

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LONGIS® 20 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Each film-coated tablet contains 20 mg tadalafil.

Excipients: Lactose monohydrate (bovine source) 182 mg

For excipients, refer to section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Yellow, convex, round film-coated tablets with the "T20" logo on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the treatment of erectile dysfunction.

For LONGIS® to be effective, sexual stimulation is required.

LONGIS® is not indicated for use in women.

4.2 Posology and method of administration

Posology/frequency and duration of use:

Use in adult males

The generally recommended dose is 10 mg, taken at least 30 minutes before the planned sexual activity. If 10 mg of tadalafil does not provide sufficient effect, the dose may be increased to 20 mg.

A maximum of one dose should be taken per day.

The 10 mg or 20 mg doses of tadalafil should be taken before the planned sexual activity and are not recommended for continuous daily use.

Products containing 20 mg tadalafil (excluding scored tablets) is not appropriate to divide the product for use.

Method of administration:

The tablets are taken orally.

Additional information for special populations

Renal/Liver impairment:

No dose adjustment is necessary for patients with mild to moderate renal impairment.

Tadalafil use is not recommended in patients with severe renal impairment (see Section 4.4 and 5.2).

In patients with severe liver impairment (Child-Pugh Class C), there is limited clinical data on

the safety of LONGIS®. If LONGIS® is prescribed to these patients, a detailed individual benefit/risk assessment should be conducted by the prescribing physician (see Section 4.4 and 5.2).

Diabetic male patients:

No dose adjustment is necessary in diabetic patients.

Pediatric population:

LONGIS® should not be used in individuals under 18 years of age.

Geriatric population:

No dose adjustment is necessary in elderly males.

4.3 Contraindications

LONGIS® is contraindicated in patients with hypersensitivity to the active substance or any of the excipients.

In clinical studies, tadalafil has been shown to enhance the hypotensive effects of nitrates. This is thought to be due to the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, LONGIS® is contraindicated in patients taking organic nitrates in any form (see Section 4.5).

Compounds used for erectile dysfunction, including LONGIS®, should not be used in men with heart disease where sexual activity is not recommended. Physicians should consider the potential cardiac risks associated with sexual activity in individuals with a history of cardiovascular disease.

The following groups of patients with cardiovascular disease were not included in clinical studies, and therefore tadalafil use is contraindicated in these patients:

- Patients who have had a myocardial infarction in the past 90 days
- Patients with unstable angina or those who experience angina during sexual activity
- Patients with heart failure classified as "Class 2" or worse according to the New York Heart Association within the last 6 months
- Patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension
- Patients who have had a stroke within the last 6 months

In patients who have lost vision in one eye due to non-arteritic anterior ischemic optic neuropathy (NAION), LONGIS® is contraindicated, regardless of whether this episode was associated with previous PDE5 inhibitor use (see Section 4.4).

PDE5 inhibitors, including tadalafil, are contraindicated when used in combination with guanylate cyclase stimulators, such as riociguat, as this may lead to symptomatic hypotension (see Section 4.5).

4.4 Special warnings and precautions for use

Before starting treatment with LONGIS®, erectile dysfunction should be diagnosed, and the underlying potential causes should be identified. This should be done by reviewing the patient's medical history and conducting a physical examination, before considering pharmacological treatment.

Since there is a certain cardiac risk associated with sexual activity, physicians should consider their patients' cardiovascular condition before initiating any treatment for erectile dysfunction. Tadalafil has vasodilatory properties that can cause mild and transient decreases in blood pressure (see Section 5.1) and can enhance the hypotensive effects of nitrates (see Section 4.3).

Erectile dysfunction assessment should include the identification of underlying potential causes, followed by appropriate medical evaluation to determine the suitable treatment. The effectiveness of LONGIS® in patients who have undergone pelvic surgery or non-nerve-sparing radical prostatectomy is unknown.

Cardiovascular

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina, ventricular arrhythmias, stroke, transient ischemic attacks, chest pain, palpitations, and tachycardia, have been reported during post-marketing surveillance and clinical trials. Most of the patients who reported these events had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events were directly related to these risk factors, LONGIS®, sexual activity, or a combination of these or other factors.

