25 mm

25 mm

Rx Prescription only

Tadalafil STELLA

1. Name of the medicinal product

Tadalafil STELLA 10 mg

Tadalafil STELLA 20 mg

2. Special notice and recommendation

Keep out of reach of children

Read the package insert carefully before use

3. Qualitative and quantitative composition

Each film-coated tablet Tadalafil STELLA 10 mg contains:

Tadalafil.....10 mg

Each film-coated tablet Tadalafil STELLA 20 mg contains:

Tadalafil.....20 mg

4. Pharmaceutical form

Film-coated tablet

Tadalafil STELLA 10 mg:

Yellow, oblong film - coated tablets, biconvex, engraved with logo " " on one side and scored on the other side.

Dimension: About 5.6 mm x 11.6 mm.

Thickness: About 3.4 mm.

The tablet can be divided into equal doses.

Tadalafil STELLA 20 mg:

Yellow, almond-shaped, film - coated tablet, biconvex, engraved with "T20" on one side and plain on the other side.

Dimension: About 7.8 mm x 12.6 mm.

Thickness: About 4.80 mm.

5. Indications

Treatment of erectile dysfunction in adult males.

In order for tadalafil to be effective, sexual stimulation is required.

Tadalafil is not indicated for use by women.

6. Administration and dosage

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 10 and 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 Tadalafil (i.e., at least twice weekly) a once daily regimen with the lowest doses of Tadalafil 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 dose may be decreased to 2.5 mg once a day based on individual tolerability.
 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.

Men with hepatic impairment

The recommended dose of Tadalafil is 10 mg 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 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.

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.

7. Contraindications

- Hypersensitivity to the active substance or to any of the excipients in the drug products.
- 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 use of tadalafil is contraindicated in the following groups of patients with cardiovascular disease:
 + 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.
- 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.

8. 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.
- 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 who are taking alpha$_1$ 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.

Hepatic impairment

There is limited clinical data on the safety of single-dose administration of tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). If tadalafil is prescribed, 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 STELLA contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take the medicinal product.

9. Pregnancy and lactation

Tadalafil is not indicated for use by women.

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 of tadalafil 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. Tadalafil should not be used during breast feeding.

10. Effects on abillity 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.

11. Drug interactions

Effects of other substances on tadalafil

Cytochrome P450 inhibitors: Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole, increased tadalafil exposure (AUC) and C_{max}, relative to the AUC and C_{max} values for tadalafil alone. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil exposure (AUC) 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 coadministered 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 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.

25 mm

25 mm

Effects of tadalafil on other medicinal products

Nitrates: Tadalafil was shown to augment the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated.

Doxazosin: The co-administration of doxazosin (4 and 8 mg daily) and tadalafil 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.

Alpha-blockers: 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.

Antihypertensive medicinal products [calcium-channel blockers, angiotensin converting enzyme (ACE) inhibitors, beta-adrenergic receptor blockers, thiazide diuretics, and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium-channel blockers, beta-blockers, and/or alpha-blockers)]: Tadalafil had no clinically significant interaction with any of these antihypertensive medicinal products.

Riociguat: Riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated.

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. 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 (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after coadministration 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 did not potentiate the increase in bleeding time caused by acetylsalicylic acid.

Antidiabetic medicinal products: Specific interaction studies with antidiabetic medicinal products were not conducted.

12. Adverse reactions

Summary of the safety profile

The most commonly reported adverse reactions in patients taking tadalafil for the treatment were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of tadalafil. The adverse reactions reported were transient, and generally mild or moderate.

Tabulated summary of adverse reactions

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, non-arteritic 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

*Most of the patients had pre-existing cardiovascular risk factors.

Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

Data in patients over 65 years of age receiving tadalafil are limited. Diarrhoea was reported more frequently in patients over 65 years of age. Dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

13. Overdosage and management

Single doses up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patient. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted, as required. Hemodialysis contributes negligibly to tadalafil elimination.

14. 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.

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 > 10,000-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.

15. 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 13,000-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

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) 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. 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 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 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 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. 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.

16. Packaging

Tadalafil STELLA 10 mg:

Blister of 2 tablets. Box of 1 blister.

Blister of 2 tablets. Box of 7 blisters.

Tadalafil STELLA 20 mg:

Blister of 2 tablets. Box of 1 blister.

17. Storage condition, shelf-life

The expiry date of this pack is printed on the box. Do not use this pack after this date.

Do not store above 30ºC.

18. Name, address of manufacturer

STELLAPHARM J.V. CO., LTD. – BRANCH 1
(A Joint Venture Company of Auxilto GmbH, Germany)
No. 40 Tu Do Avenue, Vietnam - Singapore Industrial Park,
An Phu Ward, Thuan An Town, Binh Duong Province, Vietnam
Tel: (+84 274) 3767 470 Fax: (+84 274) 3767 469

Date of revision: July 2nd, 2024

MALTAD10110724