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CYLERT®

(PEMOLINE)
Rx only

CYLERT SHOULD NOT BE USED BY PATIENTS UNTIL THERE HAS BEEN A COMPLETE DISCUSSION OF THE RISKS AND BENEFITS OF CYLERT THERAPY AND WRITTEN INFORMED CONSENT HAS BEEN OBTAINED (SEE **PATIENT INFORMATION/CONSENT FORM**). A SUPPLY OF PATIENT INFORMATION/ CONSENT FORMS AS PRINTED AT THE END OF THIS INSERT IS AVAILABLE, FREE OF CHARGE, BY CALLING (847) 937-7302. PERMISSION TO USE THE PATIENT INFORMATION/CONSENT FORM BY PHOTOCOPY REPRODUCTION IS HEREBY GRANTED BY ABBOTT LABORATORIES.

Because of its association with life threatening hepatic failure, CYLERT should not ordinarily be considered as first line drug therapy for ADHD (see INDICATIONS AND USAGE). Because CYLERT provides an observable symptomatic benefit, patients who fail to show substantial clinical benefit within 3 weeks of completing dose titration, should be withdrawn from CYLERT therapy.

Since CYLERT's marketing in 1975, 15 cases of acute hepatic failure have been reported to the FDA. While the absolute number of reported cases is not large, the rate of reporting ranges from 4 to 17 times the rate expected in the general population. This estimate may be conservative because of under reporting and because the long latency between initiation of CYLERT treatment and the occurrence of hepatic failure may limit recognition of the association. If only a portion of actual cases were recognized and reported, the risk could be substantially higher.

Of the 15 cases reported as of December 1998, 12 resulted in death or liver transplantation, usually within four weeks of the onset of signs and symptoms of liver failure. The earliest onset of hepatic abnormalities occurred six months after initiation of CYLERT. Although some reports described dark urine and nonspecific prodromal symptoms (e.g., anorexia, malaise, and gastrointestinal symptoms), in other reports it was not clear if any prodromal symptoms preceded the onset of jaundice.

Treatment with CYLERT should be initiated only in individuals without liver disease and with normal baseline liver function tests. It is not clear if baseline and periodic liver function testing are predictive of these instances of acute liver failure; however it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Accordingly, the following liver monitoring program is recommended: Serum ALT (SGPT) levels should be determined at baseline, and every two weeks thereafter. If CYLERT therapy is discontinued and then restarted, liver function test monitoring should be done at baseline and reinitiated at the frequency above.

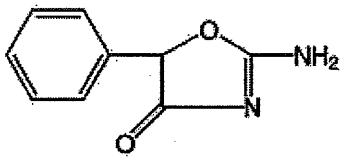
CYLERT should be discontinued if serum ALT (SGPT) is increased to a clinically significant level, or any increase ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure (see PRECAUTIONS).

The physician who elects to use CYLERT should obtain written informed consent from the patient prior to initiation of CYLERT therapy (see PATIENT INFORMATION/CONSENT FORM).

DESCRIPTION

CYLERT (pemoline) is a central nervous system stimulant. Pemoline is structurally dissimilar to the amphetamines and methylphenidate.

It is an oxazolidine compound and is chemically identified as 2-amino-5-phenyl-2-oxazolin-4-one. Pemoline has the following structural formula:



Pemoline is a white, tasteless, odorless powder, relatively insoluble (less than 1 mg/mL) in water, chloroform, ether, acetone, and benzene; its solubility in 95% ethyl alcohol is 2.2 mg/mL.

CYLERT (pemoline) is supplied as tablets containing 18.75 mg, 37.5 mg or 75 mg of pemoline for oral administration. CYLERT is also available as chewable tablets containing 37.5 mg of pemoline.

Inactive Ingredients

18.75 mg tablet: corn starch, gelatin, lactose, magnesium hydroxide, polyethylene glycol and talc.

37.5 mg tablet: corn starch, FD&C Yellow No. 6, gelatin, lactose, magnesium hydroxide, polyethylene glycol and talc.

37.5 mg chewable tablet: corn starch, FD&C Yellow No. 6, magnesium hydroxide, magnesium stearate, mannitol, polyethylene glycol, povidone, talc and artificial flavor. 75 mg tablet: corn starch, gelatin, iron oxide, lactose, magnesium hydroxide, polyethylene glycol and talc.

CLINICAL PHARMACOLOGY

CYLERT (pemoline) has a pharmacological activity similar to that of other known central nervous system stimulants; however, it has minimal sympathomimetic effects. Although studies indicate that pemoline may act in animals through dopaminergic mechanisms, the exact mechanism and site of action of the drug in man is not known.

