

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 5 mg film-coated tablets.
Vivanza 10 mg film-coated tablets
Vivanza 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of 5 mg film-coated tablets contains 5 mg of vardenafil (as hydrochloride).
Each tablet of 10 mg film-coated tablets contains 10 mg of vardenafil (as hydrochloride).
Each tablet of 20 mg film-coated tablets contains 20 mg of vardenafil (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Vivanza 5 mg film-coated tablets

Orange round tablets marked with 'v' on one side and "5" on the other side.

Vivanza 10 mg film-coated tablets

Orange round tablets marked with 'v' on one side and "10" on the other side.

Vivanza 20 mg film-coated tablets

Orange round tablets marked with 'v' on one side and "20" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult men. Erectile dysfunction is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

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

4.2 Posology and method of administration

Posology

Use in 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. Vivanza 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).

Special populations

Elderly (≥ 65 years old)

Dose adjustments are not required in elderly patients. However, an increase to a maximum 20 mg dose should be carefully considered depending on the individual tolerability (see sections 4.4 and 4.8).

Hepatic impairment

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 subsequently be increased. The maximum dose recommended in patients with moderate hepatic impairment (Child-Pugh B) is 10 mg (see sections 4.3 and 5.2).

Renal impairment

No dose 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.

Paediatric population

Vivanza is not indicated for individuals below 18 years of age. There is no relevant indication for use of Vivanza in children.

Use in patients using other medicinal products

Concomitant use of CYP3A4 inhibitors

When used in combination with the CYP3A4 inhibitors such as erythromycin or clarithromycin, the dose of vardenafil should not exceed 5 mg (see section 4.5).

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Vivanza is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous phosphodiesterase 5 (PDE5) inhibitor exposure (see section 4.4).

Medicinal products 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),
- end stage 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 the potent CYP3A4 inhibitors ketoconazole and itraconazole (oral form) is contraindicated in men older than 75 years.

Concomitant use of vardenafil with HIV protease inhibitors such as ritonavir and indinavir is contraindicated, as they are very potent inhibitors of CYP3A4 (see section 4.5).

The co-administration of PDE5 inhibitors, including vardenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

4.4 Special warnings and 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). Patients with left ventricular outflow obstruction, e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators including Type 5 phosphodiesterase inhibitors.

Medicinal products 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 Vivanza film-coated tablets with vardenafil orodispersible tablets or other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Tolerability of the maximum dose of 20 mg may be lower in elderly patients (≥ 65 years old) (see sections 4.2 and 4.8).

Concomitant use of alpha-blockers

The concomitant use of alpha-blockers and vardenafil may lead to symptomatic hypotension in some patients because both are vasodilators. Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5 mg film-coated tablets. Vardenafil may be administered at any time with tamsulosin or with alfuzosin. With other alpha-blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly (see section 4.5). In those patients already taking an optimized dose of vardenafil, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking vardenafil.

Concomitant use of CYP3A4 inhibitors

Concomitant use of vardenafil with potent CYP3A4 inhibitors such as itraconazole and ketoconazole (oral form) should be avoided as very high plasma concentrations of vardenafil are reached if the medicinal products are combined (see sections 4.5 and 4.3).

Vardenafil dose adjustment might be necessary if moderate CYP3A4 inhibitors such as erythromycin and clarithromycin, are given concomitantly (see sections 4.5 and 4.2).

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

Effect on QTc interval

Single oral doses of 10 mg and 80 mg of vardenafil have been shown to prolong the QTc interval by a mean of 8 msec and 10 msec, respectively. And single doses of 10 mg vardenafil co-administered concomitantly with 400 mg gatifloxacin, an active substance with comparable QT effect, showed an additive QTc effect of 4 msec when compared to either active substance alone. The clinical impact of these QT changes is unknown (see section 5.1).

The clinical relevance of this finding is unknown and cannot be generalised to all patients under all circumstances, as it will depend on the individual risk factors and susceptibilities that may be present at any time in any given patient. Medicinal products that may prolong QTc interval, including vardenafil, are best avoided in patients with relevant risk factors, for example, hypokalaemia, congenital QT

prolongation, concomitant administration of antiarrhythmic medicinal products in Class 1A (e.g. quinidine, procainamide), or Class III (e.g. amiodarone, sotalol).

Effect on vision

Visual defects and cases of non-arteritic ischemic optic neuropathy (NAION) have been reported in connection with the intake of Vivanza and other PDE5 inhibitors. The patient should be advised that in the case of sudden visual defect, he should stop taking Vivanza and consult immediately a physician (see section 4.3).

Effect on bleeding

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 three times a day), a potent CYP 3A4 inhibitor, with vardenafil (10 mg film-coated tablets) 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}).

Co-administration of vardenafil with ritonavir (600 mg twice daily) resulted in a 13-fold increase in vardenafil C_{max} and a 49-fold increase in vardenafil AUC_{0-24} when co-administered with vardenafil 5 mg. The interaction is a consequence of blocking hepatic metabolism of vardenafil by ritonavir, a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. Ritonavir significantly prolonged the half-life of vardenafil to 25.7 hours (see section 4.3).

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) can be expected to produce vardenafil plasma levels comparable to those produced by ketoconazole. Concomitant use of vardenafil with potent CYP3A4 inhibitors such as itraconazole and ketoconazole (oral use) should be avoided (see sections 4.3 and 4.4). In men older than 75 years the concomitant use of vardenafil with itraconazole or ketoconazole is contraindicated (see section 4.3)

Co-administration of erythromycin (500 mg three times a day), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max} . Although a specific interaction study has not been conducted, the co-administration of clarithromycin can be expected to result in similar effects on vardenafil AUC and C_{max} . When used in combination with a moderate CYP 3A4 inhibitor such as erythromycin or clarithromycin, vardenafil dose adjustment might be necessary (see sections 4.2 and 4.4). Cimetidine (400 mg twice daily), 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 H2-antagonist ranitidine (150 mg twice daily), 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 CYP3A4 inhibitors, diuretics and medicinal products 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. Vardenafil 20 mg film-coated tablets potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 1 and 4 hours after vardenafil administration to healthy middle aged subjects. No effect on blood pressure was observed when nitroglycerin was taken 24 hours after administration of a single dose of vardenafil 20 mg film-coated tablets. 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).

Nicorandil is a hybrid of potassium channel opener and nitrate. Due to the nitrate component, it has the potential to have serious interaction with vardenafil.

Since alpha-blocker monotherapy can cause marked lowering of blood pressure, especially postural hypotension and syncope, interaction studies were conducted with vardenafil. In two interaction studies with healthy normotensive volunteers after forced titration of the alpha-blockers tamsulosin or terazosin to high doses, hypotension (in some cases symptomatic) was reported in a significant number of subjects after co-administration of vardenafil. Among subjects treated with terazosin, hypotension was observed more frequently when vardenafil and terazosin were given simultaneously than when the dosing was separated by a time interval of 6 hours.

Based on the results of interaction studies conducted with vardenafil in patients with benign prostatic hyperplasia (BPH) on stable tamsulosin, terazosin or alfuzosin therapy:

- When vardenafil (film-coated tablets) was given at doses of 5, 10 or 20 mg on a background of stable therapy with tamsulosin, there was no symptomatic reduction in blood pressure, although 3/21 tamsulosin treated subjects exhibited transient standing systolic blood pressures of less than 85 mmHg.
- When vardenafil 5 mg (film-coated tablets) was given simultaneously with terazosin 5 or 10 mg, one of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when vardenafil 5 mg and terazosin administration was separated by 6 hours.
- When vardenafil (film-coated tablets) was given at doses of 5 or 10 mg on a background of stable therapy with alfuzosin, compared to placebo, there was no symptomatic reduction in blood pressure.

Therefore, concomitant treatment should be initiated only if the patient is stable on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5 mg. Vivanza may be administered at any time with tamsulosin or alfuzosin. With other alpha-blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly (see section 4.4).

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 film-coated tablets). 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 film-coated tablets) 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).

Riociguat

Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including vardenafil, is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Vivanza is not indicated for use by women. There are no studies of vardenafil in pregnant women. There are no fertility data available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The adverse reactions reported with Vivanza film-coated tablets or vardenafil 10 mg orodispersible tablets in clinical trials were generally transient and mild to moderate in nature. The most commonly reported adverse drug reaction occurring in $\geq 10\%$ of patients is headache.

Adverse reactions are listed according to the MedDRA frequency convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and not known (can not be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The following adverse reactions have been reported:

System organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (can not be estimated from the available data)
Infection and infestations				Conjunctivitis	
Immune system disorders			Allergic oedema and angioedema	Allergic reaction	
Psychiatric disorders			Sleep disorder	Anxiety	
Nervous system disorders	Headache	Dizziness	Somnolence Paraesthesia and dysaesthesia	Syncope Seizure Amnesia	
Eye disorders			Visual disturbance Ocular hyperemia Visual colour distortions Eye pain and eye discomfort Photophobia	Increase in intraocular pressure Lacrimation increased	Non-arteritic anterior ischemic optic neuropathy Visual defects
Ear and labyrinth disorders			Tinnitus Vertigo		Sudden deafness
Cardiac disorders			Palpitation Tachycardia	Myocardial infarction Ventricular tachy-arrythmias Angina pectoris	
Vascular disorders		Flushing		Hypertension Hypotension	
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Dyspnoea Sinus congestion	Epistaxis	
Gastrointestinal disorders		Dyspepsia	Gastro-oesophageal reflux disease Gastritis Gastrointestinal and abdominal pain Diarrhoea Vomiting Nausea Dry mouth		
Hepatobilliary disorders			Increase in transaminases	Increase in gamma-glutamyl transferase	

System organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (can not be estimated from the available data)
Skin and subcutaneous tissue disorders			Erythema Rash	Photosensitivity reaction	
Musculoskeletal and connective tissue disorders			Back Pain Increase in creatine phosphokinase Myalgia Increased muscle tone and cramping		
Renal and urinary disorders					Haematuria
Reproductive system and breast disorders			Increase in erection	Priapism	Penile Haemorrhage Haemospermia
General disorders and administration site conditions			Feeling unwell	Chest pain	

Penile haemorrhage, haemospermia and haematuria have been reported in clinical trials and spontaneous post-marketing data with the use of all PDE5 inhibitors, including vardenafil.

