



SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HARDCIS 20 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Active substance:

Tadalafil _____ 20 mg

Excipient(s) with known effect:

Lactose monohydrate (from cow's milk) _____ 249 mg

Lactose monohydrate (from bovine milk) _____ 2.86 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Yellow, almond-shaped, film-coated tablet with one side blank and the '20' printed on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It is indicated for the treatment of erectile dysfunction.

HARDCIS requires sexual stimulation to be effective.

HARDCIS is not indicated for use by women.

4.2. Posology and method of administration

Posology/frequency and duration of administration

In adult men

In general, the recommended dose is 10 mg (2 x 5 mg) taken at least 30 minutes prior to anticipated sexual activity.

In those patients in whom tadalafil 10 mg (2 x 5 mg) does not produce an adequate effect, 20 mg might be tried.

The maximum dose frequency is once per day.

Tadalafil 10 mg (2 x 5 mg) and 20 mg is intended for use before anticipated sexual activity and it is not recommended for continuous daily use.

For products containing 20 mg tadalafil (except for notched tablets), it is not appropriate to use the medicine by dividing it.

Method of administration

For oral use.



Additional information for special populations

Renal / Hepatic impairment

Dose adjustments are not required in patients with mild to moderate renal impairment. Tadalafil is not recommended for use in patients with severe renal impairment (see Sections 4.4 and 5.2).

There is limited clinical data on the safety of tadalafil in patients with severe hepatic impairment (Child-Pugh Class C). If HARDCIS is prescribed to these patients, a detailed individual benefit/risk assessment should be performed by the prescribing physician (see Sections 4.4 and 5.2).

Men with diabetes:

Dose adjustments are not required in diabetic patients.

Pediatric population:

HARDCIS should not be used in people under 18 years of age.

Geriatric population:

Dose adjustments are not required in elderly patients.

4.3. Contraindications

Contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

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/cGMP pathway. Therefore, HARDCIS use in patients who are using any form of organic nitrate is contraindicated (see section 4.5).

Compounds used for the treatment of erectile dysfunction, including HARDCIS, 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 in:

- 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 mmHg), or uncontrolled hypertension,
- Patients with a stroke within the last 6 months.

HARDCIS 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 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 HARDCIS

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. 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).

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 HARDCIS is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing 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 HARDCIS, to sexual activity, or to a combination of these or other factors.

In patients who are taking alpha₁ blockers, concomitant administration of HARDCIS may lead to symptomatic hypotension in some patients (see section 4.5). 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 HARDCIS 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 patients should be advised that in case of sudden visual defect, they should stop taking HARDCIS and consult a physician immediately (see section 4.3).

Decreased 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.

Hepatic 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). If HARDCIS is prescribed to these patients, 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.

Compounds for the treatment of erectile dysfunction, including HARDCIS, 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 anemia, multiple myeloma or leukemia).

Use with CYP3A4 inhibitors

Caution should be exercised when prescribing HARDCIS 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 4.5).

HARDCIS and other treatments for erectile dysfunction

The safety and efficacy of using tadalafil and other PDE5 inhibitors or other erectile dysfunction treatments in combination have not been studied. Patients should be informed not to take HARDCIS with such combinations.

Lactose

Patients with hereditary problems such as galactose intolerance, Lapp lactase deficiency, or impaired glucose-galactose absorption should not use this medication.

In post-marketing experience, retinal vein occlusion has been reported very rarely. The causal relationship between tadalafil and retinal vein occlusion has not been investigated. Physicians need to pay attention to the fact that the risk of retinal vein occlusion is higher in patients with increased blood viscosity, especially in the elderly.

4.5. Interactions with other medicinal products and other forms of interaction

Interaction studies with tadalafil have been conducted as described below.

Effects of other substances on tadalafil

Cytochrome P450 inhibitors

Tadalafil is principally metabolized 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, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) exposure (AUC) 2-fold with no change in C_{max} .



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 was shown to augment the hypotensive effects of nitrates. Therefore, administration of HARDCIS 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 HARDCIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of HARDCIS before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate hemodynamic 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 12 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 favorable 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 (ARI)

In a clinical trial that compared tadalafil 5 mg co-administered 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-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered 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 co-administration with tadalafil. In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximize 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 metabolized medicinal products

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products metabolized 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 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 did not potentiate the increase in bleeding time caused by acetylsalicylic acid.

Antidiabetic medicinal products

Specific interaction studies with antidiabetic medicinal products were not conducted.

Additional information on special populations

Pediatric population

HARDCIS is not indicated for use in pediatric patients. No data regarding safety and efficacy in patients under 18 years of age have been established.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category is B.

HARDCIS is not indicated for use by women.

Women of childbearing potential / Birth Control (Contraception)

The physician should be informed when pregnancy is suspected or present.

Pregnancy

There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of HARDCIS during pregnancy.

Breast-feeding

HARDCIS is not indicated for use by women. It is not known whether tadalafil passes into breast milk. Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. HARDCIS should not be used during breast feeding.



Reproductive ability / Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7. Effects on ability to drive and use machines

HARDCIS has negligible influence on the ability to drive or use machines. 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 HARDCIS, before driving or using machines.