In patients taking alpha1 blockers, simultaneous administration of LONGIS® may cause symptomatic hypotension in some individuals (see Section 4.5). The combination of tadalafil and doxazosin is not recommended.

Visual

Impairments Associated with the Use of LONGIS® and Other PDE5 Inhibitors

Cases of visual disturbances, including Central Serous Chorioretinopathy (CSCR) and NAION, have been reported in association with the use of LONGIS® and other PDE5 inhibitors. Most cases of CSCR resolved spontaneously after discontinuation of tadalafil treatment. Regarding NAION, an analysis of observational data indicates an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. This may apply to all patients exposed to tadalafil; therefore, patients should be advised to discontinue LONGIS® and seek immediate medical attention if they experience sudden vision changes, blurred vision, and/or visual impairment (see Section 4.3).

Decreased or Sudden Hearing Loss

Sudden hearing loss has been reported after tadalafil use. Although other risk factors (such as

age, diabetes, hypertension, and a history of previous hearing loss) may be present, patients should be advised to stop taking tadalafil and seek immediate medical assistance if they experience sudden hearing loss or a decrease in hearing.

Liver Impairment

There is limited clinical data on the safety of a single dose of LONGIS® in patients with severe liver impairment (Child-Pugh Class C). If LONGIS® is prescribed to these patients, a detailed individual benefit/risk assessment should be performed by the prescribing physician.

Priapism and Penile Anatomical Deformities

Patients who experience an erection lasting 4 hours or more should seek immediate medical help. If priapism is not treated promptly, it can cause damage to penile tissue and result in permanent impotence.

In patients with anatomical deformities of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease) or conditions that may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), erectile dysfunction treatments, including LONGIS®, should be used with caution.

Use with CYP3A4 Inhibitors

In patients using potent CYP3A4 inhibitors (such as ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin), an increase in tadalafil exposure (AUC) has been observed when these drugs are used together. Therefore, caution is advised when prescribing LONGIS® in such cases (see Section 4.5).

LONGIS® and Other Erectile Dysfunction Treatments

The safety and efficacy of combining LONGIS® with other PDE5 inhibitors or other erectile dysfunction treatments have not been studied. Patients should be informed not to take LONGIS® with such combinations.

Lactose

LONGIS® contains lactose monohydrate from bovine sources. Patients with rare hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not use this medicine.

Post-Marketing Experience

Retinal vein occlusion has been reported very rarely in post-marketing experience. The causal relationship between tadalafil and retinal vein occlusion has not been investigated. Physicians should be aware that the risk of retinal vein occlusion is higher in older patients and those with increased blood viscosity.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

As outlined below, interaction studies with tadalafil have been conducted.

Effects of Other Substances on Tadalafil

Cytochrome P450 Inhibitors

Tadalafil is primarily metabolized by CYP3A4. Ketoconazole, a selective CYP3A4 inhibitor (200 mg daily), increased tadalafil exposure (AUC) by 2 times and C_{max} by 15% compared to tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil exposure (AUC) by 4 times and C_{max} by 22% compared to tadalafil alone. Ritonavir, a protease inhibitor that inhibits CYP3A4, CYP2C9, CYP2C19, and CYP2D6 (200 mg twice daily), increased tadalafil exposure (AUC) by 2 times without altering C_{max}. Although specific interactions have not been studied, other protease inhibitors like saquinavir, and other CYP3A4 inhibitors such as erythromycin, clarithromycin, itraconazole, and grapefruit juice, are expected to increase tadalafil plasma concentrations, and caution should be taken when used together (see Section 4.4).

As a result, the incidence of adverse reactions listed in Section 4.8 may be increased.

Transporters

The role of transporters (e.g., P-glycoprotein) in the disposition of tadalafil is not well understood. Therefore, drug interactions via inhibition of these transporters are possible.

Cytochrome P450 Inducers

Rifampicin, a CYP3A4 inducer, decreased tadalafil exposure (AUC) by 88% compared to tadalafil alone (10 mg). This decreased exposure is expected to reduce the efficacy of tadalafil; however, the extent of the reduction in efficacy is unknown. Other CYP3A4 inducers, such as phenobarbital, phenytoin, and carbamazepine, may reduce tadalafil plasma concentrations.