At the 20 mg dose Vivanza film-coated tablets, elderly (≥ 65 years old) patients had higher frequencies of headaches (16.2% versus 11.8%) and dizziness (3.7% versus 0.7%) than younger patients (<65 years old). In general, the incidence of adverse reactions (especially “dizziness”) has been shown to be slightly higher in patients with a history of hypertension.

Post-marketing reports of another medicinal product of this class

Vascular disorders

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in Appendix V**.

4.9 Overdose

In single dose volunteer studies, doses up to and including 80 mg vardenafil (film-coated tablets) per day were tolerated without exhibiting serious adverse reactions.

When vardenafil was administered in higher doses and more frequently than the recommended dose regimen (40 mg film-coated tablets twice daily) 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: Urologicals, Drugs used in erectile dysfunction, ATC code: G04BE09.

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.

A single dose, double blind, crossover, randomised trial in 59 healthy males compared the effects on the QT interval of vardenafil (10 mg and 80 mg), sildenafil (50 mg and 400 mg) and placebo. Moxifloxacin (400 mg) was included as an active internal control. Effects on the QT interval were measured one hour post-dose (average t_{max} for vardenafil). The primary objective of this study was to rule out a greater than 10 msec effect (i.e. to demonstrate lack of effect) of a single 80 mg oral dose of vardenafil on QTc interval compared to placebo, as measured by the change in Fridericia's correction formula ($QTcF=QT/RR^{1/3}$) from baseline at the 1 hour post-dose time point. The vardenafil results showed an

increase in QTc (Fridericia) of 8 msec (90% CI: 6-9) and 10 msec (90% CI: 8-11) at 10 and 80 mg doses compared to placebo and an increase in QTci of 4 msec (90% CI: 3-6) and 6 msec (90% CI: 4-7) at 10 and 80 mg doses compared to placebo, at one hour post-dose. At t_{max} , only the mean change in QTcF for vardenafil 80 mg was out of the study established limit (mean 10 msec, 90% CI 8-11). When using the individual correction formulae, none of the values was out of the limit.

In a separate post-marketing study of 44 healthy volunteers, single doses of 10 mg vardenafil or 50 mg sildenafil were co-administered concomitantly with 400 mg gatifloxacin, a drug with comparable QT effect. Both vardenafil and sildenafil showed an increase of Fridericia QTc effect of 4 msec (vardenafil) and 5 msec (sildenafil) when compared to either drug alone. The actual clinical impact of these QT changes is unknown.

Further information on clinical trials with vardenafil 10 mg orodispersible tablets

Efficacy and safety of vardenafil 10 mg orodispersible tablets were separately demonstrated in a broad population in two studies including 701 randomized erectile dysfunction patients who were treated up to 12 weeks. The distribution of patients in the predefined subgroups was covering elderly patients (51%), patients with history of diabetes mellitus (29%), dyslipidemia (39%) and hypertension (40%).

In pooled data from the two vardenafil 10 mg orodispersible tablets trials, IIEF-EF domain scores were significantly higher with vardenafil 10 mg orodispersible tablet versus placebo.

A percentage of 71% of all sexual attempts reported in the clinical trials had successful penetration compared to 44% of all attempts in the placebo group. These results were also reflected in subgroups, in elderly patients (65%), in patients with history of diabetes mellitus (63%), patients with history of dyslipidemia (66%) and hypertension (70%) of all sexual attempts reported had successful penetration.

About 63% of all reported sexual attempts with vardenafil 10 mg orodispersible tablets were successful in terms of erection maintenance compared to about 26% of all placebo-controlled sexual attempts. In the predefined subgroups 57% (elderly patients), 56% (patients with history of diabetes mellitus), 59% (patients with history of dyslipidemia) and 60% (patients with history of hypertension) of all reported attempts with vardenafil 10 mg orodispersible tablets were successful in terms of maintenance of erection.

Further information on clinical trials

In clinical trials vardenafil was administered to over 17,000 men with erectile dysfunction (ED) aged 18 - 89 years, many of whom had multiple co-morbid conditions. Over 2,500 patients have been treated with vardenafil for six months or longer. Of these, 900 patients 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%), hyperlipidemia (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 trials in CNS diseases (except spinal cord injury), 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 (film-coated tablets) 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 (film-coated tablets) 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 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.

In a flexible-dose clinical trial in patients with Spinal Cord Injury, 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. The number of patients who returned to a normal IIEF domain score (≥ 26) were 53% on vardenafil compared to 9% on placebo. The response rates for the ability to obtain and maintain an erection were 76% and 59% on vardenafil compared to 41% and 22% on placebo for patients who completed three months treatment which were clinically and statistically significant ($p < 0.001$).

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Bioequivalence studies have shown that vardenafil 10 mg orodispersible tablet is not bioequivalent to vardenafil 10 mg film-coated tablets; therefore, the orodispersible formulation should not be used as an equivalent to vardenafil 10 mg film-coated tablets.

Absorption

In vardenafil film-coated tablets, 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 film-coated tablets are 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.

Vardenafil is rapidly absorbed after administration of vardenafil 10 mg orodispersible tablets without water. The median time to reach C_{max} varied between 45 to 90 minutes and was similar or slightly delayed (by 8 to 45 min) compared to the film-coated tablets. Mean vardenafil AUC was increased by

21 to 29% (middle aged and elderly ED patients) or 44% (young healthy subjects) with 10 mg orodispersible tablets compared to film coated tablets as a result of local oral absorption of a small amount of drug in the oral cavity. There was no consistent difference in mean C_{max} between orodispersible tablets and film coated tablets.

In subjects taking vardenafil 10 mg orodispersible tablets with a high fat meal no effect on vardenafil AUC and t_{max} was observed, while vardenafil C_{max} was reduced by 35% in the fed condition. Based on these results vardenafil 10 mg orodispersible tablets can be taken with or without food.

If vardenafil 10 mg orodispersible tablets are taken with water, the AUC is reduced by 29%, C_{max} remains unchanged and median t_{max} is shortened by 60 minutes compared to intake without water. Vardenafil 10 mg orodispersible tablets must be taken without liquid.

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.

Biotransformation

Vardenafil in film-coated tablets 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%.

The mean terminal half-life of vardenafil in patients receiving vardenafil 10 mg orodispersible tablets ranged between 4 – 6 hours. The elimination half-life of the metabolite M1 is between 3 to 5 hours, similar to parent drug.

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 taking vardenafil film-coated tablets had a 52% higher AUC, and a 34% higher C_{max} than younger males (see section 4.2).

Vardenafil AUC and C_{max} in elderly patients (65 years or over) taking vardenafil orodispersible tablets were increased by 31 to 39% and 16 to 21%, respectively, in comparison to patients aged 45 years and below. Vardenafil was not found to accumulate in the plasma in patients aged 45 years and below or 65 years or over following once-daily dosing of vardenafil 10 mg orodispersible tablets over ten days.

Renal impairment

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 has not been studied in patients requiring dialysis (see section 4.3).

Hepatic impairment

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 by 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) has not been studied (see section 4.3).

5.3 Preclinical safety data

Non-clinical 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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 2, 4, 8, 12 and 20 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/249/001-004, 013
EU/1/03/249/005-008, 014
EU/1/03/249/009-012, 015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 March 2003

Date of latest renewal: 4 March 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 10 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 10 mg of vardenafil (as hydrochloride).

Excipients:

7.96 mg sorbitol (E420), and 1.80 mg aspartame (E951) per orodispersible tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet.

White round tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult men. Erectile dysfunction is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

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

4.2 Posology and method of administration

Posology

Vivanza 10 mg orodispersible tablet is not bioequivalent to Vivanza 10 mg film-coated tablet (see section 5.1). The maximum dose for Vivanza orodispersible tablet is 10 mg/day.

Use in adult men

Vivanza 10 mg orodispersible tablets are taken as needed approximately 25 to 60 minutes before sexual activity.

Special populations

Elderly (≥ 65 years old)

Dose adjustments are not required in elderly patients. However, an increase to a maximum dose of Vivanza 20 mg film-coated tablets should be carefully considered depending on the individual tolerability (see sections 4.4 and 4.8).

Hepatic impairment

Vivanza 10 mg orodispersible tablets are not indicated as a starting dose in patients with mild hepatic impairment (Child-Pugh A).

Patients with mild hepatic impairment should start treatment with Vivanza 5 mg film-coated tablets. Based on tolerability and efficacy, the dose may be increased to Vivanza 10 mg and 20 mg film-coated tablets, or Vivanza 10 mg orodispersible tablets.

The maximum dose recommended in patients with moderate hepatic impairment (Child-Pugh B) is Vivanza 10 mg as film-coated tablets (see section 5.2).

Vivanza 10 mg orodispersible tablets are not for use in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C; see section 4.3).

Renal impairment

No dose 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 Vivanza 5 mg film-coated tablets should be considered. Based on tolerability and efficacy, the dose may be increased to Vivanza 10 mg and 20 mg film-coated tablets, or Vivanza 10 mg orodispersible tablets. Vivanza orodispersible tablet is not for use in patients with end-stage renal failure (see section 4.3).

Paediatric population

Vivanza orodispersible tablets are not indicated for individuals below 18 years of age. There is no relevant indication for use of Vivanza orodispersible tablets in children and adolescents.

Use in patients using other medicinal products

Concomitant use of moderate or potent CYP 3A4 inhibitors

Vardenafil dose adjustment is necessary if moderate or potent CYP 3A4 inhibitors are given concomitantly (see section 4.5).

