PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIAVOR 5 - 5 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CIAVOR 5 film-coated tablet contains 5 mg tadalafil. Excipient with known effect:

Each coated tablet contains 121 mg lactose (as monohydrate). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light yellow, almond shaped tablets debossed with identification code “F48” on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

CIAVOR is indicated for the treatment of erectile dysfunction. In order for CIAVOR to be effective, sexual stimulation is required.

4.2. Posology and method of administration

For oral use.

In adult men: The recommended dose is 2,5 to 5 mg taken once a day at approximately the same time of day.

In men with renal impairment: Dosage adjustments are not required in patients with mild or moderate renal impairment. Once-a-day dosing of CIAVOR is not recommended in patients with severe renal impairment.

4.3. Contraindications

A known hypersensitivity to tadalafil or to any of the components of the tablet. Administration of CIAVOR to patients who are using any form of organic nitrate. Patients with severe hepatic insufficiency (Child-Pugh Class C).

Previous experience of partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes.

Previous experience of unilateral or bilateral decrease or loss of hearing with or without associated vestibular symptoms.

4.4. Special warnings and precautions for use

Sexual activity carries a potential cardiac risk for patients with pre-existing cardiovascular disease. CIAVOR should not be used in men with cardiac disease for whom sexual activity is inadvisable.

The following groups of patients with cardiovascular disease were not included in clinical trials, and the use of CIAVOR in these patients is not recommended:

- 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.

Special precautions:

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment.

Doctors should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and should report the episode to their physician.

Non-arteritic anterior ischaemic optic neuropathy (NAION) is a cause of decreased vision including permanent loss of vision. There are postmarketing reports of NAION in temporal association with the use of all PDE5 inhibitors. Currently it is not possible to determine whether NAION is related directly to the use of PDE5 inhibitors or other factors. Physicians should advise patients to stop use of CIAVOR and seek medical attention in the event of a sudden loss of vision. Physicians should also discuss with patients that individuals who have already experienced NAION are at increased risk of NAION.

Physicians should advise their patients to stop taking CIAVOR and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of CIAVOR. It is not possible to determine whether these events are related directly to the use of CIAVOR or to other factors. (See Section 4.8)

The safety and efficacy of combinations of CIAVOR and other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Priapism has been reported with PDE5 inhibitors, including CIAVOR. 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.

CIAVOR should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anaemia, multiple myeloma, or leukaemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

In a clinical pharmacology study, administration of CIAVOR to patients with moderate renal failure (creatinine clearance = 31 to 50 ml/min) was determined to be safe but appeared to be less well tolerated in terms of back pain than in patients with mild renal failure (creatinine clearance = 51 to 80 ml/min) and healthy subjects.

Due to increased CIAVOR exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of CIAVOR is not recommended in patients with severe renal impairment.

Safety and efficacy of once-a-day administration in patients with hepatic insufficiency have not been established.

Caution should be exercised when prescribing CIAVOR to patients who are taking □-[1] blockers, such as doxazosin, as simultaneous administration may lead to symptomatic hypotension in some patients.

In a clinical pharmacology study of 18 healthy volunteers who received a single dose of CIAVOR, no symptomatic hypotension was observed with simultaneous administration of tamsulosin, an α-[1A] blocker (see Section 4.5).

CIAVOR has systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing CIAVOR, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects.

4.5. Interaction with other medicines and other forms of interaction

CIAVOR does not inhibit or induce CYP450 isoforms, including CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

CIAVOR is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (400 mg daily), increased CIAVOR 20 mg single-dose exposure (AUC) by 312% and Cmax by 22% and ketoconazole (200 mg daily) increased CIAVOR 10 mg single-dose exposure (AUC) by 107% and Cmax by 15% relative to the AUC and Cmax values for CIAVOR alone.

Ritonavir (200 mg twice daily) an inhibitor of CYP3A4, 2C9, 2C19 and 2D6, increased CIAVOR single-dose exposure (AUC) by 124% with no change in Cmax. Although specific interactions have not been studied, other HIV protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors such as erythromycin and itraconazole, would likely increase CIAVOR exposure.

A selective CYP3A4 inducer, rifampicin (rifampicin, 600 mg daily), reduced CIAVOR single-dose exposure (AUC) by 88% and Cmax by 46%, relative to the AUC and Cmax values for CIAVOR alone. It can be expected that concomitant administration of other CYP3A4 inducers will also decrease plasma concentrations of CIAVOR.

The reduced exposure of CIAVOR with the co-administration of rifampin can be anticipated to decrease the efficacy of once-a-day-dosed CIAVOR; the magnitude of decreased efficacy is unknown. It can be expected that concomitant administration of other CYP3A4 inducers will also decrease plasma concentrations of CIAVOR.

Antihypertensive medications:

CIAVOR has systemic vasodilatory properties and may augment the blood pressure lowering effects of antihypertensive agents. Additionally, in patients taking multiple antihypertensive agents whose hypertension was not well controlled, greater reductions in blood pressure were observed. These reductions were not associated with hypotensive symptoms in the vast majority of patients. Appropriate clinical advice should be given to patients when they are treated with antihypertensive medications and CIAVOR.

α-adrenergic blockers: CIAVOR had no clinically significant effect on blood pressure changes due to tamsulosin, an α-adrenergic receptor blocking agent.

When CIAVOR was administered to healthy subjects taking doxazosin (8 mg daily), an α-[1]-adrenergic blocker, there was an augmentation of the blood pressure lowering effect of doxazosin. The number of patients with potentially clinically significant standing blood pressure decreases was greater for the combination. Some patients experienced dizziness. There were no cases of syncope. Lower doses of doxazosin have not been studied.