Effects of Tadalafil on Other Medicinal Products

Nitrates

In clinical studies, tadalafil has been shown to enhance the hypotensive effects of nitrates. Therefore, the use of LONGIS® in patients taking any form of organic nitrate is contraindicated (see Section 4.3). According to the results of a clinical study in 150 subjects, who received 20 mg tadalafil daily for 7 days and sublingual nitroglycerin 0.4 mg at different times, the drug interaction lasted for more than 24 hours, and was undetectable 48 hours after the last dose of tadalafil. Therefore, in patients where nitrate application is medically necessary in life-threatening situations and a dose of LONGIS® has been prescribed, it is important to ensure that at least 48 hours have passed since the last dose of LONGIS® before applying nitrates. In such cases, nitrates should only be administered under close medical supervision and with appropriate hemodynamic monitoring.

Antihypertensives (Including Calcium Channel Blockers)

The concurrent administration of doxazosin (4 mg and 8 mg daily) and tadalafil (5 mg and 20 mg single dose daily) significantly enhances the blood pressure-lowering effect of this alpha-blocker. This effect can persist for at least 12 hours and may be symptomatic, including syncope. Therefore, this combination is not recommended (see Section 4.4).

Interaction studies with a limited number of healthy volunteers have shown no such effects with alfuzosin and tamsulosin. However, caution is advised when using tadalafil in patients treated with alpha-blockers, especially in the elderly. Treatment should begin with the lowest dose and be adjusted gradually.

In clinical pharmacology studies, the potential of tadalafil to enhance the hypotensive effects of antihypertensive drugs has been investigated. This research included calcium channel blockers (amlodipine), angiotensin-converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendroflumethiazide), and angiotensin II receptor blockers (in various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (at doses of 20 mg and in studies with angiotensin II blockers and amlodipine, or 10 mg in other studies) showed no clinically significant interactions with any of the aforementioned antihypertensive categories.

In another clinical pharmacology study, tadalafil (20 mg) was combined with four different classes of antihypertensive drugs. In patients taking multiple antihypertensive drugs, changes in standing blood pressure were somewhat associated with blood pressure control. In well-controlled blood pressure patients, the reduction was minimal and similar to that seen in healthy volunteers. In volunteers with poorly controlled blood pressure, although the reduction was greater, it was not associated with hypotensive symptoms in the majority of subjects. In patients concurrently taking antihypertensive drugs, tadalafil 20 mg can induce a blood pressure reduction, which, except with alpha-blockers (as noted above), is generally very low and clinically insignificant. Analysis of Phase 3 clinical trial data has shown no difference in adverse effects between patients receiving tadalafil with antihypertensive drugs or alone. However, patients should be advised that when treated with antihypertensive medications, there may be a possible decrease in blood pressure.

Riociguat

Preclinical studies have shown that when PDE5 inhibitors are used in combination with riociguat, they produce an additional blood pressure-lowering effect. Clinical studies have demonstrated that riociguat increases the hypotensive effects of PDE5 inhibitors. No evidence of a positive clinical effect of this combination has been found in the studied population. Therefore, the use of riociguat in combination with PDE5 inhibitors, including tadalafil, is contraindicated (see Section 4.3).

5-Alpha Reductase Inhibitors (ARI)

In a clinical study comparing 5 mg tadalafil used with 5 mg finasteride for the relief of BPH symptoms to placebo plus 5 mg finasteride, no new adverse reactions were identified. However, a drug-drug interaction study in accordance with the guidelines evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been conducted. Caution should be exercised when using tadalafil in combination with 5-alpha reductase inhibitors.

CYP1A2 Substrates (e.g., Theophylline)

In a clinical pharmacology study, 10 mg tadalafil did not show any pharmacokinetic interaction when administered with theophylline, a non-selective phosphodiesterase inhibitor. The only observed pharmacodynamic effect was a small increase in heart rate (3.5 beats per minute). Although this effect was small and not clinically significant in this study, it should be considered when these medications are used together.

