に関連する使用上の注意」の項参照） 4．（省略） 5・患者に本剤を用いた陣痛誘発、陣痛促進、分娩促進の必要性及び危険性を十分説明し、同意を得てから本剤を使用すること。 本剤の使用にあたっては、添付文書を熟読すること。
（記載なし）	用法及び用量に関連する使用上の注意 陣痛誘発、陣痛促進、分娩促進の目的で本剤を投与する際は、精密持続点滴装置を用いて投与すること。
2．重要な基本的注意 （省略）	2．重要な基本的注意 3）薬剤の使用の有無によらず、分娩時には母体の生命を脅かす緊急状態（子宮破裂、羊水塞栓、脳内出血、くも膜下出血、常位胎盤早期剥離、子癇、分娩時大量出血等）が起こることがあるため、本剤を用いた陣痛誘発、陣痛促進、分娩促進にあたっては、分娩監視装置を用いた分娩監視に加えて、定期的にバイタルサインのモニターを行うなど、患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。

【改訂案】　ジノプロストン

現　　行	改 訂 案
■　警告 過強陣痛や強直性子宮収縮により、胎児仮死、子宮破裂、頸管裂傷、羊水塞栓等が起こることがあり、母体あるいは児が重篤な転帰に至った症例が報告されているので、本剤の投与にあたっては以下の事項を遵守し慎重に行うこと。 (1) 患者及び胎児の状態を十分観察して、本剤の有益性及び危険性を考慮した上で、慎重に適応を判断すること。特に子宮破裂、頸管裂傷等は経産婦、帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので注意すること。 (2) （省略） (3) （省略） 本剤の使用にあたっては，添付文書を熟読すること.	■　警告 過強陣痛や強直性子宮収縮により、胎児仮死、子宮破裂、頸管裂傷、羊水塞栓等が起こることがあり、母体あるいは児が重篤な転帰に至った症例が報告されているので、本剤の投与にあたっては以下の事項を遵守し慎重に行うこと。 (1) 母体及び胎児の状態を十分観察して、本剤の有益性及び危険性を考慮した上で、慎重に適応を判断すること。特に子宮破裂、頸管裂傷等は経産婦、帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので注意すること。 (2) （省略） (3) （省略） (4)患者に本剤を用いた陣痛誘発、陣痛促進の必要性及び危険性を十分説明し、同意を得てから本剤を使用すること。 本剤の使用にあたっては，添付文書を熟読すること.
2．重要な基本的注意 （省略）	2．重要な基本的注意 3）薬剤の使用の有無によらず、分娩時には母体の生命を脅かす緊急状態（子宮破裂、羊水塞栓、脳内出血、くも膜下出血、常位胎盤早期剥離、子癇、分娩時大量出血等）が起こることがあるため、本剤を用いた陣痛誘発、陣痛促進にあたっては、分娩監視装置を用いた分娩監視に加えて、定期的にバイタルサインのモニターを行うなど、患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。

ASKA

10-2231
CF

**2010年6月 改訂(第7版)
*2010年3月 改訂

日本標準商品分類番号 872414

日本薬局方 オキシトシン注射液

処方せん医薬品注)

アトニン®-O注1単位
アトニン®-O注5単位

ATONIN®-O INJECTION 1u, 5u

	1単位	5単位
承認番号	21700AMZ00472	21700AMZ00473
薬価収載	1957年5月	
販売開始	1954年6月	
再評価結果	1993年3月	

貯　法：凍結を避け冷所保存
有効期限：製造後36カ月

注）注意－医師等の処方せんにより使用すること

【警　告】

本剤を分娩誘発,微弱陣痛の治療の目的で使用するにあたって過強陣痛や強直性子宮収縮により，胎児仮死，子宮破裂，頸管裂傷，羊水塞栓等が起こることがあり，母体あるいは児が重篤な転帰に至った症例が報告されているので，本剤の投与にあたっては以下の事項を遵守し慎重に行うこと．

** 1. 母体及び胎児の状態を十分観察して，本剤の有益性及び危険性を考慮した上で，慎重に適応を判断すること．特に子宮破裂，頸管裂傷等は経産婦，帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので，注意すること．
2. 分娩監視装置を用いて，胎児の心音，子宮収縮の状態を十分に監視すること．
** 3. 本剤の感受性は個人差が大きく，少量でも過強陣痛になる症例も報告されているので，ごく少量からの点滴より開始し，陣痛の状況により徐々に増減すること．また，精密持続点滴装置を用いて投与すること．(「用法・用量」及び〈用法・用量に関連する使用上の注意〉の項参照)
4. プロスタグランジン製剤($PGF_{2\alpha}$, PGE_2)との同時併用は行わないこと．また，前後して投与する場合も，過強陣痛を起こすおそれがあるので，十分な分娩監視を行い，慎重に投与すること．(「相互作用」の項参照)
** 5. 患者に本剤を用いた分娩誘発,微弱陣痛の治療の必要性及び危険性を十分説明し,同意を得てから本剤を使用すること．

本剤の使用にあたっては，添付文書を熟読すること．

【禁　忌】(次の患者には投与しないこと)

1. 既往にオキシトシン又は類似化合物に対して過敏症を起こした患者
2. **分娩誘発,微弱陣痛の治療の目的で使用するにあたって**
(1) プロスタグランジン製剤($PGF_{2\alpha}$, PGE_2)を投与中の患者(「相互作用」の項参照)
(2) 児頭骨盤不均衡
[経腟分娩が成立せず，胎児に障害を及ぼすおそれがある．]
(3) 全前置胎盤
[胎盤が胎児より先に娩出され,胎児への危険性がある．]

【原則禁忌】(次の患者には投与しないことを原則とするが，特に必要とする場合には慎重に投与すること)

分娩誘発，微弱陣痛の治療の目的で使用するにあたって

1. 前置胎盤
[出血及び胎盤の圧迫により，胎児に障害が起こることがある．]
2. 常位胎盤早期剥離
[緊急な胎児娩出が要求されるため，外科的処置の方が確実性が高い．]
3. 過強陣痛，子宮切迫破裂又は胎児仮死の場合
[子宮破裂，胎児仮死，胎児死亡のおそれがある．]

【組成・性状】

販売名	アトニン-O注1単位	アトニン-O注5単位
成　分	日局オキシトシン	
含　量	1管1mL中 1オキシトシン単位	1管1mL中 5オキシトシン単位
添加物	1管1mL中 クロロブタノール5mg，pH調節剤	
剤形・性状	アンプル(無色澄明の水性注射液)	
pH	2.5～4.5	
浸透圧比	約0.1(生理食塩液に対する比)	

【効能・効果】

子宮収縮の誘発，促進並びに子宮出血の治療の目的で，次の場合に使用する．

分娩誘発，微弱陣痛，弛緩出血，胎盤娩出前後，子宮復古不全，帝王切開術（胎児の娩出後），流産，人工妊娠中絶

【用法・用量】

原則として点滴静注法によること．

1. 分娩誘発，微弱陣痛
点滴静注法
オキシトシンとして，通常5～10単位を5％ブドウ糖注射液（500mL）等に混和し，点滴速度を1～2ミリ単位／分から開始し，陣痛発来状況及び胎児心拍等を観察しながら適宜増減する．なお，点滴速度は20ミリ単位／分を超えないようにすること．

2. 弛緩出血,胎盤娩出前後,子宮復古不全,流産,人工妊娠中絶
(1) **点滴静注法**
オキシトシンとして，通常5～10単位を5％ブドウ糖注射液（500mL）等に混和し，子宮収縮状況等を観察しながら適宜増減する．
(2) **静　注　法**（弛緩出血及び胎盤娩出前後の場合）
5～10単位を静脈内に緩徐に注射する．
(3) **筋　注　法**
5～10単位を筋肉内に緩徐に注射する．

3. 帝王切開術（胎児の娩出後）
(1) **点滴静注法**
オキシトシンとして，通常5～10単位を5％ブドウ糖注射液（500mL）等に混和し，子宮収縮状況等を観察しながら適宜増減する．
(2) **筋　注　法**
5～10単位を筋肉内に緩徐に注射する．
(3) **子宮筋注法**
5～10単位を子宮筋層内へ直接投与する．

＜用法・用量に関連する使用上の注意＞

1. 筋注法,静注法は調節性に欠けるので,弛緩出血に用いる場合か，又はやむを得ない場合にのみ使用を考慮すること．
2. **分娩誘発，微弱陣痛の治療の目的で使用する場合は，以下の点に留意すること．**
(1) **本剤に対する子宮筋の感受性は個人差が大きく，少量でも過強陣痛になる症例があることなどを考慮し，できる限り少量(2ミリ単位／分以下)から投与を開始し，陣痛発来状況及び胎児心音を観察しながら適宜増減すること．過強陣痛等は，点滴開始初期に起こることが多いので，特に注意が必要である．**
(2) **点滴速度をあげる場合は，一度に1～2ミリ単位／分の範囲で，30分以上経過を観察しつつ徐々に行うこと．点滴速度を20ミリ単位／分にあげても有効陣痛に至らないときは，それ以上あげても効果は期待できないので増量しないこと．**
** (3) **本剤を投与する際は，精密持続点滴装置を用いて投与すること．**

【使用上の注意】

1. **慎重投与**（次の患者には，母体，胎児の全身状態及び子宮収縮の観察を十分に行い，慎重に投与すること）
(1) 胎児仮死の疑いがある患者
[胎児仮死，胎児死亡のおそれがある．]

(2) 妊娠中毒症，心・腎・血管障害のある患者
［大量投与で血圧下降による臓器虚血を来すおそれがある．また，本剤は弱いバソプレシン様作用（血管収縮作用及び抗利尿作用）を有し，血圧上昇及び水貯留があらわれることがある．］
(3) 児頭骨盤不均衡の疑いのある患者，胎位胎勢異常による難産，軟産道強靭症の患者
［経腟分娩が困難で過強陣痛が起こりやすい．］
(4) 帝王切開術及び広範囲子宮手術の既往のある患者，経産婦
［このような患者では一般に子宮破裂が起こりやすい．］
(5) 高年初産婦
［このような患者では一般に軟産道の伸展不良により分娩障害が起こりやすい．］
(6) 多胎妊娠
［胎位胎勢異常のことがある．］

2. 重要な基本的注意
(1) オキシトシンに対する子宮筋の感受性が高い場合，過強陣痛，胎児仮死があらわれることがあるので，このような場合には投与を中止するか，又は減量すること．
(2) 本剤を投与する際には，Bishop score等により頸管が熟化していることを確認した後，本剤を投与することが望ましい．また，頸管熟化剤との同時投与は避けること．
** (3) 薬剤の使用の有無によらず，分娩時には母体の生命を脅かす緊急状態（子宮破裂，羊水塞栓，脳内出血，くも膜下出血，常位胎盤早期剥離，子癇，分娩時大量出血等）が起こることがあるため，本剤を用いた分娩誘発，微弱陣痛の治療にあたっては，分娩監視装置を用いた分娩監視に加えて，定期的にバイタルサインのモニターを行うなど，患者の状態を十分に観察し，異常が認められた場合には適切な処置を行うこと．

