TADILAS FILM-COATED TABLETS P I

1. NAME OF THE MEDICINAL PRODUCT

Tadilas 5 mg film-coated tablets
Tadilas 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tadilas 5 mg film-coated tablets
Each film-coated tablet contains 5 mg tadalafil.

Tadilas 20 mg film-coated tablets
Each film-coated tablet contains 20 mg tadalafil.

Excipient with known effect:

Tadilas 5 mg film-coated tablets
Each film-coated tablet contains 0.750 mg lactose monohydrate.

Tadilas 20 mg film-coated tablets
Each film-coated tablet contains 3.000 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

5 mg film-coated tablets: Light yellow, biconvex, oval, film-coated tablets, scored on one side and with sign 5 on the other side. Film-coated tablets are approximately 9 mm long and 6 mm wide. The tablet can be divided into equal doses.

20 mg film-coated tablets: Brown yellow, biconvex, oval, film-coated tablets, scored on one side and with sign 20 on the other side. Film-coated tablets are approximately 14 mm long and 9.5 mm wide. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction (ED) in adult males. In order for tadalafil to be effective for the treatment of erectile dysfunction, sexual stimulation is required.

Treatment of the signs and symptoms of benign prostatic hyperplasia (BHP). If Tadilas is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks.

Treatment of erectile dysfunction and the signs and symptoms of benign prostatic hyperplasia (ED/BPH).

Tadilas is not indicated for use by women.

4.2 Posology and method of administration

Posology

Erectile dysfunction
Tadilas for Use as Needed
The recommended dose is 10 mg taken prior to anticipated sexual activity. In those patients in whom tadalafil 10 mg does not produce an adequate effect, the maximum dose is 20 mg and the maximum dosing frequency is once per day. It may be taken from 30 minutes to 36 hours prior to sexual activity. Tadalafil 10 mg and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

Tadilas for Once Daily Use
In patients who anticipate a frequent use of Tadilas (i.e. at least twice weekly) a once daily regimen with the lowest doses of Tadilas might be considered suitable, based on patient choice and the physician's judgement. In these patients the recommended starting dose is 2.5 mg once a day, taken at approximately the same time every day, without regard to timing of sexual activity. The dose may be increased to 5 mg once a day, based on individual efficacy and tolerability. The appropriateness of continued use of the daily regimen should be reassessed periodically.

Benign prostatic hyperplasia
The recommended dose is 5 mg, taken at approximately the same time every day. When therapy for BPH is initiated with Tadilas and finasteride, the recommended dose of Tadilas is 5 mg, taken at approximately the same time every day for up to 26 weeks.

Erectile Dysfunction and Benign Prostatic Hyperplasia
The recommended dose is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.

Elderly men
Dose adjustments are not required in elderly patients.

Men with renal impairment
Tadilas for Use as Needed
- Mild (creatinine clearance 51 to 80 ml/min): No dose adjustment is required.
- Moderate (creatinine clearance 31 to 50 ml/min): A starting dose of 5 mg not more than once per day is recommended and the maximum dose is 10 mg not more than once in every 48 hours.
- Severe (creatinine clearance < 30 ml/min or on hemodialysis): The maximum dose is 5 mg not more than once in every 72 hours (see section 4.4 and 5.2).

Tadilas for Once Daily Use
- Mild (creatinine clearance 51 to 80 ml/min): No dose adjustment is required.
- Moderate (creatinine clearance 31 to 50 ml/min): No dose adjustment is required.
- Severe (creatinine clearance < 30 ml/min or on hemodialysis): Tadilas for once daily use is not recommended (see section 4.4 and 5.2).

Men with hepatic impairment
Tadilas for Use as Needed
The recommended dose is 10 mg taken prior to anticipated sexual activity. There is limited clinical data on the safety of Tadilas in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

Tadilas for Once Daily Use
Once-a-day dosing has not been extensively evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician (see section 4.4 and 5.2).

Men with diabetes
Dose adjustments are not required in diabetic patients.

Paediatric population
Tadilas should not be used in individuals below 18 years of age.

Patients taking CYP3A4 Inhibitors
Tadilas for Use as Needed
For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of Tadilas is 10 mg, not to exceed once every 72 hours (see section 4.4 and 4.5)

Tadilas for Once Daily Use
For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of Tadilas is 2.5 mg (see section 4.4 and 4.5)

Method of administration
For oral use. Tadilas 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.

In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated (see section 4.5).

