

Body System	Very Common (≥ 10%)	Common (>1% < 10%)	Uncommon (> 0.1% < 1%)*	Rare (> 0.01% < 0.1%)*
Digestive		Dyspepsia Nausea		
Nervous System		Dizziness		Hypertonia
Cardiovascular	Flushing		Hypertension	Hypotension Syncope
Respiratory		Rhinitis		
Body as a Whole	Headache		Photosensitivity reaction	
Special senses			Abnormal vision	
Urogenital				Erectile disturbance

\*For adverse reactions reported in <1% of patients, only those which warrant special attention, because of their possible association with serious disease states or of otherwise clinical relevance, and which have been reported in >2 cases are listed.

In addition, two cases of priapism have been observed in a Phase I clinical study with 40 mg vardenafil (twice the maximum recommended dose).

In a study evaluating visual function with twice the maximum recommended dose of vardenafil, some patients were found to have mild and transient impairment of colour discrimination in the blue/green range and in the purple range one hour after dosing. These changes had improved by six hours and no changes were present at 24 hours. The majority of these patients had no subjective visual symptoms.

Serious cardiovascular events, including cerebrovascular haemorrhage, myocardial infarction, sudden cardiac death, transient ischaemic attack and ventricular arrhythmia have been reported post marketing in temporal association with another medicinal product in this class.

#### 4.9 Overdose

In single dose volunteer studies, doses up to and including 80 mg per day were tolerated without exhibiting serious adverse reactions.

When vardenafil was administered in higher doses and more frequently than the recommended dosing regimen (40 mg b.i.d.) cases of severe back pain have been reported. This was not associated with any muscle or neurological toxicity.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance, as vardenafil is highly bound to plasma proteins and not significantly eliminated in the urine.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal product used in erectile dysfunction, ATC code: G04B E09

Vardenafil is an oral therapy for the improvement of erectile function in men with erectile dysfunction. In the natural setting, i.e. with sexual stimulation it restores impaired erectile function by increasing blood flow to the penis.

Penile erection is a haemodynamic process. During sexual stimulation, nitric oxide is released. It activates the enzyme guanylate cyclase, resulting in an increased level of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. This in turn results in smooth muscle relaxation, allowing increased inflow of blood into the penis. The level of cGMP is regulated by the rate of synthesis via guanylate cyclase and by the rate of degradation via cGMP hydrolysing phosphodiesterases (PDEs).

Vardenafil is a potent and selective inhibitor of the cGMP specific phosphodiesterase type 5 (PDE5), the most prominent PDE in the human corpus cavernosum. Vardenafil potently enhances the effect of endogenous nitric oxide in the corpus cavernosum by inhibiting PDE5. When nitric oxide is released in response to sexual stimulation, inhibition of PDE5 by vardenafil results in increased corpus cavernosum levels of cGMP. Sexual stimulation is therefore required for vardenafil to produce its beneficial therapeutic effects.

*In vitro* studies have shown that vardenafil is more potent on PDE5 than on other known phosphodiesterases (>15-fold relative to PDE6, >130-fold relative to PDE1, >300-fold relative to PDE11, and >1000-fold relative to PDE2, PDE3, PDE4, PDE7, PDE8, PDE9 and PDE10).

In a penile plethysmography (RigiScan) study, vardenafil 20 mg produced erections considered sufficient for penetration (60% rigidity by RigiScan) in some men as early as 15 minutes after dosing. The overall response of these subjects to vardenafil became statistically significant, compared to placebo, 25 minutes after dosing.