3. 相互作用
［併用禁忌］（併用しないこと）
分娩誘発，微弱陣痛の治療の目的で使用するにあたって

薬剤名等	臨床症状・措置方法	機序・危険因子
** プロスタグランジン製剤（$PGF_{2\alpha}$，PGE_1） プロスタルモンF注射液 プロスタグランジンE_1錠等	同時併用により，過強陣痛を起こしやすい．	本剤及びこれらの薬剤の有する子宮収縮作用が併用により増強される．

［併用注意］（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
プロスタグランジン製剤（$PGF_{2\alpha}$，PGE_2）	両剤を前後して使用する場合は，過強陣痛を起こすおそれがあるので十分な分娩監視を行い投与する．	本剤及びこれらの薬剤の有する子宮収縮作用が併用により増強される．
シクロホスファミド	本剤の作用が増強されることがある．	機序不明

4. 副作用
本剤は使用成績調査等の副作用発現頻度が明確となる調査を実施していない（再審査対象外）．
(1) 重大な副作用（頻度不明）
1) ショック：ショックを起こすことがあるので，観察を十分に行い，チアノーゼ，虚脱等の異常が認められた場合には投与を中止し，適切な処置を行うこと．
2) 過強陣痛，子宮破裂，頸管裂傷，羊水塞栓症，微弱陣痛，弛緩出血：過強陣痛，子宮破裂，頸管裂傷，羊水塞栓症，微弱陣痛，弛緩出血等があらわれることがある．
3) 胎児仮死：胎児仮死を起こすことがあるので，観察を十分に行うこと．
(2) その他の副作用

	頻度不明
過敏症	過敏症状
新生児	新生児黄疸
循環器	不整脈，静脈内注射後一過性の血圧下降，血圧上昇等
消化器	悪心，嘔吐等
投与部位	疼痛，硬結
その他	水中毒症状

5. 過量投与
症　状：オキシトシンの過量投与の症状は子宮筋の感受性が高い場合にあらわれやすい．
子宮の過強収縮により過強陣痛，子宮破裂，頸管裂傷，胎児仮死があらわれることがある．大量を点滴静注した場合には水中毒により昏睡，痙攣を来すことがある．
処　置：子宮の過強収縮があらわれた場合は直ちに投与を中止する．過強陣痛が持続し，子宮破裂，胎児仮死の危険がある場合には，緊急帝王切開の適用も考慮する．
水中毒の場合；投与を中止し，水分摂取の制限，利尿，高張液の投与，電解質バランスの補正を行う．
痙攣の場合；抗痙攣剤を投与する．

6. 適用上の注意
(1) 投与速度
静脈内注射は血圧等に注意しながら徐々に行うこと（特に麻酔剤，昇圧剤等を併用する場合）．
(2) 筋肉内注射時
筋肉内注射にあたっては，組織・神経等への影響を避けるため，下記の点に注意すること．
1) 筋肉内投与はやむを得ない場合にのみ，必要最小限に行うこと．
なお，特に同一部位への反復注射は行わないこと．
2) 神経走行部位を避けること．
3) 注射針を刺入したとき，激痛を訴えたり血液の逆流をみた場合は直ちに針を抜き，部位をかえて注射すること．
(3) その他
本品はワンポイントカットアンプルであるが，アンプルのカット部分をエタノール綿等で清拭してからカットすることが望ましい．

【薬効薬理】[1,2]
子宮筋に作用して子宮の律動的な収縮を起こさせる．

【有効成分に関する理化学的知見】
一般名：オキシトシン
Oxytocin［JAN］
分子式：$C_{43}H_{66}N_{12}O_{12}S_2$
化学構造式：Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2
分子量：1007.19
性　状：白色の粉末である．水に極めて溶けやすく，エタノール（99.5）に溶けやすい．塩酸試液に溶ける．
本品0.10 g を新たに煮沸し冷却した水10mLに溶かした液のpHは4.0～6.0である．
吸湿性である．

【包　装】
アトニン-O注 1単位：10管
アトニン-O注 5単位：10管，50管

【主要文献】
1) 勝田信夫：現代の薬理学，P.257（金原出版 1968）
2) 平井　修 他：産婦人科の世界，7：868，1955

*【文献請求先・製品情報お問い合わせ先】
あすか製薬株式会社　くすり相談室
〒108-8532　東京都港区芝浦二丁目5番1号
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販売
武田薬品工業株式会社
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FujiPharma

※※2010年6月改訂（第9版）
※2009年8月改訂

日本標準商品分類番号
872414

貯法
冷所保存・禁凍結

使用期限
3年（外箱に表示）

脳下垂体後葉ホルモン
※処方せん医薬品㊟

日本薬局方　オキシトシン注射液

オキシトシン注射液5単位「F」

OXYTOCIN injection

承認番号	21900AMX01370000
薬価収載	2007年12月
販売開始	1996年8月

注）注意—医師等の処方せんにより使用すること

※※【警告】
本剤を分娩誘発、微弱陣痛の治療の目的で使用するにあたって過強陣痛や強直性子宮収縮により、胎児仮死、子宮破裂、頸管裂傷、羊水塞栓等が起こることがあり、母体あるいは児が重篤な転帰に至った症例が報告されているので、本剤の投与にあたっては以下の事項を遵守し慎重に行うこと。
1．母体および胎児の状態を十分観察して、本剤の有益性および危険性を考慮した上で、慎重に適応を判断すること。特に子宮破裂、頸管裂傷等は経産婦、帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので、注意すること。
2．分娩監視装置を用いて、胎児の心音、子宮収縮の状態を十分に監視すること。
3．本剤の感受性は個人差が大きく、少量でも過強陣痛になる症例も報告されているので、ごく少量からの点滴より開始し、陣痛の状況により徐々に増減すること。また、精密持続点滴装置を用いて投与すること。（「用法・用量」および《用法・用量に関連する使用上の注意》の項参照）
4．プロスタグランジン製剤（$PGF_{2\alpha}$，PGE_2）との同時併用は行わないこと。また、前後して投与する場合も、過強陣痛を起こすおそれがあるので、十分な分娩監視を行い、慎重に投与すること。（「3．相互作用」の項参照）
5．患者に本剤を用いた分娩誘発、微弱陣痛の治療の必要性および危険性を十分説明し、同意を得てから本剤を使用すること。
本剤の使用にあたっては、添付文書を熟読すること。

【禁忌（次の患者には投与しないこと）】
1．既往にオキシトシンまたは類似化合物に対して過敏症を起こした患者
2．分娩誘発、微弱陣痛の治療の目的で使用するにあたって
（1）プロスタグランジン製剤（$PGF_{2\alpha}$，PGE_2）を投与中の患者（「3．相互作用」の項参照）
（2）児頭骨盤不均衡［経腟分娩が成立せず、胎児に障害を及ぼすおそれがある。］
（3）全前置胎盤［胎盤が胎児より先に娩出され、胎児への危険性がある。］

【原則禁忌（次の患者には投与しないことを原則とするが、特に必要とする場合には慎重に投与すること）】
分娩誘発、微弱陣痛の治療の目的で使用するにあたって
1．前置胎盤［出血および胎盤の圧迫により、胎児に障害が起こることがある。］
2．常位胎盤早期剥離［緊急な胎児娩出が要求されるため、外科的処置の方が確実性が高い。］
3．過強陣痛、子宮切迫破裂または胎児仮死の場合［子宮破裂、胎児仮死、胎児死亡のおそれがある。］

【組成・性状】

販売名	オキシトシン注射液5単位「F」
有効成分	日局　オキシトシン
含量	5単位
容量	1mL
添加物	クロロブタノール　5mg pH調整剤　適量
pH	2.5～4.5
浸透圧比（生理食塩液に対する比）	約0.1
色調・性状	無色澄明の水性注射液
剤形	注射剤（アンプル）

【効能・効果】
子宮収縮の誘発、促進ならびに子宮出血の治療の目的で、次の場合に使用する。
分娩誘発、微弱陣痛、弛緩出血、胎盤娩出前後、子宮復古不全、帝王切開術（胎児の娩出後）、流産、人工妊娠中絶

【用法・用量】
原則として点滴静注法によること。
1．分娩誘発、微弱陣痛
点滴静注法
オキシトシンとして、通常5～10単位を5%ブドウ糖注射液（500mL）等に混和し、点滴速度を1～2ミリ単位／分から開始し、陣痛発来状況および胎児心拍等を観察しながら適宜増減する。なお、点滴速度は20ミリ単位／分を超えないようにすること。
2．弛緩出血、胎盤娩出前後、子宮復古不全、流産、人工妊娠中絶
（1）点滴静注法
オキシトシンとして、通常5～10単位を5%ブドウ糖注射液（500mL）等に混和し、子宮収縮状況等を観察しながら適宜増減する。
（2）静注法（弛緩出血および胎盤娩出前後の場合）
5～10単位を静脈内に緩徐に注射する。
（3）筋注法
5～10単位を筋肉内に緩徐に注射する。
3．帝王切開術（胎児の娩出後）
（1）点滴静注法
オキシトシンとして、通常5～10単位を5%ブドウ糖注射液（500mL）等に混和し、子宮収縮状況等を観察しながら適宜増減する。
（2）筋注法
5～10単位を筋肉内に緩徐に注射する。
（3）子宮筋注法
5～10単位を子宮筋層内へ直接投与する。

《用法・用量に関連する使用上の注意》
1．筋注法、静注法は調節性に欠けるので、弛緩出血に用いる場合か、またはやむを得ない場合にのみ使用を考慮すること。
2．分娩誘発、微弱陣痛の治療の目的で使用する場合は、以下の点に留意すること。
（1）本剤に対する子宮筋の感受性は個人差が大きく、少

量でも過強陣痛になる症例があることなどを考慮し、できる限り少量（2ミリ単位／分以下）から投与を開始し、陣痛発来状況および胎児心音を観察しながら適宜増減すること。過強陣痛等は、点滴開始初期に起こることが多いので、特に注意が必要である。

（2）点滴速度をあげる場合は、一度に1～2ミリ単位／分の範囲で、30分以上経過を観察しつつ徐々に行うこと。
点滴速度を20ミリ単位／分にあげても有効陣痛に至らないときは、それ以上あげても効果は期待できないので増量しないこと。

※※（3）本剤を投与する際は、精密持続点滴装置を用いて投与すること。

【使用上の注意】

1．慎重投与（次の患者には、母体、胎児の全身状態および子宮収縮の観察を十分に行い、慎重に投与すること）

（1）胎児仮死の疑いがある患者［胎児仮死、胎児死亡のおそれがある。］

（2）妊娠中毒症、心・腎・血管障害のある患者［大量投与で血圧下降による臓器虚血をきたすおそれがある。また、本剤は弱いバソプレシン様作用（血管収縮作用および抗利尿作用）を有し、血圧上昇および水貯留があらわれることがある。］

（3）児頭骨盤不均衡の疑いのある患者、胎位胎勢異常による難産、軟産道強靭症の患者［経腟分娩が困難で過強陣痛が起こりやすい。］

（4）帝王切開術および広範囲子宮手術の既往のある患者、経産婦［このような患者では一般に子宮破裂が起こりやすい。］

（5）高年初産婦［このような患者では一般に軟産道の伸展不良により分娩障害が起こりやすい。］

（6）多胎妊娠［胎位胎勢異常のことがある。］

2．重要な基本的注意

（1）オキシトシンに対する子宮筋の感受性が高い場合、過強陣痛、胎児仮死があらわれることがあるので、このような場合には投与を中止するか、または減量すること。

（2）本剤を投与する際には、Bishop score等により頸管が熟化していることを確認した後、本剤を投与することが望ましい。また、頸管熟化剤との同時投与は避けること。

