SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

MYESED 20 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each film coated tablet contains 20 mg tadalafil.

Excipients:

Lactose SD	260.70 mg (sourced from cow's milk)
Lactose monohydrate	6.40 mg (sourced from cow's milk)

See 6.1 for excipients.

3. PHARMACEUTICAL FORM

Film coated tablet
Yellow and almond-shaped film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
It is indicated for the treatment of erectile dysfunction.

Sexual stimulation is required in order for MYESED to be effective.

MYESED is not indicated for use by women.

4.2 Posology and method of administration

Posology / administration frequency and time:
Use in adult men
The generally recommended dose is 10 mg taken at least 30 minutes before anticipated sexual activity. In patients in whom 10 mg tadalafil does not show an adequate effect, the dose may be increased to 20 mg.
The maximum dose frequency is 1 tablet per day.

20 mg tadalafil tablets are intended for use prior to anticipated sexual activity and they are not recommended for continuous daily use.

It is not recommended to divide MYESED.

Method of administration:
Take tablets orally.

Additional information for specific populations
Renal/Hepatic Failure:
Dose adjustment is not necessary in patients with mild to moderate renal failure. Tadalafil use is not recommended for 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 insufficiency (Child-Pugh Class C). If MYESED is prescribed to such patients, a careful benefit/risk evaluation should be undertaken by the prescribing physician (see Section 5.2).

Diabetes:
Dose adjustment is not necessary for patients with diabetes.

Pediatric population:
MYESED should not be used by individuals younger than 18 years old.

Geriatric population:
Dose adjustment is not necessary for old patients.

4.3 Contraindications
It is contraindicated for patients with hypersensitivity to any of the active substances or the excipients.

It was shown in clinical studies that tadalafil increases 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, the use of MYESED by patients who are using any form of organic nitrate is contraindicated (see section 4.5).

The substances including MYESED used for the treatment of erectile dysfunction should not be used by men with cardiac disease for whom sexual activity is not recommended. Physicians should consider the potential cardiac risks of sexual activity in patients with previous cardiovascular disease.

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

- Patients with myocardial infarction within the last 90 days,
- Patients with unstable angina or angina occurring during sexual intercourse,
- Patients with New York Heart Association "Class 2" or greater heart failure in the last 6 months,
- Patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension,
- Patients who had a stroke within the last 6 months.

MYESED is contraindicated in patients who have loss of vision in one eye due to 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).
Co-administration of PDE5 inhibitors, including tadalafil, with guanylate cyclase stimulators such as riosiguat is contraindicated as it leads to potential symptomatic hypotension (see section 4.5).

4.4 Special warnings and precautions for use

Before treatment with MYESED

Before pharmacological treatment is considered, the medical history of patient should be reviewed and physical examination should be performed to diagnose erectile dysfunction and determine potential underlying causes.

As there is a particular level of cardiac risk associated with sexual activity, physicians should consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction. Tadalafil has vasodilator properties which may cause mild and transient decreases in blood pressure (see section 5.1) and it potentiates the hypotensive effect of nitrates (see section 4.3).

Evaluation of erectile dysfunction should include identification of potential underlying causes and appropriate treatment after appropriate medical evaluation. It is not known whether tadalafil is effective in patients undergoing pelvic surgery or non-nerve-sparing radical prostatectomy.

Cardiovascular

Serious cardiovascular events such as myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia have been reported during post marketing period and in clinical trials. Most of the patients reported these events had a history of cardiovascular risk factors. However, it is not possible to determine definitively whether these events are related directly to these risk factors, to Tadalafil, to sexual activity, or to a combination of these or other factors.

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

Visual

Visual defects and cases of NAION have been reported in connection with the use of Tadalafil and other PDE5 inhibitors. Analysis of observational data suggests an increased risk of acute NAION after exposure to tadalafil or other PDE5 inhibitors in men with erectile dysfunction. As this may apply to all patients exposed to tadalafil, patients should be advised to discontinue MYESED and consult a physician immediately in case of sudden visual impairment (see section 4.3).

Decreased or sudden hearing loss

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

Impairment of liver function

There is limited clinical data on the safety of the single-dose administration of Tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). If MYESED is prescribed to such patients, a detailed 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 seek immediate medical assistance. Penile tissue damage may occur and permanent loss of potency may result if priapism is not treated immediately.

Substances used for the treatment of erectile dysfunction including MYESED 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).

Concomitant use with CYP3A4 inhibitors
Caution should be exercised when prescribing MYESED 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).

