novugen

TADIGRA

Tadalafil

1. NAME OF THE MEDICINAL PRODUCT

Tadigra 20mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of Tadalafil. Excipient with known effect:
Each coated tablet contains 290.800 mg lactose (as monohydrate). For the full list of excipients, see section List of excipients.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Yellow, almond-shaped biconvex film coated tablet debossed with "N" on one side and "44" on other side.

4. CLINICAL PARTICULARS

4.1 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.
Tadigra is not indicated for use by women.

4.2 Posology and method of administration

Posology
Adult men
In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without 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 dose frequency is once per day.
Tadalafil 20 mg 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 Tadigra (i.e., at least twice weekly) a once daily regimen with the lowest doses of Tadigra might be considered suitable, based on patient choice and the physician's judgement.
In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day.
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 10 mg is the maximum recommended dose. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment (see sections Special warnings and precautions for use and Pharmacokinetic properties).
Men with hepatic impairment
The recommended dose of Tadigra is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of TADIGRA 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 10 mg of tadalafil to patients with hepatic impairment. Once-a-day dosing 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 Special warnings and precautions for use and Pharmacokinetic properties).
Men with diabetes
Dose adjustments are not required in diabetic patients.
Paediatric population
There is no relevant use of Tadigra in the paediatric population with regard to the treatment of erectile dysfunction.
Method of administration
Tadigra film-coated tablet is for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section List of excipients. Administration of Tadigra to patients who are using any form of organic nitrate is contraindicated. (see section Interaction with other medicinal products and other forms of interaction).
Tadigra, 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 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 (< 90/50 mm Hg), or uncontrolled hypertension,
- patients with a stroke within the last 6 months.

Tadigra 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 section Special warnings and precautions for use).
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 (see section Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Before treatment with Tadigra
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 (see section Pharmacodynamic properties) 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 Tadigra 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 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 Tadigra, 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 Tadigra may lead to symptomatic hypotension in some patients (see section Interaction with other medicinal products and other forms of interaction). 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 Tadigra 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 Tadigra and consult a physician immediately (see section Contraindications).
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
Due to increased tadalafil exposure (AUC) and the lack of ability to influence clearance by dialysis, once-a-day dosing of Tadigra is not recommended in patients with severe renal impairment.
There is limited data on the safety of single-dose administration of Tadigra in patients with severe hepatic insufficiency (Child-Pugh Class C). 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 Tadigra 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.
Tadigra, 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 Tadigra 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 (see section Interaction with other medicinal products and other forms of interaction).
Tadigra and other treatments for erectile dysfunction
The safety and efficacy of combinations of Tadigra and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take Tadigra in such combinations.
Lactose
Tadigra contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other substances on tadalafil
Cytochrome P450 inhibitors
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 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 (see section Special warnings and precautions for use).
Consequently, the incidence of the adverse reactions listed in section Undesirable effects 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 (10 mg). 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
Tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of Tadigra to patients who are using any form of organic nitrate is contraindicated (see section Contraindications). 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 8 mg daily) and tadalafil (5 mg daily dose and 20 mg 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 (see section Special warnings and precautions for use).
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.
Riociguat
Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated (see section Contraindications).
5- alpha reductase inhibitors
Caution should be exercised when tadalafil is co- administered with 5-ARIs.
CYP1A2 substrates (e.g. theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor), there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small increase in heart rate. 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 (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol.
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 (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.
Aspirin
Tadalafil (10 mg and 20 mg) 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
Tadigra is not indicated for use by women.
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 Tadigra during pregnancy.
Breastfeeding
Tadigra should not be used during breast feeding.
Fertility
A decrease in sperm concentration was seen in some men (see sections Pharmacodynamic properties).

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

4.8 Undesirable effects
Summary of the safety profile
The most commonly reported adverse reactions in patients taking Tadigra for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of Tadigra. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with Tadigra once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated summary of adverse reactions
The table below lists the adverse reactions for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

Very common	Common	Uncommon	Rare
Immune system disorders			
		Hypersensitivity reactions	Angioedema
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures, Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non- arteritic anterior ischemic optic neuropathy (NAION), Retinal vascular occlusion
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris, Ventricular arrhythmia
Vascular disorders			
	Flushing	Hypotension[2], Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux	
Skin and subcutaneous tissue disorders			
		Rash	Urticaria, Stevens-Johnson syndrome, Exfoliative dermatitis, Hyperhydrosis (sweating)
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia, Pain in extremity		
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
		Prolonged erections	Priapism, Penile haemorrhage, Haematospermia
General disorders and administration site conditions			
		Chest pain[1], Peripheral oedema, Fatigue	Facial oedema[2], Sudden cardiac death[1]

(1) Most of the patients had pre-existing cardiovascular risk factors (see section Special warnings and precautions for use).
(2) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.
Description of selected adverse reactions
Most of these ECG abnormalities were not associated with adverse reactions.
Other special populations
Data in patients over 65 years of age receiving tadalafil, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited.

4.9 Overdose
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.

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 absence of sexual stimulation.
Pharmacodynamic effects
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 > 10,000-fold 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.

5.2 Pharmacokinetic properties
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 Tadigra 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 l, 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).
Linearity/non-linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, 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
This effect of age is not clinically significant and does not warrant a dose adjustment.
Renal insufficiency
Haemodialysis contributes negligibly to tadalafil elimination.
Hepatic insufficiency
If Tadigra 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Lactose Monohydrate, Croscarmellose Sodium, Hydroxypropylcellulose, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Magnesium Stearate.
Film-coat:
Opadry II Complete Film Coating System 32K620003 Yellow

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Please refer to the expiry date on the product labels.

6.4 Special precautions for storage
Store below 30°C

6.5 Nature and contents of container
Alu/Alu blisters in cartons of 2, 4 or 8 film-coated tablets. Not all packs sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MANUFACTURER

Manufactured by:
Novugen Pharma Sdn.Bhd.
No.27, Jalan Lengkuk Teknologi 2,
Taman Teknologi Enstek Fasa 1,
71760 Bandar Baru Enstek,
Negeri Sembilan.

PRODUCT REGISTRATION HOLDER
Novugen Pharma Sdn. Bhd.
No.3, Jalan Jururancang U1/21,
Hicom Glenmarie Industrial Park
40150 Shah Alam, Selangor

8 DATE OF REVISION
16 August 2024