※※（3）薬剤の使用の有無によらず、分娩時には母体の生命を脅かす緊急状態（子宮破裂、羊水塞栓、脳内出血、くも膜下出血、常位胎盤早期剥離、子癇、分娩時大量出血等）が起こることがあるため、本剤を用いた分娩誘発、微弱陣痛の治療にあたっては、分娩監視装置を用いた分娩監視に加えて、定期的にバイタルサインのモニターを行うなど、患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。

3．相互作用

（1）併用禁忌（併用しないこと）
分娩誘発、微弱陣痛の治療の目的で使用するにあたって

薬剤名等	臨床症状・措置方法	機序・危険因子
プロスタグランジン製剤（$PGF_{2\alpha}$，PGE_2） プロスタルモン・F注射液1000 プロスタルモン・F注射液2000 プロスタグランジンE_2錠0.5mg等	同時併用により、過強陣痛を起こしやすい。	本剤およびこれらの薬剤の有する子宮収縮作用が併用により増強される。

（2）併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
プロスタグランジン製剤（$PGF_{2\alpha}$，PGE_2）	両剤を前後して使用する場合は、過強陣痛を起こすおそれがあるので十分な分娩監視を行い投与する。	本剤およびこれらの薬剤の有する子宮収縮作用が併用により増強される。
シクロホスファミド	本剤の作用が増強されることがある。	機序不明

4．副作用

本剤は使用成績調査等の副作用発現頻度が明確となる調査を実施していない。

（1）重大な副作用（頻度不明）

1）ショック：ショックを起こすことがあるので、観察を十分に行い、チアノーゼ、虚脱等の異常が認められた場合には投与を中止し、適切な処置を行うこと。

2）過強陣痛、子宮破裂、頸管裂傷、羊水塞栓症、微弱陣痛、弛緩出血：過強陣痛、子宮破裂、頸管裂傷、羊水塞栓症、微弱陣痛、弛緩出血等があらわれることがある。

3）胎児仮死：胎児仮死を起こすことがあるので、観察を十分に行うこと。

（2）その他の副作用

	頻度不明
過敏症	過敏症状
新生児	新生児黄疸
循環器	不整脈、静脈内注射後一過性の血圧下降、血圧上昇等
消化器	悪心、嘔吐等
投与部位	疼痛、硬結
その他	水中毒症状

5．過量投与

症　状：オキシトシンの過量投与の症状は子宮筋の感受性が高い場合にあらわれやすい。
子宮の過強収縮により過強陣痛、子宮破裂、頸管裂傷、胎児仮死があらわれることがある。
大量を点滴静注した場合には水中毒により昏睡、けいれんをきたすことがある。

処　置：子宮の過強収縮があらわれた場合は直ちに投与を中止する。過強陣痛が持続し、子宮破裂、胎児仮死の危険がある場合には、緊急帝王切開の適用も考慮する。
水中毒の場合；投与を中止し、水分摂取の制限、利尿、高張液の投与、電解質バランスの補正を行う。
けいれんの場合；抗けいれん剤を投与する。

6．適用上の注意

（1）投与速度
静脈内注射は血圧等に注意しながら徐々に行うこと（特に麻酔剤、昇圧剤等を併用する場合）。

（2）筋肉内注射時：筋肉内注射にあたっては、組織・神経等への影響を避けるため下記の点に注意すること。

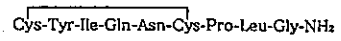
1）筋肉内投与はやむを得ない場合にのみ、必要最小限に行うこと。
同一部位への反復注射は行わないこと。

2）神経走行部位を避けること。

3）注射針を刺入したとき、激痛を訴えたり血液の逆流をみた場合は直ちに針を抜き、部位を変えて注射すること。

（3）アンプルカット時：本品はワンポイントカットアンプルであるが、アンプルのカット部分をエタノール綿等で清拭してからカットすることが望ましい。

【有効成分に関する理化学的知見】
一般名：オキシトシン（Oxytocin）
構造式：



分子式：$C_{43}H_{66}N_{12}O_{12}S_2$
分子量：1007.19
性　状：白色の粉末である。
水に極めて溶けやすく、エタノール(99.5)に溶けやすい。塩酸試液に溶ける。本品0.10gを新たに煮沸し冷却した水10mLに溶かした液のpHは4.0～6.0である。吸湿性である。

【取扱い上の注意】
安定性試験
最終包装製品を用いた長期保存試験(冷所、なりゆき湿度、3年)の結果、外観および含量等は規格の範囲内であり、オキシトシン注射液5単位「F」は規定条件の市場流通下において3年間安定であることが確認された。[1)]

【包　装】
5単位/1mL　10アンプル

【主要文献】
1）富士製薬工業株式会社　社内資料（安定性試験）

【文献請求先】
主要文献に記載の社内資料につきましても下記にご請求下さい。
富士製薬工業株式会社　富山工場　学術情報課
〒939-3515　富山県富山市水橋辻ヶ堂1515番地
(TEL) 076-478-0032
(FAX) 076-478-0336

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5CF1006X

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*2010年6月改訂

日本標準商品分類番号 872499

	プロスタルモン・F注射液1000	プロスタルモン・F注射液2000
承認番号	14800AMZ00036	21300AMZ00520
薬価収載	1974年2月	2001年9月
販売開始	1974年3月	2001年11月
再審査結果	1988年3月(プロスタルモン・F注射液1000)	
効能追加	1981年12月(プロスタルモン・F注射液1000)	

プロスタグランジン$F_{2\alpha}$製剤

劇薬、処方せん医薬品注)

プロスタルモン®・F注射液1000

劇薬、処方せん医薬品注)

プロスタルモン®・F注射液2000

《PROSTARMON®・F》

ジノプロスト注射液

貯　法：遮光、室温保存
使用期限：外箱に表示(3年)

〔警　告〕

本剤を妊娠末期における陣痛誘発、陣痛促進、分娩促進の目的で使用するにあたって

過強陣痛や強直性子宮収縮により、胎児仮死、子宮破裂、頸管裂傷、羊水塞栓等が起こることがあり、母体あるいは児が重篤な転帰に至った症例が報告されているので、本剤の投与にあたっては以下の事項を遵守し慎重に行うこと。

* 1．母体及び胎児の状態を十分観察して、本剤の有益性及び危険性を考慮した上で、慎重に適応を判断すること。特に子宮破裂、頸管裂傷等は経産婦、帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので、注意すること。

2．分娩監視装置を用いて、胎児の心音、子宮収縮の状態を十分に監視すること。

* 3．本剤の感受性は個人差が大きく、少量でも過強陣痛になる症例も報告されているので、ごく少量からの点滴より開始し、陣痛の状況により徐々に増減すること。また、精密持続点滴装置を用いて投与すること。(「用法・用量」、「用法・用量に関連する使用上の注意」の項参照)

4．オキシトシン、ジノプロストン(PGE_2)との同時併用は行わないこと。また、前後して投与する場合も、過強陣痛を起こすおそれがあるので、十分な分娩監視を行い、慎重に投与すること。(「相互作用」の項参照)

* 5．患者に本剤を用いた陣痛誘発、陣痛促進、分娩促進の必要性及び危険性を十分説明し、同意を得てから本剤を使用すること。

本剤の使用にあたっては、添付文書を熟読すること。

〔禁忌(次の患者には投与しないこと)〕

本剤を妊娠末期における陣痛誘発、陣痛促進、分娩促進の目的で使用するにあたって

1．骨盤狭窄、児頭骨盤不均衡、骨盤位等の胎位異常のある患者〔正常な経腟分娩が進行せず、母体及び胎児への障害を起こすおそれがある。〕
2．全前置胎盤〔胎盤が胎児より先に娩出され、胎児への危険性が予想される。〕
3．気管支喘息又はその既往歴のある患者〔気管支を収縮させ気道抵抗を増加し、喘息発作を悪化又は誘発するおそれがある。〕
4．オキシトシン、ジノプロストン(PGE_2)を投与中の患者(「相互作用」の項参照)
5．本剤の成分に対し過敏症の既往歴のある患者

〔禁忌(次の患者には投与しないこと)〕

本剤を腸管蠕動亢進の目的で使用するにあたって

1．本剤の成分に対し過敏症の既往歴のある患者
2．気管支喘息又はその既往歴のある患者〔気管支を収縮させ気道抵抗を増加し、喘息発作を悪化又は誘発するおそれがある。〕
3．妊婦又は妊娠している可能性のある婦人(「妊婦、産婦、授乳婦等への投与」の項参照)

〔禁忌(次の患者には投与しないこと)〕

本剤を治療的流産の目的で使用するにあたって

1．前置胎盤、子宮外妊娠等で、操作により出血の危険性のある患者〔経腟分娩ができず、大量出血のおそれがある。〕
2．骨盤内感染による発熱のある患者〔炎症、感染を増悪させるおそれがある。〕
3．気管支喘息又はその既往歴のある患者〔気管支を収縮させ気道抵抗を増加し、喘息発作を悪化又は誘発するおそれがある。〕
4．本剤の成分に対し過敏症の既往歴のある患者

〔原則禁忌(次の患者には投与しないことを原則とするが、特に必要とする場合には慎重に投与すること)〕

本剤を妊娠末期における陣痛誘発、陣痛促進、分娩促進の目的で使用するにあたって

1．前置胎盤〔出血及び胎盤の圧迫により、胎児に障害を起こすおそれがある。〕
2．常位胎盤早期剝離〔緊急な胎児娩出が要求されるため、外科的処置の方が確実性が高い。〕
3．胎児仮死のある患者〔子宮収縮により胎児の症状を悪化させるおそれがある。〕

〔組成・性状〕

販売名	プロスタルモン・F注射液1000	プロスタルモン・F注射液2000
成分	ジノプロスト	
含量	1,000μg	2,000μg
容量	1mL	2mL
添加物(1アンプル中)	クエン酸ナトリウム水和物0.3mg、酢酸ナトリウム水和物3.4mg、等張化剤、pH調節剤	クエン酸ナトリウム水和物0.6mg、酢酸ナトリウム水和物6.8mg、等張化剤、pH調節剤
剤形	注射剤(アンプル)	
pH	7.0～9.5	
浸透圧比	0.9～1.1	
性状	無色澄明の液	

〔効能・効果〕

Ⅰ．静脈内注射投与
1．妊娠末期における陣痛誘発・陣痛促進・分娩促進
2．下記における腸管蠕動亢進
●胃腸管の手術における術後腸管麻痺の回復遷延の場合
●麻痺性イレウスにおいて他の保存的治療で効果が認められない場合

Ⅱ．卵膜外投与
治療的流産

注)処方せん医薬品：注意－医師等の処方せんにより使用すること

〔用法・用量〕

Ⅰ．注射投与

1．妊娠末期における陣痛誘発・陣痛促進・分娩促進には
通常1～2mLを静脈内に点滴または持続注入する。

＊(1) 点滴静注
本剤1mLに5%ブドウ糖注射液または糖液を加えて500mLに希釈し、通常ジノプロストとして0.1μg/kg/分の割合で点滴静注する。なお、希釈する輸液の量及び種類は患者の状態に応じて適切に選択する。

