WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB361 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg clofazimine.

Excipients with known effect:

Each tablet contains about 12.5 mg of castor oil polyoxyl hydrogenated and 48.5 mg of betadex (cyclodextrin).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB361 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

[TB361 trade name] is indicated as a second-line antimycobacterial drug when first-line drugs cannot be used because of resistance or intolerance (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official treatment guidelines for tuberculosis e.g. WHO guidelines and local health authorities' guidelines.

4.2 Posology and method of administration

Posology

Adults and adolescents

Adults and adolescents 15 years or older and weighing ≥30 kg
The usual dose is 2 tablets (100 mg) once daily.

For patients weighing <30 kg, use the dose recommendations for children and adolescents younger than 15 years.

Special populations

Patients with renal impairment
No dose adjustment is required in patient with renal impairment.

Patients with hepatic impairment
Clofazimine is partially metabolized by the liver. It should be used with caution in patients with hepatic impairment (Child-Pugh Class A, B, and C) (see section 4.4).

Paediatric population

Children and adolescents younger than 15 years
The usual dose in children is 2-5 mg/kg body weight, up to a maximum dose of 100 mg/day.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

[TB361 trade name] should be given on alternated days in case 1 tablet (50 mg) exceeds the dose calculated from the weight-based dose according to the table below.

Child's weight	Dose range	Number of tablets
5–15 kg	10–75 mg	1 tablet every other day
16–23 kg	32–115 mg	1 tablet once daily
24–30 kg	48–150 mg	2 tablets once daily
over 30 kg	100 mg	as for adults and adolescents 15 years or older: 2 tablets once daily

Method of administration

[TB361 trade name] is administered orally, and should be taken with water and swallowed whole. [TB361 trade name] should be taken with food to avoid stomach upset and improve absorption.

Missed dose and vomiting after a dose
It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [TB361 trade name] and reduce its effectiveness.

If the patient vomits within 1 hour of taking [TB361 trade name], the patient should take an extra dose. If vomiting occurs more than an hour after taking the dose, the patient does not need to take an extra dose and can take the next dose as usual when it is due.

4.3 Contraindications

Hypersensitivity to clofazimine or to any of the excipients contained in the formulation.

4.4 Special warnings and precautions for use

Abdominal Obstruction and Other Gastrointestinal Adverse Reactions
Clofazimine may accumulate in various organs as crystals, including the mesenteric lymph nodes and histiocytes at the lamina propria of the intestinal mucosa, spleen and liver. Deposition in the intestinal mucosa may lead to intestinal obstruction that may necessitate exploratory laparotomy. Splenic infarction, gastrointestinal bleeding, and death have been reported. If a patient complains of pain in the abdomen, nausea, vomiting, or diarrhea, initiate appropriate medical investigations and consider discontinuing the drug.

QT Prolongation
Cases of Torsade de Pointes with QT prolongation have been reported in patients receiving clofazimine in combination with QT prolonging medications, such as bedaquiline, delamanid, fluoroquinolones, efavirenz and several other antiretrovirals for the treatment of HIV, or azole anti-fungals. Monitor ECGs in patients taking [TB361 trade name] and such medications concomitantly, and consider discontinuation of [TB361 trade name] if clinically significant ventricular arrhythmia is noted or if the QTcF interval is 500 ms or greater. If syncope occurs, obtain an ECG to detect QT prolongation.
The use of the combination of moxifloxacin with bedaquiline and clofazimine (three drugs that strongly prolong the QT interval) in the tuberculosis treatment-regimen should be avoided.

Skin and Body Fluid Discolouration and Other Skin Reactions
Clofazimine causes orange-pink to brownish-black discolouration of the skin, as well as discoloration of the conjunctivae, tears, sweat, sputum, urine and faeces. Advise patients that skin discoloration is likely to occur and that it may take several months or years to reverse after the conclusion of therapy. Advise patients to avoid the sun and use strong sunscreens.