Method of administration

For oral use.

The orodispersible tablet should be placed in the mouth on the tongue, where it will rapidly disintegrate, and then swallowed. Vivanza orodispersible tablets must be taken without liquid and immediately upon release from the blister.

Vivanza orodispersible tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Vivanza is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous phosphodiesterase 5 (PDE5) inhibitor exposure (see section 4.4).

Medicinal products 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),
- end stage 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 the potent CYP3A4 inhibitors ketoconazole and itraconazole (oral form) is contraindicated in men older than 75 years.

Concomitant use of vardenafil with HIV protease inhibitors such as ritonavir and indinavir is contraindicated, as they are very potent inhibitors of CYP3A4 (see section 4.5).

The co-administration of PDE5 inhibitors, including vardenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

4.4 Special warnings and 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). Patients with left ventricular outflow obstruction, e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators including Type 5 phosphodiesterase inhibitors.

Medicinal products 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 Vivanza orodispersible tablets with Vivanza film-coated tablets or other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Tolerability of the maximum dose of Vivanza 20 mg film-coated tablets may be lower in elderly patients (≥ 65 years old) (see sections 4.2 and 4.8).

Concomitant use of alpha-blockers

The concomitant use of alpha-blockers and vardenafil may lead to symptomatic hypotension in some patients because both are vasodilators. Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5 mg film-coated tablets. Patients treated with alpha-blockers should not use Vivanza 10 mg orodispersible tablets as a starting dose. Vardenafil may be administered at any time with tamsulosin or with alfuzosin. With other alpha-blockers a time separation of dose should be considered when vardenafil is prescribed concomitantly (see section 4.5). In those patients already taking an optimised dose of vardenafil, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking vardenafil.

Concomitant use of CYP 3A4 inhibitors

Concomitant use of vardenafil with potent CYP 3A4 inhibitors such as itraconazole and ketoconazole (oral form) should be avoided as very high plasma concentrations of vardenafil are reached if the medicinal products are combined (see sections 4.5 and 4.3).

Vardenafil dose adjustment might be necessary if moderate CYP 3A4 inhibitors such as erythromycin and clarithromycin, are given concomitantly (see section 4.2 and 4.5).

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

Effect on QTc interval

Single oral doses of 10 mg and 80 mg of vardenafil have been shown to prolong the QTc interval by a mean of 8 msec and 10 msec, respectively. And single doses of 10 mg vardenafil co-administered concomitantly with 400 mg gatifloxacin, an active substance with comparable QT effect, showed an additive QTc effect of 4 msec when compared to either active substance alone. The clinical impact of these QT changes is unknown (see section 5.1).

The clinical relevance of this finding is unknown and cannot be generalised to all patients under all circumstances, as it will depend on the individual risk factors and susceptibilities that may be present at any time in any given patient. Medicinal products that may prolong QTc interval, including vardenafil,

are best avoided in patients with relevant risk factors, for example, hypokalaemia, congenital QT prolongation, concomitant administration of antiarrhythmic medicinal products in Class IA (e.g. quinidine, procainamide), or Class III (e.g. amiodarone, sotalol).

Effect on vision

Visual defects and cases of non-arteritic ischemic optic neuropathy (NAION) have been reported in connection with the intake of Vivanza and other PDE5 inhibitors. The patient should be advised that in the case of sudden visual defect, he should stop taking Vivanza orodispersible tablets and consult immediately a physician (see section 4.3).

Effect on bleeding

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.

Aspartame

Vivanza 10 mg orodispersible tablets contain aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria.

Sorbitol

Vivanza 10 mg orodispersible tablets contain sorbitol. Patients with rare hereditary problems of fructose intolerance should not take Vivanza 10 mg orodispersible tablets.

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 reduce vardenafil clearance.

In vivo studies

Co-administration of the HIV protease inhibitor indinavir (800 mg three times a day), a potent CYP3A4 inhibitor, with vardenafil (10 mg film-coated tablet) 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}).

Co-administration of vardenafil with ritonavir (600 mg twice daily) resulted in a 13-fold increase in vardenafil C_{max} and a 49-fold increase in vardenafil AUC_{0-24} when co-administered with vardenafil 5 mg. The interaction is a consequence of blocking hepatic metabolism of vardenafil by ritonavir, a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. Ritonavir significantly prolonged the half-life of vardenafil to 25.7 hours (see section 4.3).

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) can be expected to produce vardenafil plasma levels comparable to those produced by ketoconazole. Concomitant use of vardenafil with potent CYP 3A4 inhibitors such as itraconazole and ketoconazole (oral use) should be avoided (see sections 4.3 and 4.4). In men older than 75 years the concomitant use of vardenafil with itraconazole or ketoconazole is contraindicated (see section 4.3).

Co-administration of erythromycin (500 mg three times a day), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max} . Although a specific interaction study has not been conducted, the co-administration of clarithromycin can be expected to result in similar effects on vardenafil AUC and C_{max} . When used in combination with a moderate CYP 3A4 inhibitor such as erythromycin or clarithromycin, vardenafil dose adjustment might be necessary (see sections 4.2 and 4.4).

Cimetidine (400 mg twice daily), 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 H2-antagonist ranitidine (150 mg twice daily), 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 medicinal products 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. Vardenafil 20 mg film-coated tablets potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 1 and 4 hours after vardenafil administration to healthy middle aged subjects. No effect on blood pressure was observed when nitroglycerin was taken 24 hours after administration of a single dose of vardenafil 20 mg film-coated tablet. However, there is no information on the possible potentiation of the hypotensive effects of nitrates by vardenafil in patients, and concomitant use of Vivanza orodispersible tablets and nitrates is therefore contraindicated (see section 4.3).

Nicorandil is a hybrid of potassium channel opener and nitrate. Due to the nitrate component it has the potential to have serious interaction with vardenafil.

Since alpha-blocker monotherapy can cause marked lowering of blood pressure, especially postural hypotension and syncope, interaction studies were conducted with vardenafil. In two interaction studies with healthy normotensive volunteers after forced titration of the alpha-blockers tamsulosin or terazosin to high doses, hypotension (in some cases symptomatic) was reported in a significant number of subjects after co-administration of vardenafil. Among subjects treated with terazosin, hypotension was observed more frequently when vardenafil and terazosin were given simultaneously than when the dosing was separated by a time interval of 6 hours.

Based on the results of interaction studies conducted with vardenafil in patients with benign prostatic hyperplasia (BPH) on stable tamsulosin, terazosin or alfuzosin therapy:

- When vardenafil (film-coated tablets) was given at doses of 5, 10 or 20 mg on a background of stable therapy with tamsulosin, there was no symptomatic reduction in blood pressure, although 3/21 tamsulosin treated subjects exhibited transient standing systolic blood pressures of less than 85 mmHg.
- When vardenafil 5 mg (film-coated tablets) was given simultaneously with terazosin 5 or 10 mg, one of 21 patients experienced symptomatic postural hypotension. Hypotension was not observed when vardenafil 5 mg and terazosin administration was separated by 6 hours.
- When vardenafil (film-coated tablets) was given at doses of 5 or 10 mg on a background of stable therapy with alfuzosin, compared to placebo, there was no symptomatic reduction in blood pressure.

Therefore, concomitant treatment should be initiated only if the patient is stable on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5mg. Vivanza may be administered at any time with tamsulosin or alfuzosin. With other alpha-blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly (see section 4.4).

Vivanza 10 mg orodispersible tablets should not be taken as starting dose in patients treated with alpha-blockers (see section 4.4).

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 film-coated tablets). 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 film-coated tablet) 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).

Riociguat

Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including vardenafil, is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Vivanza is not indicated for use by women. There are no studies of vardenafil in pregnant women. There are no fertility data available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The adverse reactions reported with Vivanza film-coated tablets or 10 mg orodispersible tablets in clinical trials were generally transient and mild to moderate in nature. The most commonly reported adverse drug reaction occurring in $\geq 10\%$ of patients is headache.

Adverse reactions are listed according to the MedDRA frequency convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and not known (can not be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The following adverse reactions have been reported:

System organ class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Not known (can not be estimated from the available data)
Infection and infestations				Conjunctivitis	
Immune system disorders			Allergic oedema and angioedema	Allergic reaction	
Psychiatric disorders			Sleep disorder	Anxiety	
Nervous system disorders	Headache	Dizziness	Somnolence Paraesthesia and dysaesthesia	Syncope Seizure Amnesia	
Eye disorders			Visual disturbance Ocular hyperaemia Visual colour distortions Eye pain and eye discomfort Photophobia	Increase in intraocular pressure Lacrimation increased	Non-arteritic anterior ischemic optic neuropathy Visual defects
Ear and labyrinth disorders			Tinnitus Vertigo		Sudden deafness
Cardiac disorders			Palpitation Tachycardia	Myocardial infarction Ventricular tachy-arrhythmias Angina pectoris	
Vascular disorders		Flushing		Hypotension Hypertension	
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Dyspnoea Sinus congestion	Epistaxis	

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (can not be estimated from the available data)
Gastrointestinal disorders		Dyspepsia	Gastro-oesophageal reflux disease Gastritis Gastrointestinal and abdominal pain Diarrhoea Vomiting Nausea Dry mouth		
Hepatobiliary disorders			Increase in transaminases	Increase in gamma-glutamyl transferase	
Skin and subcutaneous tissue disorders			Erythema Rash	Photosensitivity reaction	
Musculoskeletal and connective tissue disorders			Back pain Increase in creatine phosphokinase Myalgia Increased muscle tone and cramping		
Renal and urinary disorders					Haematuria
Reproductive system and breast disorders			Increase in erection	Priapism	Penile Haemorrhage Haemospermia
General disorders and administration site conditions			Feeling unwell	Chest pain	

Penile haemorrhage, haemospermia and haematuria have been reported in clinical trials and spontaneous post-marketing data with the use of all PDE5 inhibitors, including vardenafil.