＊(2) シリンジポンプによる静注(持続注入)
本剤1mLに生理食塩液を加えて50mLに希釈し、通常ジノプロストとして0.1μg/kg/分(0.05～0.15μg/kg/分)の割合で静注する。

(3) 症状により適宜増減する。

2．腸管蠕動亢進には

(1) 通常1回ジノプロストとして1,000～2,000μg(本剤1～2mL)を輸液500mLに希釈し、1～2時間(10～20μg/分の投与速度)で1日2回静脈内に点滴注射する。

(2) 本剤の投与は、手術侵襲の程度ならびに他の処置などを考慮して慎重に行うこと。

(3) 3日間投与しても効果が認められないときは直ちに投与を中止し他の療法にきりかえる。

(4) 症状、体重により適宜増減する。

Ⅱ．卵膜外投与

治療的流産には

1．妊娠12週以降
本剤1mLに生理食塩液を加え4mLに希釈し、この液を子宮壁と卵膜の間に数回に分け注入投与する。

(1) 薬液注入カテーテルの固定
通常フォーリーカテーテルを用いる。カテーテルを子宮頸管を通じ挿入、カテーテルのバルーン部が子宮口を通過して、子宮下部まで到達した後、バルーン部に生理食塩液を充満、内子宮口を閉鎖し、カテーテルの脱出と腟への薬液漏出を防止する。次にカテーテルを大腿部内側へテープで固定する。

(2) 薬液の注入

1)初回量
希釈液(ジノプロスト250μg/mL)1mLを注入し、薬液がカテーテル内に残らないように引き続きカテーテルの内腔量を若干上回る生理食塩液を注入する(通例、16号カテーテルでは約3.5mL)。

2)2回目以降
本剤の2回目以降の注入投与は、原則として2時間ごとに希釈液3～4mL(750～1,000μg)を反復投与するが、初回投与による子宮収縮、その他の反応が強すぎる場合には、次回の投与量を2mL(500μg)に減量または4時間後に投与する。

3)本剤の投与は原則として2時間々隔で行うが、本剤による効果及びその他の反応を観察しながら適宜投与量及び投与間隔を1～4時間の間で調節する。

4)本投与法においては薬剤注入の度に、カテーテルの内腔量を若干上回る生理食塩液を引き続き注入することに注意すること。

2．妊娠12週未満
胞状奇胎、合併症で全身麻酔が困難な症例、頸管拡張の困難な症例又はその場合の除去術の前処置に使用する。その際本剤の注入は、硫酸アトロピン、鎮痛剤の投与後、前麻酔効果があらわれてから行うことが望ましい。

(1) チューブの挿入
通常F4～5号の合成樹脂製の細いチューブを用い、使用前にチューブ内腔に生理食塩液を満たしておく。チューブを鉗子ではさみ、外子宮口より子宮腔内にゆっくりと約7cm位まで挿入する。
直視下で薬液の注入を行う以外は、チューブの排出をふせぐためチューブをとりかこむようにガーゼを腟腔内につめる。注射器をチューブに接続し、また、チューブを大腿部内側にテープで固定する。

(2) 薬液の注入

1)分割注入法
妊娠12週以降の場合に準じ、本剤1mLに生理食塩液を加え4mLに希釈した液を用い分割注入する。

●初回量は希釈液1mL(ジノプロスト250μg/mL)を注入し、また薬液がチューブ内に残らないように引き続きチューブ内腔量を若干上回る生理食塩液を注入する。

●2回目以降の注入は、原則として1時間ごとに希釈液3～4mL(750～1,000μg)を反復投与するが、初回投与による子宮収縮、その他の反応が強すぎる場合には、次回の投与量を2mL(500μg)に減量または投与時間々隔をおくらせる。

●本剤の投与は原則として総投与量3,000μgとし、また1時間々隔で行うが、本剤による効果及びその他の反応を観察しながら適宜に投与量及び投与時間々隔を調節する。

●本投与法においては薬剤注入の度にチューブの内腔量を若干上回る生理食塩液を引き続き注入することに注意する。

2)一回注入法

●通常ジノプロスト1,000μg/1mL含有注射剤を希釈しないで、一回に2,000～3,000μg(2～3mL)をゆっくり注入する。本剤による効果及びその反応を観察しながら適宜に投与量を増減する。

●注入後チューブの内腔量を若干上回る生理食塩液を引き続き注入する。チューブは薬液注入が終了すれば抜きとる。

＊〈用法・用量に関連する使用上の注意〉
陣痛誘発、陣痛促進、分娩促進の目的で本剤を投与する際は、精密持続点滴装置を用いて投与すること。

〔使用上の注意〕

Ⅰ．静脈内注射投与

1．妊娠末期における陣痛誘発・陣痛促進・分娩促進の場合

(1) 慎重投与(次の患者には慎重に投与すること)

1)緑内障、眼圧亢進のある患者〔動物実験(ウサギ)で眼圧上昇が報告されている。[1)]〕

2)心疾患のある患者〔血管収縮作用により心機能を悪化させるおそれがある。〕

3)高血圧症のある患者〔血圧上昇作用がある。〕

4)帝王切開又は子宮切開等の既往歴のある患者〔子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。〕

5)多胎妊娠、経産婦の患者〔子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。〕

(2) 重要な基本的注意

1)心室細動、心停止、ショック、気管支収縮があらわれることがあるので、投与中は循環・呼吸器に対する観察を行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

2)本剤を投与する際には、Bishop score等により頸管が熟化していることを確認した後、本剤を投与することが望ましい。また、頸管熟化剤との同時投与は避けること。

＊3)薬剤の使用の有無によらず、分娩時には母体の生命を脅かす緊急状態(子宮破裂、羊水塞栓、脳内出血、くも膜下出血、常位胎盤早期剥離、子癇、分娩時大量出血等)が起こることがあるため、本剤を用いた陣痛誘発、陣痛促進、分娩促進にあたっては、分娩監視装置を用いた分娩監視に加えて、定期的にバイタルサインのモニターを行うなど、患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。

(3) 相互作用

1)併用禁忌(同時併用しないこと)

薬剤名等	臨床症状・措置方法	機序・危険因子
オキシトシン アトニン－O ジノプロストン(PGE2) プロスタグランジンE2錠0.5mg	これらの薬剤と同時併用することにより過強陣痛を起こしやすい。	本剤は子宮収縮作用を有するため、類似の作用を持つ薬剤を併用することにより作用を増強する。

2)併用注意(前後して使用する場合は注意すること)

薬剤名等	臨床症状・措置方法	機序・危険因子
陣痛誘発・促進剤 オキシトシン ジノプロストン(PGE2)	これらの薬剤と前後して使用する場合も、過強陣痛を起こしやすいので、十分な分娩監視を行い慎重に投与すること。	本剤は子宮収縮作用を有するため、類似の作用を持つ薬剤を前後して使用することにより作用を増強する。

(4) 副作用

承認時の臨床試験及び市販後調査において副作用集計の対象となった3,149例中370例(11.7%)に499件の副作用(臨床検査値の異常を含む)が認められた。

主なものは、母体側においては過強陣痛14件(0.4%)、顔面潮紅99件(3.1%)、嘔気・嘔吐145件(4.6%)、下痢11件(0.3%)、頭痛・頭重22件(0.7%)等であり、胎児側においては羊水混濁48件(1.5%)、切迫仮死徴候35件(1.1%)、徐脈42件(1.3%)、頻脈25件(0.8%)等であった。

(承認時及び1980年8月までの副作用頻度報告結果)

1)重大な副作用

①心室細動、心停止、ショック

心室細動、心停止、ショック(いずれも頻度不明※)があらわれることがあるので、異常が認められた場合には投与を中止し、適切な処置を行うこと。

②呼吸困難

喘鳴、呼吸困難等(頻度不明※)があらわれることがあるので、このような場合には投与を中止すること。

③過強陣痛

過強陣痛(0.4%)があらわれることがある。また、それに伴い子宮破裂、頸管裂傷をきたしたとの報告があるので、観察を十分に行い、異常が認められた場合には、投与を中止し適切な処置を行うこと。

④胎児仮死徴候

胎児に仮死徴候〔児切迫仮死徴候(1.1%)、徐脈(1.3%)、頻脈(0.8%)、羊水の混濁(1.5%)〕をきたすことがあるので、観察を十分に行い、異常が認められた場合には、減量又は投与を中止すること。投与を中止してもこのような症状が認められる場合には、急速遂娩等の適切な処置を行うこと。

2)その他の副作用

	1～5%未満	1%未満	頻度不明※
循環器	顔面潮紅	頻脈、血圧上昇	血圧下降、動悸
消化器	嘔気・嘔吐	下痢	
注射部(注)		血管痛、静脈炎、発赤	
その他		頭痛・頭重、発汗、悪寒、発熱、手指のしびれ	

※：頻度不明は自発報告による。

注)：発現した場合には、投与部位をかえるなど処置を行うこと。

(5) 適用上の注意

1)投与経路：本剤は、用法・用量にしたがって、静脈内に点滴又は持続注入にのみ使用すること。

2)アンプルカット時：本剤はワンポイントカットアンプルであるが、アンプルカット部分をエタノール綿等で清拭しカットすることが望ましい。

(6) その他の注意

1)適応外であるが、分娩後の弛緩出血の治療あるいは帝王切開時の出血防止の目的で本剤を子宮筋注した症例において、心停止、心室性頻拍、心室性期外収縮、肺水腫があらわれたとの報告がある。

2)動物実験(ラット)において、大量投与により心筋障害が生じたとの報告がある。[2)]

3)動物実験(ラット)により催奇形作用が認められている。[2)]

2．腸管蠕動亢進の場合

(1) 慎重投与(次の患者には慎重に投与すること)

1)緑内障、眼圧亢進のある患者〔動物実験(ウサギ)で眼圧上昇が報告されている。[1)]〕

2)心疾患のある患者〔血管収縮作用により心機能を悪化させるおそれがある。〕

3)高血圧症のある患者〔血圧上昇作用がある。〕

4)幼児〔使用経験が少なく安全性が確立していない。〕

(2) 重要な基本的注意

心室細動、心停止、ショック、気管支収縮があらわれることがあるので、投与中は循環・呼吸器に対する観察を行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

(3) 副作用

承認時の臨床試験及び市販後調査において副作用集計の対象となった10,481例中638例(6.1%)に951件の副作用(臨床検査値の異常を含む)が認められた。

主なものは心悸亢進24件(0.2%)、顔面潮紅36件(0.3%)、血圧上昇10件(0.1%)、血圧下降4件(0.04%)、悪心105件(1.0%)、嘔気・嘔吐156件(1.5%)、腹痛219件(2.1%)、腹部膨満感51件(0.5%)、下痢107件(1.0%)、頭痛7件(0.07%)、発汗22件(0.2%)、血管痛99件(0.9%)等であった。

(再審査終了時)