There is neither specific evidence which clearly establishes the mechanism whereby CYLERT produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Pemoline is rapidly absorbed from the gastrointestinal tract. Approximately 50% is bound to plasma proteins. The serum half-life of pemoline is approximately 12 hours. Peak serum levels of the drug occur within 2 to 4 hours after ingestion of a single dose. Multiple dose studies in adults at several dose levels indicate that steady state is reached in approximately 2 to 3 days. In animals given radiolabeled pemoline, the drug was widely and uniformly distributed throughout the tissues, including the brain.

Pemoline is metabolized by the liver. Metabolites of pemoline include pemoline conjugate, pemoline dione, mandelic acid, and unidentified polar compounds. CYLERT is excreted primarily by the kidneys with approximately 50% excreted unchanged and only minor fractions present as metabolites.

CYLERT (pemoline) has a gradual onset of action. Using the recommended schedule of dosage titration, significant clinical benefit may not be evident until the third or fourth week of drug administration.

INDICATIONS AND USAGE

CYLERT (pemoline) is indicated in Attention Deficit Hyperactivity Disorder (ADHD). Because of its association with life threatening hepatic failure, CYLERT should not ordinarily be considered as first line therapy for ADHD (see **BOXED WARNING**).

CYLERT (pemoline) therapy should be part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

CONTRAINDICATIONS

CYLERT (pemoline) is contraindicated in patients with known hypersensitivity or idiosyncrasy to the drug. CYLERT should not be administered to patients with impaired hepatic function (see **BOXED WARNING** and **ADVERSE REACTIONS**).

WARNINGS

Decrements in the predicted growth (i.e., weight gain and/or height) rate have been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

PRECAUTIONS

General:

Clinical experience suggests that in psychotic children, administration of CYLERT may exacerbate symptoms of behavior disturbance and thought disorder.

CYLERT should be administered with caution to patients with significantly impaired renal function.

Information for Patients:

Patients should be informed that CYLERT therapy has been associated with liver abnormalities ranging from reversible liver function test increases that do not cause any symptoms to liver failure, which may result in death. Patients should be informed that the risk of liver failure in the general population is relatively rare; however patients taking CYLERT are at a greater risk of developing liver failure than that expected in the general population. At present, there is no way to predict who is likely to develop liver failure; however only patients without liver disease and with normal baseline liver function tests should initiate CYLERT therapy. Patients should be advised to follow their doctors directives for liver function tests prior to and during CYLERT therapy. Patients should be advised to be alert for signs of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they should occur.

The physician who elects to use CYLERT should obtain written informed consent from patients prior to initiation of CYLERT therapy (see **PATIENT INFORMATION/CONSENT FORM**.)

Laboratory Tests:

Since CYLERT's market introduction, there have been reports of elevated liver enzymes associated with its use. Many of these patients had this increase detected several months after starting CYLERT. Most patients were asymptomatic, with the increase in liver enzymes returning to normal after CYLERT was discontinued.

Treatment with CYLERT should be initiated only in individuals without liver disease and with normal baseline liver function tests. It is not clear if baseline and periodic liver function testing are predictive of these instances of acute liver failure; however it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Accordingly, the following liver monitoring program is recommended.

Serum ALT (SGPT) levels should be determined at baseline, and every two weeks thereafter. If CYLERT therapy is discontinued and then restarted, liver function test monitoring should be done at baseline and reinitiated at the frequency above. CYLERT should be discontinued if serum ALT (SGPT) is increased to a clinically significant level, or any increase ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure (see **BOXED WARNING**).

Drug Interactions:
The interaction of CYLERT (pemoline) with other drugs has not been studied in humans. Patients who are receiving CYLERT concurrently with other drugs, especially drugs with CNS activity, should be monitored carefully.

Decreased seizure threshold has been reported in patients receiving CYLERT concomitantly with *antiepileptic medications*.

Carcinogenesis:
Long-term studies have been conducted in rats with doses as high as 150 mg/kg/day for eighteen months. There was no significant difference in the incidence of any neoplasm between treated and control animals.

Mutagenesis:
Data are not available concerning long-term effects on mutagenicity in animals or humans.

Impairment of Fertility:
The results of studies in which rats were given 18.75 and 37.5 mg/kg/day indicated that pemoline did not affect fertility in males or females at those doses.

Pregnancy:
Teratogenic effects: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses of 18.75 and 37.5 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic effects:
Studies in rats have shown an increased incidence of stillbirths and cannibalization when pemoline was administered at a dose of 37.5 mg/kg/day. Postnatal survival of offspring was reduced at doses of 18.75 and 37.5 mg/kg/day.

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 CYLERT is administered to a nursing woman.

Pediatric Use:
Safety and effectiveness in children below the age of 6 years have not been established.

Long-term effects of CYLERT in children have not been established (see **WARNINGS**).

CNS stimulants, including pemoline, have been reported to precipitate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and