PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

INCRAFLO 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg tadalafil.

Each film-coated tablet contains 249,00 mg lactose per tablet.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

INCRAFLO 20 mg are yellow coloured, almond shaped, film-coated tablets, debossed with "20" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Use in adult men: the recommended maximum dose of INCRAFLO 20 mg 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.

Method of administration

For oral use.

4.3 Contraindications

INCRAFLO 20 mg is contraindicated in:

- hypersensitivity to tadalafil or to any of the excipients of INCRAFLO 20 mg (see section 6.1).
- patients who are using any form of organic nitrate.
- patients with severe hepatic insufficiency (Child-Pugh Class C).

The following groups of patients with cardiovascular disease were excluded in clinical trials, and 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 dysrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension.
- patients with a stroke within the last 6 months.

INCRAFLO 20 mg is contraindicated in patients who have loss of vision in one or both eyes because of non-arteritic anterior ischemic optic neuropathy (NAION) regardless whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

The combination of tadalafil and guanylate cyclase stimulators, such as riociguat, is contraindicated because it may lead to symptomatic hypotension (see section 4.5).

4.4 Special warnings and precautions for use

Before treatment with INCRAFLO 20 mg

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

Medical practitioner 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 medical practitioner.

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

Cardiovascular

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

Caution should be exercised when prescribing INCRAFLO 20 mg to patients who are taking α-1 blockers, such as prazosin and doxazosin, as simultaneous administration may lead to symptomatic hypotension in some patients (see section 4.5).

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

Vision

Non-arteritic anterior ischemic optic neuropathy (NAION) is a cause of decreased vision including permanent loss of vision. There are post-marketing reports of NAION in temporal association with the use of all PDE5 inhibitors, including INCRAFLO 20 mg. Currently it is not possible to determine whether NAION is related directly to the use of PDE5 inhibitors or other factors. Medical practitioners should advise patients to stop use of INCRAFLO 20 mg and seek medical attention in the event of a sudden loss of vision. Medical practitioners should also inform patients that individuals who have already experienced NAION should not use INCRAFLO 20 mg or other PDE5 inhibitors again (see section 4.3).

Decreased or sudden hearing loss

Medical practitioners should advise their patients to stop taking INCRAFLO 20 mg, 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 INCRAFLO 20 mg. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors (See section 4.8).

Hepatic impairment

Once-a day administration has not been evaluated in patients with hepatic insufficiency. It is therefore contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Renal impairment

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.

Priapism and anatomical deformation of the penis

Priapism has been reported with PDE5 inhibitors, including INCRAFLO 20 mg. 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.

INCRAFLO 20 mg should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anaemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

Use with CYP3A4 inhibitors

Caution should be exercised when prescribing INCRAFLO 20 mg 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 4.5).

INCRAFLO 20 mg and other treatments for erectile dysfunction

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

INCRAFLO 20 mg contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take INCRAFLO 20 mg.

4.5 Interactions with other medicines and other forms of interactions

Effects of other medicines on INCRAFLO 20 mg

Cytochrome P450 inhibitors

INCRAFLO 20 mg is principally metabolized by CYP3A4. Ketoconazole, a selective inhibitor of CYP3A4 increases INCRAFLO 20 mg plasma concentrations.

Ritonavir, an inhibitor of CYP3A4, 2C9, 2C19 and 2D6, increases INCRAFLO 20 mg plasma concentrations. 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 INCRAFLO 20 mg plasma concentrations.

Cytochrome P450 inducers

Rifampicin, a selective CYP3A4 inducer, reduces INCRAFLO 20 mg plasma concentrations. It can be expected that concomitant administration of other CYP3A4 inducers will also decrease plasma concentrations of INCRAFLO 20 mg.

Antacids

Although the apparent rate of absorption of INCRAFLO 20 mg is reduced with simultaneous administration of an antacid (magnesium hydroxide/ aluminium hydroxide), the INCRAFLO 20 mg plasma concentrations are not changed.

H_2-antagonists

An increase in gastric pH resulting from administration of nizatidine, and H_2-antagonist, had no significant effect in INCRAFLO 20 pharmacokinetics.

Effects of INCRAFLO 20 mg on other medicines

Nitrates

In clinical studies, tadalafil was shown to increase the hypotensive effects of nitrates. Therefore, administration of INCRAFLO 20 mg to patients who are using any form of organic nitrate is contra-indicated (see section 4.3).

Antihypertensive medicines

When tadalafil was administered to healthy subjects taking doxazosin (8 mg daily), an α-1-adrenergic blocker there was an increase of the blood pressure lowering effect of doxazosin. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore, this combination is not recommended (see section 4.4).

INCRAFLO 20 mg had no clinically significant effect on blood pressure changes due to tamsulosin, an α-adrenergic receptor blocking medicine.

INCRAFLO 20 mg has systemic vasodilatory properties and may increase the blood pressure lowering effects of antihypertensive medicines. Additionally, in patients taking multiple antihypertensive medicines 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 medicines and INCRAFLO 20 mg.