Tadalafil must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:
- patients with myocardial infarction within the last 90 days,
- patients with unstable angina or angina occurring during sexual intercourse,
- patients with New York Heart Association Class 2 or greater heart failure in the last 6 months,
- patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension,
- patients with a stroke within the last 6 months.

Tadalafil 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 type 5 (PDE5) inhibitor exposure (see section 4.4).

The co-administration of PDE5 inhibitors, including tadalafil, 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

Before treatment with tadalafil

A medical history and physical examination should be undertaken to diagnose erectile dysfunction or benign prostatic hyperplasia 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. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1) and as such potentiates the hypotensive effect of nitrates (see section 4.3).

Prior to initiating treatment with tadalafil for benign prostatic hyperplasia patients should be examined to rule out the presence of carcinoma of the prostate and carefully assessed for cardiovascular conditions (see section 4.3).

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment. It is not known if tadalafil is effective in patients who have undergone pelvic surgery or radical non-nervesparing prostatectomy.

Cardiovascular

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. 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 tadalafil, to sexual activity, or to a combination of these or other factors.

In patients receiving concomitant antihypertensive medicinal products, tadalafil may induce a blood pressure decrease. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

In patients who are taking alpha$_1$ blockers, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients (see section 4.5). Therefore, the combination of tadalafil and doxazosin is not recommended.

Vision

Visual defects and cases of NAION have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. Analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the patient should be advised that in case of sudden visual defect, he should stop taking tadalafil and consult a physician immediately (see section 4.3).

Decrease or sudden hearing loss

Cases of sudden hearing loss have been reported after the use of tadalafil. Although other risk factors were present in some cases (such as age, diabetes, hypertension and previous hearing loss history) patients should be advised to stop taking tadalafil and seek prompt medical attention in the event of sudden decrease or loss of hearing.

Renal and hepatic impairment

Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.

There is limited clinical data on the safety of single-dose administration of tadalafil in patients with severe hepatic impairment (Child-Pugh Class C). Once-a-day administration has not been evaluated in patients with hepatic impairment. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Priapism and anatomical deformation of the penis
Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Tadalafil 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).

Use with CYP3A4 inhibitors
Caution should be exercised when prescribing tadalafil to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.2 and 4.5).

Tadalafil and other treatments for erectile dysfunction
The safety and efficacy of combinations of tadalafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take tadalafil in such combinations.

Lactose
Tadilas contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were conducted with 10 mg and/or 20 mg tadalafil, as indicated below. With regard to those interaction studies where only the 10 mg tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.

Effects of other medicinal products on tadalafil

Cytochrome P450 inhibitors
Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) exposure (AUC) 4-fold and C_{max} by 22 %.
Ritonavir 500 mg or 600 mg twice daily at steady state, an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20 mg single-dose exposure (AUC) by 32% with a 30% reduction in C_{max}, relative to the values for tadalafil 20 mg alone. Ritonavir 200 mg twice daily, increased tadalafil 20 mg single-dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice should be co-administered with caution as they would be expected to increase plasma concentrations of tadalafil (see section 4.4).
Consequently the incidence of the adverse reactions listed in section 4.8 might be increased.

Transporters
The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. Therefore there is the potential of drug interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
A CYP3A4 inducer, rifampicin, reduced tadalafil AUC by 88 %, relative to the AUC values for tadalafil alone (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown.
Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease

plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

Nitrates
In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical study in which 150 subjects receiving daily doses of tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Thus, in a patient prescribed any dose of tadalafil (2,5 mg – 20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended (see section 4.4).
In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However, caution should be exercised when using tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers – see above) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

Riociguat
Preclinical studies showed an 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 tadalafil, is contraindicated (see section 4.3).

5- alpha reductase inhibitors (5-ARIs)
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus

finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of tadalafil and 5-ARIs has not been performed, caution should be exercised when tadalafil is coadministered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by coadministration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol). Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40 % alcohol [vodka] in an 80-kg male) but in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Cytochrome P450 metabolised medicinal products
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products metabolised by CYP450 isoforms. Studies have confirmed that tadalafil does not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.

CYP2C9 substrates (e.g. R-warfarin)
Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

Aspirin
Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by aspirin.

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

Digoxin
Co-administration of tadalafil 40 mg once per day for 10 days did not have a significant effect on the steady-state pharmacokinetics of digoxin 0.25 mg/day in healthy subjects.

4.6 Pregnancy

Tadalafil is not indicated for use by women. No clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive or use machines have been performed. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to tadalafil, before driving or using machines.