Vardenafil causes mild and transient decreases in blood pressure which, in the majority of the cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 20 mg and 40 mg vardenafil were - 6.9 mmHg under 20 mg and - 4.3 mmHg under 40 mg of vardenafil, when compared to placebo. These effects are consistent with the vasodilatory effects of PDE5-inhibitors and are probably due to increased cGMP levels in vascular smooth muscle cells. Single and multiple oral doses of vardenafil up to 40 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

#### Further information on clinical trials

In clinical studies vardenafil was administered to over 3750 men with erectile dysfunction (ED) aged 18 - 89 years, many of whom had multiple co-morbid conditions. Over 1630 patients have been treated with LEVITRA for six months or longer. Of these, over 730 have been treated for one year or longer. The following patient groups were represented: elderly (22%), patients with hypertension (35%), diabetes mellitus (29%), ischaemic heart disease and other cardiovascular diseases (7%), chronic pulmonary disease (5%), hyperlipidaemia (22%), depression (5%), radical prostatectomy (9%). The following groups were not well represented in clinical trials: elderly (>75 years, 2.4%), and patients with certain cardiovascular conditions (see Section 4.3). No clinical studies in spinal cord injury or other CNS diseases, patients with severe renal or hepatic impairment, pelvic surgery (except nerve-sparing prostatectomy) or trauma or radiotherapy and hypoactive sexual desire or penile anatomic deformities have been performed.

Across the pivotal trials, treatment with vardenafil resulted in an improvement of erectile function compared to placebo. In the small number of patients who attempted intercourse up to four to five hours after dosing the success rate for penetration and maintenance of erection was consistently greater than placebo.

In fixed dose studies in a broad population of men with erectile dysfunction, 68% (5 mg), 76% (10 mg) and 80% (20 mg) of patients experienced successful penetrations (SEP 2) compared to 49% on placebo over a three month study period. The ability to maintain the erection (SEP 3) in this broad ED population was given as 53% (5 mg), 63% (10 mg) and 65% (20 mg) compared to 29% on placebo.

In pooled data from the major efficacy trials, the proportion of patients experiencing successful penetration on vardenafil were as follows: psychogenic erectile dysfunction (77-87%), mixed erectile dysfunction (69-83%), organic erectile dysfunction (64-75%), elderly (52-75%), ischaemic heart disease (70-73%), hyperlipidemia (62-73%), chronic pulmonary disease (74-78%), depression (59-69%), and patients concomitantly treated with antihypertensives (62-73%).

In a clinical trial in patients with diabetes mellitus, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 61% and 49% on 10 mg and 64% and 54% on 20 mg vardenafil compared to 36% and 23% on placebo for patients who completed three months treatment.

In a clinical trial in patients post-prostatectomy patients, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 47% and 37% on 10 mg and 48% and 34% on 20 mg vardenafil compared to 22% and 10% on placebo for patients who completed three months treatment.

The safety and efficacy of vardenafil was maintained in long term studies.

## 5.2 Pharmacokinetic properties

### Absorption

Vardenafil is rapidly absorbed with maximum observed plasma concentrations reached in some men as early as 15 minutes after oral administration. However, 90% of the time, maximum plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 15 %. After oral dosing of vardenafil AUC and  $C_{max}$  increase almost dose proportionally over the recommended dose range (5 – 20 mg).

When vardenafil is taken with a high fat meal (containing 57% fat), the rate of absorption is reduced, with an increase in the median  $t_{max}$  of 1 hour and a mean reduction in  $C_{max}$  of 20%. Vardenafil AUC is not affected. After a meal containing 30% fat, the rate and extent of absorption of vardenafil ( $t_{max}$ ,  $C_{max}$  and AUC) are unchanged compared to administration under fasting conditions.

### Distribution

The mean steady state volume of distribution for vardenafil is 208 l, indicating distribution into the tissues. Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteins (approximately 95% for vardenafil or M1). For vardenafil as well as M1, protein binding is independent of total drug concentrations.

Based on measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.00012% of the administered dose may appear in the semen of patients.

### Metabolism

Vardenafil is metabolised predominantly by hepatic metabolism via cytochrome P450 (CYP) isoform 3A4 with some contribution from CYP3A5 and CYP2C isoforms.

