For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only

Tadalafil tablets

Tagra

Composition

Tagra - 10
Each film-coated tablet contains
Tadalafil USP ..... 10 mg

Tagra - 20
Each film-coated tablet contains
Tadalafil USP ..... 20 mg

Dosage Form
Film coated tablets

Pharmacology

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.

Pharmacodynamic effects
Studies *in vitro* have shown that 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 >10,000fold 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 administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8mmHg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6mmHg, respectively), and no significant change in heart rate.

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Across all clinical studies, reports of changes in colour vision were rare (<0.1%).

Three studies were conducted in men to assess the potential effect on spermatogenesis of tadalafil 10mg (one 6-month study) and 20mg (one 6-month and one 9-month study) administered daily. In two of these studies decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters, such as motility, morphology, and FSH.

Erectile dysfunction
Three clinical studies were conducted in 1054 patients in an at-home setting to define the period of responsiveness to tadalafil. 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 patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.

In a 12-week study performed in 186 patients (142 tadalafil, 44 placebo) with erectile dysfunction secondary to spinal cord injury, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with tadalafil 10 or 20 mg (flexible-dose, on demand) of 48% as compared to 17% with placebo.

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

For once-a-day evaluation of tadalafil at doses of 2.5, 5, and 10 mg 3 clinical studies were initially conducted involving 853 patients of various ages (range 21-82 years) and 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. Most patients in these three studies were responders to previous on-demand treatment with PDE5 inhibitors. In a subsequent study, 217 patients who were treatment-naive to PDE5 inhibitors were randomised 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
Tadalafil was studied in 4 clinical studies of 12 weeks duration enrolling over 1500 patients with signs and symptoms of benign prostatic hyperplasia. The improvement in the total international prostate symptom score with tadalafil 5mg in the four studies were -4.8, -5.6, -6.1 and -6.3 compared to -2.2, -3.6, -3.8 and -4.2 with placebo. The improvements in total international prostate symptom score occurred as early as 1 week. In one of the studies, which also included tamsulosin 0.4 mg 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 5 mg 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 5 mg compared to 48.3% with placebo.

The maintenance of the effect was evaluated in an open-label extension to one of the studies, which 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

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. 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 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.
Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

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 13,000fold 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 2.5 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).

Linearity/Non-Linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5mg 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 subjects without erectile dysfunction.

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

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

Hepatic Insufficiency
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). If tadalafil is 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. 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 subjects. This difference in exposure does not warrant a dose adjustment.

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.
Tadalafil tablets are not indicated for use by women.

Dosage and Method of Administrations

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.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

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.

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 for the treatment of erectile dysfunction 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. (See sections warnings and precautions.)

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 is available as 10 and 20 mg film-coated tablets for oral use.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.
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 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 (see warnings and precautions).

Warnings and 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 (see section contraindications).

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 (see section contraindications).

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 whetherthese 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