1)重大な副作用

①心室細動、心停止、ショック

心室細動、心停止、ショック(いずれも頻度不明※)があらわれることがあるので、異常が認められた場合には投与を中止し、適切な処置を行うこと。

②呼吸困難

喘鳴、呼吸困難等(頻度不明※)があらわれることがあるので、このような場合には投与を中止すること。

2)その他の副作用

	0.1～5%未満	0.1%未満
循環器	心悸亢進、顔面潮紅	血圧上昇、血圧下降、胸内苦悶、不整脈、頻脈
過敏症		発疹等
消化器	嘔気・嘔吐、腹痛、下痢、腹部膨満感、腹部不快感	鼓腸
注射部(注)	血管痛、静脈炎、発赤	
その他	発汗	しびれ感、冷汗、口渇、頭痛、発熱

※：頻度不明は自発報告による。

注)：発現した場合には、投与部位をかえるなど処置を行うこと。

(4) 高齢者への投与

一般に高齢者では、心機能等生理機能が低下しているので減量するなど注意すること。

(5) 妊婦、産婦、授乳婦等への投与

妊婦又は妊娠している可能性のある婦人には投与しないこと。〔子宮収縮を起こす可能性がある。また、動物実験(ラット)で催奇形作用が報告されている。[2)]〕

(6) 適用上の注意

1) 投与速度：本剤投与により副作用があらわれた場合には、速やかに投与速度を遅くするか、あるいは投与を中止すること。

2) アンプルカット時：本剤はワンポイントカットアンプルであるが、アンプルカット部分をエタノール綿等で清拭しカットすることが望ましい。

(7) その他の注意

動物実験(ラット)において、大量投与により心筋障害が生じたとの報告がある。[2]

Ⅱ．卵膜外投与

治療的流産の場合

(1) 慎重投与(次の患者には慎重に投与すること)

1) 緑内障、眼圧亢進のある患者〔動物実験(ウサギ)で眼圧上昇が報告されている。[1]〕

2) 心疾患のある患者〔血管収縮作用により心機能を悪化させるおそれがある。〕

3) 高血圧症のある患者〔血圧上昇作用がある。〕

4) 頸管炎又は腟炎のある患者〔炎症、感染を増悪させるおそれがある。〕

5) 帝王切開又は子宮切開等の既往歴のある患者〔子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。〕

6) 多胎妊娠、経産婦の患者〔子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。〕

(2) 重要な基本的注意

1) 心室細動、心停止、ショック、気管支収縮があらわれることがあるので、投与中は循環・呼吸器に対する観察を行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

2) 本投与法においてカテーテルの挿入後、カテーテルを通じて持続的な出血を見る場合は、胎盤付着部への穿刺による場合があるのでカテーテルを抜き去り投与を中止すること。

3) 妊娠12週未満での投与において、子宮内容物の完全な排出に至らない場合又は総投与量3,000μgを投与しても十分な効果が認められない場合は、直ちに器械的子宮内容物除去術に切り替えること。

(3) 相互作用

併用注意(前後して使用する場合は注意すること)

薬剤名等	臨床症状・措置方法	機序・危険因子
陣痛誘発・促進剤 オキシトシン ゲメプロスト	これらの薬剤と前後して使用する場合は、異常収縮に注意し、観察を十分に行い慎重に投与すること。	本剤は子宮収縮作用を有するため、類似の作用を持つ薬剤を前後して使用することにより作用を増強する。

(4) 副作用

承認時の臨床試験及び市販後調査において副作用集計の対象となった509例中171例(33.6%)に295件の副作用(臨床検査値の異常を含む)が認められた。

主なものは顔面潮紅44件(8.6%)、血圧上昇23件(4.5%)、動悸17件(3.3%)、嘔気・嘔吐115件(22.6%)、悪心9件(1.8%)、下痢15件(2.9%)、発熱17件(3.3%)、頭痛・頭重26件(5.1%)等であった。(承認時及び1981年3月までの副作用頻度報告結果)

1) 重大な副作用

①心室細動、心停止、ショック

心室細動、心停止、ショック(いずれも頻度不明※)があらわれることがあるので、異常が認められた場合には投与を中止し、適切な処置を行うこと。

②呼吸困難

喘鳴、呼吸困難等(頻度不明※)があらわれることがあるので、このような場合には投与を中止すること。

2) その他の副作用

	10%以上	5～10%未満	5%未満
循環器		顔面潮紅	血圧上昇、血圧下降、動悸、胸内苦悶、四肢冷感
消化器	嘔気・嘔吐		下痢
皮　膚			発疹
その他		頭痛・頭重	発熱、全身倦怠感、耳鳴

※：頻度不明は自発報告による。

(5) 適用上の注意

アンプルカット時：本剤はワンポイントカットアンプルであるが、アンプルカット部分をエタノール綿等で清拭しカットすることが望ましい。

(6) その他の注意

1) 動物実験(ラット)において、大量投与により心筋障害が生じたとの報告がある。[2]

2) 動物実験(ラット)により催奇形作用が認められている。[2]

〔薬物動態〕

(参考)動物における吸収・分布・代謝・排泄〔ラット〕

^{3}H-PGF$_{2\alpha}$をラットに静脈内投与すると、^{3}Hは血中から速やかに肝・腎等、各臓器に移行し、その後速やかに各組織から消失する。そして投与60分後に尿中へ投与量の47.0%、糞中へ1.5%、24時間後で尿中へ55.7%、糞中へ35.4%排泄される。[3]

〔臨床成績〕

1．妊娠末期における陣痛誘発・陣痛促進・分娩促進

(1) 分娩誘発を目的とする妊娠週数38週以上42週以内の妊婦を対象として比較臨床試験を行い、本剤の陣痛誘発効果、分娩促進効果が報告されている。[4]

(2) 比較臨床試験を含む臨床試験において陣痛誘発、陣痛促進の有効率は87.2%(265/304例)、分娩促進の有効率は69.4%(211/304例)である。[5]

2．腸管蠕動亢進

(1) 開腹術を行った患者を対象として二重盲検比較試験を行い、本剤の術後腸管麻痺改善効果が報告されている。[6]

(2) 二重盲検比較試験を含む臨床試験において、腸管蠕動促進の有効率は77.2%(179/232例)である。[7]

3．治療的流産

母体保護法にもとづき人工妊娠中絶を行う妊娠12週以降177例、12週未満107例の妊婦を対象とした臨床試験において、本剤の流産効果の有効率はそれぞれ80.2%(142/177例)、99.1%(106/107例)である。[8]

〔薬効薬理〕

1．作用機序

PGF$_{2\alpha}$は生理的な子宮収縮作用を有し、妊娠各期において効果的な子宮収縮を起こすため、妊娠末期には点滴静注により陣痛誘発・分娩促進に、妊娠初期・中期には卵膜外注入により治療的流産に有用であることが認められている。また、PGF$_{2\alpha}$は消化管の縦走筋・輪状筋に作用し、蠕動運動亢進作用をもたらすことが認められ、臨床的にも排ガス時間の短縮、術後腸管麻痺の改善に効果が認められている。

2．薬理作用

(1) 子宮に対する作用

ラット摘出子宮平滑筋に対し0.6ng/mL以上の濃度で収縮作用を示す(*in vitro*)。[1]

1) 分娩誘発作用

●妊娠21日目のラットに静脈内持続注入(5～10μg/kg/分)すると子宮の自動収縮を増強する。[9]

●妊娠21日目のラットに静脈内持続注入(0.5～5.0μg/kg/分)すると第1児分娩までの時間は非投与群と比較して有意

に短縮する。[9]

●妊娠末期の妊婦に静脈内持続注入(0.05～0.15μg/kg/分)すると内圧の低い不規則陣痛から次第に規則的陣痛に移行し、自然陣痛発来時の子宮収縮に類似している。[10]

2) 流産誘発作用

妊娠中期のラットに羊膜外投与(0.25～1.0mg/kg)すると、子宮収縮作用を示し、流産が認められる。また血中プロゲステロン濃度は減少する。[11]

(2) 消化管に対する作用

モルモット摘出胃・回腸・結腸平滑筋に対し1ng/mLの濃度で収縮作用を示す(*in vitro*)。[12]

1) 腸管輸送能亢進作用

腸管運動麻痺ラットに静脈内持続注入(10～20μg/kg/分)したとき、腸管運動麻痺を緩解し、腸管輸送能の有意の亢進が認められる。[12]

2) 胃腸管運動亢進作用

麻酔下の絶食犬の空腸、回腸、結腸のバルーンによる内圧測定及び筋電図所見では静脈内持続注入(5～10μg/kg/分)で内圧の上昇、蠕動運動の誘発が認められる。[12]

3) 術後消化管運動亢進作用

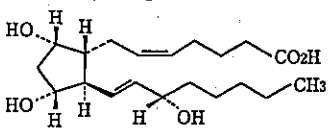
筋電図所見によれば、消化管術後患者の胃、十二指腸、空腸、回腸、結腸に運動抑制がみられるが、$PGF_{2\alpha}$の静脈内持続注入(0.3～0.5μg/kg/分)により、消化管各部位に用量依存性の著明な運動亢進を認め、この作用は投与中止後5～10分で消失する。[13]

〔有効成分に関する理化学的知見〕

一般名：ジノプロスト(Dinoprost)

化学名：(5*Z*)-7-{(1*R*, 2*R*, 3*R*, 5*S*)-3, 5-Dihydroxy-2-[(1*E*, 3*S*)-3-hydroxyoct-1-en-1-yl]-cyclopentyl}hept-5-enoic acid

構造式：



分子式：$C_{20}H_{34}O_5$

分子量：354.48

性　状：本品は白色のろう状の塊又は粉末、若しくは無色～淡黄色澄明の粘稠性のある液で、においはない。
本品は*N*,*N*-ジメチルホルムアミドに極めて溶けやすく、メタノール、エタノール(99.5)又はジエチルエーテルに溶けやすく、水に極めて溶けにくい。

〔包　　装〕

プロスタルモン・F注射液1000　1mL：10管、50管

プロスタルモン・F注射液2000　2mL：10管

〔主 要 文 献〕

1) 川崎晃義ほか：応用薬理，5：955, 1971
2) 松岡康夫ほか：医薬品研究，2：403, 1971
3) 西堀　勉ほか：医薬品研究，2：397, 1971
4) 澤崎千秋ほか：産科と婦人科，39：595, 1972
5) 小野薬品工業：〈妊娠末期における陣痛誘発・陣痛促進・分娩促進〉臨床成績集計(社内資料)
6) 草間　悟ほか：臨床評価，8：215, 1980
7) 小野薬品工業：〈腸管蠕動亢進〉臨床成績集計(社内資料)
8) 小野薬品工業：〈治療的流産〉臨床成績集計(社内資料)
9) 松本公一郎ほか：応用薬理，5：941, 1971
10) 坂元正一ほか：産科と婦人科，38：120, 1971
11) 松本公一郎ほか：応用薬理，10：753, 1975
12) 無量林堯ほか：現代医療，11：1651, 1979
13) 福西茂二ほか：日本平滑筋学会雑誌，13：141, 1977

〔文献請求先〕

主要文献に記載の社内資料につきましても下記にご請求下さい。

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PGF-ハN

FujiPharma

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872499

プロスタグランジン$F_{2\alpha}$製剤
※劇薬・処方せん医薬品注)