In humans the one major circulating metabolite (M1) results from desethylation of vardenafil and is subject to further metabolism with a plasma elimination half life of approximately 4 hours. Parts of

M1 are in the form of the glucuronide in systemic circulation. Metabolite M1 shows a phosphodiesterase selectivity profile similar to vardenafil and an *in vitro* potency for phosphodiesterase type 5 of approximately 28% compared to vardenafil, resulting in an efficacy contribution of about 7%.

#### Elimination

*The total body clearance of vardenafil is 56 l/h with a resultant terminal half life of approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the faeces (approximately 91-95% of the administered dose) and to a lesser extent in the urine (approximately 2-6% of the administered dose).*

#### Pharmacokinetics in special patient groups

##### Elderly

Hepatic clearance of vardenafil in healthy elderly volunteers (65 years and over) was reduced as compared to healthy younger volunteers (18 - 45 years). On average elderly males had a 52% higher AUC, and a 34% higher C<sub>max</sub> than younger males (see Section 4.2).

##### Renal insufficiency

In volunteers with mild to moderate renal impairment (creatinine clearance 30 – 80 ml/min), the pharmacokinetics of vardenafil were similar to that of a normal renal function control group. In volunteers with severe renal impairment (creatinine clearance < 30 ml/min) the mean AUC was increased by 21% and the mean C<sub>max</sub> decreased by 23%, compared to volunteers with no renal impairment. No statistically significant correlation was observed between creatinine clearance and vardenafil exposure (AUC and C<sub>max</sub>) (see Section 4.2). Vardenafil pharmacokinetics have not been studied in patients requiring dialysis (see section 4.3).

##### Hepatic insufficiency

In patients with mild to moderate hepatic impairment (Child-Pugh A and B), the clearance of vardenafil was reduced in proportion to the degree of hepatic impairment. In patients with mild hepatic impairment (Child-Pugh A), the mean AUC and C<sub>max</sub> increased 17% and 22% respectively, compared to healthy control subjects. In patients with moderate impairment (Child-Pugh B), the mean AUC and C<sub>max</sub> increased 160% and 133% respectively, compared to healthy control subjects (see Section 4.2). The pharmacokinetics of vardenafil in patients with severely impaired hepatic function (Child-Pugh C) have not been studied (see Section 4.3).

### 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Tablet core:

Crospovidone,  
Magnesium Stearate,  
Microcrystalline cellulose,  
Silica, colloidal anhydrous.

#### Film coat:

Macrogol 400,

Hypromellose,  
Titanium dioxide (E171),  
Ferric oxide yellow (E172),  
Ferric oxide red (E172)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

No special precautions for storage.

**6.5 Nature and contents of container**

PP/Aluminium foil blisters in cartons of 2, 4, 8 and 12 tablets.

Not all pack sizes may be marketed.

**6.6 Instructions for use and handling**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Bayer AG,  
D-51368 Leverkusen,  
Germany

**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

## 1. NAME OF THE MEDICINAL PRODUCT

LEVITRA 20 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg vardenafil (as hydrochloride trihydrate)

For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet

Orange round tablets marked with the BAYER-cross on one side and 20 on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for LEVITRA to be effective, sexual stimulation is required.

LEVITRA is not indicated for use by women.

### 4.2 Posology and method of administration

Oral use.

#### Adult men

The recommended dose is 10 mg taken as needed approximately 25 to 60 minutes before sexual activity. Based on efficacy and tolerability the dose may be increased to 20 mg or decreased to 5 mg. The maximum recommended dose is 20 mg. The maximum recommended dosing frequency is once per day. LEVITRA can be taken with or without food. The onset of activity may be delayed if taken with a high fat meal (see Section 5.2).

#### Elderly men

Since vardenafil clearance is reduced in elderly patients (see Section 5.2) a first dose of 5 mg should be used. Based on efficacy and tolerability the dose may be increased to 10 mg and 20 mg.

#### Children and adolescents

LEVITRA is not indicated for individuals below 18 years of age.

#### Use in patients with impaired hepatic function

A starting dose of 5 mg should be considered in patients with mild and moderate hepatic impairment (Child-Pugh A-B). Based on tolerability and efficacy, the dose may be increased to 10 mg and then 20 mg (see section 5.2).