In clinical studies, CIAVOR was shown to augment the hypotensive effects of nitrates. Therefore, administration of CIAVOR to patients who are using any form of organic nitrate is contraindicated (see 4.3. Contraindications).

Alcohol: CIAVOR did not affect alcohol concentrations and alcohol did not affect CIAVOR concentrations. At high doses of alcohol (0,7 g/kg), the addition of CIAVOR did not induce statistically significant mean blood pressure decreases. In some subjects, postural dizziness and orthostatic hypotension were observed. When CIAVOR was administered with lower doses of alcohol (0,6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone.

Antacids: Simultaneous administration of an antacid (magnesium hydroxide/aluminium hydroxide) and CIAVOR reduced the apparent rate of absorption of CIAVOR without altering exposure (AUC) to CIAVOR.

H_2-antagonists: An increase in gastric pH resulting from administration of nizatidine, an H2-antagonist, had no significant effect on CIAVOR pharmacokinetics.

Warfarin: CIAVOR had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did CIAVOR affect changes in prothrombin time induced by warfarin.

Aspirin: CIAVOR did not potentiate the increase in bleeding time caused by aspirin.

Theophylline: CIAVOR had no clinically significant effect on the pharmacokineticsor pharmacodynamics of theophylline, a CYP1A2 substrate.

4.6. Fertility, pregnancy and lactation

The safety and efficacy of CIAVOR in pregnancy and lactation have not been established.

4.7. Effects on ability to drive and use machines

Patients should be aware of how they react to CIAVOR, before driving or operating machinery.

4.8. Undesirable effects

Side effects:

The following adverse events were reported in clinical trials:

	Frequency of occurrence		
Body system	**≥ 10 %**	**≥ 1 % and < 10 %**	**≥ 0,1 % and < 1 %**
Digestive system		Dyspepsia	
Musculoskeletal System		Back pain Myalgia	
Cardiovascular System		Flushing	
Respiratory System		Nasal congestion	
Nervous System		Headache	

SPONTANEOUS DATA

In postmarketing surveillance, adverse events that have been reported in temporal association in patients taking CIAVOR include:

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, stroke, chest pain, palpitations and tachycardia, have been reported postmarketing in temporal association with the use of CIAVOR. 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 CIAVOR, to sexual activity, or to a combination of these or other factors.

Hypotension (more commonly reported when CIAVOR is given to patients who are already taking antihypertensive agents), hypertension and syncope.

Gastrointestinal: Abdominal pain and gastroesophageal reflux.

Skin and subcutaneous tissues: Hyperhidrosis (sweating).

Ophthalmologic: Blurred vision, irreversible uni- or bilateral non-arteritic anterior ischaemic optic neuropathy (NAION) with loss of some vision or blindness, retinal vein occlusion, visual field defect.

Otologic: A sudden unilateral or bilateral decrease or loss of hearing (sensorineural deafness) with or without associated vestibular symptoms has been reported with the use of PDE5 inhibitors including CIAVOR. There is insufficient information regarding the reversibility of the hearing loss and the role of underlying risk factors for hearing loss in individual subjects.

Urogenital: Priapism and prolonged erection.

Nervous System: Migraine.

Respiratory System: Epistaxis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications https://www.sahpra.org.za/Publications/Index/8.

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 CIALIS elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 7.1.5 Vasodilators – peripheral

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction, ATC Code: G04BE08.

Tadalafil improves impaired erectile dysfunction by increasing blood flow to the penis, in response to sexual stimulation. 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.

Tadalafil at doses of 2,5; 5 and 10 mg taken once a day has been evaluated in 3 clinical studies 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, 76 and 85% of patients reported that tadalafil 5 mg taken once a day improved their erections as compared to 29 and 30% with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections while taking tadalafil once a day. In the primary efficacy studies, 62 and 69% of intercourse attempts in the general population studies were successful in tadalafil 5 mg-treated patients as compared to 34 and 39% with placebo. Tadalafil 5 mg significantly improves erectile function over the 24-hour period between the doses.

5.2. Pharmacokinetic properties

Absorption: Tadalafil is well absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) is achieved at a median time of 2 hours after dosing.

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 L. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Less than 0,0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism: Tadalafil is predominantly metabolised by the cytochrome P450 CYP3A4 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 half-life is 17,5 hours in healthy subjects. Tadalafil is excreted predominantly as 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 in 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 subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment, tadalafil exposure (AUC) was higher than

in healthy subjects. In subjects with renal insufficiency, including those on haemodialysis, tadalafil exposure AUC was higher than in healthy subjects.

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. No dose adjustment is required in these patients. No data are available in patients with severe hepatic impairment (Child-Pugh Class C).

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

CIAVOR film-coated tablets contain the following inactive ingredients: Lactose monohydrate, croscarmellose sodium, hydroxypropylcellulose, microcrystalline cellulose, sodium laurylsulphate, magnesium stearate, hypromellose, triacetin, titanium dioxide (E171), iron oxide (E172) and talc.

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

24 months

6.4. Special precautions for storage

Store below 25ºC. Store in original package.

6.5. Nature and contents of container

CIAVOR 5 (Tablets), are available in aluminium/PVC/PE/PCTFE blisters, with a clear plastic web film, in cartons of 14 or 28 tablets. Each blister contains 14 tablets and there are either one or two blisters per carton.

Not all packs sizes may be marketed.

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand,

1686

8. REGISTRATION NUMBER(S)

48/7.1.5/0657

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 July 2021

10. DATE OF REVISION OF THE TEXT

11 November 2024