CLEAN PROPOSED PROFESSIONAL INFORMATION JUNE 2021

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CLEAN AMENDED PROPOSED PROFESSIONAL INFORMATION JUNE 2021

SCHEDULING STATUS: **S4**

1. NAME OF THE MEDICINE

CLOFAZIMINE TABLETS MACLEODS 50 mg (Film-coated tablets)

CLOFAZIMINE TABLETS MACLEODS 100 mg (Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CLOFAZIMINE TABLETS MACLEODS 50 mg

Each film-coated tablet contains 50 mg clofazimine.

CLOFAZIMINE TABLETS MACLEODS 100 mg

Each film-coated tablet contains 100 mg clofazimine.

Sugar free.

Excipients: For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

CLOFAZIMINE TABLETS MACLEODS 50 mg

Light brown coloured, circular shaped, biconvex, film-coated tablets plain on both sides.

CLOFAZIMINE TABLETS MACLEODS 100 mg

Light brown coloured, oval shaped, biconvex, film-coated tablets with score line on one side and plain surface on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Multidrug-resistant Tuberculosis (MDR-TB):

CLOFAZIMINE TABLETS MACLEODS is indicated for the treatment of pulmonary multidrug-resistant tuberculosis, MDR35 TB in adults and children 10 years and older, including Rifampicin resistant tuberculosis (RR-TB).

Leprosy:

CLOFAZIMINE TABLETS MACLEODS, used only in combination with rifampicin and dapsone, is indicated as treatment for multibacillary (MB) forms of leprosy, including erythema nodosum leprosum (ENL).

Multidrug therapy (MDT) is necessary in order to prevent the emergence of resistant strains of *Mycobacterium leprae.*

4.2 Posology and method of administration

Posology:

Multibacillary leprosy

CLOFAZIMINE TABLETS MACLEODS is administered as part of a multidrug therapy, in combination with dapsone and rifampicin for the treatment of multibacillary leprosy. Multidrug therapy (MDT) is necessary in order to prevent the emergence of resistant strains of *Mycobacterium leprae.*

For the treatment of leprosy, the WHO recommends the following regimens:

MDT dosage

	Dapsone	Rifampicin	CLOFAZIMINE TABLETS MACLEODS (clofazimine)
Adults and adolescents (15 years and above)	Days 1-28 100 mg once daily as self-medication	Day 1 only of each cycle* 600 mg under supervision	Day 1 only of each cycle* 300 mg under supervision and Days 2-28 50 mg once daily as self-medication
Children (10 to 14	Days 1-28	Day 1 only of each	Day 1 only of each

years)	50 mg once daily as self-medication	cycle* 450 mg under supervision	cycle* 150 mg under supervision and Days 2-28 50 mg on alternate days (i.e. day 3, 5, 7,..) as self-medication

This triple combination should be administered for 12 months (i.e.*12 consecutive 28-day treatment cycles). An additional 12 months of this triple combination may be necessary for MB patients showing evidence of relapse.

Children below 10 years

The dose should be adjusted according to body weight: 1 to 2 mg/kg clofazimine + 10 to 20 mg/kg rifampicin + 1 to 2 mg/kg dapsone. As an example, **CLOFAZIMINE TABLETS MACLEODS** once a month under supervision + 50 mg twice a week as self- medication + rifampicin 300 mg once a month under supervision + dapsone 25 mg once a day as self-medication.

Treatment of children below 10 years of age is possible only if dapsone tablets of 25 mg are commercially available.

Patients with erythema nodosum leprosum (ENL)

Adults and children

If the patient develops erythema nodosum leprosum, treatment with dapsone and rifampicin should be continued as before, and the dosage of **CLOFAZIMINE TABLETS MACLEODS** should be raised to 200 to 300 mg per day, given under medical supervision. These high daily doses must not be given for longer than 3 months (see section 4.4). The dose of **CLOFAZIMINE TABLETS MACLEODS** should be gradually reduced, first to 100 mg twice daily for 12 weeks and then to 100 mg once daily for a

further 12 to 24 weeks.

Multidrug-resistant tuberculosis (MDR-TB)

Dosage:

For the treatment of pulmonary MDR-TB:

Adults and adolescents:

• For adults weighing at least 30 kg, the recommended dosage is 100 mg/day.

• For adults weighing less than 30 kg, the recommended dosage is 50 mg/day.