4.8. Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions in patients taking tadalafil 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.

Listed summary of adverse reactions

The list below demonstrates 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.

The adverse reactions listed below are presented by MedDRA system-organ class and absolute frequency. Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Immune system disorders

Uncommon: Hypersensitivity reactions

Rare: Angioedema²

Nervous system disorders

Common: Headache

Uncommon: Dizziness

Rare: Stroke¹ (including hemorrhagic events), syncope, transient ischemic attacks¹, migraine², seizures², transient amnesia

Eye disorders

Uncommon: Blurred vision, sensations described as eye pain

Rare: Visual field defect, swelling of eyelid, conjunctival hyperemia, non-arteritic anterior ischemic optic neuropathy (NAION)², retinal vascular occlusion²

Ear and labyrinth disorders

Uncommon: Tinnitus

Rare: Sudden hearing loss

Cardiac disorders¹

Uncommon: Tachycardia, palpitations



Rare: Myocardial infarction, unstable angina pectoris², ventricular arrhythmia²

Vascular disorders

Common: Flushing

Uncommon: Hypotension³, hypertension

Respiratory, thoracic and mediastinal disorders

Common: Nasal congestion

Uncommon: Dyspnea, epistaxis

Gastrointestinal disorders

Common: Dyspepsia

Uncommon: Abdominal pain, vomiting, nausea, gastro-esophageal reflux

Skin and subcutaneous tissue disorders

Uncommon: Rash

Rare: Urticaria, Stevens-Johnson syndrome², exfoliative dermatitis², hyperhidrosis (sweating)

Musculoskeletal, connective tissue and bone disorders

Common: Back pain, myalgia, pain in extremity

Renal and urinary disorders

Uncommon: Hematuria

Reproductive system and breast disorders

Uncommon: Prolonged erections,

Rare: Priapism, penile hemorrhage, hematospermia

General disorders and administration site conditions

Uncommon: Chest pain¹, peripheral edema, fatigue

Rare: Facial edema², sudden cardiac death^{1,2}

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).

(2) Post-marketing 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.

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, diarrhea 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 diarrhea were reported more frequently in patients over 75 years of age.

Reporting of suspected adverse reactions

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

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. Hemodialysis 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 erectile dysfunction in the absence of sexual stimulation.

Pharmacodynamic effects

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. 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

According to the results of three clinical studies involving 1054 patients that investigated the response period to tadalafil used before intercourse, tadalafil's effect in providing successful sexual intercourse and erection started as early as 16 minutes after dose administration and lasted for 36 hours, significantly more so than placebo.

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 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal



decrease of 0.2/4.6 mm Hg, respectively), and no significant change in heart rate.

In a study to assess the effects of tadalafil on vision, no impairment of color 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 color 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.

Tadalafil, in doses ranging from 2 to 100 mg, was evaluated in 16 clinical trials involving 3250 patients of varying ages (age range: 21-86) and ethnicities with erectile dysfunction of varying severity (mild, moderate, and severe) and etiology. The majority of patients reported erectile dysfunction lasting at least one year. In primary efficacy studies conducted in the general population, 81% of patients reported improved erections with tadalafil, compared to 35% with placebo. In addition, patients with erectile dysfunction in all severity categories reported that tadalafil improved their erections (86%, 83%, and 72% with tadalafil, compared to 45%, 42%, and 19% with placebo, respectively, for mild, moderate, and severe). In primary efficacy studies, 75% of attempts at sexual intercourse were successful in patients treated with tadalafil, compared to 32% with placebo.

In a 12-week study of 186 patients with spinal cord injury and erectile dysfunction (142 tadalafil, 44 placebo), the mean number of successful attempts at sexual intercourse per patient was 17% in the placebo group, while tadalafil 10 mg or 20 mg significantly improved erectile function by 48% in patients treated with tadalafil (pre-intercourse, flexible dose).

5.2. Pharmacokinetic properties

General properties

Absorption

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) 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 HARDCIS 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 liters, 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 metabolized 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 feces (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.

In patients with erectile dysfunction, pharmacokinetics determined using a population approach are similar to pharmacokinetics in volunteers 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 hemodialysis patients, C_{max} was 41% higher than that observed in healthy subjects. Hemodialysis 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 (Child-Pugh Class C). If HARDCIS has been prescribed, a detailed benefit/risk assessment should be performed by the prescribing physician.

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 fetotoxicity 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 drug 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

Lactose monohydrate (from cow's milk)
Microcrystalline cellulose (pH 101)
Hydroxypropyl cellulose-L
Sodium lauryl sulfate
Croscarmellose sodium
Magnesium stearate

Opadry II Yellow 32K520009

Lactose monohydrate (from bovine milk)
Hypromellose
Titanium dioxide
Iron oxide yellow
Triacetin
Talc

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Keep at room temperature below 25°C.

6.5. Nature and contents of container

The primary packaging material used is a blister pack made of transparent PVC-PVDC foil on one side and aluminum on the other. The blisters are packaged in cardboard boxes. Each box contains packs of 2, 4, or 8 tablets, along with package leaflet.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1



34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER(S)

252/84

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 29.08.2013

Renewal of the authorization :

10. DATE OF REVISION OF THE TEXT