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

Lactose
MYESED contains lactose. Patients with rare hereditary problems such as galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Retinal vein occlusion was reported very rarely in post-marketing experience. The causality relationship between tadalafil and retinal vein occlusion was not studied. Physicians should be careful that the risk of retinal vein occlusion is higher in patients with increased blood viscosity, especially in older patients.

4.5 Interactions with other medical products and other forms of interaction
As stated below, interaction studies were performed on tadalafil.

Effects of other substances on tadalafil

Cytochrome P450 inhibitors
Tadalafil is metabolized principally by CYP3A4. Ketoconazole (400 mg daily) which is a selective inhibitor of CYP3A4 increased tadalafil (20 mg) exposure (AUC) 4-fold and C_{max} by 22%, compared to AUC and C_{max} values obtained by tadalafil alone. 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 coadministered 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
Rifampicin, which is a CYP3A4 inducer, reduced the AUC value of tadalafil by 88% compared to the AUC values obtained by tadalafil alone (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; however, the magnitude of decreased efficacy is unknown. Other CYP3A4 inducers such as phenobarbital, phenytoin and carbamazepine may also decrease the plasma concentrations of tadalafil.

The effect of tadalafil on other medical products

Nitrates
It was shown in clinical studies that tadalafil increases the hypotensive effects of nitrates. Therefore, the use of MYESED by 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, drug interaction lasted for more than 24 hours and it was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Therefore, in a patient prescribed any dose of MYESED and nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of MYESED before nitrate administration is considered. In such cases, nitrates should only be administered under close medical supervision with appropriate hemodynamic monitoring.

Antihypertensives (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 especially in elder patients. Treatments should be initiated at minimal dosage and adjusted progressively.

In clinical pharmacology studies, the potential for tadalafil to increase the hypotensive effects of antihypertensive medicinal products was investigated. 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 the classes stated above. 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 a certain degree of blood-pressure control. In this regard, the reduction was minimal in the study subjects whose blood pressure was well controlled and similar to that seen in healthy subjects. The reduction was greater in study subjects whose blood pressure was not controlled 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 the section 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 alone or with 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.

Riosiguat
In preclinical studies, PDE5 inhibitors, when used in combination with riosiguat, showed an additional lowering effect on systemic blood pressure. In clinical studies, riosiguat has been shown to enhance the hypotensive effects of PDE5 inhibitors. There is no evidence of a favorable clinical effect of the combination in the population studied. Concomitant use of riosiguat with PDE5 inhibitors, including tadalafil, is contraindicated (see section 4.3).

5-alpha reductase inhibitors (ARI)
No new adverse reactions were identified in a clinical study comparing 5 mg finasteride used in combination with 5 mg tadalafil for the relief of BPH symptoms with placebo plus 5 mg finasteride. However, a regulatory 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 using tadalafil in combination with 5-alpha reductases.

CYP1A2 substrates (e.g. theophylline)
In a clinical pharmacology study, there were no pharmacokinetic interactions when tadalafil 10 mg was administered with theophylline, a non-selective phosphodiesterase inhibitor. The only pharmacodynamic effect seen was a small increase in pulse rate (3.5 beats/min). Although this effect was small and not clinically significant in this study, it should be taken into account when these medicinal products are used together.

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

Alcohol
Alcohol concentrations (mean maximum blood concentration 0.08%) were not affected by coadministration with tadalafil. In addition, no changes in tadalafil concentrations were seen 3 hours after coadministration 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 increase 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 postural dizziness and orthostatic hypotension were observed in some volunteers. 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 functions was not increased by tadalafil (10 mg).

Medicinal products metabolized by cytochrome P450
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 affect the increase in bleeding time caused by acetyl salicylic acid.

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

Additional information for specific populations:

Pediatric population:
MYESED is not indicated for use by pediatric patients. There is no data on the safety and efficacy on patients younger than 18 years old.

4.6 Pregnancy and lactation
Pregnancy category: B
MYESED is not indicated for use by women.

Fertile women / Birth control (Contraception)
Physician should be informed in case of pregnancy or suspected pregnancy.

Pregnancy
There are limited data on the use of tadalafil by 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). It is recommended to avoid the use of MYESED during pregnancy as a precautionary measure.

Lactation
MYESED is not indicated for use by women. It is not known if tadalafil transfers into breast milk or not. Available pharmacodynamic/toxicological data obtained from animals have shown excretion of tadalafil in milk. The risk of transferring to suckling child through breast milk cannot be prevented. MYESED should not be used during breast feeding.