Children (10 years of age and over):

• For children weighing at least 30 kg, the recommended dosage is 2-5 mg/kg/day, not exceeding 100 mg/day.

• For children weighing less than 30 kg, the recommended dosage is 2-5 mg/kg/day, not exceeding 50 mg/day. If a dose lower than 50 mg/day is required, the 50 mg dose can be given every other day.

Dosing in special populations

Safety and efficacy have not been established in HIV infected patients on antiretroviral therapy

Renal impairment

There are no data available in patients with renal impairment.

Caution is advised when administered to patients with renal impairment.

Hepatic impairment

There are no data available in patients with hepatic impairment. **CLOFAZIMINE TABLETS MACLEODS** should not be administered to patients with hepatic impairment (see section 4.4 and section 5).

No dosing recommendations can be made in the following groups of patients as efficacy and safety have not been established:

• Patients co-infected with HIV and treated for HIV infection

• Patients with hepatic impairment

• Women who are pregnant

• Patients co-infected with hepatitis B and/ or C

Method of administration

It is recommended to take **CLOFAZIMINE TABLETS MACLEODS** during a meal or with a glass of milk to ensure maximum absorption.

4.3 Contraindications

- **CLOFAZIMINE TABLETS MACLEODS** is contraindicated in patients with known hypersensitivity to clofazimine or any of the excipients of **CLOFAZIMINE TABLETS MACLEODS,** listed in section 6.1.
- Patients with acquired or congenital QT interval prolongation including torsades de Pointes (see section 4.4).
- Concomitant use with medicines known to prolong QTc interval up to the time intervals known to induce serious dysrhythmias.

4.4 Special warnings and precautions for use

Accumulation of clofazimine

Deposition of large amounts of clofazimine in the intestinal mucosa causes irritations resulting in gastrointestinal disorders (e.g. abdominal pain (sometimes intermittent), nausea, vomiting and diarrhoea), usually of moderate intensity but sometimes more severe in case of higher dosage (200-300 mg/day) and prolonged (more than 6 months). Clofazimine has a heterogeneous distribution profile in the body and its elimination is slow. Clofazimine mainly accumulates in adipose tissue, the reticuloendothelial system (macrophages, histiocytes and spleen) and in the skin. The adverse effects of clofazimine are mainly related to its reuptake by tissues and organs. Therefore, administration of large doses over long periods should be avoided. Daily doses of **CLOFAZIMINE TABLETS**

MACLEODS greater than 100 mg should be administered as short as possible (< 3 months) and only under close medical supervision.

After prolonged administration of high doses, clofazimine can accumulate in several organs, body fluids and tissues in the form of crystals. In the viscera, the most important deposits are in the jejunum and then the spleen. Deposition of crystals in the mesenteric lymph nodes, and / or histiocytes of the laminapropria of the jejunal mucosa, may lead to intestinal obstruction. Deaths following the occurrence of gastrointestinal adverse events have been reported. If gastrointestinal disturbances occur during treatment, the dose or the time taken should be reduced. Symptoms may regress slowly when treatment is stopped. In case of persistent diarrhoea or vomiting, the patient must be hospitalised.

Modification of the colour of the skin and body fluids

Medical practitioners should be informed that cutaneous dyschromia due to **CLOFAZIMINE TABLETS MACLEODS** may cause depression (2 cases of suicide in a depressive context have been reported).

Patients should be advised of possible abnormal discoloration of the conjunctiva, tear fluid, sweat, sputum, urine, faeces, sperm, breast milk, hair and reddish to dark brown skin discoloration. Patients should be informed that the skin colour is reversible but it may take several months or years to disappear after discontinuation of treatment with **CLOFAZIMINE TABLETS MACLEODS**.

Torsades de pointe and QT prolongation

Cases of Torsades de Pointes with QT prolongation have been reported in patients receiving CLOFAZIMINE TABLETS MACLEODS mostly at doses higher than usually recommended or in combination with other QT-prolonging medicines (such as bedaquiline, fluoroquinolones, delamanid, rilpivirine, lopinavir, atazanavir, nelfinavir, saquinavir). Concomitant administration with other medicines known to prolong QTc interval up to the time intervals known to induce serious dysrhythmias is contraindicated (see section 4.3 and section 4.5). CLOFAZIMINE TABLETS MACLEODS should be discontinued if the QTc prolongation exceeds 500 milliseconds (ms) and/or the Qtc prolongation exceeds 60 milliseconds (ms) from baseline or if

the patient develops dysrhythmias. Patients receiving CLOFAZIMINE TABLETS MACLEODS at recommended doses and/or doses higher than usually recommended and/or in combination with QT-prolonging medicines, should have regular clinical monitoring at baseline and regular ECGs performed to monitor for QT prolongation and cardiac dysrhythmias.