4.8 Undesirable effects

The most commonly reported adverse reactions in patients taking tadalafil for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of tadalafil. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with tadalafil once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

The table below lists the adverse reactions observed from spontaneous reporting and in placebo controlled clinical trials (comprising a total of 8022 patients on tadalafil and 4422 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

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 very rare (<1/10,000) and not known (cannot be estimated from the available data).

Very common	**Common**	**Uncommon**	**Rare**
Immune system disorders			
		Hypersensitivity reactions	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures[2], Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischaemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss[4]
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]
Vascular disorders			
	Flushing	Hypotension[3], Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal	

		reflux	
Skin and subcutaneous tissue disorders			
		Rash	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhidrosis (sweating)
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia, Pain in extremity		
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
		Prolonged erections	Priapism, Penile haemorrhage, Haematospermia
General disorders and administration site conditions			
		Chest pain[1], Peripheral oedema, Fatigue	Facial oedema[2], Sudden cardiac death[1,2]

[1] Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).
[2] Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
[3] More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.
[4] Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil.

Description of selected adverse reactions
A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations
Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with tadalafil taken on demand for the treatment of erectile dysfunction, diarrhoea was reported more frequently in patients over 65 years of age. In clinical trials with tadalafil 5 mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

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.

4.9 Overdose

Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses.
In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: urologicals, drugs used in erectile dysfunction, ATC code: G04BE08.

Mechanism of action
Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the treatment of ED in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The resulting vascular relaxation increases blood perfusion which may be the mechanism by which symptoms of benign prostatic hyperplasia are reduced. These vascular effects may be complemented by inhibition of bladder afferent nerve activity and smooth muscle relaxation of the prostate and bladder.

Pharmacodynamic effects
Studies in vitro have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in the smooth muscle of the corpus cavernosum, prostate and bladder as well as in vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, cerebellum and pancreas. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4 enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10,000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety
Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mmHg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mmHg, respectively), and no significant change in heart rate.

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Across all clinical studies, reports of changes in colour vision were rare (< 0.1%).

Three studies were conducted in men to assess the potential effect on spermatogenesis of tadalafil 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered daily. In two of these studies decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.

Erectile Dysfunction
For tadalafil on-demand, three clinical studies were conducted in 1,054 patients in an at-home setting to define the period of responsiveness. Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to

placebo as early as 16 minutes following dosing.

In a 12-week study performed in 186 patients (142 tadalafil, 44 placebo) with ED secondary to spinal cord injury, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with tadalafil 10 mg or 20 mg (flexible-dose, on-demand) of 48% as compared to 17% with placebo.

For once-a-day evaluation of tadalafil at doses of 2.5 mg, 5 mg and 10 mg, three clinical studies were initially conducted involving 853 patients of various ages (range 21-82 years) and ethnicities, with ED of various severities (mild, moderate, severe) and etiologies. In the two primary efficacy studies of general populations, the mean per-subject proportion of successful intercourse attempts were 57 and 67% on tadalafil 5 mg, 50% on tadalafil 2.5 mg as compared to 31 and 37% with placebo. In the study in patients with ED secondary to diabetes, the mean per-subject proportion of successful attempts were 41 and 46% on tadalafil 5 mg and 2.5 mg, respectively, as compared to 28% with placebo. Most patients in these three studies were responders to previous on-demand treatment with PDE5 inhibitors. In a subsequent study, 217 patients who were treatment-naive to PDE5 inhibitors were randomised to tadalafil 5 mg one a day vs placebo. The mean per-subject proportion of successful sexual intercourse attempts was 68% for tadalafil patients compared to 52% for patients on placebo.

Tadalafil at doses of 2 mg to 100 mg has been evaluated in 16 clinical studies involving 3,250 patients, including patients with ED of various severities (mild, moderate, severe), etiologies, ages (range 21-86 years), and ethnicities. Most patients reported ED of at least 1 year in duration. In the primary efficacy studies of general populations, 81% of patients reported that tadalafil improved their erections as compared to 35 % with placebo. Also, patients with ED in all severity categories reported improved erections whilst taking tadalafil (86%, 83%, and 72% for mild, moderate, and severe, respectively, as compared to 45%, 42%, and 19% with placebo). In the primary efficacy studies, 75% of intercourse attempts were successful in tadalafil treated patients as compared to 32% with placebo.

Benign Prostatic Hyperplasia

Tadalafil was studied in 5 clinical studies (LVHG, LVHJ, LVHR, LVID of 12 weeks duration and LVIW of 26 weeks duration).