At the 20 mg dose Vivanza film-coated tablets, elderly (≥ 65 years old) patients had higher frequencies of headaches (16.2% versus 11.8%) and dizziness (3.7% versus 0.7%) than younger patients (<65 years old). In general, the incidence of adverse reactions (especially “dizziness”) has been shown to be slightly higher in patients with a history of hypertension.

Post-marketing reports of another medicinal product of this class

Vascular disorders

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in Appendix V**.

4.9 Overdose

In single dose volunteer studies, doses up to and including 80 mg vardenafil (film-coated tablets) per day were tolerated without exhibiting serious adverse reactions.

When vardenafil was administered in higher doses and more frequently than the recommended dose regimen (40 mg film-coated tablets twice daily) 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: Urologicals, Drugs used in erectile dysfunction, ATC code: G04BE09.

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.

A single dose, double blind, crossover, randomised trial in 59 healthy males compared the effects on the QT interval of vardenafil (10 mg and 80 mg), sildenafil (50 mg and 400 mg) and placebo. Moxifloxacin (400 mg) was included as an active internal control. Effects on the QT interval were measured one hour post-dose (average t_{max} for vardenafil). The primary objective of this study was to rule out a greater than 10 msec effect (i.e. to demonstrate lack of effect) of a single 80 mg oral dose of vardenafil on QTc interval compared to placebo, as measured by the change in Fridericia's correction formula ($QTcF=QT/RR^{1/3}$) from baseline at the 1 hour post-dose time point. The vardenafil results showed an increase in QTc (Fridericia) of 8 msec (90% CI: 6-9) and 10 msec (90% CI: 8-11) at 10 and 80 mg doses compared to placebo and an increase in QTci of 4 msec (90% CI: 3-6) and 6 msec (90% CI: 4-7) at 10 and 80 mg doses compared to placebo, at one hour post-dose. At t_{max} , only the mean change in QTcF for vardenafil 80 mg was out of the study established limit (mean 10 msec, 90% CI 8-11). When using the individual correction formulae, none of the values were out of the limit.

In a separate post-marketing study of 44 healthy volunteers, single doses of 10 mg vardenafil or 50 mg sildenafil were co-administered concomitantly with 400 mg gatifloxacin, a drug with comparable QT effect. Both vardenafil and sildenafil showed an increase of Fridericia QTc effect of 4 msec (vardenafil) and 5 msec (sildenafil) when compared to either drug alone. The actual clinical impact of these QT changes is unknown.

Further information on clinical trials with Vardenafil 10 mg orodispersible tablets

Efficacy and safety of vardenafil 10 mg orodispersible tablets were separately demonstrated in a broad population in two studies including 701 randomized erectile dysfunction patients who were treated up to 12 weeks. The distribution of patients in the predefined subgroups was covering elderly patients (51%), patients with history of diabetes mellitus (29%), dyslipidemia (39%) and hypertension (40%).

In pooled data from the two vardenafil 10 mg orodispersible tablets trials, IIEF-EF domain scores were significantly higher with vardenafil 10 mg orodispersible tablet versus placebo.

A percentage of 71% of all sexual attempts reported in the clinical trials had successful penetration compared to 44% of all attempts in the placebo group. These results were also reflected in subgroups, in elderly patients (65%), in patients with history of diabetes mellitus (63%), patients with history of dyslipidemia (66%) and hypertension (70%) of all sexual attempts reported had successful penetration.

About 63% of all reported sexual attempts with vardenafil 10 mg orodispersible tablets were successful in terms of erection maintenance compared to about 26% of all placebo-controlled sexual attempts. In the predefined subgroups 57% (elderly patients), 56% (patients with history of diabetes mellitus), 59% (patients with history of dyslipidemia) and 60% (patients with history of hypertension) of all reported attempts with vardenafil 10 mg orodispersible tablets were successful in terms of maintenance of erection.

Further information on clinical trials

In clinical trials vardenafil was administered to over 17,000 men with erectile dysfunction (ED) aged 18 - 89 years, many of whom had multiple co-morbid conditions. Over 2,500 patients were treated with vardenafil for 6 months or longer. Of these, 900 patients 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%), hyperlipidemia (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 trials in CNS diseases (except spinal cord injury), 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 (film-coated tablets) 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 (film-coated tablets) 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 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.

In a flexible-dose clinical trial in patients with Spinal Cord Injury, 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. The number of patients who returned to a normal IIEF domain score (≥ 26) were 53% on vardenafil compared to 9% on placebo. The response rates for the ability to obtain and maintain an erection were 76% and 59% on vardenafil compared to 41% and 22% on placebo for patients who completed three months treatment which were clinically and statistically significant ($p < 0.001$).

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Bioequivalence studies have shown that vardenafil 10 mg orodispersible tablet is not bioequivalent to vardenafil 10 mg film-coated tablet; therefore, the orodispersible formulation should not be used as an equivalent to vardenafil 10 mg film-coated tablets.

Absorption

In vardenafil film-coated tablets, 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 Vivanza film-coated tablets are 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.

Vardenafil is rapidly absorbed after administration of 10 mg orodispersible tablets without water. The median time to reach C_{max} varied between 45 to 90 minutes and was similar or slightly delayed (by 8 to 45 min) compared to the film-coated tablets. Mean vardenafil AUC was increased by 21 to 29% (middle aged and elderly ED patients) or 44% (young healthy subjects) with 10 mg orodispersible tablets compared to film coated tablets as a result of local oral absorption of a small amount of drug in the oral cavity. There was no consistent difference in mean C_{max} between orodispersible tablets and film coated tablets.

In subjects taking vardenafil 10 mg orodispersible tablets with a high fat meal no effect on vardenafil AUC and t_{max} was observed, while vardenafil C_{max} was reduced by 35% in the fed condition. Based on these results Vivanza 10 mg orodispersible tablets can be taken with or without food.

If Vivanza 10 mg orodispersible tablets are taken with water, the AUC is reduced by 29%, C_{max} remains unchanged and median t_{max} is shortened by 60 minutes compared to intake without water. Vivanza 10 mg orodispersible tablets must be taken without liquid.

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.

Biotransformation

Vardenafil in Vivanza film-coated tablets 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%.

The mean terminal half-life of vardenafil in patients receiving Vivanza 10 mg orodispersible tablets ranged between 4 – 6 hours. The elimination half-life of the metabolite M1 is between 3 to 5 hours, similar to parent drug.

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 taking Vivanza film-coated tablets had a 52% higher AUC, and a 34% higher C_{max} than younger males (see section 4.2).

Vardenafil AUC and C_{max} in elderly patients (65 years or over) taking vardenafil orodispersible tablets were increased by 31 to 39% and 16 to 21%, respectively, in comparison to patients aged 45 years and below. Vardenafil was not found to accumulate in the plasma in patients aged 45 years and below or 65 years or over following once-daily dosing of vardenafil 10 mg orodispersible tablets over ten days.

Renal impairment

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 has not been studied in patients requiring dialysis (see section 4.3).

Hepatic impairment

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 by 17% and 22% respectively, compared to healthy control subjects. In patients with moderate impairment (Child-Pugh B), the mean AUC and C_{max} increased by 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) has not been studied (see section 4.3).

5.3 Preclinical safety data

Non-clinical 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

Aspartame (E951)
Peppermint flavour.
Magnesium stearate.
Crospovidone.
Mannitol (E421)
Silica colloidal hydrated.
Sorbitol (E420)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from humidity and light.

6.5 Nature and contents of container

4 x 1 orodispersible tablets in alu/alu perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/249/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 March 2003

Date of latest renewal: 4 March 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- D. CONDITION OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 5 mg film-coated tablets
vardenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg vardenafil (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets
20 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/249/001 2 tablets
EU/1/03/249/002 4 tablets
EU/1/03/249/003 8 tablets
EU/1/03/249/004 12 tablets
EU/1/03/249/013 20 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vivanza 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 5 mg film-coated tablets
vardenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 10 mg film-coated tablets
vardenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg vardenafil (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets
20 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/249/005 2 tablets
EU/1/03/249/006 4 tablets
EU/1/03/249/007 8 tablets
EU/1/03/249/008 12 tablets
EU/1/03/249/014 20 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vivanza 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 10 mg film-coated tablets
vardenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 20 mg film-coated tablets
vardenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg vardenafil (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets
20 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/249/009 2 tablets
EU/1/03/249/010 4 tablets
EU/1/03/249/011 8 tablets
EU/1/03/249/012 12 tablets
EU/1/03/249/015 20 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vivanza 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 20 mg film-coated tablets
vardenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 10 mg orodispersible tablets
vardenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg vardenafil (as hydrochloride).

3. LIST OF EXCIPIENTS

Contains aspartame (E951) and sorbitol (E420).
Read the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4 x 1 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use. Dissolve in the mouth

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from humidity and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/249/016 4 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vivanza 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Vivanza 10 mg orodispersible tablets
vardenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Vivanza 5 mg film-coated tablets Vardenafil

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vivanza is and what it is used for
2. What you need to know before you take Vivanza
3. How to take Vivanza
4. Possible side effects
5. How to store Vivanza
6. Contents of the pack and other information

1. What Vivanza is and what it is used for

Vivanza contains vardenafil, a member of a class of medicines called phosphodiesterase type 5 inhibitors. They are used for the treatment of erectile dysfunction in adult men, a condition which implies difficulties in getting or keeping an erection.

At least one in ten men has trouble getting or keeping an erection at some time. There may be physical or psychological causes, or a mixture of both. Whatever the cause is, due to muscle and blood vessel changes not enough blood stays in the penis to make it hard and keep it hard.

Vivanza will only work when you are sexually stimulated. It reduces the action of the natural chemical in your body, which makes erections go away. Vivanza allows an erection to last long enough for you to satisfactorily complete sexual activity.

