Size : 120x340 mm
Code No. :
Reason of artwork : New/Export (Registration)
Insert as per new Guideline
Country : Malawi

Front side

340.00 mm

120.00 mm

For the use of a Registered Medical Practitioner or a Hospital only.

TADAFORCE

Tadalafil Tablets USP

COMPOSITION

Each film coated tablet contains:
Tadalafil USP.....20 mg
Colours: Yellow Oxide of Iron & Titanium Dioxide USP

PHARMACEUTICAL FORM

Tablet

THERAPEUTIC 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.

DOSAGE AND ADMINISTRATION

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.

CONTRAINDICATIONS

Hypersensitivity to the active substance.
In clinical studies, 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 tablet to patients who are using any form of organic nitrate is contraindicated.
Tablet, must not be used in men with cardiac disease for whom sexual activity is inadvisable.
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 uncontrolled arrhythmias, hypotension (<90/50 mmHg), or uncontrolled hypertension.
- Patients with a stroke within the last 6 months.

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

SPECIAL WARNINGS AND PRECAUTIONS

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, sexual activity, or to a combination of these or other factors.
In patients who are taking alpha$_1$ blockers, concomitant administration 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 and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking and consult a physician immediately.

Renal and hepatic impairment
Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing is not recommended in patients with severe renal impairment. 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 it 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. It 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 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.

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

DRUG INTERACTIONS

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 (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.

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
In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. Therefore, administration to patients who are using any form of organic nitrate is contraindicated. Based on the results of a clinical study in which 150 subjects received 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 , where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

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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.
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 notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg 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 (3.5 bpm) 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 80 kg 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.

Aspirin
Tadalafil (10mg and 20mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid.

PREGNANCY AND LACTATION

Pregnancy
There are limited data from the use of tadalafil in pregnant women. Animal studies 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 during pregnancy.

Breastfeeding
Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. It should not be used during breast feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tadalfil has negligible influence on the ability to drive or 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 before driving or using machines.

UNDESIRABLE EFFECTS

Headache, Flushing, Nasal congestion, Dyspepsia, Gastroesophageal reflux, Back pain, Myalgia, Pain in extremity.

OVERDOSAGE

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.

PHARMACODYNAMIC PROPERTIES

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.

PHARMACOKINETIC 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.

Distribution
The mean volume of distribution is approximately 63 litres, 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.

Metabolism
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.

Elimination
The mean oral clearance for tadalafil is 2.5 l/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).

STORAGE CONDITIONS

Store below 30°C, protected from light & moisture.

Keep all medicines out of reach of children.

PRESENTATION

4 Tablets packed in Alu -PVC Blister.

Product from
Unosource Pharma Ltd.

Manufactured by:
Akums Drugs & Pharmaceuticals Ltd.
19,20,21, Sector-6A, I.I.E., SIDCUL,
Ranipur, Haridwar-249 403, INDIA.