Other skin reactions associated with clofazimine-therapy include ichthyosis, dry skin and pruritus.

Psychological Effects of Skin Discolouration
Skin discoloration due to clofazimine therapy has been reported to result in depression and suicide. Advise patients regarding skin discolouration and monitor for depression or suicidal ideation during [TB361 trade name] therapy.

Liver function
Clofazimine is partially metabolized by the liver. [TB361 trade name] should be used with caution in patients with hepatic impairment (Child-Pugh Class A, B, and C). Serum liver enzymes (ALT, ALP, AST, GGT) should be periodically monitored throughout treatment.

Resistance
Clofazimine must be used in conjunction with adequate doses of other antituberculous drugs. The use of clofazimine alone allows the rapid development of strains resistant to it.

Excipients

[TB361 trade name] contains castor oil polyoxyl hydrogenated, which may cause stomach upset and diarrhea.

[TB361 trade name] also contains betadex (cyclodextrin). At high doses cyclodextrins can cause reversible diarrhoea and cecal enlargement in animals.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Effect on substrates of CYP3A
Concomitant use of [TB361 trade name] may increase concentrations of drugs that are substrates of CYP3A4/5 which may increase the risk of toxicity of these drugs. Monitor for toxicities of these drugs when used concomitantly with [TB361 trade name].

Drugs that Prolong QT Interval
Using clofazimine with drugs that prolong the QT interval may cause additive QT prolongation (e.g. bedaquiline, delamanid, fluoroquinolones, efavirenz and several other antiretrovirals for the treatment of HIV, or azole anti-fungals). Monitor ECGs for QT prolongation when [TB361 trade name] is administered with other drugs known to prolong the QT interval (see section 4.4).

No clinically significant differences in clofazimine pharmacokinetics have been observed when used concomitantly with bedaquiline, cycloserine, dapsone, ethionamide, para-aminosalicylic acid, pyrazinamide, and pyridoxine.
In patients receiving high doses of clofazimine (300 mg daily) and isoniazid (300 mg daily), elevated concentrations of clofazimine were detected in plasma and urine, although skin concentrations were found to be lower, however the clinical consequences are unknown.

No clinically significant differences in the pharmacokinetics of the following drugs were observed when used concomitantly with clofazimine: dapsone or rifampicin.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential
Pregnancy should be avoided in women treated with clofazimine. Adequate contraceptive measures should be taken during treatment and for at least 4 months after stopping treatment with [TB361 trade name].

Pregnancy
There are no adequate and well-controlled studies of [TB361 trade name] administration in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

The skin of infants born to pregnant mothers who had received clofazimine during pregnancy is pigmented at birth. Limited data is available regarding the reversibility of discoloration. Based on previous observations, discoloration gradually faded over the first year.

[TB361 trade name] should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Lactation
Clofazimine is excreted in human milk, giving it a pink colour. Clofazimine might increase skin pigmentation in nursing infants.

A risk to the newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from [TB361 trade name] therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effects [TB361 trade name] on human male or female fertility.

Animal studies indicate effects of clofazimine on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Vision problems, dizziness, and fatigue have been reported during treatment with clofazimine. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

The following undesirable effects have been recorded mainly with the use of clofazimine in the treatment of leprosy. Reliable information on frequency of occurrence in the treatment of tuberculosis is not available.

The following reactions are common:

Skin:	Pigmentation from pink to brownish-black in 75% to 100% of the patients within a few weeks of treatment; ichthyosis and dryness; rash and pruritus.
Gastrointestinal:	Abdominal and epigastric pain, diarrhea, nausea, vomiting, gastrointestinal intolerance.
Ocular:	Diminished vision, conjunctival and corneal pigmentation due to clofazimine crystal deposits; dryness; burning; itching; irritation.
Other:	Discoloration of urine, feces, sputum, sweat; elevated blood sugar; elevated erythrocyte sedimentation rate (ESR).