2. What you need to know before you take Vivanza

Do not take Vivanza

- If you are allergic to vardenafil or any of the other ingredients of this medicine (listed in section 6). Signs of an allergic reaction include a rash, itching, swollen face or lips and shortness of breath.
- If you are taking medicines containing nitrates, such as glycerol trinitrate for angina, or nitric oxide donors, such as amyl nitrite. Taking these medicines with Vivanza could seriously affect your blood pressure.
- If you are taking ritonavir or indinavir, medicines used to treat human immunodeficiency virus (HIV) infections.
- If you are over 75 years of age and are taking ketoconazole or itraconazole, anti-fungal medicines.
- If you have a severe heart or liver problem.
- If you are having kidney dialysis.
- If you have recently had a stroke or heart attack.
- If you have or have had low blood pressure.
- If your family has a history of degenerative eye diseases (such as retinitis pigmentosa)

- If you have ever had a condition involving loss of vision due to damage to the optic nerve from insufficient blood supply known as non-arteritic ischemic optic neuropathy (NAION).
- If you are taking riociguat. This drug is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors, such as Vivanza have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking Vivanza.

Take special care with Vivanza

- If you have heart trouble. It may be risky for you to have sex.
- If you suffer from irregular heart beat (cardiac arrhythmia) or inherited heart diseases affecting your electrocardiogram.
- If you have a physical condition affecting the shape of the penis. This includes conditions called angulation, Peyronie's disease and cavernosal fibrosis.
- If you have an illness that can cause erections which won't go away (priapism). These include sickle cell disease, multiple myeloma and leukaemia.
- If you have stomach ulcers (also called gastric or peptic ulcers)
- If you have a bleeding disorder (such as haemophilia)
- If you are using any other treatments for erection difficulties, including vardenafil in orodispersible tablets (see section: Other medicines and Vivanza).
- If you experience sudden decrease or loss of vision, stop taking Vivanza and contact your doctor immediately.

Children and adolescents

Vivanza is not intended for use by children or adolescents under 18.

Other medicines and Vivanza

Please tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription.

Some medicines may cause problems, especially these:

- Nitrates, medicines for angina, or nitric oxide donors, such as amyl nitrite. Taking these medicines with Vivanza could seriously affect your blood pressure. Talk to a doctor without taking Vivanza.
- Medicine for the treatment of arrhythmias, such as quinidine, procainamide, amiodarone or sotalol.
- Ritonavir or indinavir, medicines for HIV. Talk to a doctor without taking Vivanza.
- Ketoconazole or itraconazole, anti-fungal medicines.
- Erythromycin or clarithromycin, macrolide antibiotics.
- Alpha-blockers, a type of medicine used to treat high blood pressure and enlargement of the prostate (as benign prostatic hyperplasia).
- Riociguat.

Do not use Vivanza film-coated tablets combined with any other treatment for erectile dysfunction, including Vivanza orodispersible tablets.

Vivanza with food, drink and alcohol

- You can take Vivanza with or without food – but preferably not after a heavy or high-fat meal as this may delay the effect.
- Don't drink grapefruit juice when you use Vivanza. It can interfere with the usual effect of the medicine.
- Alcoholic drink can make erection difficulties worse.

Pregnancy and breast-feeding

Vivanza is not for use by women.

Driving and using machines

Vivanza might make some people feel dizzy or affect their vision. If you feel dizzy, or if your vision is affected after taking Vivanza don't drive or operate any tools or machines.

3. How to take Vivanza

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is 10 mg.

Take a Vivanza tablet about 25 to 60 minutes before sexual activity. With sexual stimulation, you may achieve an erection anywhere from 25 minutes up to four to five hours after taking Vivanza.

- Swallow one tablet with a glass of water

Do not take Vivanza film-coated tablets with any other forms of Vivanza.

Do not take Vivanza more than once a day.

Tell your doctor if you think Vivanza is too strong or too weak. He or she may suggest a switch to an alternative vardenafil formulation with a different dose, depending on how well it works for you.

If you take more Vivanza than you should

Men who take too much Vivanza may experience more side effects or may get severe back pain. If you take more Vivanza than you should, tell your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the effects are mild or moderate.

Partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes has been experienced by patients. Stop taking Vivanza and contact your doctor immediately.

Sudden decrease or loss of hearing has been reported.

The chance of having a side effect is described by the following categories:

Very common:

may affect more than 1 in 10 users

- Headache

Common:

may affect up to 1 in 10 users

- Dizziness
- Flushing
- Blocked or runny nose
- Indigestion

Uncommon:

may affect up to 1 in 100 users

- Swelling of skin and mucous tissue including swollen face, lips or throat
- Sleep disorder
- Numbness and impaired perception of touch
- Sleepiness

- Effects on vision; redness of the eye, effects on colour vision, eye pain and discomfort, light sensitivity
- Ringing in the ears; vertigo
- Fast heart beat or pounding heart
- Breathlessness
- Stuffy nose
- Acid reflux, gastritis, abdominal pain, diarrhoea, vomiting; feeling sick (*nausea*), dry mouth
- Raised levels of liver enzymes in your blood
- Rash, reddened skin
- Back or muscle pain, increase in blood of a muscle enzyme (*creatine phosphokinase*), muscle stiffness
- Prolonged erections
- Malaise

Rare:

may affect up to 1 in 1,000 users

- Inflammation of the eyes (*conjunctivitis*)
- Allergic reaction
- Anxiety
- Fainting
- Amnesia
- Seizure
- Increase pressure in the eye (*glaucoma*), lacrimation increased
- Effects on the heart (such as heart attack, altered heart beat or angina)
- High or low blood pressure
- Nose bleed
- Effect on results of blood tests to check liver function
- Sensitivity of the skin to sun light
- Painful erections
- Chest pain

Very rare or not known:

may affect less than 1 in 10,000 users or frequency cannot be estimated from the available data

- Blood in the urine (*Haematuria*)
- Penile bleeding (*Penile Haemorrhage*)
- Presence of blood in the semen (*Haematospermia*)

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly **via the national reporting system listed in Appendix V**. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vivanza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vivanza contains

- The active substance is vardenafil. Each tablet contains 5 mg of vardenafil (as hydrochloride).
- The other ingredients of the tablets are:
Tablet core: crospovidone, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica.
Film coat: macrogol 400, hypromellose, titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172).

What Vivanza looks like and contents of the pack

Vivanza 5 mg film-coated tablets are orange marked with a 'v' on one side and the strength (5) on the other side. The tablets are provided in blister packs containing 2, 4, 8, 12 or 20 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

Bayer S.A./N.V.

Tél/Tel: +32-(0)2-535 63 11

България

Байер България ЕООД

Тел.: +359 02 81 401 01

Česká republika

GlaxoSmithKline s.r.o.

Tel: +420 2 22001111

Danmark

Bayer A/S

Tlf: +45 45 23 50 00

Deutschland

Jenapharm GmbH & Co. KG

Tel: +49 (0)3641 64 8888

Eesti

GlaxoSmithKline Eesti OÜ

Tel: +372 6676900

Ελλάδα

Bayer Ελλάς ABEE

Τηλ: +30 210 61 87 500

España

Bayer Hispania S.L.

Tel: +34-93-495 65 00

France

Bayer HealthCare

Tél (N° vert) : +33-(0)800 87 54 54

Hrvatska

Bayer d.o.o.

Tel: + 385-(0)1-6599 900

Ireland

Bayer Limited

Tel: +353 1 2999313

Ísland

Icepharma hf.

Sími: +354-540 8000

Italia

Bayer S.p.A.

Tel: +39 02 397 81

Κύπρος

Bayer Ελλάς ABEE

Τηλ: +30 210 618 75 00

Latvija

GlaxoSmithKline Latvia SIA

Tel: +371-67312687

Lietuva

UAB “GlaxoSmithKline Lietuva”

Tel: +37 05 264 90 00

Luxembourg/Luxemburg

Bayer S.A./N.V.

Tél/Tel: +32-(0)2-535 63 11

Magyarország

Bayer Hungária KFT.

Tel.: +36 14 87-4100

Malta

Alfred Gera and Sons Ltd.

Tel: +35 621 44 62 05

Nederland

Bayer B.V.

Tel: +31-(0)297-28 06 66

Norge

Bayer AS

Tlf: +47-23 13 05 00

Österreich

Bayer Austria Ges. m. b. H.

Tel: +43-(0)1-711 46-0

Polska

Bayer Sp. z o.o.

Tel.: +48 22 572 35 00

Portugal

Bayer Portugal, Lda.

Tel: +351 21 416 42 00

România

GlaxoSmithKline (GSK) S.R.L.

Tel: +40 21 3028 208

Slovenija

Bayer d. o. o.

Tel: +386 (0)1 58 14 400

Slovenská republika

GlaxoSmithKline Slovakia s.r.o.

Tel: +421 (0)2 48261111

Suomi/Finland

Bayer Oy

Puh/Tel: +358 20 785 21

Sverige

Bayer AB

Tel: +46 (0)8 580 223 00

United Kingdom

Bayer plc

Tel: +44 (0) 118 206 3000

This leaflet was last revised in {month YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

Package Leaflet: Information for the user

Vivanza 10 mg film-coated tablets Vardenafil

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vivanza is and what it is used for
2. What you need to know before you take Vivanza
3. How to take Vivanza
4. Possible side effects
5. How to store Vivanza
6. Contents of the pack and other information

1. What Vivanza is and what it is used for

Vivanza contains vardenafil, a member of a class of medicines called phosphodiesterase type 5 inhibitors. They are used for the treatment of erectile dysfunction in adult men, a condition which implies difficulties in getting or keeping an erection.

At least one in ten men has trouble getting or keeping an erection at some time. There may be physical or psychological causes, or a mixture of both. Whatever the cause is, due to muscle and blood vessel changes not enough blood stays in the penis to make it hard and keep it hard.

Vivanza will only work when you are sexually stimulated. It reduces the action of the natural chemical in your body, which makes erections go away. Vivanza allows an erection to last long enough for you to satisfactorily complete sexual activity.

