Tyra®

Tadalafil

DESCRIPTION:
Tyra® contains tadalafil which is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).
Inactive ingredients: Lactose, croscarmellose sodium, sodium laurilsulphate, hypromellose, microcrystalline cellulose, magnesium stearate, iron oxide yellow (E172), triacetin, titanium dioxide.

PHARMACOLOGY:
Pharmacodynamic
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 absence of sexual stimulation. 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 PDE1, PDE2 and PDE4 enzymes which are found in the heart, brain, blood vessels, liver and other organs.
Pharmacokinetics
Absorption: Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) 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 **Tyra®** 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 liters, 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 13,000-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 2.5 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).
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: Tadalafil exposure (AUC) is approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis, when single dose tadalafil (5 mg - 20 mg) is administered. In haemodialysis patients, Cmax 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 10 mg is administered. There is limited clinical data on the safety of tadalafil in patients with severe hepatic insufficiency (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 10 mg of tadalafil to patients with hepatic impairment.
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 order for **Tyra®** to be effective, sexual stimulation is required.
Tyra® is not indicated for use by women.

CONTRAINDICATIONS:
Tadalafil augments 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 **Tyra®** to patients who are using any form of organic nitrate is contra-indicated.
Agents for the treatment of erectile dysfunction, including **Tyra®**, should 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 has not been studied in these patient populations and is therefore contraindicated in:
- 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.

Tyra® is contra-indicated 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.
Tyra® should not be used in patients with hypersensitivity to the active substance or to any of the excipients.

SIDE EFFECTS:
The most commonly reported side effects are headache and dyspepsia, see tables below.

Table 1	
Very common side effects (> 1/10)	
System organ class	Side effect
Nervous system	headache
Gastrointestinal	dyspepsia

Table 2	
Common side effects (> 1/100, < 1/10)	
System organ class	Side effect
Nervous system	dizziness
Vascular	flushing
Respiratory, thoracic and mediastinal	nasal congestion
Musculoskeletal and connective tissue	back pain myalgia

Swelling of eyelids, sensations described as eye pain and conjunctival hyperaemia are uncommon side effects.
The side effects reported with tadalafil were transient, and generally mild or moderate.
Side effect data are limited in patients over 75 years of age.
In postmarketing surveillance, side effects that have been reported in patients taking tadalafil include:
Nervous system: Migraine.
Body as a whole: Hypersensitivity reactions including rash, urticaria, facial oedema, stevens-johnson syndrome, and exfoliative dermatitis.
Cardiovascular and cerebrovascular: 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 whom these events have been reported had pre-existing cardiovascular risk factors. Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), hypertension, and syncope.
Eye disorders: Blurred vision, visual field defect, retinal vascular occlusion. non-arteritic anterior ischemic optic neuropathy (NAION) has been reported at an unknown frequency.
Respiratory system: Epistaxis.
Skin and subcutaneous tissue: Hyperhidrosis (sweating).
Gastrointestinal: Abdominal pain and gastro-oesophageal reflux.
Urogenital: Priapism and prolonged erection.

WARNINGS AND PRECAUTIONS:
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 potentiate the hypotensive effect of nitrates.
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.
Visual defects and cases of non-arteritic anterior ischemic optic neuropathy have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking tadalafil and consult a physician immediately.
There is limited clinical data on the safety of tadalafil in patients with severe hepatic insufficiency (Child-Pugh class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.
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.
Agents for the treatment of erectile dysfunction, including 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).
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 with spinal cord injuries and patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.
Tyra® should not be administered to patients with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
In patients who are taking alpha (1)-blockers, such as doxazocin, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients. Therefore, the combination of tadalafil and alpha blockers is not recommended.
Caution should be exercised when prescribing tadalafil to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin), as increased tadalafil a exposure (AUC) has been observed if the drugs are combined.
The safety and efficacy of combinations of tadalafil and other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.
Tyra® 20 mg tablet contains:
Lactose monohydrate: If the patient has been told by the doctor that he has intolerance to some sugars, he should contact his doctor before taking this medicinal product.
Use during pregnancy and lactation:
Tyra® is not indicated for use by women. There are no studies of tadalafil in pregnant women.
There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1000 mg/kg/day.
Effects on ability to drive and use machines:
Tyra® is expected to have no or negligible influence on the ability to drive and or use machines.
No specific studies have been performed to evaluate a potential effect. Dizziness has been reported, thus, patients should be aware of how they react to tadalafil, before driving or operating machinery.