Riociguat

Studies have shown an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. Riociguat has been shown to increase the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination.

Riociguat should not be used concomitantly with PDE5 inhibitors such as tadalafil (see section 4.3).

5- alpha reductase inhibitors

No new adverse reactions were identified when tadalafil was co-administered with finasteride. However, as a formal 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

INCRAFLO 20 mg had no clinically significant effect on the pharmacokinetics or pharmacodynamics of theophylline, a CYP1A2 substrate.

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

INCRAFLO 20 mg does not affect alcohol concentrations and alcohol does not affect INCRAFLO 20 mg concentrations.

Cytochrome P450 metabolised medicinal products

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

CYP2C9 substrates (e.g. R-warfarin)

INCRAFLO 20 mg had no clinically significant effect on plasma concentrations of *S*-warfarin of *R*-warfarin (CYP2C9 substrate), nor did INCRAFLO 20 mg affect changes in prothrombin time induced by warfarin.

Aspirin

INCRAFLO 20 mg did not potentiate the increase in bleeding time caused by aspirin.

4.6 Fertility, pregnancy and lactation

INCRAFLO 20 mg is not indicated for use by women.

Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men.

4.7 Effects on ability to drive and use machines

Patients should be aware of how they react to INCRAFLO 20 mg before driving or operating heavy machinery.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of INCRAFLO 20 mg. The adverse reactions reported were transient, and generally mild or moderate.

Summary of adverse reactions

The following side effects were reported in clinical trials:

Immune system disorders

Less frequently: Hypersensitivity reactions, angiodema[1]

Nervous system disorders

Frequently: Headache, dizziness

Less frequently: Stroke[1] (including haemorrhagic events), syncope, transient ischaemic attacks[1], migraine[2], seizures[2], transient amnesia

Eye disorders

Less frequently: Blurred vision, sensations described as eye pain, visual field defect, swelling of eyelids, conjunctival hyperaemia, irreversible uni- or bilateral non-arteritic anterior ischemic optic neuropathy (NAION) with loss of some vision or blindness[2], retinal vascular occlusion[2]

Cardiac disorders:

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations and tachycardia, have been reported post-marketing in temporal association with the use of tadalafil[2]. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to determine whether these events are related directly to the risk factors, to tadalafil, to sexual activity, or to a combination of these or other factors[2]

Ear and labyrinth disorders

Less frequently: Tinnitus, sudden hearing loss

Vascular disorders

Frequently: Flushing

Less frequently: Hypotension[3], hypertension

Respiratory, thoracic and mediastinal disorders

Frequently: Nasal congestion

Less frequently: Dyspnoea, epistaxis

Gastrointestinal disorders

Frequently: Dyspepsia

Less frequently: Abdominal pain, vomiting, nausea, gastro-oesophageal reflux

Skin and subcutaneous tissue disorders

Less frequently: rash, urticaria, Stevens-Johnson syndrome[2], exfoliative dermatitis[2], hyperhidrosis (sweating)

Musculoskeletal, connective tissue and bone disorders

Frequently: Back pain, myalgia, pain in extremity

Renal and urinary disorders

Less frequently: Haematuria

Reproductive system and breast disorders:

Less frequently: Prolonged erection, priapism, penile haemorrhage, haematospermia

General disorders:

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 (see section 4.4).
(2) Post-marketing 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 as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

Although there is limited data in patients over 65 years of age, in clinical trials with tadalafil taken on demand for the treatment of erectile dysfunction, diarrhoea was reported more frequently in patients over 65 years of age. In clinical trials with tadalafil 5 mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care 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

Adverse events were similar to those seen at lower doses when single doses of up to 500 mg of INCRAFLO 20 mg have been given to healthy subjects and multiple daily doses up to 100 mg have been given to patients.

Should an overdose occur, symptomatic and supportive treatment should be instituted. Haemodialysis contributes negligible to INCRAFLO 20 mg 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.

Mechanism of action

Tadalafil increases blood flow to the penis, resulting in improved erectile function, 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.

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, 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.

5.2 Pharmacokinetic properties

Absorption

Tadalafil is rapidly absorbed after oral administration and the mean maximum plasma concentrations occur within 2 hours after oral administration.

Tadalafil may be taken with or without food, as food does not influence the rate and extent of absorption. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution

Mean volume of distribution of tadalafil is approximately 63 litres, and it is 94 % bound to plasma proteins. Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation

Tadalafil is predominantly metabolised by the cytochrome P450 CYP3A4 isoform with methylcatechol glucuronide as the major circulating metabolite. This metabolite is at least 13000-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 in healthy subjects is approximately 17,5 hours. 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.

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.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, microcrystalline cellulose, hydroxypropylcellulose, sodium lauryl sulphate, croscarmellose sodium, magnesium stearate, Opadry II 32K520009 Yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store at or below 30 °C in the original package.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

Aluminium/PVC/PVDC blisters strips containing 1, 2, 4 or 10 tablets and packed into a cardboard carton.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein, Cape Town

7800

8. REGISTRATION NUMBERS

48/7.1.5/0034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10. DATE OF REVISION OF THE TEXT