The following reactions are less frequent:

Skin:	Phototoxicity, erythroderma, acneiform eruptions, monilial cheilosis.
Gastrointestinal:	Bowel obstruction, gastrointestinal bleeding, anorexia, constipation, weight loss, hepatitis, jaundice, eosinophilic enteritis, enlarged liver.
Ocular:	Maculopathy (bull's eye retinopathy).
Nervous:	Dizziness, drowsiness, fatigue, headache, giddiness, neuralgia, taste disorder.
Psychiatric:	Depression and suicide secondary to skin discoloration.
Laboratory:	Elevated levels of albumin, serum bilirubin, and aspartate aminotransferase (AST); eosinophilia; hypokalemia.
Other:	Splenic infarction, thromboembolism, anemia, cystitis, bone pain, edema, fever, lymphadenopathy, vascular pain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

No specific data are available on the treatment of overdosage with clofazimine. In case of overdose, supportive symptomatic treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, ATC Code J04BA01

Clofazimine is an antimycobacterial drug.

Mechanism of action
Clofazimine may interfere with the proton-motive force and bacterial ATP production by membrane interaction with the respiratory chain or phospholipids. The delayed activity might therefore be due to the need to saturate the lipid-rich bacterial membrane, the time needed to disrupt the proton-motive force and/or the need to deplete energy stores before antimicrobial activity is observed.

Mechanisms of resistance
There is no cross-resistance with rifampicin or dapsone.

5.2 Pharmacokinetic properties

No pharmacokinetic data are available for [TB361 trade name].

The absorption characteristics of a proportionally similar medicine (Clofazimine 100 mg tablets from Macleods Pharmaceuticals Ltd., India) have been determined after administration of single tablets (100 mg clofazimine) in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**
Maximum concentration (C_{max})	137 ± 62 ng/ml
Area under the curve ($AUC_{0\text{-}72h}$), a measure of the extent of absorption	3216 ± 1036 ng·h/ml
Time to attain maximum concentration (t_{max})	5.80 ± 1.47 h

* Arithmetic mean

Pharmacokinetics of Clofazimine
The pharmacokinetics of [TB361 trade name] have not been studied in patients with tuberculosis. Data in the table below are based on data available from the use of clofazimine in patients with leprosy. Clofazimine pharmacokinetic parameters in patients with tuberculosis may differ from those in leprosy patients.

General	
	Average serum concentration of clofazimine in leprosy patients treated with 100 mg daily was 0.7 µg/mL.
Absorption	
Absorption	Clofazimine absorption ranges from 45% to 62% in leprosy patients
Oral bioavailability	NA*
Food effect	Median T_{max} of clofazimine decreases from 12 hours to 8 hours under fed conditions relative to the fasted state.
Distribution	
Volume of distribution (mean)	NA

Plasma proteinbinding *in vitro*	Clofazimine is bound to alpha- and primarily to beta-lipoproteins in serum, and the binding was saturable at plasma concentrations of approximately 10 µg /mL. Binding to gamma-globulin and albumin was negligible.
Tissue distribution	Clofazimine is lipophilic and deposits predominantly in fatty tissue and in cells of the reticuloendothelial system. It is taken up by macrophages throughout the body and clofazimine crystals have predominantly been found in the mesenteric lymph nodes, adrenals, subcutaneous fat, liver, bile, gall bladder, spleen, small intestine, muscles, bones, and skin. In patient studies, clofazimine has shown good penetration in tissue but not in cavities. Target tissue concentrations may be much higher than can be inferred from plasma measurements (with the exception of caseating tissue in a cavity).
Metabolism	
	Limited information. Three clofazimine metabolites were found in urine following repeated oral doses of clofazimine.
Elimination	
Elimination half life	25 days (range 6.5 to 160 days) following repeated oral doses of 50 or 100 mg clofazimine in leprosy patients.
Excretion	After a single dose of 300 mg clofazimine, elimination of unchanged clofazimine and its metabolites was negligible in a 24-hour urine collection. Part of the ingested drug recovered from the feces may represent excretion via the bile. A small amount is also eliminated in the sputum, sebum, and sweat.
Drug interactions *(in vitro*)	Clofazimine inhibits the metabolism of CYP2C8, CYP2D6, CYP3A4/5 drug substrates.

