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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB364 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 100 mg clofazimine.

Excipients with known effect:

Each capsule contains about 20 mg of soybean oil, 48 mg glycerin, 0.0073 mg methylparaben and 0.0041 mg propylparaben.

3. PHARMACEUTICAL FORM

Soft capsules.

Brown opaque, oval soft capsule filled with brick red to brown suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB364 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

[TB364 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 1 capsule (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.

[TB364 trade name] should be given on alternated days in case 1 capsule (100 mg) exceeds the dose calculated from the weight based dose according to the table below.

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

Child's weight	Dose range	Number of capsules
5–9 kg	10–45 mg	1 capsule every Monday, Wednesday, and Friday
10–15 kg	20–75 mg	1 capsule every other day
16–23 kg	32–115 mg	1 capsule every other day
24–30 kg	48–150 mg	1 capsule once daily
over 30 kg	100 mg	as for adults and adolescents 15 years or older: 1 capsule once daily

Method of administration

[TB364 trade name] is administered orally, and should be taken with water and swallowed whole. [TB364 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 [TB364 trade name] and reduce its effectiveness.

If the patient vomits within 1 hour of taking [TB364 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 [TB364 trade name] and such medications concomitantly, and consider discontinuation of [TB364 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 [TB364 trade name]-therapy.

Liver function
Clofazimine is partially metabolized by the liver. [TB364 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

[TB364 trade name] contains soybean oil. People allergic to peanut or soya should not use this medicinal product.

[TB364 trade name] also contains glycerin, which may cause headache, stomach upset and diarrhea.

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 [TB364 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 [TB364 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 [TB364 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 [TB364 trade name].

Pregnancy
There are no adequate and well-controlled studies of [TB364 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.

[TB364 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 [TB364 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 [TB364 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

The absorption characteristics of [TB364 trade name] have been determined after administration of single capsules (100 mg clofazimine) in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**
Maximum concentration (C_{max})	162 ± 88 ng/ml
Area under the curve (AUC_{0-72h}), a measure of the extent of absorption	3227 ± 1263 ng·h/ml
Time to attain maximum concentration (t_{max})	6.15 ± 2.56 h

* Arithmetic mean

Pharmacokinetics of Clofazimine
The pharmacokinetics of [TB364 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

Capsule fill:
Soybean oil
Canola oil
Hydrogenated vegetable oil
White beeswax
Lecithin
Butylated hydroxytoluene

Capsule shell:
Gelatin
Glycerin
Ethyl vanillin

Black iron oxide
Red iron oxide
Methylparaben
Propylparaben

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

White HDPE bottle with 1g silica gel stick and closed with white low density polyethylene cap.

Pack sizes: 100 capsules.

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

Dong-A ST Co. Ltd.
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Dongdaemun-gu
Seoul 130 708
Republic of Korea

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB364

9. DATE OF PREQUALIFICATION

26 January 2021

10. DATE OF REVISION OF THE TEXT

February 2021
Section 6 was updated in August 2025.

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]

WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. Available at: https://www.who.int/publications/i/item/9789240006997 [accessed 9 November 2020]

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/pqweb/medicines