Treatment compliance

CLOFAZIMINE TABLETS MACLEODS should never be given as monotherapy to treat leprosy. **CLOFAZIMINE TABLETS MACLEODS** should be administered in combination with rifampicin and dapsone (see section 4.2). Multidrug therapy is necessary to prevent the development of resistant strains of *Mycobacterium leprae*.

Patients should be informed of the importance of good adherence to prescribed therapy to prevent the emergence of treatment resistance. Irregular administration of treatment and poor compliance can delay healing or make it incomplete, causing the patient to become a source of infection. Poor compliance can eventually lead to the development of infirmities and deformities. Whenever possible, it is necessary to ensure that non-observant patients are correctly assessed, receive appropriate health education and that their treatment is well supervised.

Patients should be educated to recognise the signs of a response to treatment and relapse of the disease upon discontinuation of treatment, and should be made aware of the importance of promptly informing their healthcare provider upon manifestations of these symptoms.

Leprosy reactions

WHO recommends never interrupting multidrug therapy in leprosy reactions, (see section 4.2) the dose of **CLOFAZIMINE TABLETS MACLEODS** to be administered in patients who develop chronic or corticodeficant leprosy glandular leprosy (ENL) reactions. Some data indicate that the frequency and severity of an ENL would tend to decrease in patients with multibacillary leprosy treated with multidrug therapy. This could be related to the anti-inflammatory properties of clofazimine. However, transient

and unexplained increases in the number of adverse reactions have also been observed in patients with multibacillary leprosy, most commonly in the first year of multidrug therapy.

Leprosy reactions usually respond satisfactorily to conventional anti-inflammatory medicines (prednisolone).

4.5 Interaction with other medicines and other forms of interaction

Dapsone

CLOFAZIMINE TABLETS MACLEODS appears to have no important effects on the pharmacokinetics of dapsone, although a transient increase in the urinary excretion of dapsone occurred in a few patients. Limited data suggesting that dapsone inhibits the anti-inflammatory activity of **CLOFAZIMINE TABLETS MACLEODS** have not been confirmed. If leprosy-associated inflammatory reactions develop in patients being treated with dapsone and **CLOFAZIMINE TABLETS MACLEODS**, it is still advisable to continue treatment with both medicines.

Rifampicin

CLOFAZIMINE TABLETS MACLEODS reduces rifampicin absorption in leprosy patients, increasing the time it takes for the peak serum concentration to be reached and prolonging the elimination half-life. Total exposure (AUC) of rifampicin was not affected, so this interaction is unlikely to be clinically significant.

Isoniazid

In volunteers receiving clofazimine (150 mg daily) and standard doses of isoniazid (300 mg daily), elevated concentrations of **CLOFAZIMINE TABLETS MACLEODS** were detected in plasma and urine, compared to clofazimine alone.

Interaction with QT prolonging medicines

Cases of Torsades de Pointes with QT prolongation have been reported in patients receiving **CLOFAZIMINE TABLETS MACLEODS** in combination with QT prolonging medicines. Caution is

recommended when clofazimine is administered with other medicines (e.g: bedaquiline, fluoroquinolones, delamanid, azithromycin, rilpivirine, lopinavir, atazanavir, nelfinavir, saquinavir) with known QT interval prolonging potential (see section 4.3 and section 4.4).

Effects of CLOFAZIMINE TABLETS MACLEODS on CYP3A (CYP3A4 and CYP3A5) substrates:

As **CLOFAZIMINE TABLETS MACLEODS** is predicted to be a moderate to strong inhibitor of CYP3A (CYP3A4 and CYP3A5) substrates, caution should be exercised while co-administering **CLOFAZIMINE TABLETS MACLEODS** with other medicines which are CYP3A substrates.

No clinical interaction studies have been performed with other CYP3A substrates. Clofazimine inhibits the CYP3A enzyme in vitro. Based on Physiologically Based Pharmacokinetic Modelling (PBPK) modeling results, clofazimine is predicted to be a moderate to strong CYP3A inhibitor.