Study LVHG randomised 1,058 patients to receive either tadalafil 2.5 mg, 5 mg, 10 mg or 20 mg for once daily use or placebo. Study LVHJ randomised 325 patients to receive either tadalafil 5 mg for once daily use or placebo. Patients with multiple co-morbid condtition such as diabetes mellitus, hypertension and other cardiovascular disease were included.

In each of these trials (LVHG, LVHJ), tadalafil 5 mg for once daily use resulted in statistically significant improvement in the total International Prostate Symptom Score (IPSS) compared to placebo. Mean total IPSS showed a decrease starting at the first scheduled observation (4 weeks) in Study LVHJ and remained decreased through 12 weeks. In the long-term open-label extension phase of the controlled study LVHG, in which patients received tadalafil 5 mg for up to 1 year after the 12-week double-blind treatment period, the improvement in total IPSS induced by tadalafil at week 12 of double-blind treatment was maintained over 1 year.

In study LVHR, tadalafil for once daily use was also shown to be effective in treating ED and the symptoms of BPH in patients with both conditions based on results from one of the placebo-controlled, double-blind, parallel-arm efficacy and safety studies which specifically assessed the efficacy and safety of tadalafil for once daily use in this population. In this ED and BPH study, tadalafil 5 mg demonstrated statistical superiority over placebo for total IPSS and for the International Index of Erectile Function Erectile Function (IIEF EF) domain score (mean treatment difference, 4.7; $p< 0.001$). The mean per-subject proportion of successful sexual intercourse attempts in this study was 71.9% for tadalafil 5 mg patients compared to 48.3% patients on placebo.

Study LVID randomised 511 patients to receive either tadalafil 5 mg, tamsulosin 0.4 mg or placebo. Tadalafil 5 mg resulted in statistically significant improvement in total IPSS. The efficacy of tadalafil

5 mg in treating BPH was observed as early as 1 week of therapy and was maintained through 12 weeks. Tadalafil 5 mg for once daily use also improved measures of ED after 12 weeks of treatment compared with placebo in sexually active subjects with ED in the Primary Analysis Population, as demonstrated by statistically significant improvements in IIEF EF domain score (mean difference of the change, 4.0; p< 0.001).

Data for Study LVHG, LVHJ, LVHR and LVID are shown below.

Study	**Treatment arm**	**No. of patients**	**Total IPSS**		
			Baseline Value (±SD)	**Change from baseline**	**Difference (95% CI) vs placebo**
LVHG	tadalafil 5 mg	205	17.3 (±5.97)	-4.8	-2.6[a] (-3.7, -1.5)
	placebo	205	17.1 (±6.36)	-2.2	
LVHJ	tadalafil 5 mg	160	17.1 (±6.06)	-5.6	-1.9[b] (-3.2, -0.6)
	placebo	164	16.6 (±5.99)	-3.6	
LVHR	tadalafil 5 mg	206	18.5 (±5.78)	-6.1	-2.3[a] (-3.5, -1.2)
	placebo	194	18.2 (±5.33)	-3.8	
LVID	tadalafil 5 mg	171	17.2 (±4.91)	-6.3	-2.1[c] (-3.3, -0.8)
	tamsulosin 0.4 mg	168	16.8 (±5.31)	-5.7	-1.5[d] (-2.8, -0.2)
	placebo	172	17.4 (±5.97)	-4.2	-

[a] p< 0.001 vs placebo
[b] p= 0.004 vs placebo
[c] p= 0.001 vs placebo
[d] p= 0.023 vs placebo