プロスモン注1000μg
プロスモン注2000μg

ジノプロスト注射液
PROSMON injection

貯法
遮光・室温保存

使用期限
外箱に表示（3年）

	プロスモン注1000μg	プロスモン注2000μg
承認番号	21900AMX01714000	21900AMX01698000
薬価収載	2007年12月	2007年12月
販売開始	1984年6月	1992年7月

注）注意－医師等の処方せんにより使用すること

※※【警告】
本剤を妊娠末期における陣痛誘発、陣痛促進、分娩促進の目的で使用するにあたって
過強陣痛や強直性子宮収縮により、胎児仮死、子宮破裂、頸管裂傷、羊水塞栓等が起こることがあり、母体あるいは児が重篤な転帰に至った症例が報告されているので、本剤の投与にあたっては以下の事項を遵守し慎重に行うこと。
1．母体および胎児の状態を十分観察して、本剤の有益性および危険性を考慮した上で、慎重に適応を判断すること。特に子宮破裂、頸管裂傷等は経産婦、帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので、注意すること。
2．分娩監視装置を用いて、胎児の心音、子宮収縮の状態を十分に監視すること。
3．本剤の感受性は個人差が大きく、少量でも過強陣痛になる症例も報告されているので、ごく少量からの点滴より開始し、陣痛の状況により徐々に増減すること。また、精密持続点滴装置を用いて投与すること。（「用法・用量」、《用法・用量に関連する使用上の注意》の項参照）
4．オキシトシン、ジノプロストン（PGE_2）との同時併用は行わないこと。また、前後して投与する場合も、過強陣痛を起こすおそれがあるので、十分な分娩監視を行い、慎重に投与すること。（「相互作用」の項参照）
5．患者に本剤を用いた陣痛誘発、陣痛促進、分娩促進の必要性および危険性を十分説明し、同意を得てから本剤を使用すること。

本剤の使用にあたっては、添付文書を熟読すること。

【禁忌（次の患者には投与しないこと）】
本剤を妊娠末期における陣痛誘発、陣痛促進、分娩促進の目的で使用するにあたって
1．骨盤狭窄、児頭骨盤不均衡、骨盤位等の胎位異常のある患者［正常な経腟分娩が進行せず、母体および胎児への障害を起こすおそれがある。］
2．全前置胎盤［胎盤が胎児より先に娩出され、胎児への危険性が予想される。］
3．気管支喘息またはその既往歴のある患者［気管支を収縮させ気道抵抗を増加し、喘息発作を悪化または誘発するおそれがある。］
4．オキシトシン、ジノプロストン（PGE_2）を投与中の患者（「相互作用」の項参照）
5．本剤の成分に対し過敏症の既往歴のある患者

【禁忌（次の患者には投与しないこと）】
本剤を腸管蠕動亢進の目的で使用するにあたって
1．本剤の成分に対し過敏症の既往歴のある患者
2．気管支喘息またはその既往歴のある患者［気管支を収縮させ気道抵抗を増加し、喘息発作を悪化または誘発するおそれがある。］
3．妊婦または妊娠している可能性のある女性
（「妊婦、産婦、授乳婦等への投与」の項参照）

【禁忌（次の患者には投与しないこと）】
本剤を治療的流産の目的で使用するにあたって
1．前置胎盤、子宮外妊娠等で、操作により出血の危険性のある患者［経腟分娩ができず、大量出血のおそれがある。］
2．骨盤内感染による発熱のある患者［炎症、感染を増悪させるおそれがある。］
3．気管支喘息またはその既往歴のある患者［気管支を収縮させ気道抵抗を増加し、喘息発作を悪化または誘発するおそれがある。］
4．本剤の成分に対し過敏症の既往歴のある患者

【原則禁忌（次の患者には投与しないことを原則とするが、特に必要とする場合には慎重に投与すること）】
本剤を妊娠末期における陣痛誘発、陣痛促進、分娩促進の目的で使用するにあたって
1．前置胎盤［出血および胎盤の圧迫により、胎児に障害を起こすおそれがある。］
2．常位胎盤早期剥離［緊急な胎児娩出が要求されるため、外科的処置の方が確実性が高い。］
3．胎児仮死のある患者［子宮収縮により胎児の症状を悪化させるおそれがある。］

【組成・性状】

販売名		プロスモン注1000μg	プロスモン注2000μg
有効成分		日局 ジノプロスト	
含量		1,000μg	2,000μg
容量		1mL	2mL
添加物	クエン酸ナトリウム水和物	33.3mg	66.6mg
	酢酸ナトリウム水和物	1.4mg	2.8mg
pH		6.5～8.5	
浸透圧比（生理食塩液に対する比）		約1	
色調・性状		無色澄明の水性注射液	
剤形		注射剤（アンプル）	

【効能・効果】
Ⅰ．静脈内注射投与
1．妊娠末期における陣痛誘発・陣痛促進・分娩促進
2．下記における腸管蠕動亢進
●胃腸管の手術における術後腸管麻痺の回復遷延の場合
●麻痺性イレウスにおいて他の保存的治療で効果が認められない場合
Ⅱ．卵膜外投与
治療的流産

【用法・用量】
Ⅰ．注射投与
1．妊娠末期における陣痛誘発・陣痛促進・分娩促進には通常1～2mLを静脈内に点滴または持続注入する。
※※（1）点滴静注
本剤1mLに5％ブドウ糖注射液または糖液を加えて500mLに希釈し、通常ジノプロストとして0.1μg/kg/分の割合で点滴静注する。なお、希釈する輸液の量及び種類は患者の状態に応じて適切に選択する。

※※(2) シリンジポンプによる静注（持続注入）
本剤１mLに生理食塩液を加えて50mLに希釈し、通常ジノプロストとして0.1μg/kg/分（0.05μg～0.15μg/kg/分）の割合で静注する。
(3) 症状により適宜増減する。
2．腸管蠕動亢進には
(1) 通常１回ジノプロストとして1,000～2,000μg（本剤１～２mL）を輸液500mLに希釈し、１～２時間（10～20μg/分の投与速度）で１日２回静脈内に点滴注射する。
(2) 本剤の投与は、手術侵襲の程度ならびに他の処置などを考慮して慎重に行うこと。
(3) ３日間投与しても効果が認められないときは直ちに投与を中止し他の療法にきりかえる。
(4) 症状、体重により適宜増減する。

II．卵膜外投与
治療的流産には
1．妊娠12週以降
本剤１mLに生理食塩液を加え４mLに希釈し、この液を子宮壁と卵膜の間に数回に分け注入投与する。
(1) 薬液注入カテーテルの固定
通常フォーリーカテーテルを用いる。カテーテルを子宮頸管を通じ挿入、カテーテルのバルーン部が子宮口を通過して、子宮下部まで到達した後、バルーン部に生理食塩液を充満、内子宮口を閉鎖し、カテーテルの脱出と膣への薬液漏出を防止する。次にカテーテルを大腿部内側へテープで固定する。
(2) 薬液の注入
1) 初回量
希釈液（ジノプロスト250μg/mL）１mLを注入し、薬液がカテーテル内に残らないように引き続きカテーテルの内腔量を若干上回る生理食塩液を注入する（通例、16号カテーテルでは約3.5mL）。
2) ２回目以降
本剤の２回目以降の注入投与は、原則として２時間ごとに希釈液３～４mL（750～1,000μg）を反復投与するが、初回投与による子宮収縮、その他の反応が強すぎる場合には、次回の投与量を２mL（500μg）に減量または４時間後に投与する。
3) 本剤の投与は原則として２時間間隔で行うが、本剤による効果およびその他の反応を観察しながら適宜投与量および投与間隔を１～４時間の間で調節する。
4) 本投与法においては薬剤注入の度に、カテーテルの内腔量を若干上回る生理食塩液を引き続き注入することに注意すること。
2．妊娠12週未満
胞状奇胎、合併症で全身麻酔が困難な症例、頸管拡張の困難な症例またはその場合の除去術の前処置に使用する。その際本剤の注入は、アトロピン硫酸塩水和物、鎮痛剤の投与後、前麻酔効果があらわれてから行うことが望ましい。
(1) チューブの挿入
通常Ｆ４～５号の合成樹脂製の細いチューブを用い、使用前にチューブ内腔に生理食塩液を満たしておく。チューブを鉗子ではさみ、外子宮口より子宮腔内にゆっくりと約７cm位まで挿入する。
直視下で薬液の注入を行う以外は、チューブの排出をふせぐためチューブをとりかこむようにガーゼを膣腔内につめる。注射器をチューブに接続し、また、チューブを大腿部内側にテープで固定する。
(2) 薬液の注入
1) 分割注入法
妊娠12週以降の場合に準じ、本剤１mLに生理食塩液を加え４mLに希釈した液を用い分割注入する。
●初回量は希釈液１mL（ジノプロスト 250μg/mL）を注入し、また薬液がチューブ内に残らないように引き続きチューブ内腔量を若干上回る生理食塩液を注入する。
●２回目以降の注入は、原則として１時間ごとに希釈液３～４mL(750～1,000μg)を反復投与するが、初回投与による子宮収縮、その他の反応が強すぎる場合には、次回の投与量を２mL(500μg)に減量または投与時間間隔をおくらせる。
●本剤の投与は原則として総投与量3,000μgとし、また１時間間隔で行うが、本剤による効果およびその他の反応を観察しながら適宜に投与量および投与時間間隔を調節する。
●本投与法においては薬剤注入の度にチューブの内腔量を若干上回る生理食塩液を引き続き注入することに注意する。
2) 一回注入法
●通常ジノプロスト1,000μg/１mL含有注射剤を希釈しないで、一回に2,000～3,000μg（２～３mL）をゆっくり注入する。
本剤による効果およびその反応を観察しながら適宜に投与量を増減する。
●注入後チューブの内腔量を若干上回る生理食塩液を引き続き注入する。チューブは薬液注入が終了すれば抜きとる。

※※**《用法・用量に関連する使用上の注意》**
陣痛誘発、陣痛促進、分娩促進の目的で本剤を投与する際は、精密持続点滴装置を用いて投与すること。

【使用上の注意】
I．静脈内注射投与
1．妊娠末期における陣痛誘発・陣痛促進・分娩促進の場合
(1) 慎重投与（次の患者には慎重に投与すること）
1) 緑内障、眼圧亢進のある患者［動物実験（ウサギ）で眼圧上昇が報告されている。］
2) 心疾患のある患者［血管収縮作用により心機能を悪化させるおそれがある。］
3) 高血圧症のある患者［血圧上昇作用がある。］
4) 帝王切開または子宮切開等の既往歴のある患者［子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。］
5) 多胎妊娠、経産婦の患者［子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。］
(2) 重要な基本的注意
1) 心室細動、心停止、ショック、気管支収縮があらわれることがあるので、投与中は循環・呼吸器に対する観察を行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。
2) 本剤を投与する際には、Bishop score等により頸管が熟化していることを確認した後、本剤を投与することが望ましい。また、頸管熟化剤との同時投与は避けること。
※※3) 薬剤の使用の有無によらず、分娩時には母体の生命を脅かす緊急状態（子宮破裂、羊水塞栓、脳内出血、くも膜下出血、常位胎盤早期剥離、子癇、分娩時大量出血等）が起こることがあるため、本剤を用いた陣痛誘発、陣痛促進、分娩促進にあたっては、分娩監視装置を用いた分娩監視に加えて、定期的にバイタルサインのモニ