Ethinylestradiol and Terbutaline

It has been shown that tadalafil increases the oral bioavailability of ethinylestradiol. Although the clinical outcome of this is uncertain, a similar increase might be expected with the oral administration of terbutaline.

Alcohol

Alcohol concentrations (average maximum blood concentration of 0.08%) were not affected by concurrent administration with tadalafil. Additionally, no changes in tadalafil concentrations were observed 3 hours after concurrent alcohol administration. Alcohol was administered in a manner that maximized alcohol absorption (without food, up to 2 hours after evening alcohol intake). Tadalafil (20 mg) did not increase the average blood pressure drop caused by alcohol (0.7 g/kg or approximately 180 ml of 40% alcohol [vodka] in a man weighing 80 kg); however, some volunteers experienced postural dizziness and orthostatic hypotension. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), no hypotension was observed, and dizziness occurred with a similar frequency as with alcohol alone. The effect of alcohol on cognitive functions was not enhanced by tadalafil (10 mg).

Cytochrome P450 Metabolized Drugs

Tadalafil is not expected to clinically inhibit or induce the clearance of drugs metabolized by CYP450 isoforms. Studies have confirmed that tadalafil does not inhibit or induce CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9, or CYP2C19 isoforms.

CYP2C9 Substrates (e.g., R-warfarin)

Tadalafil has no clinically significant effect on the exposure (EAA) of S-warfarin or R-warfarin (CYP2C9 substrate), nor has it caused any change in the prothrombin time induced by warfarin.

Aspirin

Tadalafil has not affected the extension of bleeding time caused by acetylsalicylic acid.

Antidiabetic Medications

Specific interaction studies with antidiabetic medications have not been conducted.

Additional Information for Special Populations:

Pediatric Population:

LONGIS® is not indicated for use in pediatric patients. There is no data available on the safety and efficacy in patients under 18 years of age.

4.6 Pregnancy and Lactation

Pregnancy Category: B

LONGIS® is not indicated for use by women.

Women of Childbearing Potential / Contraception

Women should be informed in case of suspected or confirmed pregnancy.

Pregnancy Period

There is limited data on the use of tadalafil in pregnant women. Animal studies do not show any direct or indirect harmful effects on pregnancy, embryonal/fetal development, labor, or postnatal development (see Section 5.3). As a precautionary measure, the use of LONGIS® should be avoided during pregnancy.

Lactation Period

LONGIS® is not indicated for use by women. It is unknown whether tadalafil passes into breast milk. Available pharmacodynamic/toxicological data in animals suggest that tadalafil passes into milk. The risk of transfer to the infant through breast milk cannot be excluded. LONGIS® should not be used during lactation.

Fertility

Effects suggesting infertility were observed in dogs. However, two clinical studies suggest that this effect was not observed in humans, despite a decrease in sperm concentration in some men (see Sections 5.1 and 5.3).

4.7 Effects on the Ability to Drive and Use Machines

The effects of LONGIS® on the ability to drive and use machinery are minimal. Although the frequency of dizziness was similar between the placebo and tadalafil in clinical trials, patients should be aware of how they respond to LONGIS® before driving or operating machinery.

4.8 Undesirable Effects

Summary of the Safety Profile

The most commonly reported undesirable effects in patients using LONGIS® are headache, dyspepsia, back pain, and myalgia, with the incidence increasing as the dose of LONGIS® is increased. The reported undesirable effects were generally temporary and mild to moderate in severity.

Summary of Adverse Reactions

The following list provides adverse reactions observed in spontaneous reports and placebo-controlled clinical studies (a total of 8022 patients with tadalafil and 4422 patients with placebo), including erectile dysfunction with on-demand and once-daily treatment, and benign prostatic hyperplasia with once-daily treatment.

The listed undesirable effects are categorized by the MedDRA system organ class and their absolute frequency. Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$); Unknown (cannot be estimated from the available data).

