CIATUFF

Tadalafil Tablets 10 mg and 20 mg

Rx Only

NAME OF DRUG PRODUCT	:	Tadalafil Tablets 10 mg Tadalafil Tablets 20 mg
(TRADE) NAME OF PRODUCT	:	CIATUFF 10 CIATUFF 20
STRENGTH	:	10 mg and 20 mg
PHARMACEUTICAL DOSAGE FORM	:	Tablet

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Tadalafil Tablets 10 mg: Each film-coated tablet contains 10 mg of Tadalafil Ph. Eur.

Tadalafil Tablets 20 mg: Each film-coated tablet contains 20 mg of Tadalafil Ph. Eur.

PHARMACEUTICAL FORM

Tadalafil Tablets 10 mg: Light yellow colored, oval shaped, film-coated tablets debossed with '10' on one side and 'TL' on other side.

Tadalafil Tablets 20 mg: Yellow colored, oval shaped, film-coated tablets debossed with '20' on one side and 'TL' on other side.

CLINICAL PARTICULARS

Therapeutic 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.

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 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 (see sections warnings and precautions and pharmacokinetics).

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 (see sections warnings and precautions and pharmacokinetics).

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 tablet for oral use.

Contraindications

Tadalafil is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients used in Tadalafil tablets.

Tadalafil may 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:

- 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.

Special Warnings and Precautions for use:

Before treatment with Tadalafil:

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 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-nervesparing 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, may occur in most of the patients who 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 alpha1 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 may occur 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.

Decreased or sudden hearing loss:

Cases of sudden hearing loss may occur 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:

Tadalafil 20 mg: 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, 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.

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

Interaction with other drugs and other forms of interactions:

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.

Consequently the incidence of the adverse reactions listed in 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 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 may augment the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated. In a patient prescribed any dose of tadalafil (2.5 mg - 20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers):

In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha-blockers - see above) is, in general, minor and not likely to be clinically relevant. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

Riociguat:

May show an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, 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:

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Black A/s: 110 x 500 mm

AUROBINDO Packaging Development	Product Name: Ciatuff Tablets	Component: Leaflet	Item Code: P1526931	Date & Time: 19.03.2021 & 09.45 am
	Customer / Country: Malaysia_U7	Version No.: 02	Reason Of Issue: Submission	Reviewed / Approved by
Team Leader: Kiran Kumar	Dimensions: 110 x 500 mm	No. of Colours : 01		
Initiator: Shirisha N				
Artist: SCDESIGNERS	Pharmacode: 26931	26931		Sign / Date
Additional Information :				

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 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor), there will be 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 (10 mg or 20 mg). 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).

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.

Use in pregnancy and lactation:

Tadalafil is not indicated for use by women. As a precautionary measure, it is preferable to avoid the use of Tadalafil during pregnancy. Tadalafil should not be used during breast feeding.

Fertility: A decrease in sperm concentration may occur in some men.

Effects on ability to drive and use machines:

Tadalafil has negligible influence on the ability to drive or use machines.

Undesirable effects:

Summary of the safety profile

The most commonly reported adverse reactions in patients taking Tadalafil for the treatment of erectile dysfunction 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. The majority of headaches reported with Tadalafil once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

The adverse reactions are listed below.

Very Common	Common	Uncommon	Rare
Immune system disorders			
		Hypersensitivity reactions	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (Including haemorrhagic events), Syncope, Transient ischaemic attacks1, Migraine[2], Seizures[2], Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hypaeremia, Non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]
Vascular disorders			
	Flushing	Hypotension[3], 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[2], Exfoliative dermatitis[2], 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[1,2]

(1) Most of the patients had pre-existing cardiovascular risk factors.

(2) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.

(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

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 for the treatment of erectile dysfunction 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.

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.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties:

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.

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.

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.

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).

PHARMACEUTICAL PARTICULARS:

List of Excipients: Copovidone, Polyoxyl 40 hydrogenated castor oil, Lactose Monohydrate, Silica Colloidal Anhydrous, Microcrystalline cellulose, Croscarmellose Sodium, Magnesium Stearate, Opadry Yellow.

Incompatibilities:

Not Applicable

Shelf-life: Please refer outer package.

Special precautions for storage:

Do not store above 30°C. Protect from moisture.

Keep out of the reach of children.

Presentation:

Blisters of 4 tablets are packed in a printed carton along with a package insert.

Pack Size: 1 x 4's Blister Pack.
2 x 4's Blister Pack.

MANUFACTURED BY:

AUROBINDO

Aurobindo Pharma Limited, Unit-VII (SEZ),

TSIIC, Plot No. S1, Survey No. 411/P, 425/P, 434/P, 435/P & 458/P, Green Industrial Park, Polepally Village, Jedcherla Mandal, Mahaboobnagar District, Telangana State, India

Product Registration Holder in Malaysia:

Synerrv Sdn Bhd,

SO-29-2, Menara 1, KL ECO City, Jalan Bangsar, KG Haji Abdullah Hukum,

59200 Kuala Lumpur Wilayah Persekutuan Kuala Lumpur, Malaysia.

DATE OF PREPARATION OF THIS LEAFLET

March 2021.

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