ターを行うなど、患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。

（3）相互作用

1）併用禁忌（同時併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
オキシトシン アトニン-O ジノプロストン（PGE_2） プロスタグランジンE_2錠 0.5mg	これらの薬剤と同時併用することにより過強陣痛を起こしやすい。	本剤は子宮収縮作用を有するため、類似の作用を持つ薬剤を併用することにより作用を増強する。

2）併用注意（前後して使用する場合は注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
陣痛誘発・促進剤 オキシトシン ジノプロストン（PGE_2）	これらの薬剤と前後して使用する場合も、過強陣痛を起こしやすいので、十分な分娩監視を行い慎重に投与すること。	本剤は子宮収縮作用を有するため、類似の作用を持つ薬剤を前後して使用することにより作用を増強する。

（4）副作用

本剤は使用成績調査等の副作用発現頻度が明確となる調査を実施していない。

1）重大な副作用（頻度不明）

①心室細動、心停止、ショック：心室細動、心停止、ショックがあらわれることがあるので、異常が認められた場合には投与を中止し、適切な処置を行うこと。

②呼吸困難：喘鳴、呼吸困難等があらわれることがあるので、このような場合には投与を中止すること。

③過強陣痛：過強陣痛があらわれることがある。また、それに伴い子宮破裂、頸管裂傷をきたしたとの報告があるので、観察を十分に行い、異常が認められた場合には、投与を中止し適切な処置を行うこと。

④胎児仮死徴候：胎児に仮死徴候（児切迫仮死徴候、徐脈、頻脈、羊水の混濁）をきたすことがあるので、観察を十分に行い、異常が認められた場合には、減量または投与を中止すること。投与を中止してもこのような症状が認められる場合には、急速遂娩等の適切な処置を行うこと。

2）その他の副作用

	頻度不明
循環器	顔面潮紅、頻脈、血圧上昇、血圧下降、動悸
消化器	嘔気・嘔吐、下痢
注射部[注]	血管痛、静脈炎、発赤
その他	頭痛・頭重、発汗、悪寒、発熱、手指のしびれ

注)発現した場合には、投与部位を変えるなど処置を行うこと。

（5）適用上の注意

1）投与経路：本剤は、用法・用量にしたがって、静脈内に点滴または持続注入にのみ使用すること。

2）アンプルカット時：本品はワンポイントカットアンプルであるが、アンプルのカット部分をエタノール綿等で清拭してからカットすることが望ましい。

（6）その他の注意

1）適応外であるが、分娩後の弛緩出血の治療あるいは帝王切開時の出血防止の目的で本剤を子宮筋注した症例において、心停止、心室性頻拍、心室性期外収縮、肺水腫があらわれたとの報告がある。

2）動物実験（ラット）において、大量投与により心筋障害が生じたとの報告がある。

3）動物実験（ラット）により催奇形作用が認められている。

2．腸管蠕動亢進の場合

（1）慎重投与（次の患者には慎重に投与すること）

1）緑内障、眼圧亢進のある患者［動物実験（ウサギ）で眼圧上昇が報告されている。］

2）心疾患のある患者［血管収縮作用により心機能を悪化させるおそれがある。］

3）高血圧症のある患者［血圧上昇作用がある。］

4）幼児［使用経験が少なく安全性が確立していない。］

（2）重要な基本的注意

心室細動、心停止、ショック、気管支収縮があらわれることがあるので、投与中は循環・呼吸器に対する観察を行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

（3）副作用

本剤は使用成績調査等の副作用発現頻度が明確となる調査を実施していない。

1）重大な副作用（頻度不明）

①心室細動、心停止、ショック：心室細動、心停止、ショックがあらわれることがあるので、異常が認められた場合には投与を中止し、適切な処置を行うこと。

②呼吸困難：喘鳴、呼吸困難等があらわれることがあるので、このような場合には投与を中止すること。

2）その他の副作用

	頻度不明
循環器	心悸亢進、顔面潮紅、血圧上昇、血圧下降、胸内苦悶、不整脈、頻脈
過敏症	発疹等
消化器	嘔気・嘔吐、腹痛、下痢、腹部膨満感、腹部不快感、鼓腸
注射部[注]	血管痛、静脈炎、発赤
その他	発汗、しびれ感、冷汗、口渇、頭痛、発熱

注)発現した場合には、投与部位を変えるなど処置を行うこと。

（4）高齢者への投与

一般に高齢者では、心機能等生理機能が低下しているので減量するなど注意すること。

（5）妊婦、産婦、授乳婦等への投与

妊婦または妊娠している可能性のある女性には投与しないこと。［子宮収縮を起こす可能性がある。また、動物実験（ラット）で催奇形作用が報告されている。］

（6）適用上の注意

1）投与速度：本剤投与により副作用があらわれた場合には、速やかに投与速度を遅くするか、あるいは投与を中止すること。

2）アンプルカット時：本品はワンポイントカットアンプルであるが、アンプルのカット部分をエタノール綿等で清拭してからカットすることが望ましい。

（7）その他の注意

動物実験（ラット）において、大量投与により心筋障害が生じたとの報告がある。

II．卵膜外投与

治療的流産の場合

（1）慎重投与（次の患者には慎重に投与すること）

1）緑内障、眼圧亢進のある患者［動物実験（ウサギ）で眼圧上昇が報告されている。］

2）心疾患のある患者［血管収縮作用により心機能を悪化させるおそれがある。］

3）高血圧症のある患者［血圧上昇作用がある。］

4）頸管炎または膣炎のある患者［炎症、感染を増悪させるおそれがある。］

5）帝王切開または子宮切開等の既往歴のある患者［子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。］

6）多胎妊娠、経産婦の患者［子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。］

（2）重要な基本的注意

1）心室細動、心停止、ショック、気管支収縮があらわれることがあるので、投与中は循環・呼吸器に対する観察を行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。

2）本投与法においてカテーテル挿入後、カテーテルを通じて持続的な出血をみる場合は、胎盤付着部への穿刺による場合があるのでカテーテルを抜き去り投与を中止すること。

3）妊娠12週未満での投与において、子宮内容物の完全な排出に至らない場合または総投与量3,000μgを投与しても十分な効果が認められない場合は、直ちに器械的子宮内容物除去術に切り替えること。

（3）相互作用

併用注意（前後して使用する場合は注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
陣痛誘発・促進剤 オキシトシン ゲメプロスト	これらの薬剤と前後して使用する場合は、異常収縮に注意し、観察を十分に行い慎重に投与すること。	本剤は子宮収縮作用を有するため、類似の作用を持つ薬剤を前後して使用することにより作用を増強する。

（4）副作用

本剤は使用成績調査等の副作用発現頻度が明確となる調査を実施していない。

1）重大な副作用（頻度不明）

①心室細動、心停止、ショック：心室細動、心停止、ショックがあらわれることがあるので、異常が認められた場合には投与を中止し、適切な処置を行うこと。

②呼吸困難：喘鳴、呼吸困難等があらわれることがあるので、このような場合には投与を中止すること。

2）その他の副作用

	頻度不明
循環器	顔面潮紅、血圧上昇、血圧下降、動悸、胸内苦悶、四肢冷感
消化器	嘔気・嘔吐、下痢
皮　膚	発疹
その他	頭痛・頭重、発熱、全身けん怠感、耳鳴

（5）適用上の注意

アンプルカット時：本品はワンポイントカットアンプルであるが、アンプルのカット部分をエタノール綿等で清拭してからカットすることが望ましい。

（6）その他の注意

1）動物実験（ラット）において、大量投与により心筋障害が生じたとの報告がある。

2）動物実験（ラット）により催奇形作用が認められている。

【薬物動態】

女性に9β－^{3}H－$PGF_{2\alpha}$を静脈内投与し、5hr後に85～95%の^{3}Hを尿中に回収した。尿中にはβ酸化、ω酸化15位アルコールの脱水素、二重結合の還元された炭素数16の代謝物、5α、7α-Dihydroxy-11-keto-16-carboxy-tetraprostanoic acidを確認した。[1]

【薬効薬理】

1．消化管に広く存在し消化管運動を調節する。

2．消化管縦走筋・輪状筋に作用し蠕動運動亢進作用をもたらす。[2]

3．排ガス時間の短縮、術後腸管麻痺を改善する。[3]

4．自然分娩発来機序と密接な関連を有し、分娩の進行に重要な役割をもっている。[4),5]

5．生理的な子宮収縮作用と収縮動態を示す。[6),7]

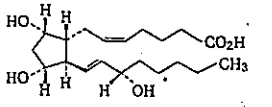
6．分娩時後の弛緩性出血が少なく、分娩第Ⅲ期時間の短縮、出血量の減少効果がある。[8]

【有効成分に関する理化学的知見】

一般名：ジノプロスト（Dinoprost）

化学名：(5*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(1*E*,3*S*)-3-hydroxyoct-1-en-1-yl]cyclopentyl}hept-5-enoic acid

構造式：



分子式：$C_{20}H_{34}O_5$

分子量：354.48

性　状：白色のろう状の塊または粉末、若しくは無色～淡黄色澄明の粘稠性のある液で、においはない。*N,N*－ジメチルホルムアミドに極めて溶けやすく、メタノール、エタノール(99.5)またはジエチルエーテルに溶けやすく、水に極めて溶けにくい。

【取扱い上の注意】

安定性試験

最終包装製品を用いた長期保存試験（室温、相対湿度50～65%、遮光、3年）の結果、外観および含量等は規格の範囲内であり、プロスモン注1000μgおよびプロスモン注2000μgは通常の市場流通下において3年間安定であることが確認された。[9]

【包　装】

プロスモン注1000μg　1,000μg/1mL　10アンプル

プロスモン注2000μg　2,000μg/2mL　10アンプル

【主要文献】

1）E.Grastrom,B.Samuelsson：J.Am,chem.Soc.,91, 3398, 1969

2）福西茂二ほか：日本平滑筋学会雑誌，13：141,1977

3）川口富司ほか：日本平滑筋学会雑誌，21：419,1985

4）産婦人科PG研究会：産と婦，39：588，1972

5）野嶽幸正ほか：産と婦，42：896，1975

6）Karim,S.M.M.,et al：J.Obst.Gyn,Brit.Cwlth.,76：769, 1969

7）坂元正一ほか：Acta.obst,et Gyn,Jap.,18, 87,1971

8）坂田寿衛ほか：産婦人科の世界，33：437，1981

9）富士製薬工業株式会社　社内資料（安定性試験）

【文献請求先】

主要文献に記載の社内資料につきましても下記にご請求下さい。

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日本標準商品分類番号
872499

陣痛誘発・促進剤

プロスタグランジンE$_2$錠0.5mg「科研」

PROSTAGLANDIN E$_2$
ジノプロストン錠

規制区分
劇薬 処方せん医薬品(注意ー医師等の処方せんにより使用すること)

貯法
室温保存、気密容器
使用期限
外箱に表示

	プロスタグランジンE2錠0.5mg「科研」
承認番号	21900AMX01175000
薬価収載	2007年12月
販売開始	1984年3月
再審査結果	1991年12月