Immune System Disorders

Uncommon: Hypersensitivity reactions

Rare: Angioedema

Nervous System Disorders

Common: Headache

Uncommon: Dizziness

Rare: Stroke (including hemorrhagic events), syncope, transient ischemic attacks, migraine, seizures, transient amnesia

Eye Disorders

Uncommon: Blurred vision, eye pain

Rare: Visual field defect, eyelid swelling, conjunctival hyperemia, Non-arteritic Anterior Ischemic Optic Neuropathy (NAION), retinal vascular occlusion

Unknown: Central Serous Chorioretinopathy

Ear and Inner Ear Disorders

Uncommon: Tinnitus

Rare: Sudden hearing loss

Cardiac Disorders

Uncommon: Tachycardia, palpitations

Rare: Myocardial infarction, unstable angina pectoris, ventricular arrhythmia

Vascular Disorders

Common: Flushing

Uncommon: Hypotension, hypertension

Respiratory, Thoracic, and Mediastinal Disorders

Common: Nasal congestion

Uncommon: Dyspnea, epistaxis

Gastrointestinal Disorders

Common: Dyspepsia

Uncommon: Abdominal pain, vomiting, nausea, gastroesophageal reflux

Skin and Subcutaneous Tissue Disorders

Uncommon: Rash

Rare: Urticaria, Stevens-Johnson syndrome, exfoliative dermatitis, hyperhidrosis (sweating)

Musculoskeletal and Connective Tissue and Bone Disorders

Common: Back pain, myalgia, pain in the extremities

Renal and Urinary Disorders

Uncommon: Hematuria

Reproductive System and Breast Disorders

Uncommon: Prolonged erections

Rare: Priapism, penile hemorrhage, hematospermia

General and Application Site Conditions

Uncommon: Chest pain, peripheral edema, fatigue

Rare: Facial edema, sudden cardiac death

(1) The majority of patients reporting these events had pre-existing cardiovascular risk factors (see Section 4.4).

(2) Some adverse events not observed in placebo-controlled trials were reported during post-marketing surveillance.

(3) These events were reported more frequently in patients receiving tadalafil alongside antihypertensive medications.

Description of Selected Adverse Reactions

Compared to placebo, patients treated with tadalafil once daily reported a slightly higher frequency of EKG abnormalities, primarily sinus bradycardia. Most of these EKG abnormalities were not associated with undesirable effects.

Other Special Populations

Data from clinical studies on patients aged 65 and older using tadalafil for the treatment of both erectile dysfunction and benign prostatic hyperplasia is limited. In clinical trials for erectile dysfunction treatment with tadalafil, diarrhea was reported more frequently in patients over 65 years old. In clinical trials for benign prostatic hyperplasia treated with a single daily dose of 5 mg tadalafil, dizziness and diarrhea were reported more frequently in patients over 75 years old.

Reporting of Suspected Adverse Reactions

The reporting of suspected post-marketing drug adverse reactions is of great importance.

Reporting allows for the continuous monitoring of the drug's benefit/risk balance. Healthcare professionals are required to report any suspected adverse reactions to the Turkish Pharmacovigilance Center (TÜFAM).

Website: www.titck.gov.tr

Email: tufam@titck.gov.tr
Phone: 0 800 314 00 08
Fax: 0 312 218 35 99

4.9 Overdose and Treatment

Healthy volunteers have been administered single doses up to 500 mg and multiple daily doses up to 100 mg. Adverse events observed were similar to those seen with lower doses. In the case of an overdose, standard supportive measures should be taken as necessary. Hemodialysis has a negligible effect on the elimination of tadalafil.

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 and reversible inhibitor of phosphodiesterase type 5 (PDE5) specific to cyclic guanosine monophosphate (cGMP). When sexual stimulation occurs and triggers local nitric oxide release, tadalafil's inhibition of PDE5 leads to an increase in cGMP levels in the corpus cavernosum. This results in the relaxation of smooth muscles and increased blood flow to the penile tissue, thereby facilitating an erection. Tadalafil has no effect in the absence of sexual stimulation.