#### Use in patients with impaired renal function

No dosage adjustment is required in patients with mild to moderate renal impairment.

In patients with severe renal impairment (creatinine clearance < 30 ml/min), a starting dose of 5 mg should be considered. Based on tolerability and efficacy the dose may be increased to 10 mg and 20 mg.

#### Use in patients using other medicinal products

When used in combination with the CYP 3A4 inhibitor erythromycin, the dose of vardenafil should not exceed 5 mg (see Section 4.5).

### 4.3 Contraindications

The coadministration of vardenafil with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see Section 4.5 and 5.1).

Agents for the treatment of erectile dysfunction should generally not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure [New York Heart Association III or IV]).

The safety of vardenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available: severe hepatic impairment (Child-Pugh C), endstage renal disease requiring dialysis, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction (within the last 6 months), unstable angina and known hereditary retinal degenerative disorders such as retinitis pigmentosa.

Concomitant use of vardenafil with potent CYP3A4 inhibitors (ritonavir, indinavir, ketoconazole and itraconazole (oral form)) is contraindicated in men older than 75 years.

Hypersensitivity to vardenafil or to any of the excipients.

### 4.4 Special warnings and special precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity (see Section 4.3). Vardenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see Section 5.1).

Agents for the treatment of erectile dysfunction should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

The safety and efficacy of combinations of vardenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

The concomitant use of vardenafil with alpha-blockers may lead to symptomatic hypotension in some patients. Until further information is available, the concomitant use of vardenafil and alpha-blockers is not recommended.

Concomitant use of vardenafil with potent CYP 3A4 inhibitors (ritonavir, indinavir, itraconazole and ketoconazole (oral form)) should be avoided as very high plasma concentrations of vardenafil are reached if the drugs are combined (see Section 4.5 and 4.3).

Vardenafil dose adjustment might be necessary if the CYP 3A4 inhibitors, erythromycin, is given concomitantly (see Section 4.5 and Section 4.2).

Concomitant intake of grapefruit juice is expected to increase the plasma concentrations of vardenafil. The combination should be avoided (see Section 4.5).

Vardenafil has not been studied in patients with spinal cord injury or other CNS disease, hypoactive sexual desire and in patients who have undergone pelvic surgery (except nerve-sparing prostatectomy), pelvic trauma or radiotherapy.

*In vitro* studies with human platelets indicate that vardenafil has no antiaggregatory effect on its own, but at high (super-therapeutic) concentrations vardenafil potentiates the antiaggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, vardenafil had no effect on bleeding time alone or in combination with acetylsalicylic acid (see section 4.5). There is no safety information available on the administration of vardenafil to patients with bleeding disorders or active peptic ulceration. Therefore vardenafil should be administered to these patients only after careful benefit-risk assessment.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### Effects of other medicinal products on vardenafil

###### *In vitro studies:*

Vardenafil is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these isoenzymes may reduce vardenafil clearance.

###### *In vivo studies:*

Co-administration of the HIV protease inhibitor indinavir (800 mg t.i.d.), a potent CYP3A4 inhibitor, with vardenafil (10 mg) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil  $C_{max}$ . At 24 hours, the plasma levels of vardenafil had fallen to approximately 4% of the maximum vardenafil plasma level ( $C_{max}$ ) (see Section 4.4).

Co-administration of ketoconazole (200 mg), a potent CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 10-fold increase in vardenafil AUC and a 4-fold increase in vardenafil  $C_{max}$  (see Section 4.4).

Although specific interaction studies have not been conducted, the concomitant use of other potent CYP3A4 inhibitors (such as itraconazole or ritonavir) can be expected to produce vardenafil plasma levels comparable to those produced by ketoconazole and indinavir. Concomitant use of vardenafil with potent CYP 3A4 inhibitors (ritonavir, indinavir, itraconazole and ketoconazole (oral form)) should be avoided (see Section 4.4).