Fertility
In dogs, effects that may indicate inability to reproduce have been observed. Although sperm concentration decreased in some males, two clinical studies suggested that this effect was not observed in humans (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines
No study was performed for the effects on ability to drive and 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 MYESED before driving or using machines.

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse effects in patients taking MYESED are headache, dyspepsia, back pain and myalgia, with the incidence increasing with increasing MYESED dose. Reported adverse effects were transient and generally mild or moderate in severity.

The summary of adverse reactions
The list below shows the side effects observed in spontaneous reporting and placebo-controlled clinical trials (a total of 8022 patients with MYESED and 4422 patients with placebo) in the pre-coital and once-daily treatment of erectile dysfunction and once-daily treatment of benign prostatic hyperplasia.

The side effects listed below are given according to MedDRA system-organ class and absolute frequency. Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), unknown (cannot be estimated with available data).

Immune system diseases
Uncommon : Hypersensitivity reactions
Rare : Angioedema[2]

Nervous system diseases
Very common : Headache
Common : 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 defects, sensations described as eye pain, swelling of eyelids, conjuctival hyperemia, non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]

Ear and inner ear diseases
Rare : Sudden hearing loss
Uncommon : Tinnitus

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

Vascular diseases
Common : Flushing
Uncommon : Hypotension[3], hypertension

Respiratory and thoracic disorders and mediastinal diseases
Common : Nasal congestion
Rare : Epistaxis, Dyspnea

Gastrointestinal diseases
Common : Dyspepsia
Uncommon : Abdominal pain, gastro-esophageal reflux, vomiting, nausea

Skin and subcutaneous tissue disorders

Uncommon : Rash,

Rare : Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], hyperhidrosis (sweating)

Musculoskeletal disorders and connective tissue and bone diseases

Common : Back pain, myalgia, pain in the extremities

Kidney and urinary tract diseases

Uncommon : Hematuria

Reproductive system and breast disorders

Uncommon : Prolonged erection

Rare : Priapism, penile hemorrhage, hematospermia

General disorders and diseases related with administration site

Uncommon : Chest pain[1], peripheral edema, fatigue

Rare : Facial edema[2], sudden cardiac death[1,3]

(1) Most of the patients reported these events had a history of cardiovascular risk factors (see section 4.4).
(2) Post marketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) They were reported more frequently when tadalafil was given to patients using antihypertensive medicinal products.

Description of selected adverse reactions

When compared with placebo, ECG anomalies and sinus bradycardia primarily were reported slightly higher in patients treated with tadalafil more than once a day. Most of these ECG abnormalities are not associated with undesired effects.

Other special populations

Data from clinical trials in patients over 65 years of age using tadalafil involving the treatment of both erectile dysfunction and benign prostatic hyperplasia are limited. In clinical trials using tadalafil for the treatment of erectile dysfunction, diarrhea was reported more frequently in patients over 65 years of age. In clinical trials using tadalafil 5 mg once daily in 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

Post-authorization reporting of suspected adverse drug reactions is of great importance. Reporting enables continuous monitoring of the benefit/risk balance of the drug. Healthcare professionals should report any suspected adverse reactions to the Turkish Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9 Overdose and treatment

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. The contribution of hemodialysis to tadalafil elimination is at negligible level.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used for erectile dysfunction.
ATC Code: G04BE08

Mechanism of Action

Tadalafil is the selective and reversible inhibitor of phosphodiesterase type 5 (PDE5) specific to cyclic guanosine monophosphate (cGMP). When sexual stimulation causes the local release of nitric oxide, the inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in the relaxation of smooth muscles and inflow of blood into penile tissue, therefore causing erection. Tadalafil has no effect when there is no sexual stimulation.

Pharmacodynamic effects

In vitro studies have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in smooth muscle of corpus cavernosum, vascular and visceral smooth muscles, skeletal muscle, thrombocytes, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is over than 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 over than 10,000-fold more potent for PDE5 than for PDE3 which an enzyme found in the heart and blood vessels. Compared to PDE3, the selectivity of PDE5 is significant as PDE3 is an enzyme associated with cardiac contractility. In additional, tadalafil is approximately 700- fold more potent for PDE5 than for PDE6 which is an enzyme found in the retina and responsible for phototransduction. Tadalafil is also over than 10,000-fold more potent for PDE5 than the enzymes from PDE7 to PDE10.

Clinical efficacy and safety

The results of 3 clinical studies investigating 1054 patients for their response periods to tadalafil used before sexual intercourse demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse compared to placebo as early as 16 minutes following dosing and continued for 36 hours.

