Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vardenafil Teva 10 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:
1.80 mg aspartame (E951) per orodispersible tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.
White to off white plain round tablets (approximately 9 mm).

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 Vardenafil Teva to be effective, sexual stimulation is required.

4.2 Posology and method of administration

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

Use in adult men
Vardenafil Teva 10 mg orodispersible tablets are taken as needed approximately 25 to 60 minutes before sexual activity.

Special populations
Elderly population (≥65 years old) Dose adjustments are not required in elderly patients. However, an increase to a maximum dose of vardenafil 20 mg film-coated tablets 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). This dose of 5 mg is not possible with this formulation; therefore, another formulation should be used. 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 vardenafil 5 mg film-

coated tablets should be considered. Based on tolerability and efficacy, the dose may be increased to vardenafil 10 mg and 20 mg film-coated tablets, or Vardenafil Teva 10 mg orodispersible tablets. Vardenafil Teva orodispersible tablet is not for use in patients with end-stage renal failure (see section 4.3).

Paediatric population
Vardenafil Teva orodispersible tablets are not indicated for individuals below 18 years of age. There is no relevant indication for use of Vardenafil Teva 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. Vardenafil orodispersible tablets must be taken without liquid and immediately upon release from the blister.
Vardenafil 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).

Vardenafil 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 inpatients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

The safety and efficacy of combinations of vardenafil orodispersible tablets with vardenafil 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 vardenafil 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 Vardenafil Teva 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 vardenafil and other PDE5 inhibitors. The patient should be advised that in the case of sudden visual defect, he should stop taking Vardenafil Teva 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
Vardenafil Teva 10 mg orodispersible tablets contain aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria.

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 AUC0-24 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 Vardenafil Teva 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. Vardenafil 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).

Vardenafil Teva 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

Vardenafil is not indicated for use by women. There are no studies of vardenafil in pregnant women. There is 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 Vardenafil Teva orodispersible tablets, before driving or operating machines.

4.8 Undesirable effects

The adverse reactions reported with vardenafil 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 ≥ 10% of patients is headache.

Adverse reactions are listed according to the MedDRA frequency convention: 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) and not known (cannot 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** (cannot 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	Headache	Dizziness	Somnolence	Syncope	

disorders			Paraesthesia and dysaesthesia	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 disorder		Nasal congestion	Dyspnoea Sinus congestion	Epistaxis	
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			Erythema Rash	Photosensitivity reaction	

disorders					

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** (cannot be estimated from the available data)
Musculoskeletal and connective tissue disorders			Back pain Increase in creatine phosphokinase Myalgia Increased Muscle tone and cramping		Haematuria
Renal and urinary disorders					
Reproductive system and breast disorders			Increase in erection	Priapism	Penile Haemorrhage Haematospermia
General disorders and administration site conditions			Feeling unwell	Chest pain	

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

At the 20mg dose vardenafil 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

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 plesthysmography (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/RR1/3) from baseline at the 1 hour post-dose time point. The vardenafil results showed an 11 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 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%), hyperlipidaemia (22%), depression (5%), radical prostatectomy (9%). The following groups were not well represented in clinical trials: elderly (>75 years, 2.4%), and patients with certain cardiovascular conditions (see section 4.3). No clinical 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%), hyperlipidaemia (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 13 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 14 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

Cellulose microcrystalline
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Magnesium stearate
Aspartame (E951)
Sodium stearyl fumarate
Peppermint flavour SD

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Product packed in oPA/Alu/PVC laminate with aluminium lidding foil blisters: 36 months
Product packed in PVC/PE.EVOH.PE/PCTFE laminate with aluminium lidding foil blisters: 24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

oPA/Alu/PVC laminate or PVC/PE.EVOH.PE/PCTFE laminate with aluminium lidding foil blisters in cartons of 4 or 8 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/049/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th January 2018

10 DATE OF REVISION OF THE TEXT