Co-administration of erythromycin (500 mg t.i.d.), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4-fold increase in vardenafil AUC and a 3-fold increase in  $C_{max}$ . When used in combination with erythromycin, vardenafil dose adjustment might be necessary (see Section 4.2 and Section 4.4). Cimetidine (400 mg b.i.d.), a non-specific cytochrome P450 inhibitor, had no effect on vardenafil AUC and  $C_{max}$  when co-administered with vardenafil (20 mg) to healthy volunteers.



Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of vardenafil (see Section 4.4).

The pharmacokinetics of vardenafil (20 mg) was not affected by co-administration with the H<sub>2</sub>-antagonist ranitidine (150-mg-b.i.d.), digoxin, warfarin, glibenclamide, alcohol (mean maximum blood alcohol level of 73 mg/dl) or single doses of antacid (magnesium hydroxide/aluminium hydroxide).

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect on vardenafil pharmacokinetics of the following concomitant medicinal products: acetylsalicylic acid, ACE-inhibitors, beta-blockers, weak CYP 3A4 inhibitors, diuretics and medications for the treatment of diabetes (sulfonylureas and metformin).

#### Effects of vardenafil on other medicinal products

There are no data on the interaction of vardenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

#### *In vivo studies:*

No potentiation of the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) was observed when vardenafil (10 mg) was given at varying time intervals (1 h to 24 h) prior to the dose of nitroglycerin in a study in 18 healthy male subjects. However, there is no information on the possible potentiation of the hypotensive effects of nitrates by vardenafil in patients, and concomitant use is therefore contraindicated (see Section 4.3). No significant interactions were shown when warfarin (25 mg), which is metabolised by CYP2C9, or digoxin (0.375 mg) was co-administered with vardenafil (20 mg). The relative bioavailability of glibenclamide (3.5 mg) was not affected when co-administered with vardenafil (20 mg). In a specific study, where vardenafil (20 mg) was co-administered with slow release nifedipine (30 mg or 60 mg) in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 6 mmHg and supine diastolic blood pressure of 5 mmHg accompanied with an increase in heart rate of 4 bpm.

When vardenafil (20 mg) and alcohol (mean maximum blood alcohol level of 73 mg/dl) were taken together, vardenafil did not potentiate the effects of alcohol on blood pressure and heart rate and the pharmacokinetics of vardenafil were not altered.

Vardenafil (10 mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid (2 x 81 mg).

#### **4.6 Pregnancy and lactation**

LEVITRA is not indicated for use by women.

#### **4.7 Effects on ability to drive and use machines**

As dizziness and abnormal vision have been reported in clinical trials with vardenafil, patients should be aware of how they react to LEVITRA, before driving or operating machinery.

#### **4.8 Undesirable effects**

Over 3750 patients have received LEVITRA in clinical trials. The adverse reactions were generally transient and mild to moderate in nature. The most commonly reported adverse drug reactions occurring in  $\geq 10\%$  of patients are headache and flushing.

The following adverse reactions have been reported in clinical trials:

Body System	Very Common (≥ 10%)	Common (>1% < 10%)	Uncommon (> 0.1% < 1%)*	Rare (> 0.01% < 0.1%)*
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Nervous System		Dizziness		Hypertonia
Cardiovascular	Flushing		Hypertension	Hypotension Syncope
Respiratory		Rhinitis		
Body as a Whole	Headache		Photosensitivity reaction	
Special senses			Abnormal vision	
Urogenital				Erectile disturbance

\*For adverse reactions reported in <1% of patients, only those which warrant special attention, because of their possible association with serious disease states or of otherwise clinical relevance, and which have been reported in >2 cases are listed.

In addition, two cases of priapism have been observed in a Phase I clinical study with 40 mg vardenafil (twice the maximum recommended dose).

In a study evaluating visual function with twice the maximum recommended dose of vardenafil, some patients were found to have mild and transient impairment of colour discrimination in the blue/green range and in the purple range one hour after dosing. These changes had improved by six hours and no changes were present at 24 hours. The majority of these patients had no subjective visual symptoms.

