pharmaniaga®

LIBEREZ

Film-Coated Tablet 5mg

LIBEREZ FILM-COATED TABLET 5MG
(TADALAFIL 5 MG)

NAME OF THE MEDICINAL PRODUCT
LIBEREZ film-coated tablet 5mg

PRODUCT DESCRIPTION
Yellow, round shape film-coated tablet and plain on both sides.

PHARMACEUTICAL FORM
Each film coated tablet contains Tadalafil 5mg.

Excipient with known effect:
Each coated tablet contains 62.20mg lactose (as monohydrate)

CLINICAL PARTICULARS
Treatment indications
Treatment of erectile dysfunction in adult males.

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

Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.

Tadalafil is not indicated for use by women.

POSOLOGY AND METHOD OF ADMINISTRATION
Erectile dysfunction in adult men
In general, the recommended dose is 10mg taken prior to anticipated sexual activity and with or without food.

In those patients in whom tadalafil 10mg does not produce an adequate effect, 20mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10mg and 20mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate 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 5mg taken once a day at approximately the same time of day. The appropriateness of continued use of the daily regimen should be reassessed periodically.

Benign Prostatic Hyperplasia in Adult Men
The recommended dose is 5mg, taken at approximately the same time every day with or without food.

For adult men being treated for both benign prostatic hyperplasia and erectile dysfunction the recommended dose is also 5mg taken at approximately the same time every day. Patients who are unable to tolerate tadalafil 5mg for the treatment of benign prostatic hyperplasia should consider an alternative therapy as the efficacy of tadalafil 2.5mg for the treatment of benign prostatic hyperplasia has not been demonstrated.

Special populations
Elderly men
Dose adjustments are not required in elderly patients.

Men with renal impairment
Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment, 10mg is the maximum recommended dose for on-demand treatment.

Once-a-day dosing of 2.5 or 5mg tadalafil both for the treatment of erectile dysfunction or benign prostatic hyperplasia is not recommended in patients with severe renal impairment.

Men with hepatic impairment
For the treatment of erectile dysfunction using on-demand tadalafil the recommended dose of tadalafil is 10mg taken prior to anticipated sexual activity and with or without food. There is limited data on the safety of tadalafil in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10mg of tadalafil to patients with hepatic impairment.

Once-a-day dosing of tadalafil 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.

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

Paediatric population
There is no relevant use of tadalafil in the paediatric population with regard to the treatment of erectile dysfunction.

Method of administration
Liberez Film-Coated Tablet 5 mg is for oral use.
Liberez Film-Coated Tablet 5mg is not able to deliver all approved dose regimen of tadalafil; other approved dosage forms and strength of tadalafil should be used in such cases.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients. 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, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated.

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

The use of tadalafil is therefore contraindicated in the following:

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

Tadalafil is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.

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.

WARNING & PRECAUTIONS

Before treatment with tadalafil

A medical history and physical examination should be undertaken to diagnose erectile dysfunction or benign prostatic hyperplasia and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure and as such potentiates the hypotensive effect of nitrates.

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.

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

Cardiovascular

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to tadalafil, to sexual activity, or to a combination of these or other factors.

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

In patients who are taking alpha[1] blockers, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients. The combination of tadalafil and doxazosin is not recommended.

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

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) and the lack of ability to influence clearance by dialysis, once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.

There is limited information on the safety of single-dose administration of tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day administration either for the treatment of erectile dysfunction or benign prostatic hyperplasia has not been evaluated in patients with hepatic insufficiency. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

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

Tadalafil should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease, or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

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

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

Lactose
Tadalafil tablet 5mg contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (less than 23mg) per tablet, that is to say essentially 'sodium free'.

INTERACTIONS WITH OTHER MEDICAMENTS
Effects of other substances on tadalafil

Cytochrome P450 inhibitors
Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200mg daily), increased tadalafil (10mg) exposure (AUC) 2-fold and C_{max} by 15%, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400mg daily) increased tadalafil (20mg) 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 (20mg) 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. Consequently, the incidence of the adverse reactions 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 (10mg). 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
Tadalafil augments the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated. Based on published data, 150 patients receiving daily doses of tadalafil 20mg for 7 days and 0.4mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Thus, in a patient prescribed any dose of tadalafil (2.5mg – 20mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8mg daily) and tadalafil (5mg daily dose and 20mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore, this combination is not recommended.

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.

Based on the reported clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medical products was examined. Major classes of

antihypertensives 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 (10mg except for studies with angiotension II receptor blockers and amlodipine in which a 20mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20mg) was studied in combination with up to 4 classes of antihypertensives. In patients taking multiple antihypertensives, the ambulatory blood pressure changes appeared to relate to the degree of blood pressure control. In patients whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of patients.

In patients receiving concomitant antihypertensive medicinal products, tadalafil 20mg 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. Based on available data, there is 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
The additive systemic blood pressure lowering effect shown when PDE5 inhibitors were combined with riociguat. Riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of this combination. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated.