Compared to placebo, there was no significant difference in systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively) measured on supine position of healthy volunteers who were administered tadalafil, and in systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively) measured in standing position, and there was no significant change in heart rate.

In a study investigating 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. In 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 (6-month study) and 20 mg (one 6-month study and one 9-month study) administered daily. In two of these studies, decreases were observed in sperm count and concentration related to tadalafil treatment not clinically significant. These effects are not associated with changes in other parameters such as motility, morphology and follicle stimulating hormones.

Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), etiologies, ages (range: 21-86 years), and ethnicities. Most patients reported erectile dysfunction lasting for at least 1 year. In the primary efficacy studies conducted on general populations, 81% of patients reported that Tadalafil improved their erections as compared to 35% with placebo. In addition, patients with erectile dysfunction in all severity categories reported improved erections while taking tadalafil (86%, 83%, and 72% for mild, moderate, and severe, respectively, as compared to 45%, 42%, and 19% with placebo). In the primary efficacy studies, 75% of intercourse attempts were successful in patients treated with tadalafil compared to 32% with placebo.

In a 12-week study performed on 186 patients (142 tadalafil, 44 placebo) with spinal cord injury and erectile dysfunction, the rate of successful attempts for sexual intercourse was 17% in placebo while tadalafil significantly improved the erectile function in patients treated with tadalafil 10 or 20 mg leading to the success rate of 48% (flexible dose before intercourse).

5.2 Pharmacokinetic properties

General properties

Absorption:

Tadalafil is rapidly 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 MYESED may be taken with or without food. The time of dosing (morning or evening) had no clinically significant effect on the rate and extent of absorption.

Distribution:

Mean distribution volume of tadalafil is approximately 63 liters, indicating that it is distributed to the 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 mainly 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. Therefore, it is not expected to be clinically active at observed metabolite concentrations.

Elimination:

In healthy subjects, the mean oral clearance for tadalafil is 2.5 L/h and the mean half-life is 17.5 hours. 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 volunteers are linear with respect to time and dose. In a dose ranging between 2.5 and 20 mg, the exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are reached within 5 days of once-daily dosing.

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

Characteristics in patients

Geriatrics:

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

Renal failure:

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 volunteers. The contribution of hemodialysis to tadalafil elimination is at negligible level.

Hepatic failure:

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Classes 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 MYESED is prescribed, a detailed benefit/risk evaluation should be undertaken by the prescribing physician for such patients.

Diabetic patients:

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

5.3 Pre-clinical safety data

Non-clinical data showed that there is no particular risk for human based on the studies performed for safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproduction toxicity.

There is no evidence for teratogenicity, embryotoxicity or phototoxicity in rats or mice administered tadalafil up to doses 1000 mg/kg daily. In a prenatal and postnatal development study performed on rats, the dose with no observed effect was 30 mg/kg. In pregnant rats, AUC for free drug calculated for this dose is approximately 18 times higher than AUC observed in human with the dose of 20 mg.

No fertility disorder was observed in male and female rats. The regression occurred in seminiferous tubule epithelium resulting with the decrease in spermatogenesis in some of the dogs administered tadalafil in the doses of 25mg/kg (resulting in maximum 3 times higher exposure [interval: 3.7-18.6] than the exposure in human administered a single dose of 20 mg) and above for 6-12 months (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 The list of excipients

Lactose SD (sourced from cow's milk)
Croscarmellose sodium
Hydroxypropyl cellulose LH 11

Sodium laurilsulfate
Microcrystalline cellulose PH 101
Magnesium Stearate
Lactose monohydrate (sourced from cow's milk)
HPMC 2910/Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)
Triacetin

6.2 Incompatibilities
There is no known incompatibility.

6.3 Shelf life
24 months

6.4 Specific precautions for storage
Keep in original package to keep away from moisture.
Keep at room temperatures below 30℃.

6.5 Nature and content of the package

2, 4 and 8 film coated tablets in PVC/PVDC/Aluminum foil blister packages within box.
All package sizes may not be marketed.

6.6 Special precautions for disposal and other handling
Unused products or waste materials should be disposed in accordance with the "Regulation for the Control of Medical Wastes" and the "Regulations for the Control of Packages and Package Wastes".

7. MARKETING AUTHORISATION HOLDER
Humanis Saglik A.S.
Istanbul/Turkey

8. MARKETING AUTHORISATION NUMBER

06374/5298/NMR/2018
09449/08811/VAR/2023

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Date of first authorization: Jul 25, 2021

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10. DATE OF REVISION OF THE TEXT

02.06.2020