Serious cardiovascular events, including cerebrovascular haemorrhage, myocardial infarction, sudden cardiac death, transient ischaemic attack and ventricular arrhythmia have been reported post marketing in temporal association with another medicinal product in this class.

#### 4.9 Overdose

In single dose volunteer studies, doses up to and including 80 mg per day were tolerated without exhibiting serious adverse reactions.

When vardenafil was administered in higher doses and more frequently than the recommended dosing regimen (40 mg b.i.d.) cases of severe back pain have been reported. This was not associated with any muscle or neurological toxicity.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance, as vardenafil is highly bound to plasma proteins and not significantly eliminated in the urine.

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*In vitro* studies have shown that vardenafil is more potent on PDE5 than on other known phosphodiesterases (>15-fold relative to PDE6, >130-fold relative to PDE1, >300-fold relative to PDE11, and >1000-fold relative to PDE2, PDE3, PDE4, PDE7, PDE8, PDE9 and PDE10).

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When vardenafil is taken with a high fat meal (containing 57% fat), the rate of absorption is reduced, with an increase in the median  $t_{max}$  of 1 hour and a mean reduction in  $C_{max}$  of 20%. Vardenafil AUC is not affected. After a meal containing 30% fat, the rate and extent of absorption of vardenafil ( $t_{max}$ ,  $C_{max}$  and AUC) are unchanged compared to administration under fasting conditions.

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Vardenafil is metabolised predominantly by hepatic metabolism via cytochrome P450 (CYP) isoform 3A4 with some contribution from CYP3A5 and CYP2C isoforms.

In humans the one major circulating metabolite (M1) results from desethylation of vardenafil and is subject to further metabolism with a plasma elimination half life of approximately 4 hours. Parts of

M1 are in the form of the glucuronide in systemic circulation. Metabolite M1 shows a phosphodiesterase selectivity profile similar to vardenafil and an *in vitro* potency for phosphodiesterase type 5 of approximately 28% compared to vardenafil, resulting in an efficacy contribution of about 7%.

### Elimination

*The total body clearance of vardenafil is 56 L/h with a resultant terminal half life of approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the faeces (approximately 91-95% of the administered dose) and to a lesser extent in the urine (approximately 2-6% of the administered dose).*

### Pharmacokinetics in special patient groups

#### Elderly

Hepatic clearance of vardenafil in healthy elderly volunteers (65 years and over) was reduced as compared to healthy younger volunteers (18 - 45 years). On average elderly males had a 52% higher AUC, and a 34% higher  $C_{max}$  than younger males (see Section 4.2).

#### Renal insufficiency

*In volunteers with mild to moderate renal impairment (creatinine clearance 30 – 80 ml/min), the pharmacokinetics of vardenafil were similar to that of a normal renal function control group. In volunteers with severe renal impairment (creatinine clearance < 30 ml/min) the mean AUC was increased by 21% and the mean  $C_{max}$  decreased by 23%, compared to volunteers with no renal impairment. No statistically significant correlation was observed between creatinine clearance and vardenafil exposure (AUC and  $C_{max}$ ) (see Section 4.2). Vardenafil pharmacokinetics have not been studied in patients requiring dialysis (see section 4.3).*

#### Hepatic insufficiency

In patients with mild to moderate hepatic impairment (Child-Pugh A and B), the clearance of vardenafil was reduced in proportion to the degree of hepatic impairment. In patients with mild hepatic impairment (Child-Pugh A), the mean AUC and  $C_{max}$  increased 17% and 22% respectively, compared to healthy control subjects. In patients with moderate impairment (Child-Pugh B), the mean AUC and  $C_{max}$  increased 160% and 133% respectively, compared to healthy control subjects (see Section 4.2). The pharmacokinetics of vardenafil in patients with severely impaired hepatic function (Child-Pugh C) have not been studied (see Section 4.3).