5 – alpha reductase inhibitors
There is no data on co-administration of tadalafil with 5-alpha reductase inhibitors (5-ARIs). Therefore, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
Based on published clinical pharmacology study, when tadalafil 10mg was administered with theophylline (non-selective phosphodiesterase inhibitor), there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5bpm) 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 (10mg or 20mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol). Tadalafil (20mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180ml of 40% alcohol [vodka] in an 80-kg male) but in some subjects, postural dizziness and orthostatic hypotension were reported. 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 (10mg).

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

CYP2C9 substrates (e.g. R-warfarin)
Tadalafil (10mg and 20mg) 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 (10mg and 20mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

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

FERTILITY, PREGNANCY AND LACTATION
Tadalafil is not indicated for use by women.

Pregnancy
There are limited data on the use of tadalafil in pregnant women. Published animal data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of tadalafil during pregnancy.

Breastfeeding
Published animal data reports excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. Tadalafil should not be used during breast feeding.

Fertility
Reported data in dogs that indicate impairment of fertility. The published data suggests that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men.

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

Very Common	**Common**	**Uncommon**	**Rare**
Immune system disorders			
		Hypersentivity reactions	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including Haemorrhagic events), Syncope, Transient Ischaemic attacks[1],

			Migraine[2], Seizures[2], Transient amnesia
Eye Disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non- arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]
Vascular disorders			
	Flushing	Hypotension[3], Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux	
Skin and subcutaneous tissue disorders			
		Rash	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis (sweating)
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia, Pain in extremity		
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
		Prolonged erections	Priapism, Penile, haemorrhage, Haematospermia

General disorders and administration site conditions			
		Chest pain[1], Peripheral oedema, Fatigue	Facial oedema[2], Sudden cardiac death[1,2]

[1] Most of the patients had pre-existing cardiovascular risk factors.
[2] Based on published data, 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
Based on available data, patients over 65 years of age receiving tadalafil either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. Based on data available, tadalafil taken on demand for the treatment of erectile dysfunction, diarrhoea was reported more frequently in patients over 65 years of age. According to available data, tadalafil 5mg taken once a day for treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

OVERDOSE
Single doses up to 500mg have been given to healthy patients, and multiple daily doses up to 100mg 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Tadalafil has negligible influence on the ability to drive or use machines even though dizziness has been reported. However, patients should be aware of how they react to tadalafil, before driving or using machines.

PHARMACOLOGICAL PROPERTIES
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.

Pharmacodynamics effects
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 treatment in healthy volunteers shows no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively), and no significance change in heart rate. Across all published clinical studies, reports of changes in colour vision were rare.

Erectile dysfunction
Based on available data, 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 ability to attain and maintain erections for effective intercourse as early as 16 minutes following dosing.

Published studies have reported once-a-day evaluation of tadalafil at doses of 2.5, 5, and 10mg involving patients of various ages (range 21-82 years), 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 5mg, 50% on tadalafil 2.5mg 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 5mg and 2.5mg, respectively, as compared to 28% with placebo. In a subsequent study, patients who were treatment-naïve to PDE5 inhibitors were randomized to tadalafil 5mg once a day vs. placebo. The mean per-subject proportion of successful sexual intercourse attempts was 68% for tadalafil patients compared to 52% for patients on placebo.

Benign prostatic hyperplasia
Published four clinical studies shows improvement in total international prostate symptom score with Tadalafil 5mg as early as 1 week. In one of the studies, which also included tamsulosin 0.4mg as an active comparator, the improvement in total international prostate symptom score with tadalafil 5mg, 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 5mg 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 5mg compared to 48.3% with placebo.

Available data also 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 5mg.

PHARMACOKINETICS
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 tadalafil may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

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

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

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

Linearity/non-linearity
Tadalafil pharmacokinetics are linear with respect to time and dose. Over a dose range of 2.5 to 20mg, 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 patients without erectile dysfunction.

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

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

Hepatic insufficiency
Tadalafil exposure (AUC) in patients with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy patients when a dose of 10mg 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 tadalafil 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 patients. This difference in exposure does not warrant a dose adjustment.

NATURE AND CONTENTS OF CONTAINER
Aluminium/ Aluminium film blister in box of 30 tablets (3 blisters x 10 tablets)

STORAGE CONDITION
Store below 30℃

SHELF LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

REGISTRATION NUMBER
MAL24096059AZ

CONTROLLED MEDICINE
UBAT TERKAWAL

KEEP MEDICINES OUT OF REACH OF CHILDREN
JAUHI UBAT-UBATAN DARI KANAK-KANAK

For further information, please consult your doctor or your pharmacist.

Revision Number: 01
Revision Date: 14 Jul 2026

PRODUCT REGISTRATION HOLDER AND MANUFACTURER
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