2. What you need to know before you take Vivanza

Do not take Vivanza

- If you are allergic to vardenafil or any of the other ingredients of this medicine (listed in section 6). Signs of an allergic reaction include a rash, itching, swollen face or lips and shortness of breath.
- If you are taking medicines containing nitrates, such as glycerol trinitrate for angina, or nitric oxide donors, such as amyl nitrite. Taking these medicines with Vivanza could seriously affect your blood pressure.
- If you are taking ritonavir or indinavir, medicines used to treat human immunodeficiency virus (HIV) infections.
- If you are over 75 years of age and are taking ketoconazole or itraconazole, anti-fungal medicines.
- If you have a severe heart or liver problem.
- If you are having kidney dialysis.
- If you have recently had a stroke or heart attack.
- If you have or have had low blood pressure.
- If your family has a history of degenerative eye diseases (such as retinitis pigmentosa)

- If you have ever had a condition involving loss of vision due to damage to the optic nerve from insufficient blood supply known as non-arteritic ischemic optic neuropathy (NAION).
- If you are taking riociguat. This drug is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors, such as Vivanza have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking Vivanza.

Take special care with Vivanza

- If you have heart trouble. It may be risky for you to have sex.
- If you suffer from irregular heart beat (cardiac arrhythmia) or inherited heart diseases affecting your electrocardiogram.
- If you have a physical condition affecting the shape of the penis. This includes conditions called angulation, Peyronie's disease and cavernosal fibrosis.
- If you have an illness that can cause erections which won't go away (*priapism*). These include sickle cell disease, multiple myeloma and leukaemia.
- If you have stomach ulcers (also called gastric or peptic ulcers)
- If you have a bleeding disorder (such as haemophilia)
- If you are using any other treatments for erection difficulties, including vardenafil in orodispersible tablets (see section: Other medicines and Vivanza).
- If you experience sudden decrease or loss of vision, stop taking Vivanza and contact your doctor immediately.

Children and adolescents

Vivanza is not intended for use by children or adolescents under 18.

Other medicines and Vivanza

Please tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription.

Some medicines may cause problems, especially these:

- Nitrates, medicines for angina, or nitric oxide donors, such as amyl nitrite. Taking these medicines with Vivanza could seriously affect your blood pressure. Talk to a doctor without taking Vivanza.
- Medicine for the treatment of arrhythmias, such as quinidine, procainamide, amiodarone or sotalol.
- Ritonavir or indinavir, medicines for HIV. Talk to a doctor without taking Vivanza.
- Ketoconazole or itraconazole, anti-fungal medicines.
- Erythromycin or clarithromycin, macrolide antibiotics.
- Alpha-blockers, a type of medicine used to treat high blood pressure and enlargement of the prostate (as benign prostatic hyperplasia)
- Riociguat.

Do not use Vivanza film-coated tablets combined with any other treatment for erectile dysfunction, including Vivanza orodispersible tablets.

Vivanza with food, drink and alcohol

- You can take Vivanza with or without food - but preferably not after a heavy or high-fat meal as this may delay the effect.
- Don't drink grapefruit juice when you use Vivanza. It can interfere with the usual effect of the medicine.
- Alcoholic drink can make erection difficulties worse.

Pregnancy and breast-feeding

Vivanza is not for use by women.

Driving and using machines

Vivanza might make some people feel dizzy or affect their vision. If you feel dizzy, or if your vision is affected after taking Vivanza don't drive or operate any tools or machines.

3. How to take Vivanza

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is 10 mg.

Take a Vivanza tablet about 25 to 60 minutes before sexual activity. With sexual stimulation, you may achieve an erection anywhere from 25 minutes up to four to five hours after taking Vivanza.

- Swallow one tablet with a glass of water.

Do not take Vivanza film-coated tablets with any other forms of Vivanza.

Do not take Vivanza more than once a day.

Tell your doctor if you think Vivanza is too strong or too weak. He or she may suggest a switch to an alternative vardenafil formulation with a different dose, depending on how well it works for you.

If you take more Vivanza than you should

Men who take too much Vivanza may experience more side effects or may get severe back pain. If you take more Vivanza than you should, tell your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the effects are mild or moderate.

Partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes has been experienced by patients. Stop taking Vivanza and contact your doctor immediately.

Sudden decrease or loss of hearing has been reported.

The chance of having a side effect is described by the following categories:

Very common:

may affect more than 1 in 10 user

- Headache

Common:

may affect up to 1 in 10 users

- Dizziness
- Flushing
- Blocked or runny nose
- Indigestion

Uncommon:

may affect up to 1 in 100 users

- Swelling of skin and mucous tissue including swollen face, lips or throat
- Sleep disorder
- Numbness and impaired perception of touch
- Sleepiness

- Effects on vision; redness of the eye, effects on colour vision, eye pain and discomfort, light sensitivity
- Ringing in the ears; vertigo
- Fast heart beat or pounding heart
- Breathlessness
- Stuffy nose
- Acid reflux, gastritis, abdominal pain, diarrhoea, vomiting; feeling sick (*nausea*), dry mouth
- Raised levels of liver enzymes in your blood
- Rash, reddened skin
- Back or muscle pain, increase in blood of a muscle enzyme (*creatine phosphokinase*), muscle stiffness
- Prolonged erections
- Malaise

Rare:

may affect up to 1 in 1,000 users

- Inflammation of the eyes (*conjunctivitis*)
- Allergic reaction
- Anxiety
- Fainting
- Amnesia
- Seizure
- Increase pressure in the eye (*glaucoma*), lacrimation increased
- Effects on the heart (such as heart attack, altered heart beat or angina)
- High or low blood pressure
- Nose bleed
- Effect on results of blood tests to check liver function
- Sensitivity of the skin to sun light
- Painful erections
- Chest pain

Very rare or not known:

may affect less than 1 in 10,000 users or frequency cannot be estimated from the available data

- Blood in the urine (*Haematuria*)
- Penile bleeding (*Penile Haemorrhage*)
- Presence of blood in the semen (*Haematospermia*)

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vivanza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vivanza contains

- The active substance is vardenafil. Each tablet contains 10 mg of vardenafil (as hydrochloride).

- The other ingredients of the tablets are:
Tablet core: crospovidone, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica.
Film coat: macrogol 400, hypromellose, titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172).

What Vivanza looks like and contents of the pack

Vivanza 10 mg film-coated tablets are orange with a ‘v’ on one side and the strength (10) on the other side. The tablets are provided in blister packs containing 2, 4, 8, 12 or 20 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

Bayer S.A./N.V.

Tél/Tel: +32-(0)2-535 63 11

България

Байер България ЕООД

Тел.: +359 02 81 401 01

Česká republika

GlaxoSmithKline s.r.o.

Tel: +420 2 22001111

Danmark

Bayer A/S

Tlf: +45 45 23 50 00

Deutschland

Jenapharm GmbH & Co. KG

Tel: +49 (0)3641 64 8888

Eesti

GlaxoSmithKline Eesti OÜ

Tel: +372 6676900

Ελλάδα

Bayer Ελλάς ABEE

Τηλ: +30 210 61 87 500

España

Bayer Hispania S.L.

Tel: +34-93-495 65 00

France

Bayer HealthCare

Tél (N° vert) : +33-(0)800 87 54 54

Hrvatska

Bayer d.o.o.

Tel: + 385-(0)1-6599 900

Ireland

Bayer Limited

Tel: +353 1 2999313

Ísland

Icepharma hf.

Sími: +354-540 8000

Italia

Bayer S.p.A.

Tel: +39 02 397 81

Κύπρος

Bayer Ελλάς ABEE

Τηλ: +30 210 618 75 00

Latvija

GlaxoSmithKline Latvia SIA

Tel: +371-67312687

Lietuva

UAB “GlaxoSmithKline Lietuva”

Tel: +37 05 264 90 00

Luxembourg/Luxemburg

Bayer S.A./N.V.

Tél/Tel: +32-(0)2-535 63 11

Magyarország

Bayer Hungária KFT.

Tel.: +36 14 87-4100

Malta

Alfred Gera and Sons Ltd.

Tel: +35 621 44 62 05

Nederland

Bayer B.V.

Tel: +31-(0)297-28 06 66

Norge

Bayer AS

Tlf: +47-23 13 05 00

Österreich

Bayer Austria Ges. m. b. H.

Tel: +43-(0)1-711 46-0

Polska

Bayer Sp. z o.o.

Tel.: +48 22 572 35 00

Portugal

Bayer Portugal, Lda.

Tel: +351 21 416 42 00

România

GlaxoSmithKline (GSK) S.R.L.

Tel: +40 21 3028 208

Slovenija

Bayer d. o. o.

Tel: +386 (0)1 58 14 400

Slovenská republika

GlaxoSmithKline Slovakia s.r.o.

Tel: +421 (0)2 48261111

Suomi/Finland

Bayer Oy

Puh/Tel: +358 20 785 21

Sverige

Bayer AB

Tel: +46 (0)8 580 223 00

United Kingdom

Bayer plc

Tel: +44 (0) 118 206 3000

This leaflet was last revised in {month YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

Package Leaflet: Information for the user

Vivanza 20 mg film-coated tablets Vardenafil

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vivanza is and what it is used for
2. What you need to know before you take Vivanza
3. How to take Vivanza
4. Possible side effects
5. How to store Vivanza
6. Contents of the pack and other information

1. What Vivanza is and what it is used for

Vivanza contains vardenafil, a member of a class of medicines called phosphodiesterase type 5 inhibitors. They are used for the treatment of erectile dysfunction in adult men, a condition which implies difficulties in getting or keeping an erection.

At least one in ten men has trouble getting or keeping an erection at some time. There may be physical or psychological causes, or a mixture of both. Whatever the cause is, due to muscle and blood vessel changes not enough blood stays in the penis to make it hard and keep it hard.

