Talfil™

(T a d a l a f i l)

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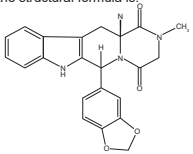
Film-coated Tablets
5mg, 10mg & 20mg

Description
Talfil (Tadalafil) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). The chemical name of Tadalafil is p y r a z i n o [1 ′ , 2 ′ : 1 , 6] p y r i d o [3 , 4 - b] i n d o l e - 1 , 4 - d i o n e , 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. Its molecular formula is $C_{22}H_{19}N_3O_4$ and the structural formula is:



Tadalafil

QUALITATIVE AND QUANTITATIVE COMPOSITION
Talfil (Tadalafil) Tablets are available for oral administration as:

Talfil Tablets 5mg
Each film-coated tablet contains:
Tadalafil… 5mg

Talfil Tablets 10mg
Each film-coated tablet contains:
Tadalafil… 10mg

Talfil Tablets 20mg
Each film-coated tablet contains:
Tadalafil… 20mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by Tadalafil has no effect in the absence of sexual stimulation.
The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The mechanism for reducing BPH symptoms has not been established.

Pharmacokinetics
Absorption
After single oral-dose administration, the maximum observed plasma concentration (C_{max}) of Tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). The rate and extent of absorption of Tadalafil are not influenced by food; thus, Tadalafil may be taken with or without food.

Distribution
The mean apparent volume of distribution following oral administration is approximately 63L, indicating that Tadalafil is distributed into tissues. At therapeutic concentrations, 94% of Tadalafil in plasma is bound to proteins. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism
Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination
The mean oral clearance for Tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Special Population
Patients with Renal Impairment
In clinical pharmacology studies using single-dose Tadalafil (5mg to 10mg), Tadalafil exposure (AUC) doubled in subjects with creatinine clearance 30 to 80mL/min. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.8-fold increase in AUC following single-dose administration of 10mg or 20mg Tadalafil.

Patients with Hepatic Impairment
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10mg is administered. There is limited clinical data on the safety of Tadalafil in patients with severe hepatic insufficiency (Child- Pugh Class C).

Geriatric
Healthy male elderly subjects (65 years or over) had a lower oral clearance of Tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered.

Pediatric
Tadalafil is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years have not been established.

Patients with Diabetes Mellitus
In male patients with diabetes mellitus after a 10mg Tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

THERAPEUTIC INDICATIONS
Talfil (Tadalafil) is indicated:
- For the treatment of Erectile Dysfunction (ED) in adult males.
- For the treatment of the signs and symptoms of Benign Prostatic Hyperplasia (BPH) in adult males.
- For the treatment of Erectile Dysfunction (ED) and the signs and symptoms of Benign Prostatic Hyperplasia (BPH).

Tadalafil is not indicated for use by women.

DOSAGE AND ADMINISTRATION
Do not split Talfil (Tadalafil) tablets; entire dose should be taken.
Talfil (Tadalafil) may be taken without regard to food.

Talfil (Tadalafil) for Use as Needed for Erectile Dysfunction
- The recommended starting dose of Talfil (Tadalafil) for use as needed in most patients is 10mg, taken prior to anticipated sexual activity.
- The dose may be increased to 20mg or decreased to 5mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.
- Tadalafil for use as needed was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of Tadalafil, this should be taken into consideration.

Talfil (Tadalafil) for Once Daily Use for Erectile Dysfunction
- The recommended starting dose of Talfil (Tadalafil) for once daily use is 2.5mg, taken at approximately the same time every day, without regard to timing of sexual activity.
- The Tadalafil dose for once daily use may be increased to 5mg, based on individual efficacy and tolerability.

Talfil (Tadalafil) for Once Daily Use for Benign Prostatic Hyperplasia
The recommended dose of Talfil (Tadalafil) for once daily use is 5mg, taken at approximately the same time every day.

Talfil (Tadalafil) for Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia
The recommended dose of Talfil (Tadalafil) for once daily use is 5mg, taken at approximately the same time every day, without regard to timing of sexual activity.

Special Population
Patients with Renal Impairment
Talfil (Tadalafil) for Use as Needed
- Creatinine clearance 30 to 50mL/min: A starting dose of 5mg not more than once per day is recommended, and the maximum dose is 10mg not more than once in every 48 hours.
- Creatinine clearance less than 30mL/min or on hemodialysis: The maximum dose is 5mg not more than once in every 72 hours.

Talfil (Tadalafil) for Once Daily Use
Erectile Dysfunction
- Creatinine clearance less than 30mL/min or on hemodialysis: Talfil (Tadalafil) for once daily use is not recommended.

Benign Prostatic Hyperplasia and Erectile Dysfunction/Benign Prostatic Hyperplasia
- Creatinine clearance 30 to 50mL/min: A starting dose of 2.5mg is recommended. An increase to 5mg may be considered based on individual response.
- Creatinine clearance less than 30mL/min or on hemodialysis: Talfil (Tadalafil) for once daily use is not recommended.

Patients with Hepatic Impairment
Talfil (Tadalafil) for Use as Needed
- Mild or moderate (Child Pugh Class A or B): The dose should not exceed 10mg once per day. The use of Talfil (Tadalafil) once per day has not been extensively evaluated in patients with hepatic impairment and therefore, caution is advised.
- Severe (Child Pugh Class C): The use of Talfil (Tadalafil) is not recommended.