※※【警　告】

過強陣痛や強直性子宮収縮により、胎児仮死、子宮破裂、頸管裂傷、羊水塞栓等が起こることがあり、母体あるいは児が重篤な転帰に至った症例が報告されているので、本剤の投与にあたっては以下の事項を遵守し慎重に行うこと。

1. 母体及び胎児の状態を十分観察して、本剤の有益性及び危険性を考慮した上で、慎重に適応を判断すること。特に子宮破裂、頸管裂傷等は経産婦、帝王切開あるいは子宮切開術既往歴のある患者で起こりやすいので、注意すること。
2. 本剤は点滴注射剤に比べ調節性に欠けるので、分娩監視装置を用いて胎児の心音、子宮収縮の状態を十分に監視出来る状態で使用すること。
3. オキシトシン、ジノプロスト($PGF_{2\alpha}$)との同時併用は行わないこと。また、前後して使用する場合も、過強陣痛を起こすおそれがあるので、十分な分娩監視を行い、慎重に投与すること。[「相互作用」の項参照]
4. 患者に本剤を用いた陣痛誘発、陣痛促進の必要性及び危険性を十分説明し、同意を得てから本剤を使用すること。

本剤の使用にあたっては、添付文書を熟読すること。

【禁忌(次の患者には投与しないこと)】

1. 骨盤狭窄、児頭骨盤不均衡、骨盤位等の胎位異常のある患者
   [正常な経腟分娩が進行せず、母体及び胎児への障害を起こすおそれがある。]
2. 前置胎盤
   [出血及び胎盤の圧迫により、胎児に障害を起こすおそれがある。]
3. 常位胎盤早期剥離
   [緊急な胎児娩出が要求されるため、外科的処置の方が確実性が高い。]
4. 胎児仮死のある患者
   [子宮収縮により胎児の症状を悪化させるおそれがある。]
5. オキシトシン、ジノプロスト($PGF_{2\alpha}$)を投与中の患者
   [「相互作用」の項参照]

【組成・性状】

有効成分	1錠中にジノプロストン0.5mgを含有する。
添加物	アメ粉、カルメロースカルシウム、結晶セルロース、酸化チタン、ステアリン酸マグネシウム、乳糖水和物、ヒプロメロース、メチルヘスペリジン、黄色5号
性　状	淡黄白色のフィルムコーティング錠である。

外形			サイズ 重量	識別コード
表面	裏面	側面		
KC 29			直径　8.2mm 厚さ　4.7mm 重量　0.215g	KC29

【効能・効果】

妊娠末期における陣痛誘発並びに陣痛促進

【用法・用量】

1. 通常1回1錠を1時間毎に6回、1日総量6錠(ジノプロストンとして3mg)を1クールとし、経口投与する。
2. 体重、症状及び経過に応じ適宜増減する。
3. 本剤の投与開始後、陣痛誘発、分娩進行効果を認めたとき、本剤の投与を中止する。
4. 1日総量ジノプロストンとして1クール3mg(6錠)を投与し、効果の認められない場合は本剤の投与を中止し、翌日あるいは以降に投与を再開する。

【使用上の注意】

1. 慎重投与(次の患者には慎重に投与すること)
   (1)緑内障、眼圧亢進のある患者
   [動物実験(ウサギ)で眼圧上昇が報告されている。]
   (2)喘息又はその既往歴のある患者
   [気管支を収縮させるとの報告がある。]
   (3)帝王切開又は子宮切開等の既往歴のある患者
   [子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。]
   (4)多胎妊娠、経産婦の患者
   [子宮が脆弱になっていることがあり、過強陣痛が生じると子宮破裂の危険がある。]
2. 重要な基本的注意
   (1)本剤は点滴注射剤に比べ、調節性に欠けるので、分娩監視装置を用いて子宮収縮の状態及び胎児心音の観察を行い、投与間隔を保つよう十分注意し、陣痛誘発効果、分娩進行効果を認めたときは中止し、過量投与にならないよう慎重に投与すること。
   (2)本剤を投与する際には、Bishop score等により頸管が熟化していることを確認した後、本剤を投与することが望ましい。また、頸管熟化剤との同時投与は避けること。
   ※※(3)薬剤の使用の有無によらず、分娩時には母体の生命を脅かす緊急状態(子宮破裂、羊水塞栓、脳内出血、くも膜下出血、常位胎盤早期剥離、子癇、分娩時大量出血等)が起こることがあるため、本剤を用いた陣痛誘発、陣痛促進にあたっては、分娩監視装置を用いた分娩監視に加えて、定期的にバイタルサインのモニターを行うなど、患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。
3. 相互作用
   (1)併用禁忌(同時併用しないこと)

薬剤名等	臨床症状・措置方法	機序・危険因子
オキシトシン アトニン-O ジノプロスト プロスタルモン・F 注射液1000、2000	これらの薬剤と同時併用することにより過強陣痛を起こしやすい。	本剤は子宮収縮作用を有するため、類似の作用を持つ薬剤を併用することにより作用を増強する。

(2)併用注意(前後して使用する場合は注意すること)

薬剤名等	臨床症状・措置方法	機序・危険因子
陣痛誘発・促進剤 オキシトシン ジノプロスト	これらの薬剤と前後して使用する場合も、過強陣痛を起こしやすいので投与間隔を保ち十分な分娩監視を行い、慎重に投与すること。	本剤は子宮収縮作用を有するため、類似の作用を持つ薬剤を前後して使用することにより作用を増強する。

4.副作用

総症例5,721例中、副作用が認められたのは144例(2.52%)190件で、母体副作用は117件(2.05%)、胎児副作用は73件(1.28%)であった。その主なものは、母体副作用では嘔気・嘔吐51件(0.89%)、顔面潮紅19件(0.33%)、過強陣痛12件(0.21%)、下痢11件(0.19%)等が、胎児副作用では羊水混濁29件(0.51%)、胎児徐脈22件(0.38%)、胎児頻脈11件(0.19%)、胎児仮死10件(0.17%)等が認められている。

(再審査結果時)

(1)重大な副作用

1)過強陣痛

過強陣痛(0.1～5%未満)があらわれることがある。また、それに伴い子宮破裂、頸管裂傷をきたすことがあるので、観察を十分に行い、異常が認められた場合には、投与を中止し適切な処置を行うこと。

2)胎児仮死徴候

胎児仮死徴候(0.1～5%未満)(仮死、徐脈、頻脈、羊水の混濁等)をきたすことがあるので、観察を十分に行い、異常が認められた場合には、投与を中止すること。投与を中止してもこのような症状があらわれた場合には、急速遂娩等の適切な処置を行うこと。

(2)その他の副作用

分類＼頻度	0.1～5%未満	0.1%未満
消化器	嘔気・嘔吐、下痢	
循環器	顔面潮紅	頻脈、血圧上昇
精神神経系		頭痛、眩暈
その他	胸部不快感	熱感、呼吸異常、発汗

5.妊婦、産婦、授乳婦等への投与

妊娠末期以外の妊婦には投与しないこと。

[動物実験(マウス)により催奇形作用が認められている。]

6.適用上の注意

(1)投与方法

本剤は経口剤のため調節性に欠けるので、医師の常時監視できる条件下で投与すること。

(2)投与経路

本剤は経口投与にのみ使用し、膣内に投与しないこと。

(3)薬剤交付時

PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。(PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することが報告されている。)

【薬物動態】[1,2]

<参考>動物における吸収・分布・代謝・排泄

^{3}H-プロスタグランジンE_2をマウス及びラットに経口投与すると、主要臓器への分布はマウスでは投与後15～30分、ラットでは投与後30分で最高値を示し、投与後60分では最高値の1/10程度に減少した。投与24時間までの尿中及び糞中への排泄率は、マウスでは83%及び11%、ラットでは67%及び24%であった。妊娠ラットにおいても生殖器官への特異的な集積はなく、投与後30分でも胎児への分布は投与量の1%以下であった。また、イヌに本剤を経口投与すると、投与1時間後に最高血中濃度を示し、6時間後にはほぼ投与前の値に戻った。

【臨床成績】[3～12]

一般臨床試験(526例)及び二重盲検比較試験(100例)の概要は次のとおりである。

1.陣痛誘発

陣痛のまったくみられない症例で、本剤により陣痛が発来したと認められたものは、初産婦で51.7%(90/174)、経産婦で62.9%(124/197)であった。

二重盲検比較試験での有効率は初産婦で41.7%(20/48)、経産婦で46.2%(24/52)であった。やや有効以上は初産婦で75.0%(36/48)、経産婦で82.7%(43/52)であった。

2.陣痛促進

陣痛促進を目的とする症例において、本剤により内診所見が改善したと認められたものは、初産婦で84.6%(115/136)、経産婦で89.7%(104/116)であった。

【薬効薬理】

1. 妊娠末期の子宮に対し収縮作用を有し、陣痛発来、分娩進行に重要な役割を果たす(ラット*in vitro*、マウス、ラット、ウサギ)[13,14](ヒト)[12]。
2. 分娩誘発に際し頸管軟化作用などの内診所見改善作用を有する(ヒト)[12]。

【有効成分に関する理化学的知見】

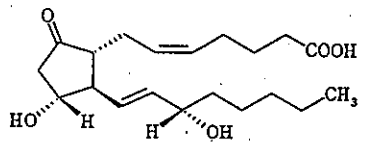
一般名：Dinoprostone(ジノプロストン)

化学名：(*Z*)-7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(1*E*)-(3*S*)-3-hydroxy-1-octenyl]-5-oxocyclopentyl]-5-heptenoic acid

分子式：$C_{20}H_{32}O_5$

分子量：352.47

※※構造式：



性　状：ジノプロストンは白色～淡黄色の結晶で、においはなく、強い苦味がある。メタノール、無水エタノール、酢酸エチル又はクロロホルムに溶けやすく、水に極めて溶けにくい。

【包　装】

(ＰＴＰ)60錠

【主要文献及び文献請求先】

<主要文献>

1)丹治昭治　他：薬理と治療, 9, 1431～1451(1981)
2)本郷久弘　他：KPEの吸収、分布、代謝および排泄に関する試験(Ⅲ)(科研製薬(株)社内資料)
3)田中俊誠　他：臨床婦人科産科, 34, 315～320(1980)
4)経塚光夫　他：産婦人科の世界, 32, 103～111(1980)
5)中山陽比古　他：産婦人科の世界, 31, 1379～1383(1979)
6)浜田哲郎　他：産婦人科の世界, 32, 615～618(1980)
7)永井生司：産婦人科の世界, 32, 609～614(1980)
8)麻生武志　他：産科と婦人科, 47, 1024～1029(1980)
9)倉智敬一　他：産婦人科治療, 41, 115～121(1980)
10)林谷誠治　他：産婦中四会誌, 28, 37～43(1980)
11)坂元　力　他：産婦人科の世界, 32, 1333～1338(1980)
12)鈴木雅洲　他：産婦人科の世界, 33, 177～190(1981)
13)讃井和子　他：薬理と治療, 9, 1351～1356(1981)
14)石崎　綺　他：基礎と臨床, 15, 1272～1276(1981)

<文献請求先>

主要文献に記載の社内資料につきましても下記にご請求ください。

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