Pharmacodynamic Effects

In vitro studies have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in the smooth muscle of the corpus cavernosum, blood vessels, and internal organs, as well as in skeletal muscles, platelets, kidneys, lungs, and the cerebellum. Tadalafil is more effective on PDE5 than on other phosphodiesterases. Its effect on PDE5 is over 10,000 times more potent than its effects on PDE1, PDE2, and PDE4 enzymes found in the heart, brain, blood vessels, liver, and other organs. Tadalafil's effect on PDE5 is more than 10,000 times greater than its effect on PDE3, an enzyme found in the heart and involved in cardiac contractility. Additionally, tadalafil's effect on PDE5 is approximately 700 times greater than its effect on PDE6, an enzyme in the retina responsible for phototransduction. Tadalafil also has a significantly higher potency (over 10,000 times more) on PDE5 compared to PDE7 to PDE10 enzymes.

Clinical Efficacy and Safety

Results from three clinical studies involving 1,054 patients, which investigated the response period of tadalafil used for pre-coital treatment, demonstrated that the successful erectile and sexual intercourse facilitating effect of tadalafil started as early as 16 minutes after dosing and lasted for up to 36 hours, significantly outperforming placebo.

Compared to Placebo-Controlled Volunteers, In a study measuring systolic and diastolic blood pressure in healthy volunteers lying on their backs, tadalafil showed no significant difference in comparison to placebo. The average maximum decrease in systolic and diastolic blood pressure was 1.6/0.8 mmHg while in a standing position, the average maximum decrease was 0.2/4.6 mmHg. Additionally, no significant change in pulse rate was observed. In a study examining the effects of tadalafil on vision, the Farnsworth-Munsell 100-hue test was used to assess color discrimination (blue/green), and no impairment was detected. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Reports of color vision changes are very rare (< 0.1%) in all clinical trials.

Studies on Spermatogenesis: To evaluate the potential effects of tadalafil 10 mg (6-month study) and 20 mg (two studies of 6 and 9 months) on spermatogenesis, three separate studies were conducted in men. In two of these studies, clinically insignificant decreases in sperm count and concentration were observed with tadalafil treatment. These effects were not associated with changes in other parameters such as motility, morphology, or FSH levels.

Clinical Studies in Erectile Dysfunction: Tadalafil, in doses ranging from 2 to 100 mg, was evaluated in 16 clinical studies involving 3,250 patients of different ages (ranging from 21 to 86) and ethnic backgrounds, all suffering from varying degrees (mild, moderate, and severe) and etiologies of erectile dysfunction. Most of the patients reported having erectile dysfunction for at least one year. In the primary efficacy studies conducted in the general population, 81% of patients reported improvement in their erections with tadalafil, compared to 35% with placebo. Additionally, patients across all severity categories (mild, moderate, and severe) reported improved erections with tadalafil (for mild, moderate, and severe erectile dysfunction, tadalafil was effective in 86%, 83%, and 72% of cases, compared to placebo with 45%, 42%, and 19%, respectively). In these primary efficacy studies, 75% of sexual intercourse attempts in patients treated with tadalafil were successful, compared to 32% with placebo.

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

5.2 Pharmacokinetic Properties

General Characteristics

Absorption:

Tadalafil is rapidly absorbed after oral administration, reaching the maximum observed mean plasma concentration (C_{max}) approximately 2 hours after drug intake. The absolute bioavailability of tadalafil after oral intake has not been determined.

The absorption rate and extent of tadalafil are not affected by food, allowing LONGIS® to be taken with or without food. The timing of drug intake (morning or evening) has no clinically significant effect on absorption rate or amount.

Distribution:

The average volume of distribution of tadalafil is approximately 63 liters, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is protein-bound. Protein binding is not affected by impaired kidney function. Less than 0.0005% of the dose administered has been observed in the semen of healthy volunteers.

Biotransformation:

Tadalafil is primarily metabolized by the cytochrome P450 (CYP) 3A4 isoform. The main metabolite circulating in the bloodstream is methylcatechol glucuronide. This metabolite is at least 13,000 times less effective on PDE5 than tadalafil. Therefore, at the concentrations of metabolites detected, they are not expected to be clinically active.