Hence, caution should be exercised with the concomitant administration of **CLOFAZIMINE TABLETS MACLEODS** and CYP3A substrates (e.g.: anti-mycobacterial medicines (bedaquiline, delamanid, clarithromycin), selected unboosted anti-retrovirals (amprenavir, delaviridine, efavirenz, etravirine, indinavir, nelfinavir, raltegravir, rilpivirine, simeprevir, maraviroc), anti-hyperlipidaemic medicines and anti-hypertension medicines (simvastatin, lovastatin, losartan, verapamil, diltiazem, nitrendipine, amlodipine, nislodipine, nifedipine, eplerenone, felodipine, lercanidipine), anti-diabetics (pioglitazone, repaglinide, saxagliptin)).

Effects of other medicines on CLOFAZIMINE TABLETS MACLEODS:

In a healthy volunteer study of a combination regimen including clofazimine, cycloserine, ethionamide, para-aminosalicyclic acid, and pyridoxine, the Cmax and Tmax values of clofazimine were similar to those reported in other studies where clofazimine was administered alone, suggesting no major effects of these medicines on the pharmacokinetics of clofazimine. In patients with pulmonary TB, where clofazimine was dosed alone and in combination with bedaquiline, pyrazinamide and pretomanid, the Cmax and AUC values of clofazimine were similar between the groups suggesting no major effects of these medicines on the pharmacokinetics of clofazimine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of clofazimine in pregnancy has not been established and experience with **CLOFAZIMINE TABLETS MACLEODS** in pregnancy is limited.

Clofazimine crosses the placenta. No teratogenic effects have been observed in the animal, but adverse effects have been reported in the foetus at high doses.

There are no clinical data available to evaluate the teratogenic or fetotoxic effect in humans. A brownish to reddish discoloration that has been reversible in a few months has been observed in neonates.

The use of **CLOFAZIMINE TABLETS MACLEODS** in pregnancy can be considered in patients with limited treatment options. Appropriate counselling of pregnant woman and her partner should be done.

Breast feeding

Safety of clofazimine in lactation has not been established.

Clofazimine passes into breast milk and skin discoloration may occur in children, therefore women using **CLOFAZIMINE TABLETS MACLEODS** should not breastfeed their infants.

Fertility

No specific recommendation regarding **CLOFAZIMINE TABLETS MACLEODS** treatment in women of childbearing age is justified on the basis of existing data.

4.7 Effects on ability to drive and use machines

CLOFAZIMINE TABLETS MACLEODS has a moderate influence on the ability to drive vehicles and use machines.

Because of the risk of dizziness, fatigue, headache and vision problems such as: decreased visual acuity, impaired peripheral vision and adjustment to day and night vision, and drowsiness and nausea associated with **CLOFAZIMINE TABLETS MACLEODS**, any patient receiving **CLOFAZIMINE**

TABLETS MACLEODS should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects

The side effects are listed below. Within each system organ class, the adverse drug reactions are ranked by frequency.

The following side effects have been reported**:**

Blood and lymphatic system disorders

Less frequent: Splenic infarction, agranulocytosis

Metabolism and nutrition disorders

Frequency unknown: Metabolic acidosis

Psychiatric disorders

Less frequent: Depression due to skin discoloration

Nervous system disorders

Less frequent: Headaches, dizziness, drowsiness

Eye disorders

Frequent: Conjunctival staining and pigmentation of the cornea, vision problems such as decreased visual acuity, visual field defect, adjustment to day and night vision, dryness and eye irritation.

Less frequent: Pigmentation of the macula, corneal deposits, decreased tear production

Cardiac disorders

Less frequent: cardiac dysrhythmia including Torsades de pointe, QT prolongation

Vascular disorders

Less frequent: Lymphoedema

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Tinted expectoration

Frequent: sputum discoloured

Hepatobiliary disorders

Less frequent: Hepatitis, increased blood bilirubin, jaundice, increased aspartate aminotransferase

Gastrointestinal disorders

Frequent: Nausea, vomiting, abdominal pain, diarrhoea, stool discolouration.

Less frequent: Decreased appetite, enteropathy by crystal deposits in the digestive mucosa, constipation, gastrointestinal bleeding, taste disorders

Frequency unknown: Bowel obstruction, abdominal discomfort

Skin and subcutaneous tissue disorders

Frequent: Abnormal staining of sweat, cutaneous dyschromism, change of hair colour, ichthyosis, dry skin, rash, itching.

