Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vardenafil Krka 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg vardenafil (as vardenafil hydrochloride trihydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Orange-brown, oval, slightly biconvex, film-coated tablets, scored on one side and engraved with 10 on the other side, dimensions 10.5 mm x 5.5 mm.The tablet can be divided into equal doses.

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 Krka 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. Vardenafil Krka 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

Vardenafil Krka is not indicated for individuals below 18 years of age. There is no relevant indication for use of Vardenafil Krka 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).

Vardenafil Krka is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic 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.

Serious cardiovascular events including sudden death, tachycardia, myocardial infarction, ventricular tachy-arrythmia, angina pectoris, and cerebrovascular disorders (including transient ischaemic attack and cerebral haemorrhage), have been reported in

temporal association with vardenafil. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to vardenafil, to sexual activity, or to a combination of these or other factors.

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 Vardenafil Krka film-coated tablets with 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).

Severe cutaneous adverse reactions
Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with vardenafil treatment (see section 4.8).
If signs and symptoms suggestive of these reactions appear, vardenafil should be withdrawn immediately and should not be restarted in this patient at any time.

Effect on vision
Visual defects, including Central Serous Chorioretinopathy (CSCR), and cases of non-arteritic ischaemic optic neuropathy (NAION) have been reported in connection with the intake of vardenafil and other PDE5 inhibitors. Analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to PDE5 inhibitors such as

vardenafil, tadalafil and sildenafil (see section 4.8). As this may be relevant for all patients exposed to vardenafil the patient should be advised that in the case of sudden visual defect, he should stop taking Vardenafil Krka and consult a physician immediately (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 CYP3A4 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 CYP3A4 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. Vardenafil Krka 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

Vardenafil Krka 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 Vardenafil Krka, before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
The adverse reactions reported with vardenafil film-coated 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.

Tabulated list of adverse reactions
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 (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:

SystemOrgan Class	Very common	Common	Uncommon	Rare	Not known
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 Transient ischaemic attack	Cerebral haemorrhage
Eye disorders			Visual disturbance Ocular hyperaemia Visual colour distortions Eye pain and eye discomfort Photophobia	Increase in intraocular pressure Lacrimation increased	Non-arteritic anterior ischaemic optic neuropathy Visual defects Central Serous Chorioretinopathy (CSCR) (see section 4.4)
Ear and labyrinth			Tinnitus Vertigo		Sudden deafness

disorders					
Cardiac disorders			Palpitation Tachycardia	Myocardial infarction Ventricular tachy-arrythmias Angina pectoris	Sudden death
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		
Hepatobiliary disorders			Increase in transaminases	Increase in gamma-glutamyl-transferase	
Skin and subcutaneous tissue disorders			Erythema Rash	Photosensitivity reaction	Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (see section 4.4)
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 Haematospermia
General disorders and administration site conditions			Feeling unwell	Chest pain	

Description of selected adverse reactions

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 20 mg 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.

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, Website: www.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 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

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.

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%.

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).

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).

Additional information
In vitro data suggest that effects of vardenafil on P-glycoprotein substrates more sensitive than digoxin cannot be excluded. Dabigatran etexilate is an example for highly sensitive intestinal P-glycoprotein substrates.

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
Cellulose, microcrystalline
Crospovidone, Type A
Silica, colloidal anhydrous
Magnesium stearate (E470b)

Film coating
Hypromellose
Macrogol 4000
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Iron oxide, red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (PVC/PVDC//Alu foil): 2, 4, 8, 12 and 20 film-coated tablets, in a box.
Unit-dose blister (PVC/PVDC//Alu foil): 2 x 1, 4 x 1, 8 x 1, 12 x 1 and 20 x 1 film-coated tablet, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/073/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th April 2017
Date of last renewal: 16th February 2022

10 DATE OF REVISION OF THE TEXT

May 2025