## 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Tablet core:

Crospovidone,  
Magnesium Stearate,  
Microcrystalline cellulose,  
Silica, colloidal anhydrous.

#### Film coat:

Macrogol 400,

Hypromellose,  
Titanium dioxide (E171),  
Ferric oxide yellow (E172),  
Ferric oxide red (E172)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

No special precautions for storage.

**6.5 Nature and contents of container**

PP/Aluminium foil blisters in cartons of 2, 4, 8 and 12 tablets.

Not all pack sizes may be marketed.

**6.6 Instructions for use and handling**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Bayer AG,  
D-51368 Leverkusen,  
Germany

**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

## バルデナフィルと $\alpha$ 遮断薬の併用禁忌措置に関する、米国における対応状況

米国では、2003年8月19日に承認されたが、その際には $\alpha$ 遮断薬を投与中の患者は禁忌とされ、承認時におけるPhase IV commitmentsとして、本薬と $\alpha$ 遮断薬との相互作用に関する臨床薬理試験を追加実施することが計画されていた。しかしながら、その後、承認時に実施中であった臨床薬理試験（試験No. 100547）の成績、第II相から第IV相臨床試験で得られた安全性データの統合解析結果及び市販後の使用成績調査結果等をFDAに提出し、本薬と $\alpha$ 遮断薬との併用投与に関する協議を行った結果、2005年5月13日に、 $\alpha$ 遮断薬を投与中の患者を禁忌から外すことが了承された。

その詳細な経緯及びFDAとの協議内容を以下に示します。

米国では、本薬の承認時（2003年8月19日）に、「健康成人男子を対象とした $\alpha$ 遮断薬との相互作用試験」（試験No. 100480及び試験No. 100481）の成績に基づいて、FDAより $\alpha$ 遮断薬を投与中の患者が「禁忌」とされ、Phase IV commitmentとして、本薬2.5 mgの $\alpha$ 遮断薬との相互作用試験及びタムロシンとテラゾシン以外の $\alpha$ 遮断薬との相互作用試験の2試験を追加実施することが指示されました。

その後、承認の直前に得られていた「 $\alpha$ 遮断薬（タムスロシンとテラゾシン）による治療で安定している良性前立腺肥大症患者を対象とした相互作用試験（試験No. 100535）」の成績に加えて、承認当時実施中であった「 $\alpha$ 遮断薬（タムスロシン）による治療で安定している良性前立腺肥大症患者を対象とした相互作用試験（試験No. 100547）」の成績が新たに得られました。これら2試験の成績から、 $\alpha$ 遮断薬による治療で安定している患者では、本薬との併用による血圧の低下は僅かであり、忍容性も良好であることが確認されたことから、2003年12月22日にこれら試験成績がFDAに提出され、本薬の $\alpha$ 遮断薬との併用投与に関する協議が改めて開始されました。

米国・バイエル社とFDAとの間で行われた一連の協議に関する概略を以下に示します。

### 2004年3月2日 第1回目の会議

新たに提出した良性前立腺肥大症患者を対象とした相互作用試験2試験の成績が、本薬と $\alpha$ 遮断薬との併用投与の可否及び $\alpha$ 遮断薬と併用する場合の本薬の適切な用量を検討するために十分な情報であるか、Phase IV commitmentとして指示された $\alpha$ 遮断薬との相互作用試験の追加実施がやはり必要であるかについて、FDAに照会した。また、添付文書における $\alpha$ 遮断薬を投与中の患者を「禁忌」から外し、併用投与に関して下記のような注意事項を追記することを提案した。

- ・本薬は $\alpha$ 遮断薬であるタムスロシン0.4 mgと併用することができる。
- ・タムスロシン以外の $\alpha$ 遮断薬と併用するには本薬の用量は5 mgを超えないこと。  
また、 $\alpha$ 遮断薬の投与から6時間以内の投与は避けること。
- ・ $\alpha$ 遮断薬による治療で患者の状態が安定している場合のみ、本薬との併用投与を開始すること。