PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

CIAVOR 20 (Tablets)

COMPOSITION:

Each film-coated tablet contains 20 mg tadalafil.

CIAVOR 20 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.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.5 Vasodilators - peripheral

PHARMACOLOGICAL ACTION:

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

Pharmacodynamics:

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.

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, PDE4 and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leucocytes, skeletal muscle 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 > 9 000-fold more potent for PDE5 than for PDE 8, 9 and 10 and 14-fold more potent for PDE5 than for PDE11. The tissue distribution and physiological effects of the inhibition of PDE8 through PDE11 have not been elucidated.

Studies on vision - In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. In addition, no effects were observed on visual acuity, electroretinograms, intraocular pressure, or pupillometry. Across all clinical studies, reports of changes in colour vision were rare (< 0,1 %).

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, including CIAVOR 20. Currently it is not possible to determine whether NAION is related directly to the use of PDE5 inhibitors or other factors. (see ‘Side Effects and Special Precautions’).

Studies on blood pressure and heart rate – Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1,6/0,8 mm Hg, respectively), in standing systolic and

diastolic blood pressure compared to placebo (mean maximal decrease of 0,2/4,6 mm Hg, respectively), and no significant change in heart rate. Larger effects were recorded among subjects receiving concomitant nitrates (see 'CONTRA-INDICATIONS').

Effects on erectile function – Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3 250 patients, including patients with erectile dysfunction of various severity (mild, moderate, severe), aetiologies (including patients with diabetes), ages (range 21-86 years) and ethnicities and duration of erectile dysfunction. In the primary efficacy studies of general populations, 81 % of patients reported that tadalafil improved their erections. In the primary efficacy studies, 75 % of intercourse attempts were successful in tadalafil-treated patients.

Two clinical studies were conducted in 571 patients in an at-home setting to define the period of responsiveness to tadalafil. Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo, as early as 16 minutes following dosing.

Pharmacokinetic properties:

Absorption: Tadalafil is rapidly absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) 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, CIAVOR 20 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.

INDICATIONS:

CIAVOR 20 is indicated for the treatment of erectile dysfunction. In order for CIAVOR 20 to be effective, sexual stimulation is required.

CONTRA-INDICATIONS:

A known hypersensitivity to tadalafil or to any of the components of the tablet.

Administration of CIAVOR 20 to patients who are using any form of organic nitrate.

Patients with severe hepatic insufficiency (Child-Pugh Class C).

CIAVOR 20 is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION) regardless whether this episode was in connection or not with previous PDE5 inhibitor exposure (See 'Special Precautions').

WARNINGS:

Sexual activity carries a potential cardiac risk for patients with pre-existing cardiovascular disease. CIAVOR 20 should not be used in men with cardiac disease for whom sexual activity is inadvisable.

Priapism has been reported with CIAVOR 20. 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.

The following groups of patients with cardiovascular disease were not included in clinical trials:

- 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 dysrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension.
- Patients with a stroke within the last 6 months.

When tadalafil, as contained in CIAVOR 20 was co-administered to healthy subjects taking doxazosin (4-8 mg dialy), an alpha[1]-adrenergic blocker, there was an augmentation of the blood- pressure-lowering effect of doxazosin.

INTERACTIONS:

Interaction with other medicinal products and other forms of interaction:

CIAVOR 20 does not inhibit or induce CYP450 isoforms, including CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

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

Ritonavir (200 mg twice daily) an inhibitor of CYP3A4, 2C9, 2C19 and 2D6, increased CIAVOR 20 single-dose exposure (AUC) by 124 % with no change in C_{max}. 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 20 exposure.

A selective CYP3A4 inducer, rifampicin (rifampicin, 600 mg daily), reduced CIAVOR 20 single-dose exposure (AUC) by 88 % and C_{max} by 46 %, relative to the AUC and C_{max} values for CIAVOR 20 alone. It can be expected that concomitant administration of other CYP3A4 inducers will also decrease plasma concentrations of CIAVOR 20.

Antihypertensive medications:

CIAVOR 20 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 20.

Alpha adrenergic blockers: When tadalafil, as contained in CIAVOR 20 was co-administered to healthy subjects taking doxazosin (4-8 mg daily), an alpha[1]-adrenergic blocker, there was an augmentation of the blood-pressure-lowering effect of doxazosin.

In clinical studies, CIAVOR 20 was shown to augment the hypotensive effects of nitrates. Therefore, administration of CIAVOR 20 to patients who are using any form of organic nitrate is contra-indicated (see 'CONTRA-INDICATIONS').