Vivanza will only work when you are sexually stimulated. It reduces the action of the natural chemical in your body, which makes erections go away. Vivanza allows an erection to last long enough for you to satisfactorily complete sexual activity.

2. What you need to know before you take Vivanza

Do not take Vivanza

- If you are allergic to vardenafil or any of the other ingredients of this medicine (listed in section 6). Signs of an allergic reaction include a rash, itching, swollen face or lips and shortness of breath.
- If you are taking medicines containing nitrates, such as glycerol trinitrate for angina, or nitric oxide donors, such as amyl nitrite. Taking these medicines with Vivanza could seriously affect your blood pressure.
- If you are taking ritonavir or indinavir, medicines used to treat human immunodeficiency virus (HIV) infections.
- If you are over 75 years of age and are taking ketaconazole or itraconazole, anti-fungal medicines.
- If you have a severe heart or liver problem.
- If you are having kidney dialysis.
- If you have recently had a stroke or heart attack.
- If you have or have had low blood pressure.
- If your family has a history of degenerative eye diseases (such as retinitis pigmentosa)

- If you have ever had a condition involving loss of vision due to damage to the optic nerve from insufficient blood supply known as non-arteritic ischemic optic neuropathy (NAION).
- If you are taking riociguat. This drug is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors, such as Vivanza have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking Vivanza.

Take special care with Vivanza

- If you have heart trouble. It may be risky for you to have sex.
- If you suffer from irregular heart beat (cardiac arrhythmia) or inherited heart diseases affecting your electrocardiogram.
- If you have a physical condition affecting the shape of the penis. This includes conditions called angulation, Peyronie's disease and cavernosal fibrosis.
- If you have an illness that can cause erections which won't go away (priapism). These include sickle cell disease, multiple myeloma and leukaemia.
- If you have stomach ulcers (also called gastric or peptic ulcers)
- If you have a bleeding disorder (such as haemophilia)
- If you are using any other treatments for erection difficulties, including vardenafil in orodispersible tablets (see section: Other medicines and Vivanza).
- If you experience sudden decrease or loss of vision, stop taking Vivanza and contact your doctor immediately.

Children and adolescents

Vivanza is not intended for use by children or adolescents under 18.

Other medicines and Vivanza

Please tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription.

Some medicines may cause problems, especially these:

- Nitrates, medicines for angina, or nitric oxide donors, such as amyl nitrite. Taking these medicines with Vivanza could seriously affect your blood pressure. Talk to a doctor without taking Vivanza.
- Medicine for the treatment of arrhythmias, such as quinidine, procainamide, amiodarone or sotalol.
- Ritonavir or indinavir, medicines for HIV. Talk to a doctor without taking Vivanza.
- Ketoconazole or itraconazole, anti-fungal medicines.
- Erythromycin or clarithromycin, macrolide antibiotics.
- Alpha-blockers, a type of medicine used to treat high blood pressure and enlargement of the prostate (as benign prostatic hyperplasia)
- Riociguat.

Do not use Vivanza film-coated tablets combined with any other treatment for erectile dysfunction, including Vivanza orodispersible tablets.

Vivanza with food, drink and alcohol

- You can take Vivanza with or without food – but preferably not after a heavy or high-fat meal as this may delay the effect.
- Don't drink grapefruit juice when you use Vivanza. It can interfere with the usual effect of the medicine.
- Alcoholic drink can make erection difficulties worse.

Pregnancy and breast-feeding

Vivanza is not for use by women.

Driving and using machines

Vivanza might make some people feel dizzy or affect their vision. If you feel dizzy, or if your vision is affected after taking Vivanza don't drive or operate any tools or machines.

3. How to take Vivanza

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is 10 mg.

Take a Vivanza tablet about 25 to 60 minutes before sexual activity. With sexual stimulation, you may achieve an erection anywhere from 25 minutes up to four to five hours after taking Vivanza.

- Swallow one tablet with a glass of water

Do not take Vivanza film-coated tablets with any other forms of Vivanza.

Do not take Vivanza more than once a day.

Tell your doctor if you think Vivanza is too strong or too weak. He or she may suggest a switch to an alternative vardenafil formulation with a different dose, depending on how well it works for you.

If you take more Vivanza than you should

Men who take too much Vivanza may experience more side effects or may get severe back pain. If you take more Vivanza than you should, tell your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the effects are mild or moderate.

Partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes has been experienced by patients. Stop taking Vivanza and contact your doctor immediately.

Sudden decrease or loss of hearing has been reported.

The chance of having a side effect is described by the following categories:

Very common:

may affect more than 1 in 10 users

- Headache

Common:

may affect up to 1 in 10 users

- Dizziness
- Flushing
- Blocked or runny nose
- Indigestion

Uncommon:

may affect up to 1 in 100 users

- Swelling of skin and mucous tissue including swollen face, lips or throat
- Sleep disorder
- Numbness and impaired perception of touch
- Sleepiness

- Effects on vision; redness of the eye, effects on colour vision, eye pain and discomfort, light sensitivity
- Ringing in the ears; vertigo
- Fast heart beat or pounding heart
- Breathlessness
- Stuffy nose
- Acid reflux, gastritis, abdominal pain, diarrhoea, vomiting; feeling sick (*nausea*), dry mouth
- Raised levels of liver enzymes in your blood
- Rash, reddened skin
- Back or muscle pain, increase in blood of a muscle enzyme (*creatine phosphokinase*), muscle stiffness
- Prolonged erections
- Malaise

Rare:

may affect up to 1 in 1,000 users

- Inflammation of the eyes (*conjunctivitis*)
- Allergic reaction
- Anxiety
- Fainting
- Amnesia
- Seizure
- Increase pressure in the eye (*glaucoma*), lacrimation increased
- Effects on the heart (such as heart attack, altered heart beat or angina)
- High or low blood pressure
- Nose bleed
- Effect on results of blood tests to check liver function
- Sensitivity of the skin to sun light
- Painful erections
- Chest pain

Very rare or not known:

may affect less than 1 in 10,000 users or frequency cannot be estimated from the available data

- Blood in the urine (*Haematuria*)
- Penile bleeding (*Penile Haemorrhage*)
- Presence of blood in the semen (*Haematospermia*)

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly **via the national reporting system listed in Appendix V**. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vivanza

Keep this medicine out of and sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vivanza contains

- The active substance is vardenafil. Each tablet contains 20 mg of vardenafil (as hydrochloride).
- The other ingredients of the tablets are:
Tablet core: crospovidone, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica.
Film coat: macrogol 400, hypromellose, titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172).

What Vivanza looks like and contents of the pack

Vivanza 20 mg film-coated tablets are orange with a 'v' on one side and the strength (20) on the other side. The tablets are provided in blister packs containing 2, 4, 8, 12 or 20 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

Bayer S.A./N.V.

Tél/Tel: +32-(0)2-535 63 11

България

Байер България ЕООД

Тел.: +359 02 81 401 01

Česká republika

GlaxoSmithKline s.r.o.

Tel: +420 2 22001111

Danmark

Bayer A/S

Tlf: +45 45 23 50 00

Deutschland

Jenapharm GmbH & Co. KG

Tel: +49 (0)3641 64 8888

Eesti

GlaxoSmithKline Eesti OÜ

Tel: +372 6676900

Ελλάδα

Bayer Ελλάς ABEE

Τηλ: +30 210 61 87 500

España

Bayer Hispania S.L.

Tel: +34-93-495 65 00

France

Bayer HealthCare

Tél (N° vert) : +33-(0)800 87 54 54

Hrvatska

Bayer d.o.o.

Tel: + 385-(0)1-6599 900

Ireland

Bayer Limited

Tel: +353 1 2999313

Ísland

Icepharma hf.

Sími: +354-540 8000

Italia

Bayer S.p.A.

Tel: +39 02 397 81

Κύπρος

Bayer Ελλάς ABEE

Τηλ: +30 210 618 75 00

Latvija

GlaxoSmithKline Latvia SIA

Tel: +371-67312687

Lietuva

UAB “GlaxoSmithKline Lietuva”

Tel: +37 05 264 90 00

Luxembourg/Luxemburg

Bayer S.A./N.V.

Tél/Tel: +32-(0)2-535 63 11

Magyarország

Bayer Hungária KFT.

Tel.: +36 14 87-4100

Malta

Alfred Gera and Sons Ltd.

Tel: +35 621 44 62 05

Nederland

Bayer B.V.

Tel: +31-(0)297-28 06 66

Norge

Bayer AS

Tlf: +47-23 13 05 00

Österreich

Bayer Austria Ges. m. b. H.

Tel: +43-(0)1-711 46-0

Polska

Bayer Sp. z o.o.

Tel.: +48 22 572 35 00

Portugal

Bayer Portugal, Lda.

Tel: +351 21 416 42 00

România

GlaxoSmithKline (GSK) S.R.L.

Tel: +40 21 3028 208

Slovenija

Bayer d. o. o.

Tel: +386 (0)1 58 14 400

Slovenská republika

GlaxoSmithKline Slovakia s.r.o.

Tel: +421 (0)2 48261111

Suomi/Finland

Bayer Oy

Puh/Tel: +358 20 785 21

Sverige

Bayer AB

Tel: +46 (0)8 580 223 00

United Kingdom

Bayer plc

Tel: +44 (0) 118 206 3000

This leaflet was last revised in {month YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

Package Leaflet: Information for the user

Vivanza 10 mg orodispersible tablets Vardenafil

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vivanza is and what it is used for
2. What you need to know before you take Vivanza
3. How to take Vivanza
4. Possible side effects
5. How to store Vivanza
6. Contents of the pack and other information

1. What Vivanza is and what it is used for

Vivanza contains vardenafil, a member of a class of medicines called phosphodiesterase type 5 inhibitors. They are used for the treatment of erectile dysfunction in adult men, a condition which implies difficulties in getting or keeping an erection.