* Information not available

No information on the pharmacokinetics of clofazimine in paediatric patients is available.

5.3 Preclinical safety data

Genotoxicity
In mutagenicity studies clofazimine was found negative in an Ames test. There is some evidence of clastogenic potential in mice.

Carcinogenicity
Long-term carcinogenicity studies in animals have not been conducted with clofazimine.

Toxicity to reproduction
Impaired female fertility (reduced number of offspring and lower proportion of implantations) was observed in one study in rats receiving clofazimine (from 9 weeks before mating until weaning) at 50 mg/kg/day. No non-clinical data on male fertility are available.

In a rat study using 25 times the usual human dose of clofazimine, there was a reduction in the number of offspring and fewer implantations. Clofazimine was not teratogenic in rats and mice at 50 mg/kg/day or in rabbits at 15 mg/kg/day. Nursing mice developed an increase in bone marrow chromosome abnormalities attributed to clofazimine in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Castor oil polyoxyl hydrogenated
Povidone
Polysorbate 80
Betadex (cyclodextrin)
Microcrystalline cellulose
Colloidal silicon dioxide
Crospovidone
Sodium stearyl fumarate

Film coat:

Hypromellose
Triacetin
Titanium dioxide
Iron oxide red
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Strip pack and HDPE bottle: 48 months

Blister pack: 36 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light. Avoid excursions above 30ºC.

6.5 Nature and contents of container

HDPE container:

Round white HDPE container closed with white polypropylene child-resistant closure with pulp and white printed liner. Pack size: 100 tablets.

Blister pack:

Clear PVC/PVDC-aluminium blister. Each blister may contain 10 or 28 tablets. 10 blisters are packed in a carton. Pack sizes: 10 x 10 tablets, and 10 x 28 tablets.

Strip pack:

Plain aluminium foil laminated with polyethene film strip. Each strip contains 10 tablets. 10 such strips are packed in a carton. Pack size: 10 x 10 tablets.

6.6 Instructions for use and handling and disposal

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB361

9. DATE OF PREQUALIFICATION

16 September 2020

10. DATE OF REVISION OF THE TEXT

November 2020

Section 6 was updated in April 2022
Section 6 was updated in April 2023

References

General reference sources for this SmPC include:

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. Available at: https://www.who.int/publications/i/item/9789240007048 [accessed 9 November 2020]

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Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. WHO 2014. Available at: http://www.who.int/tb/publications/pmdt_companionhandbook/en/ [accessed 24 November 2019]

Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis. WHO 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/260440/WHO-CDS-TB-2018.6-eng.pdf?sequence=1&isAllowed=y [accessed 24 November 2019]

FDA label Lamprene: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019500s014lbl.pdf [accessed 24 November 2019]

Further references relevant to sections of the SmPC include:

Section 4.6 and 5.3

Das RK, Roy B: Evaluation of genotoxicity of clofazimine, an antileprosy drug, in mice in vivo. I. Chromosome analysis in bone marrow and spermatocytes. Mutat Res 241:161-8, 1990.

Novartis. 2002. Lamprene prescribing information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019500s013lbl.pdf

Stenger et al., cited by Shepard TH: Catalog of teratogenic agents, 7th ed., Baltimore, Johns Hopkins University Press, 1989, p 96.

Venkatesan K, Mathur A, Girdhar A, Girdhar BK: Excretion of clofazimine in human milk in leprosy patients. Lepr Rev 68:242-6, 1997.

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/