Alcohol: CIAVOR 20 did not affect alcohol concentrations and alcohol did not affect CIAVOR 20 concentrations. At high doses of alcohol (0,7 g/kg), the addition of CIAVOR 20 did not induce statistically significant mean blood pressure decreases. In some subjects, postural dizziness and orthostatic hypotension were observed. When CIAVOR 20 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 20 reduced the apparent rate of absorption of CIAVOR 20 without altering exposure (AUC) to CIAVOR 20.

H_2-antagonists: An increase in gastric pH resulting from administration of nizatidine, an H_2-antagonist, had no significant effect on CIAVOR 20 pharmacokinetics.

Warfarin: CIAVOR 20 had no clinically significant effect on exposure (AUC) to S-warfarin or R- warfarin (CYP2C9 substrate), nor did CIAVOR 20 affect changes in prothrombin time induced by warfarin.

Aspirin: CIAVOR 20 did not potentiate the increase in bleeding time caused by aspirin.

Theophylline: CIAVOR 20 had no clinically significant effect on the pharmacokinetics or pharmacodynamics of theophylline, a CYP1A2 substrate.

PREGNANCY AND LACTATION:

The safety and efficacy of CIAVOR 20 in pregnancy and lactation have not been established.

DOSAGE AND DIRECTIONS FOR USE:

For oral use.

Use in adult men: The recommended maximum dose of CIAVOR 20 is 20 mg taken prior to anticipated sexual activity and without regard to food.

It can be taken up to 36 hours and as early as 16 minutes prior to sexual activity. Patients may initiate sexual activity at varying time points relative to dosing in order to determine their own optimal window of responsiveness.

The maximum recommended dosing frequency is once per day.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

The following adverse events were reported in clinical trials:

	Frequency of occurrence		
System organ class	Very common	Common	Uncommon
Vascular Disorders		Flushing	
Gastrointestinal Disorders		Dyspesia	
Musculoskeletal, Connetive Tissue and Bone Disorders		Back pain Myalgia	
Nervous System Disorders	Headache	Dizziness	
Respiratory, Thoracic and Mediastinal Disorders		Nasal congestion	
Eye Disorders			Conjunctival hyperaemia Sensations described as eye pain Swelling of eyelids

POST-MARKETING SURVEILLANCE DATA

In post-marketing surveillance, adverse events that have been reported in temporal association in patients taking CIAVOR 20 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 20. 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 20, to sexual activity, or to a combination of these or other factors.

Hypotension (more commonly reported when CIAVOR 20 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: Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including CIAVOR 20. These reported events may be related directly to the use of CIAVOR 20, or may be due to the patient's underlying risk factor for hearing loss, or a combination of these factors, or to other factors. (See 'Special Precautions')

Urogenital: Priapism and prolonged erection.

Nervous system: Migraine

Respiratory system: Epistaxis

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 doctor.

Nonarteritic 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, including CIAVOR 20. Currently it is not possible to determine whether NAION is related directly to the use of PDE5 inhibitors or other factors. Doctors should advise patients to stop use of CIAVOR 20 and seek medical attention in the event of a sudden loss of vision. Doctors should also inform patients that individuals who have already experienced NAION should not use CIAVOR 20 or other PDE5 inhibitors again. (See 'Contraindications').

Doctors should advise their patients to stop taking CIAVOR 20, 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 PDE5 inhibitors, including CIAVOR 20. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. (See 'Side Effects')

The safety and efficacy of combinations of CIAVOR 20 and other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

CIAVOR 20 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 tadalafil 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.

Caution should be exercised when prescribing CIAVOR 20 to patients who are taking □-[1] blockers, such as doxazosin, as simultaneous administration may lead to symptomatic hypotension in some patients (see 'Warnings').

CIAVOR 20 has systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing CIAVOR 20, doctors should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects.

CIAVOR 20 contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take CIAVOR 20.

Effects on ability to drive and use machines: Patients should be aware of how they react to CIAVOR 20, before driving or operating machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 CIAVOR 20 elimination.

IDENTIFICATION:

The tablets are yellow film-coated and almond shaped, marked 'F49' on one side.

PRESENTATION:

CIAVOR 20 (Tablets), TA 4464, are available as aluminium/PVC or aluminium PVC/PE/PCTFE blister strips packed in cartons of 2, 4 or 8 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Keep the blisters in the outer carton until required for use.

Keep out of reach of children.

REGISTRATION NUMBER:

36/7.1.5/0385

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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