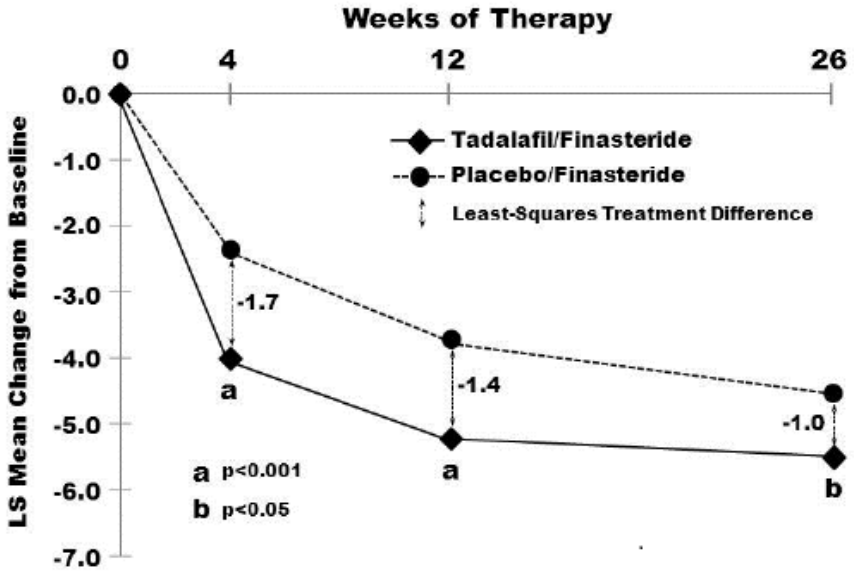
In Study LVIW, tadalafil for once daily use initiated together with finasteride was shown to be effective in treating the signs and symptoms of BPH in men with an enlarged prostate (> 30cc) for up to 26 weeks. This double-blinded, parallel-design study of 26 weeks duration randomised 696 men to initiate either tadalafil 5 mg with finasteride 5 mg or placebo with finasteride 5 mg. The study population had a mean age of 64 years (range 46-86). Patients with multiple co-morbid conditions such as ED, diabetes mellitus, hypertension and other cardiovasvular disease were included. Tadalafil with finasteride demonstrated statistically significant improvement in the signs and symptoms of BPH compared to placebo with finasteride, as measured by the total IPSS at 12 weeks, the primary study endpoint (*see* table below). Key secondary endpoints demonstrated improvement in total IPSS starting at the first scheduled observation at Week 4 (tadalafil -4.0, placebo -2.3; p< 0.001) and the score remained decreased through 26 weeks (tadalafil -5.5, placebo -4.5; p= 0.022). However, the magnitude of the treatment difference between placebo/finasteride and tadalafil/finasteride decreased from 1.7 points at Week 4 to 1.0 point at Week 26, as shown in the table and figure below. The incremental benefit of tadalafil beyond 26 weeks is unknown.

Mean Total IPSS Changes in BPH Patients in a Tadalafil for Once Daily Use Study Together with Finasteride

	n	Placebo and finasteride 5 mg (n = 350)[a]	n	tadalafil 5 mg and finasteride 5 mg (n = 345)[a]	Treatment difference	p-value[b]
Total Symptom Score (IPSS)						
Baseline[c]	349	17.4	344	17.1		
Change from Baseline to Week 4[b]	340	-2.3	330	-4.0	-1.7	< 0.001
Change from Baseline to Week 12[b]	318	-3.8	317	-5.2	-1.4	0.001
Change from Baseline to Week 26[b]	295	-4.5	308	-5.5	-1.0	0.022

[a] Overall Intention-To-Treat (ITT) population.
[b] Mixed model for repeated measurements.
[c] Unadjusted mean.

Figure: Mean Total IPSS Changes By Visit in BPH Patients Taking Tadalafil for Once Daily Use Together With Finasteride



In the 404 patients who had both ED and BPH at baseline, changes in erectile function were assessed as key secondary endpoints using the EF domain of the IIEF questionnaire. Tadalafil with finasteride (n = 203) was compared to placebo with finasteride (n = 201). A statistically significant improvement from baseline (tadalafil/finasteride 13.7, placebo/finasteride 15.1) was observed at Week 4 (tadalafil/finasteride 3.7, placebo/finasteride 1.1; p< 0.001), Week 12 (tadalafil/finasteride 4.7, placebo/finasteride 0.6; p< 0.001) and Week 26 (tadalafil/finasteride 4.7, placebo/finasteride 0.0; p< 0.001).

5.2 Pharmacokinetic properties

Absorption
Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.
The rate and extent of absorption of tadalafil are not influenced by food, thus it may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution
The mean volume of distribution is approximately 63 l, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.
Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation
Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination
The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

Linearity/non-linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once daily dosing.

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

Special populations

Elderly
Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal insufficiency
In clinical pharmacology studies using single-dose tadalafil (5 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, Cmax was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of tadalafil in patients with severe hepatic insufficiency (ChildPugh Class C). If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

Patients with diabetes
Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

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, and toxicity to reproduction.
There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free active substance at this dose was approximately 18 times the human AUC at a 20 mg dose.
There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7 – 18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also section 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose phthalate
Mannitol
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate (E470b)
Lactose monohydrate
Hypromellose
Talc (E553b)
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Tadilas 5 mg film-coated tablets
Pack sizes (blister): 28 film-coated tablets in a box.

Tadilas 20 mg film-coated tablets
Pack sizes (blister): 4 film-coated tablets in a box.

6.6 Special precautions for disposal and other handling

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

MANUFACTURER

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

DATE OF REVISION OF THE TEXT

June 2022