Less frequent: Photosensitivity reactions, acneiform dermatitis.

Frequency unknown: Exfoliative dermatitis

Renal and urinary disorders

Frequent: Chromaturia

Reproductive system and breast disorders

Frequent: Colouring of breast milk

General disorders and administrative site conditions

Less frequent: Asthenia, pyrexia, fatigue

Investigations

Frequent: Weight loss

Less frequent: Elevation of blood sugar

Reporting of suspected adverse reactions

Reporting 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

Signs and symptoms

Cases of torsade de pointes with QT prolongation have been reported following overdosage with clofazimine (see Section 4.4).

There are no specific data concerning the treatment of clofazimine overdosage.

Management of overdose

In case of overdose symptomatic and supportive treatment will be prescribed if necessary.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J04BA01

Pharmacotherapeutic group: antimycobacterial medicine, medicine for the treatment of leprosy

Mechanism of action

Clofazimine is thought to exert its anti-mycobacterial effect through multiple mechanisms. The primary mechanism of action for the antimicrobial activity of clofazimine can be postulated through its

membrane-directed activity, including the bacterial respiratory chain and ion transporters. Intracellular redox cycling, involving oxidation of reduced clofazimine, leads to the generation of antimycobacterial reactive oxygen species (ROS), superoxide-hydrogen peroxide (H_2O_2).

Secondly, interaction of clofazimine with membrane phospholipids results in the generation of antimycobacterial lysophospholipids, which promote membrane dysfunction, resulting in interference with K+ uptake. Both mechanisms result in interference with cellular energy metabolism by disrupting ATP production.

The third proposed mechanism of action is binding preferentially to mycobacterial deoxyribonucleic acid (DNA) with particular affinity to guanine bases and inhibiting mycobacterial replication and growth.

Clofazimine also displays an anti-inflammatory effect, which may contribute to the effect of clofazimine in controlling erythema nodosum leprosum (ENL) reactions.

Anti-inflammatory activity of clofazimine is primarily through inhibition of T lymphocyte activation and proliferation. Clofazimine may indirectly interfere with the proliferation of T cells by promoting the release of ROS and E-series prostaglandins (PGs), especially PGE2 from neutrophils and monocytes.

Clofazimine may also exert anti-mycobacterial activity by its effect on tissue macrophages.

Clofazimine has a tendency to concentrate selectively in cells of the reticuloendothelial system.

Clofazimine has shown apoptosis inducing properties in activated macrophages. Clofazimine has been shown to inhibit MtSerB2, a phosphatase produced by *M. tuberculosis* that is believed to help the pathogen to evade the host's immune response.

Leprosy

Clofazimine exerts a mycobacteriostatic and weakly mycobactericidal effect on *Mycobacterium leprae*.

Clofazimine appears to bind preferentially to mycobacterial DNA and inhibit mycobacterial replication and growth.

The minimum inhibitory concentration of clofazimine for *M. leprae* in mouse tissue has been estimated at between 0.1 and 1 microgram per gram; uneven tissue distribution precludes a more accurate estimate. The onset of antimicrobial activity of clofazamine is slow, and can only be demonstrated after about 50 days of therapy.

No cross-resistance occurs with dapsone and rifampicin, probably because clofazimine has a different mode of action. *M. leprae* resistant to clofazimine have been reported in isolated cases.

Multidrug-Resistant Tuberculosis (MDR-TB)

The MIC of clofazimine against drug susceptible as well as single drug-resistant, multidrug-resistant and extensively drug resistant TB strains ranges from <0.0625 µg/mL to > 1 µg/mL. The majority [84.7 % (95 % CI: 69.5 %, 93.1 %)] of the tested strains have a reported MIC value of ≤ 0.5 µg/mL for clofazimine.

Clofazimine does not show cross-resistance with isoniazid or rifampin. In vitro resistance to clofazimine in *mycobacterium tuberculosis* has been mapped to mutations in the transcriptional regulator Rv0678 which results in the upregulation of MmpS5-MmpL5, an efflux pump. These mutants show cross-resistance to bedaquiline. Two additional mutations (Rv1979c and Rv2535c) have also been associated with clofazimine resistance in vitro; however, the mechanism and clinical relevance of these mutations is yet to be determined.

5.2 Pharmacokinetic properties

Absorption

Clofazimine is absorbed slowly. Bioavailability of the micronised suspension in an oil-wax base is up to 70 % after a 100 mg dose and decreases with higher doses.

