TADAFLO™
(Tadalafil)

1. NAME OF THE PRODUCT
TADAFLO™ (Tadalafil) 10mg Tablet
TADAFLO™ (Tadalafil) 20mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
TADAFLO™ 10mg Tablet
Each film coated tablet contains:
Tadalafil……..……10mg
Also contains Lactose

TADAFLO™ 20mg Tablet
Each film coated tablet contains:
Tadalafil……..…….20mg
Also contains Lactose

3. PHARMACEUTICAL FORM
Film coated tablet

Appearance:
TADAFLO™ 10mg Tablet: Light yellow to yellow colored, almond shaped film coated tablets, plain on both sides.
TADAFLO™ 20mg Tablet: Light yellow to yellow colored, almond shaped film coated tablets, plain on both sides.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
- Treatment of erectile dysfunction in adult males.
- In order for **TADAFLO™** 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.
- **TADAFLO™** is not indicated for use by women.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
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 **TADAFLO**™ 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.
- **TADAFLO**™ 10 and 20mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use of **TADAFLO**™ (i.e., at least twice weekly) a once daily regimen with the lowest doses of **TADAFLO**™ 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 dose may be decreased to 2.5mg once a day based on individual tolerability. The appropriateness of continued use of the daily regimen should be reassessed periodically.

Benign prostatic hyperplasia in adult men: The recommended dose is 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 **TADAFLO**™ 5mg for the treatment of benign prostatic hyperplasia should consider an alternative therapy as the efficacy of **TADAFLO**™ 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 clinical 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:
Tadalafil film coated tablets is for oral use.

4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients.
- The 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 following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:

- 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 (< 90/50mmHg), or uncontrolled hypertension.
- 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.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

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 ischaemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to 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 alpha1 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. Analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the 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: Once-a-day dosing of Tadalafil is not recommended in patients with severe renal impairment due to lack of ability of clearance by dialysis. There is limited clinical data on the safety of single-dose administration of Tadalafil in patients with severe 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 contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Interaction studies were conducted with 10mg and/or 20mg tadalafil, as indicated below. With regard to those interaction studies where only the 10mg tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.

Effects of other substances on tadalafil:

Cytochrome P450 inhibitors: Tadalafil is principally metabolized by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (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}. 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: Administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated. 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. 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.

Riociguat: There is an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. Riociguat augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favorable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated.

5-alpha reductase inhibitors: In a clinical trial that compared tadalafil 5mg co-administered with finasteride 5mg to placebo plus finasteride 5mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when Tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline): When tadalafil 10mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5bpm) 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 (0.7g/kg or approximately 180ml of 40% alcohol [vodka] in an 80kg male) but in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6g/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. 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 (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.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Tadalafil is not indicated for use by women.

Fertility: Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men.

Pregnancy: There are limited data from the use of tadalafil in pregnant women. As a precautionary measure, it is preferable to avoid the use of Tadalafil during pregnancy.

Breast-feeding: A risk to the suckling child cannot be excluded. Tadalafil should not be used during breast feeding.

4.7. 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.

4.8. UNDESIRABLE EFFECTS:

Frequency convention: 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); not known (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 haemorrhagic events), syncope, transient ischaemic attacks, migraine, seizures, transient amnesia
Eye disorders:
Uncommon: Blurred vision, sensations described as eye pain
Rare: Visual field defect, swelling of eyelids, conjunctival hyperaemia, nonarteritic anterior ischaemic optic neuropathy (NAION), retinal vascular occlusion
Ear and labyrinth 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: Dyspnoea, epistaxis
Gastrointestinal disorders:
Common: Dyspepsia
Uncommon: Abdominal pain, vomiting, nausea, gastro-oesophageal reflux
Skin and subcutaneous tissue disorders:
Uncommon: Rash
Rare: Urticaria, Stevens Johnson syndrome, exfoliative dermatitis, hyperhydrosis (sweating)
Musculoskeletal, connective tissue and bone disorders:
Common: Back pain, myalgia, pain in extremity
Renal and urinary disorders:
Uncommon: Haematuria
Reproductive system and breast disorders:
Uncommon: Prolonged erections
Rare: Priapism, penile haemorrhage, haematospermia
General disorders and administration site conditions:
Uncommon: Chest pain, peripheral oedema, fatigue
Rare: Facial oedema, sudden cardiac death

4.9. OVERDOSE:

Single doses of 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. Haemodialysis contributes negligibly to tadalafil elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction

ATC Code: G04BE08.

Mechanism of action: Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the treatment of erectile dysfunction in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The resulting vascular relaxation increases blood perfusion which may be the mechanism by which symptoms of benign prostatic hyperplasia are reduced. These vascular effects may be complemented by inhibition of bladder afferent nerve activity and smooth muscle relaxation of the prostate and bladder.

5.2. PHARMACOKINETICS PROPERTIES:

Absorption: Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined. The rate and extent of absorption of tadalafil are not influenced by food, thus 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 63L, 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.

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

Elimination: The mean oral clearance for tadalafil is 2.5L/h and the mean half-life is 17.5 hours in healthy subjects. 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).

5.3. PRECLINICAL SAFETY DATA:

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction. There was no evidence of teratogenicity, embryotoxicity or fetotoxicity in rats or mice that received up to 1000mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20mg dose. There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7 – 18.6] than seen in humans given a single 20mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

TADAFLO™ 10mg Tablet:

- Microcrystalline Cellulose
- Lactose Monohydrate
- Hydroxypropyl Cellulose
- Croscarmellose Sodium
- Sodium Lauryl Sulfate
- Magnesium Stearate
- Hydroxy Propyl Methyl Cellulose
- Lactose Monohydrate
- Talcum Powder
- Titanium Dioxide
- Triacetin
- Yellow Iron oxide

TADAFLO™ 20mg Tablet:

- Microcrystalline Cellulose
- Lactose Monohydrate
- Hydroxypropyl Cellulose
- Croscarmellose Sodium
- Sodium Lauryl Sulfate

- Magnesium Stearate
- Hydroxy Propyl Methyl Cellulose
- Lactose Monohydrate
- Talcum Powder
- Titanium Dioxide
- Triacetin
- Yellow Iron oxide

6.2. INCOMPATIBILITIES:
Not applicable

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Do not store over 30°C protect from heat and moisture.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
TADAFLO™ 10mg Tablet: Alu/Alu blister, pack size is 1x10's.
TADAFLO™ 20mg Tablet: Alu/Alu blister, pack size is 1x10's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
TADAFLO™ 10mg Tablet: USP Specs.
TADAFLO™ 20mg Tablet: USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

TADAFLO™ 10mg Tablet: 135116
TADAFLO™ 20mg Tablet: 134979

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

TADAFLO™ 10mg Tablet: 7th July, 2026
TADAFLO™ 20mg Tablet: 4th June, 2026

10. DATE OF REVISION OF THE TEXT

N/A

ٹاڈافلو™ ٹیبلٹ

(ٹاڈالافِل)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