At least one in ten men has trouble getting or keeping an erection at some time. There may be physical or psychological causes, or a mixture of both. Whatever the cause is, due to muscle and blood vessel changes not enough blood stays in the penis to make it hard and keep it hard.

Vivanza will only work when you are sexually stimulated. It reduces the action of the natural chemical in your body which makes erections go away. Vivanza allows an erection to last long enough for you to satisfactorily complete sexual activity.

2. What you need to know before you take Vivanza

Do not take Vivanza

- If you are allergic to vardenafil or any of the other ingredients of this medicine (listed in section 6). Signs of an allergic reaction include a rash, itching, swollen face or lips and shortness of breath.
- If you are taking medicines containing nitrates, such as glycerol trinitrate for angina, or nitric oxide donors, such as amyl nitrite. Taking these medicines with Vivanza could seriously affect your blood pressure.
- If you are taking ritonavir or indinavir, medicines used to treat human immunodeficiency virus (HIV) infections.
- If you are over 75 years of age and are taking ketoconazole or itraconazole, anti-fungal medicines.
- If you have a severe heart or liver problem.
- If you are having kidney dialysis.
- If you have recently had a stroke or heart attack.
- If you have or have had low blood pressure.
- If your family has a history of degenerative eye diseases (such as retinitis pigmentosa).

- If you have ever had a condition involving loss of vision due to damage to the optic nerve from insufficient blood supply known as non-arteritic ischemic optic neuropathy (NAION).
- If you are taking riociguat. This drug is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors, such as Vivanza have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking Vivanza.

Take special care with Vivanza

- If you have heart trouble. It may be risky for you to have sex.
- If you suffer from irregular heart beat (cardiac arrhythmia) or inherited heart diseases affecting your electrocardiogram.
- If you have a physical condition affecting the shape of the penis. This includes conditions called angulation, Peyronie's disease and cavernosal fibrosis.
- If you have an illness that can cause erections which won't go away (priapism). These include sickle cell disease, multiple myeloma and leukaemia.
- If you have stomach ulcers (also called gastric or peptic ulcers).
- If you have a bleeding disorder (such as haemophilia).
- If you are using any other treatments for erection difficulties, including Vivanza film-coated tablets (see section: Other medicines and Vivanza).
- If you experience sudden decrease or loss of vision, stop taking Vivanza and contact your doctor immediately.

Children and adolescents

Vivanza is not intended for use by children or adolescents under 18.

Other medicines and Vivanza

Please tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription.

Some medicines may cause problems, especially these:

- Nitrates, medicines for angina, or nitric oxide donors, such as amyl nitrite. Taking these medicines with Vivanza could seriously affect your blood pressure. Talk to a doctor without taking Vivanza.
- Medicine for the treatment of arrhythmias, such as quinidine, procainamide, amiodarone or sotalol.
- Ritonavir or indinavir, medicines for HIV. Talk to a doctor without taking Vivanza.
- Ketoconazole or itraconazole, anti-fungal medicines.
- Erythromycin, or clarithromycin, macrolide antibiotics.
- Alpha-blockers, a type of medicine used to treat high blood pressure and enlargement of the prostate (as benign prostatic hyperplasia).
- Riociguat.

Do not use Vivanza orodispersible tablets combined with any other treatment for erectile dysfunction, including Vivanza film-coated tablets.

Vivanza with food, drink and alcohol

- You can take Vivanza orodispersible tablets with or without food, but do not take this medicine with any liquid.
- Don't drink grapefruit juice when you use Vivanza. It can interfere with the usual effect of the medicine.
- Alcoholic drink can make erection difficulties worse.

Pregnancy and breast-feeding

Vivanza is not for use by women.

Driving and using machines

Vivanza might make some people feel dizzy or affect their vision. If you feel dizzy, or if your vision is affected after taking Vivanza don't drive or operate any tools or machines.

Important information about some of the ingredients of Vivanza 10 mg orodispersible tablets:

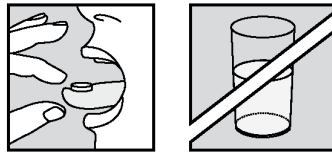
- Aspartame is a source of phenylalanine, and may be harmful for people with a disorder called phenylketonuria.
- Sorbitol: If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Vivanza orodispersible tablets

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is 10 mg.

Take Vivanza tablet about 25 to 60 minutes before sexual activity. With sexual stimulation you may achieve an erection anywhere from 25 minutes up to four to five hours after taking Vivanza.

- Do not remove the orodispersible tablet from the blister until you are going to take it. With dry hands, press gently to release the tablet on your hand. Do not crush the tablet.
- Place the entire orodispersible tablet in the mouth, on the tongue, where it will dissolve in seconds, then swallow with saliva. The orodispersible tablet must be taken without any liquid.



Do not take Vivanza orodispersible tablets with any other forms of Vivanza.

Do not take Vivanza more than once a day.

Tell your doctor if you think Vivanza is too strong or too weak. He or she may suggest a switch to an alternative Vivanza formulation with a different dose, depending on how well it works for you.

If you take more Vivanza than you should

Men who take too much Vivanza may experience more side effects or may get severe back pain. If you take more Vivanza than you should, tell your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the effects are mild or moderate.

Partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes has been experienced by patients. Stop taking Vivanza and contact your doctor immediately. Sudden decrease or loss of hearing has been reported.

The chance of having a side effect is described by the following categories:

Very common:

may affect more than 1 in 10 users

- Headache

Common:

may affect up to 1 in 10 users

- Dizziness
- Flushing
- Blocked or runny nose
- Indigestion

Uncommon:

may affect up to 1 in 100 users

- Swelling of skin and mucous tissue including swollen face, lips or throat.
- Sleep disorder
- Numbness and impaired perception of touch
- Sleepiness
- Effects on vision; redness of the eye, effects on colour vision, eye pain and discomfort, light sensitivity
- Ringing in the ears; vertigo
- Fast heart beat or pounding heart
- Breathlessness
- Stuffy nose
- Acid reflux, gastritis, abdominal pain, diarrhoea, vomiting; feeling sick (*nausea*), dry mouth
- Raised levels of liver enzymes in your blood
- Rash, reddened skin
- Back or muscle pain; increase in blood of a muscle enzyme (*creatine phosphokinase*), muscle stiffness
- Prolonged erections
- Malaise

Rare:

may affect up to 1 in 1,000 users

- Inflammation of the eyes (*conjunctivitis*)
- Allergic reaction
- Anxiety
- Fainting
- Amnesia
- Seizure
- Increased pressure in the eye (*glaucoma*), lacrimation increased
- Effects on the heart (such as heart attack, altered heart beat or angina)
- High or low blood pressure
- Nose bleed
- Effect on results of blood tests to check liver function.
- Sensitivity of the skin to sun light
- Painful erections
- Chest pain

Very rare or not known:

may affect less than 1 in 10,000 users or frequency cannot be estimated from the available data

- Blood in the urine (*Haematuria*)
- Penile bleeding (*Penile Haemorrhage*)
- Presence of blood in the semen (*Haematospermia*)

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vivanza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Store in the original package in order to protect from humidity and light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vivanza orodispersible tablets contains

- The active substance is vardenafil. Each orodispersible tablet contains 10 mg of vardenafil (as hydrochloride).
- The other ingredients of the tablets are:
Magnesium stearate, aspartame (E951), peppermint flavour, mannitol (E421) sorbitol (E420), crospovidone and silica colloidal hydrated.

What Vivanza 10 mg orodispersible tablets looks like and contents of the pack

Vivanza 10 mg orodispersible tablets are round and white. They are provided in packs of 4 x 1 orodispersible tablets in alu/alu perforated unit dose blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11

България

Байер България ЕООД
Тел.: +359-(0)2 81 401 01

Česká republika

Bayer s.r.o.
Tel: +420 266 101 111

Danmark

Bayer A/S
Tlf: +45 45 23 50 00

Deutschland

Jenapharm GmbH & Co. KG
Tel: +49 (0)3641 64 8888

Eesti

Bayer OÜ
Tel: +372 655 8565

Ελλάδα

Bayer Ελλάς ABEE
Τηλ: +30 210 61 87 500

España

Bayer Hispania S.L.
Tel: +34-93-495 65 00

France

Bayer HealthCare
Tél (N° vert) : +33-(0)800 87 54 54

Hrvatska

Bayer d.o.o.
Tel: + 385-(0)1-6599 900

Ireland

Bayer Limited
Tel: +353 1 2999313

Ísland

Icepharma hf.
Sími: +354-540 8000

Italia

Bayer S.p.A.
Tel: +39 02 397 81

Κύπρος

NOVAGEM Limited
Τηλ: +357 22 48 38 58

Latvija

SIA Bayer
Tel: +371 67 845 563

Lietuva

UAB Bayer
Tel: +37 05 23 36 868

Luxembourg/Luxemburg

Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11

Magyarország

Bayer Hungária KFT.
Tel.: +36-1-487-4100

Malta

Alfred Gera and Sons Ltd.
Tel: +35 621 44 62 05

Nederland

Bayer B.V.
Tel: +31-(0)297-28 06 66

Norge

Bayer AS
Tlf: +47-23 13 05 00

Österreich

Bayer Austria Ges. m. b. H.
Tel: +43-(0)1-711 460

Polska

Bayer Sp. z o.o.
Tel.: +48 22 572 35 00

Portugal

Bayer Portugal, Lda.
Tel: +351 21 416 42 00

România

SC Bayer SRL.
Tel: +40-21-529 59 00

Slovenija

Bayer d. o. o.
Tel: +386 1 58 14 400

Slovenská republika

Bayer, spol. s r.o.
Tel: +421 2-59 21 31 11

Suomi/Finland

Bayer Oy
Puh/Tel: +358 20 785 21

Sverige

Bayer AB
Tel: +46 (0)8 580 223 00

United Kingdom

Bayer plc
Tel: +44 (0) 118 206 3000

This leaflet was last revised in {month YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>