The time to reach peak plasma concentration (median time) of clofazimine decreases from 12 to 8 hours under fed conditions relative to the fasted state. Administration of the medicine with food increases its bioavailability in terms of AUC (area under the concentration-time curve) by about 60 %, and tends to accelerate the absorption rate.

After administration of a single oral dose of 200 mg clofazimine with a morning meal, mean (±SD) peak plasma concentrations of 0.41 (±0.14) micrograms per mL (861 (±289) pmol/g) were measured in healthy volunteers. When clofazimine is taken on an empty stomach, the peak plasma concentration was approximately 20 % lower.

After repeated administration of clofazimine to leprosy patients in daily doses of 50 mg and 100 mg, mean trough concentrations of 0.27 and 0.43 micrograms / mL (580 pmol/g and 910 pmol/g), respectively, were measured after 42 consecutive days when concentrations were still increasing. The time to achieve steady state concentration has not been studied. From modelling studies, steady state concentrations were not reached after 20 weeks of treatment. The accumulation ratios after 50 and 100 mg daily doses of clofazimine on day 42 were 9.88 and 11.61, respectively.

Distribution:

Clofazimine is highly lipophilic and accumulates mainly in adipose tissue and macrophages of the reticuloendothelial system.

After prolonged treatment, clofazimine was detected in the following organs, tissues and body secretions: subcutaneous adipose tissue, mesenteric lymph node, bile and gallbladder, adrenal gland, spleen, small intestine, liver, muscle tissue, bone and skin but never at the cerebral level. Clofazimine does not seem to pass the blood-brain barrier.

Clofazimine crosses the placental barrier and is excreted in breast milk, to which it can give a reddish colour.

In serum, clofazimine binds to alpha-, and more particularly to beta-lipoproteins, this binding is saturable at a concentration close to 10 micrograms/ml (21141 pmol/g). Clofazimine binds negligibly to gamma globulin as well as albumin.

Biotransformation:

The metabolism of clofazimine in humans is not fully understood. Three metabolites, two of which were glucuronide conjugates, were detected in the urine of treated patients.

Elimination:

The elimination of clofazimine is slow. In healthy subjects after a single 200 mg administration, the mean plasma elimination half-life of clofazimine was 10,6 (± 4,0) days.

In patients, after repeated administration of 50 and 100 mg/day, the half-life was estimated at around 25 days.

Clofazimine is excreted unchanged in the bile and then in the faeces where in about 3 days approximately 35 % of the administered dose is found.

Urinary excretion of unchanged clofazimine does not exceed 0,4 % of the administered dose after 24 hours. Urinary excretion of metabolites is approximately 0,6 % of the daily dose.

Special populations:

No pharmacokinetic data for clofazimine are available in patients with renal impairment, hepatic impairment or age.

5.3 Preclinical safety data

No long-term carcinogenicity studies were conducted with clofazimine. No mutagenic activity was detected with the Ames test but a clastogenic effect was found in the mouse.

No teratogenic effects were observed on the offspring of rodents and rabbits at doses of 50 mg / kg / day and 15 mg / kg / day of clofazimine administered orally during the gestation period, respectively. Signs of toxicity (eg delayed cranial ossification) were demonstrated in mice at a dose of 50 mg / kg / day, much higher than the doses administered in humans.

Fertility disorders were observed in a study in female rats treated with clofazimine at a dose of 50 mg / kg / day (from the 9th week preceding mating to weaning); the number of pups per litter was lower and the percentage of pups lower. These effects were not observed at lower doses (5 and 25 mg / kg / day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains: betadex, colloidal silicon dioxide, crospovidone, hydrogenated castor oil, microcrystalline cellulose, polysorbate 80, polyoxyl 40, povidone, sodium stearyl fumarate. The coating agent contains hypromellose, red iron oxide, titanium dioxide, triacetin and yellow iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blister in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack:

Tablets are packed in aluminium foil laminated on one side and laminated to PVC/PVdC on the other side.

Pack size include 10, 28, 56, 84 or 112 tablets

Strip pack:

Tablets are packed in aluminium foil laminated with polyethylene film on both sides.

Pack sizes include 6, 10, 28, 56, 84 or 112 tablets.

Not all packs and pack sizes are marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

To be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10. DATE OF REVISION OF THE TEXT