DRUG INTERACTIONS:
Effects of other medicinal products on tadalafil
Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200-mg daily), increased tadalafil (10-mg) exposure (AUC) 2-fold and Cmax by 15%, relative to the AUC and Cmax values for tadalafil alone. Ketoconazole (400-mg daily) increased tadalafil (20-mg) exposure (AUC) 4-fold and Cmax by 22%. Ritonavir, a protease inhibitor (200-mg dose given twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20-mg) exposure (AUC) 2-fold with no change in Cmax. 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 undesirable effects might be increased.
The role of transporters (for example, p-glycoprotein) in the disposition of tadalafil is not known. There is thus the potential of drug interactions mediated by inhibition of transporters.
A CYP3A4 inducer, rifampicin, reduced tadalafil AUC by 88%, relative to the AUC values for tadalafil alone (10-mg dose). It can be expected that concomitant administration of other CYP3A4 inducers, such as phenobarbital, phenytoin, and carbamazepine, will also decrease plasma concentrations of tadalafil.
Effects of tadalafil on other medicinal products
Tadalafil (10 mg and 20 mg) augments the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contra-indicated. In a patient prescribed **Tyra®**, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of **Tyra®** before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolised by CYP450 isoforms. Tadalafil does not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.
Tadalafil (10 mg and 20 mg) 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.
Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.
Tadalafil has no clinically significant interaction with any of these classes: 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). In patients receiving concomitant antihypertensive medications, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha-blockers) is, in general, minor and not likely to be clinically relevant. There is no difference in adverse events in patients taking tadalafil with or without antihypertensive medications. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medications.
In subjects receiving concomitant tadalafil (20 mg) and doxazocin (8 mg daily), an alpha (1)-adrenergic receptor blocker, there is an augmentation of the blood-pressure-lowering effect of doxazocin. This effect is present at 12 hours postdose; it generally disappeared at 24 hours. Clinically significant decrease in standing-blood-pressure is more common for the combination. Dizziness has been reported but no cases of syncope. Lower doses of doxazocin have not been studied. Therefore the combination of tadalafil and alpha blockers is not recommended. Tadalafil (10 and 20 mg) had no clinically significant effect on blood pressure changes due to tamsulosin, a selective alpha (1A)-adrenergic receptor blocking agent. It is not known how this extrapolates to other alpha (1A)-adrenergic receptor blocking agents.
When alcohol is administered in a manner to maximize the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol), alcohol concentrations (mean maximum blood concentration 0.08%) are not affected by co-administration with Tadalafil (10 mg or 20 mg). Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7g/kg or approximately 180 ml of 40% alcohol [vodka] in an 80 kg male) but, in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil is administered with lower doses of alcohol (0.6 g/kg), hypotension is not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function is not augmented by tadalafil (10 mg).
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.
No pharmacokinetic interaction was observed when tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor). 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 it should be considered when co-administering these medications.
Specific interaction studies with antidiabetic agents were not conducted.

DOSAGE AND ADMINISTRATION:
For oral use.
Use in adult men
The recommended dose is 10 mg taken prior to anticipated sexual activity and without regard to food. In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.
The maximum dosing frequency is once per day.
Tadalafil 10 and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.
Use in elderly men
Dosage adjustments are not required in elderly patients.
Use in men with impaired renal function
Dosage adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment, 10 mg is the maximum recommended dose.
Use in men with impaired hepatic function
The recommended dose of **Tyra®** is 10 mg taken prior to anticipated sexual activity and without regard to food. There is limited clinical data on the safety of **Tyra®** in patients with severe hepatic insufficiency (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 10 mg of tadalafil to patients with hepatic impairment.
Use in men with diabetes
Dosage adjustments are not required in diabetic patients.
Use in children and adolescents
Tyra® should not be used in individuals below 18 years of age

OVERDOSAGE:
Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg 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.

PRESENTATIONS:
Tyra® 20 film-coated tablets: Packs of 4 tablets. Each tablet contains 20 mg Tadalafil.

STORAGE CONDITIONS:
Store below 30°C in the original package.

This is a medicament

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold you the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and its risks.
- Do not, by yourself, interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

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