Talfil (Tadalafil) for Once Daily Use
- Mild or moderate (Child Pugh Class A or B): Talfil (Tadalafil) for once daily use has not been extensively evaluated in patients with hepatic impairment. Therefore, caution is advised if Talfil (Tadalafil) for once daily use is prescribed to these patients.
- Severe (Child Pugh Class C): The use of Talfil (Tadalafil) is not recommended.

ADVERSE REACTIONS
Common
Headache, flushing, nasal congestion, dyspepsia, back pain, myalgia and pain in extremity.

Uncommon
Hypersensitivity reactions, dizziness, blurred vision, sensations described as eye pain, tinnitus, tachycardia, palpitations, hypotension, hypertension, dyspnea, epistaxis, abdominal pain, vomiting, nausea, gastro-oesophageal reflux, rash, hematuria prolonged erections, chest pain, peripheral oedema and fatigue.

Rare
Angioedema, stroke (including hemorrhagic events), syncope, transient ischemic attacks, migraine, seizures, transient amnesia, visual field defect, swelling of eyelids, conjunctival hyperemia, non-arteritic anterior ischemic optic neuropathy (NAION), retinal vascular occlusion, sudden hearing loss, myocardial infarction, unstable angina pectoris, ventricular arrhythmia, urticaria, Stevens-Johnson Syndrome, exfoliative dermatitis,

hyperhydrosis (sweating), priapism, penile hemorrhage, hematospermia, facial oedema and sudden cardiac death.

Not Known
Central serous chorioretinopathy.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
- Tadalafil is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients of the product.
- 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.
- Tadalafil is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.
- 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.

PRECAUTIONS
Before treatment with Tadalafil
A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.
Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure and as such potentiates the hypotensive effect of nitrates.

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.
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 alpha1 blockers, concomitant administration of Tadalafil may lead to symptomatic hypotension in some patients. The combination of Tadalafil and doxazosin is not recommended.
Patients should not use Tadalafil if sex is inadvisable due to cardiovascular status

Vision
Visual defects, including Central Serous Chorioretinopathy (CSCR), and cases of NAION have been reported in connection with the intake of Tadalafil and other PDE5 inhibitors. Most cases of CSCR resolved spontaneously after stopping Tadalafil. As this may be relevant for all patients exposed to Tadalafil, the patient should be advised that in case of sudden visual defect, visual acuity impairment and/or visual distortion, he should stop taking Tadalafil and consult a physician immediately.
Tadalafil should be used with caution, and only when the anticipated benefits outweigh the risks, in patients with a history of NAION. Patients with a "crowded" optic disc may also be at an increased risk of NAION.

Decreased or Sudden Hearing Loss
Cases of sudden hearing loss have been reported after the use of Tadalafil. Patients should be advised to stop taking Tadalafil and seek prompt medical attention in the event of sudden decrease or loss of hearing.

Priapism and Anatomical Deformation of the penis
Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. 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 anemia, multiple myeloma or leukemia).

Tadalafil and other treatments for Erectile Dysfunction
The patients should be informed not to take Tadalafil with other PDE5 inhibitors or other treatments for erectile dysfunction.

Potential for Drug Interactions When Taking Tadalafil for Once Daily Use
Physicians should be aware that Tadalafil for once daily use provides continuous plasma Tadalafil levels and should consider this when evaluating the potential for interactions with medications (e.g., nitrates, alpha-blockers, anti-hypertensives and potent inhibitors of CYP3A4) and with substantial consumption of alcohol.

Counseling Patients About Sexually Transmitted Diseases
The use of Tadalafil offers no protection against sexually transmitted diseases. Counseling patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

Consideration of Other Urological Conditions Prior to Initiating Treatment for BPH
Prior to initiating treatment with Tadalafil for BPH, consideration should be given to other urological conditions that may cause similar symptoms. In addition, prostate cancer and BPH may coexist.

Effects on ability to drive and use machines
Tadalafil has negligible influence on the ability to drive or use machines. Patients should be aware of how they react to Tadalafil, before driving or using machines.

Lactose
Tadalafil tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Pregnancy and Nursing Mothers
Tadalafil is not indicated for use by women.

DRUG INTERACTIONS
Nitrates
Administration of Tadalafil to patients who are using any form of organic nitrate, is contraindicated. In a patient who has taken Tadalafil, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of Tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.

Alpha-Blockers
Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including Tadalafil, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4mg 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. 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.
Small reductions in blood pressure occurred following coadministration of Tadalafil with selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and metoprolol) compared with placebo.

Alcohol
Both alcohol and Tadalafil, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with Tadalafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Antacids
Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and Tadalafil reduced the apparent rate of absorption of Tadalafil without altering exposure (AUC) to Tadalafil.

Cytochrome P450 inhibitors
Tadalafil is principally metabolized 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 (200mg 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}. 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.

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. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of Tadalafil.

5-alpha reductase inhibitors
Caution should be exercised when Tadalafil is co-administered with 5-alpha reductase inhibitors.

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.

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.

OVERDOSAGE
Single doses up to 500mg have been given to healthy subjects, 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.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

HOW SUPPLIED
Talfil (Tadalafil) Tablets 5mg are available in blister pack of 4's.
Talfil (Tadalafil) Tablets 10mg are available in blister pack of 4's.
Talfil (Tadalafil) Tablets 20mg are available in blister pack of 4's.

Keep out of reach of children.

The expiration date refers to the product correctly stored at the required condition.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com
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