# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

HARDCIS 5 mg Film Coated Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
**Active substance:**
Tadalafil_____5 mg
**Excipient(s) with known effect:**
Lactose monohydrate (from cow's milk)_____129.5 mg
Lactose monohydrate (from bovine milk)_____1.79 mg
For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.
Yellow-colored, almond-shaped, biconvex film-coated tablets.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Indicated for the treatment of erectile dysfunction and benign prostatic hyperplasia (BPH), as well as benign prostatic hyperplasia accompanied by erectile dysfunction.

In order for HARDCIS to be effective for the treatment of erectile dysfunction, sexual stimulation is required.

HARDCIS is not indicated for use by women.

### 4.2. Posology and method of administration

**Posology/frequency and duration of administration**

Erectile dysfunction 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.

In patients who anticipate a frequent use of tadalafil (i.e., at least twice weekly) a once-daily regimen with the lowest doses of tadalafil might be considered suitable, based on patient choice and the physician's judgement.

In these patients, the recommended dose is 5 mg taken once a day but the dose may be decreased to 2.5 mg once a day based on individual tolerability. The appropriateness of continued use of the daily regimen should be reassessed periodically.

Benign prostatic hyperplasia in adult men

The recommended dose is a 5 mg tablet, taken once daily at approximately the same time every day. Patients who are unable to tolerate tadalafil 5 mg for the treatment of benign prostatic hyperplasia or for whom this dosage strength is not effective should consider an alternative therapy.

**For products containing 5 mg tadalafil (except for notched tablets), it is not appropriate to use the medicine by dividing it.**

Benign prostatic hyperplasia accompanied by erectile dysfunction in adult men

The recommended dose is a 5 mg tablet, taken once daily at approximately the same time every day. Patients who are unable to tolerate tadalafil 5 mg for the treatment of benign prostatic hyperplasia or for whom this dosage strength is not effective should consider an alternative therapy.

**For products containing 5 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 male patients with mild to moderate renal impairment. If requested for patients with severe renal impairment, 10 mg (2 x 5 mg) is the maximum recommended dose. Constant use of once-a-day dosing of 5 mg tadalafil (continuous use of daily regimen) for the treatment of erectile dysfunction or benign prostatic hyperplasia in patients with severe renal impairment is not recommended (see sections 4.4 and 5.2).

For the treatment of erectile dysfunction using on-demand tadalafil, the recommended dose is 10 mg (2 x 5 mg) taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of HARDCIS in patients with severe hepatic impairment (Child-Pugh Class C). There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

Once-a-day dosing both for the treatment of erectile dysfunction and benign prostatic hyperplasia has not been evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician (see sections 4.4 and 5.2).

Pediatric population

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

Geriatric population

Dose adjustments are not required in elderly patients.

Men with diabetes

Dose adjustments are not required in diabetic patients.

**4.3. Contraindications**

Contraindicated in patients with hypersensitivity to the active substance or to any of the excipients (see 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/cGMP pathway. Therefore, its 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 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).

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.

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).

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 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 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.

Renal and hepatic impairment
Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, administration of HARDCIS 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 insufficiency (Child-Pugh Class C). Once-a-day administration for the treatment of erectile dysfunction and benign prostatic hyperplasia has not been evaluated in patients with hepatic insufficiency. 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 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 HARDCIS in such combinations. Therefore, such combinations are not recommended.

Lactose
HARDCIS contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 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 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 (5, 10 and 20 mg) 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 (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 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*
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 (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 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 (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 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. Fertility, 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 for the treatment of erectile dysfunction or BPH 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 5 mg tadalafil dosing are experienced within the first 10 to 30 days of starting treatment.

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.

Frequency convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 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).

**Immune system disorders**
Uncommon: Hypersensitivity reactions
Rare: Angioedema[2]

**Nervous system disorders**
Common: Headache
Uncommon: Dizziness
Rare: Stroke[1] (including hemorrhagic events), syncope, transient ischemic attacks[1], migraine[2], seizures[2], transient amnesia

**Eye disorders**
Uncommon: Blurred vision, sensations described as eye pain
Rare: Visual field defect, swelling of eyelids, conjunctival hyperemia, non-arteritic anterior ischemic optic neuropathy (NAION)[2], retinal vascular occlusion[2]

**Ear and labyrinth disorders**
Uncommon: Tinnitus
Rare: Sudden hearing loss

**Cardiac disorders**[1]
Uncommon: Tachycardia, palpitations
Rare: Myocardial infarction, unstable angina pectoris[2], ventricular arrhythmia[2]

**Vascular disorders**
Common: Flushing
Uncommon: Hypotension[3], 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 syndrome[2], exfoliative dermatitis[2], 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 pain[1], peripheral edema, fatigue
Rare: Facial edema[2], 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.

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 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**
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 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.

Erectile dysfunction
For tadalafil on demand, three clinical studies were conducted in 1054 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 erectile dysfunction 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 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, 5, and 10 mg 3 clinical studies were initially conducted involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction 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 erectile dysfunction 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 randomized to tadalafil 5 mg once a day vs. placebo. The mean per-subject proportion of successful sexual intercourse attempts was 68% for tadalafil 5 mg patients compared to 52% for patients on placebo.

Benign prostatic hyperplasia
Tadalafil was studied in 4 clinical studies of 12 weeks duration enrolling over 1500 patients with signs and symptoms of benign prostatic hyperplasia. The improvement in the total international prostate symptom score with tadalafil 5 mg in the four studies were -4.8, -5.6, -6.1 and -6.3 compared to -2.2, -3.6, -3.8 and -4.2 with placebo. The improvements in total international prostate symptom score occurred as early as 1 week. In one of the studies, which also included tamsulosin 0.4 mg as an active comparator, the improvement in total international prostate symptom score with tadalafil 5 mg, tamsulosin and placebo were -6.3, -5.7 and -4.2 respectively.

One of these studies assessed improvements in erectile dysfunction and signs and symptoms of benign prostatic hyperplasia in patients with both conditions. The improvements in the erectile function domain of the international index of erectile function and the total international prostate symptom score in this study were 6.5 and -6.1 with tadalafil 5 mg compared to 1.8 and -3.8 with placebo, respectively. The mean per-subject proportion of successful sexual intercourse attempts was 71.9% with tadalafil 5 mg compared to 48.3% with placebo.

The maintenance of the effect was evaluated in an open-label extension to one of the studies, which showed that the improvement in total international prostate symptom score seen at 12 weeks was maintained for up to 1 additional year of treatment with tadalafil 5 mg.

## 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.

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 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). There are no available data about the administration of once-a-day dosing of tadalafil to patients with hepatic impairment. If HARDCIS is prescribed once-a-day, a careful individual benefit/risk evaluation should be undertaken 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
Hydroxypropyl cellulose-L
Sodium lauryl sulfate
Croscarmellose sodium
Magnesium stearate

Opadry II Yellow 32K520009
Lactose monohydrate (from bovine milk)
HPMC 2910 / Hypromellose 15cP
Iron oxide yellow
Titanium dioxide
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 and in its original package.

### 6.5. Nature and contents of container

Film-coated tablets are packaged in blisters consisting of transparent PVC/PVDC foil on one side and aluminum on the other side. The product is offered in a cardboard box containing blisters of 14 or 28 tablets, along with a 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)

2016/271

## 9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 07.04.2016
Renewal of the authorization :

## 10. DATE OF REVISION OF THE TEXT