Elimination:

In healthy volunteers, the average oral clearance of tadalafil is 2.5 L/h, with an average half-life of 17.5 hours. Tadalafil is primarily excreted as inactive metabolites, largely in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Linearity/Non-linearity:

In healthy volunteers, tadalafil pharmacokinetics are linear in terms of time and dose. Exposure (AUC) increases proportionally with dose in the range of 2.5 to 20 mg. Steady-state plasma concentrations are reached within 5 days of once-daily dosing. In patients with erectile dysfunction, pharmacokinetics determined by a population approach are similar to those in healthy volunteers without erectile dysfunction.

Characteristics in Patients:

Elderly:

In healthy elderly volunteers (aged 65 and above), the oral clearance of tadalafil was lower than in healthy volunteers aged 19 to 45 years, resulting in a 25% increase in tadalafil exposure (AUC). This age-related effect is not clinically significant and does not require dose adjustments.

Renal Impairment:

In clinical pharmacology studies where single doses of tadalafil (5-20 mg) were administered, tadalafil exposure (AUC) was approximately doubled in volunteers with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal impairment, and in dialysis patients with end-stage renal disease. In hemodialysis patients, the C_{max} values were 41% higher than those of healthy volunteers. The contribution of hemodialysis to tadalafil elimination is negligible.

Hepatic Impairment:

In patients with mild or moderate liver impairment (Child-Pugh Class A and B), tadalafil exposure (AUC) after a 10 mg dose was similar to that observed in healthy volunteers. There is limited clinical data on the safety of tadalafil in patients with severe liver impairment.

(Child-Pugh Class C). If LONGIS® is prescribed to such patients, a detailed benefit/risk assessment must be performed by the prescribing physician.

Diabetic Patients:

In diabetic patients, tadalafil exposure (AUC) is approximately 19% lower than in healthy volunteers. This difference does not necessitate any dose adjustments.

5.3 Preclinical Safety Data:

Non-clinical data, including safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity studies, do not present any specific hazard to humans.

In studies on rats or mice treated with doses of tadalafil up to 1000 mg/kg, there was no evidence of teratogenicity, embryotoxicity, or fetotoxicity. In a prenatal and postnatal development study in rats, the highest dose with no observed effect was 30 mg/kg per day. In pregnant rats, the calculated free drug AUC at this dose was approximately 18 times higher than the AUC observed in humans at the 20 mg dose.

No fertility disorders were observed in male and female rats. In dogs treated with tadalafil for 6 to 12 months at doses of 25 mg/kg per day or higher (resulting in exposure 3 times greater than the exposure observed in humans taking a 20 mg single dose), some dogs showed regression in seminiferous tubule epithelium with a decrease in spermatogenesis (see Section 5.1).

6. PHARMACEUTICAL CHARACTERISTICS

6.1 List of Excipients:

Lactose monohydrate (derived from bovine source)

Sodium croscarmellose

Hydroxypropyl cellulose

Microcrystalline cellulose

Sodium lauryl sulfate

Magnesium stearate

Hypromellose

Triacetin

Titanium dioxide

Black iron oxide

Yellow iron oxide

6.2 Incompatibilities:

Not applicable.

6.3 Shelf Life:

36 months.

6.4 Special Storage Precautions:

It should be stored in its original packaging to protect from moisture.

Store at room temperature below 25°C.

6.5 Nature and Contents of the Packaging:

2 and 4 film-coated tablet blister packs (PVC-PE-PVDC/Aluminum foil), packaged in a cardboard box with the accompanying instructions for use.

6.6 Disposal of Unused Medicinal Products and Other Special Precautions:

Unused products or waste materials should be disposed of in accordance with the "Regulation on the Control of Medical Wastes" and the "Regulation on the Control of Packaging Wastes."

7. MARKETING AUTHORIZATION HOLDER

Santa Farma Ilac San. A.S.

H. Edip Adivar/ Borucicegi Sokak. No: 16 Sisli- Istanbul, Turkey

Tel: 0212 220 64 00

Faks: 0212 222 57 59

8. MARKETING AUTHORIZATION NUMBER

221/100

9. INITIAL MARKETING AUTHORIZATION DATE / MARKETING AUTHORIZATION RENEWAL DATE

Initial authorization date: 20.11.2009

Authorization renewal date: 21.02.2019

10. PACKAGE LEAFLET RENEWAL DATE
