SUMMARY OF PRODUCT CHARACTERISTICS

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1. Name of the Medicinal Product

Clofazimine Tablet 50mg/ 100mg

2. Qualitative and Quantitative Composition

Clofazimine Tablet 50mg

Each film coated tablet contains:

Clofazimine ……50mg

Each tablet contains 12.5mg Polyoxyl 40 hydrogenated castor oil and 48.5mg betadex.

Clofazimine Tablet 100mg

Each film coated tablet contains:

Clofazimine ……100mg

Each tablet contains 25mg Polyoxyl 40 hydrogenated castor oil and 97mg betadex.

For Excipients see point 6.1

3. Pharmaceutical Form

For 50 mg- Tablet - The tablet should not be divided

For 100 mg - Tablet (scored) -The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4. Clinical Particulars

4.1 Therapeutic indications

Clofazimine is used as a second line agent in the treatment of MDR-TB in combination with other anti-tuberculotic agents.

4.2 Posology and method of administration

Clofazimine is to be used with other anti-tuberculotic agents.

Dosage

Adults: Recommend 100mg to 200mg once daily (oral).

Doses of 200mg daily for two months, then 100mg daily have been used.

Children: Limited data, WHO recommendation is based on experience and expert opinion and suggests 1mg/kg/day.

Clofazimine should be taken with meals or with milk to maximise absorption and reduce gastrointestinal adverse effects.

Do not use in children less than 2 years old unless recommended by your doctor.

Recommended to administer the product with high fat meal.

4.3 Contraindications

Known hypersensitivity to clofazimine or to any of the excipients of clofazimine.

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4.4 Special warnings and precautions for use

Severe abdominal symptoms have necessitated exploratory laparotomies in some patients receiving Clofazimine. Rare reports have included splenic infarction, bowel obstruction, and gastrointestinal bleeding. There have also been reports of death following severe abdominal symptoms. Autopsies have revealed crystalline deposits of clofazimine in various tissues including the intestinal mucosa, liver, spleen, and mesenteric lymph nodes.

Clofazimine should be used with caution in patients who have gastrointestinal problems such as abdominal pain and diarrhea. Dosages of Clofazimine of more than 100 mg daily should be given for as short a period as possible and only under close medical supervision. If a patient complains of colicky or burning pain in the abdomen, nausea, vomiting, or diarrhea, the dose should be reduced, and if necessary, the interval between doses should be increased, or the drug should be discontinued.

General: Physicians should be aware that skin discoloration due to Clofazimine may result in depression. Two suicides have been reported in patients receiving Clofazimine. For skin dryness and ichthyosis, oil can be applied to the skin.

Patients should be warned that Clofazimine may cause discoloration of the conjunctiva, lacrimal fluid, sweat, sputum, urine, faeces, nasal secretions, semen, breast milk and reddish to brownish-black discoloration of the skin. Patients should be told that discoloration of the skin, although reversible, may take several months or years to disappear after the end of therapy with Clofazimine.

Patients with pre-existing gastrointestinal disease and hepatic disease should be kept under medical supervision. If symptoms become severe, it may be necessary to reduce the dosage or to prolong the interval between doses. Liver function and creatinine clearance should be monitored.

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 reduce the daily dose of Clofazimine, or increase the dosing interval or discontinue the drug. Doses of Clofazimine Tablet of more than 100 mg daily should be given for as short a period as possible (less than 3 months) and only under close medical supervision.

QT prolongation: Cases of Torsades de Pointes with QT prolongation have been reported in patients receiving dosage regimens containing higher than 100 mg daily dose of Clofazimine Tablet or in combination with QT prolonging medications. For QT prolongation QT prolongation

Cases of Torsades de Pointes with QT prolongation have been reported in patients receiving dosage regimens containing higher than 100 mg daily dose of Clofazimine Tablet or in combination with QT prolonging medications. For QT prolongation and Torsades de Pointes cases, the patient must remain under medical surveillance. In all these patients, monitor electrocardiograms (ECGs) for QT prolongation and cardiac rhythm disturbances.

QT prolongation has also been reported in patients who were receiving Clofazimine Tablet with bedaquiline at the recommended dosage regimen for each drug. Monitor ECGs if Clofazimine Tablet is coadministered to patients receiving bedaquiline, and discontinue Clofazimine Tablet 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.

Skin and Body Fluid Discoloration and Other Skin Reactions: Clofazimine Tablet causes orange-pink to brownish-black discoloration of the skin, as well as discoloration of the conjunctivae, tears, sweat, sputum, urine and feces in 75-100% of patients. 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.

Other skin reactions associated with Clofazimine Tablet therapy include ichthyosis, dry skin and pruritus.

Psychological Effects of Skin Discoloration: Skin discoloration due to Clofazimine Tablet therapy has been reported to result in depression and suicide. Advise patients regarding skin discoloration and monitor for depression or suicidal ideation during Clofazimine therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Dapsone

Clofazimine seems 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. Preliminary data suggesting that dapsone inhibits the anti-inflammatory activity of Clofazimine have not been confirmed. If leprosy-associated inflammatory reactions develop in patients being treated with dapsone and Clofazimine, it is still advisable to continue treatment with both drugs.

Rifampicin

Clofazimine reduces rifampicin absorption in leprosy patients, increasing the time it takes for peak serum concentration to be reached and prolonging the elimination half-life. Bioavailability was not affected, so this interaction is unlikely to be clinically significant.

Isoniazid

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

4.6 Pregnancy and Lactation

Pregnancy

It has been found that Clofazimine crosses the human placenta. The skin of infants born to women who had received the drug during pregnancy was found to be deeply pigmented at birth. No evidence of teratogenicity was found in these infants. There are no adequate and well-controlled studies in pregnant women. Clofazimine should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Nursing Mothers

Clofazimine is excreted in the milk of nursing mothers. Clofazimine should not be administered to a nursing woman unless clearly indicated. Skin discoloration has been observed in breast fed neonates of mothers receiving clofazimine. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Clofazimine and any potential adverse effects on the breastfed infant from Clofazimine or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

Dizziness, decreased visual acuity, fatigue and headache have been reported under Clofazimine therapy. Patients experiencing such adverse reactions should not drive a vehicle or operate machines.

4.8 Undesirable effects

In general, clofazimine is well tolerated when administered in dosages no greater than 100 mg daily. The most consistent adverse reactions are usually dose related and are usually reversible when clofazimine is discontinued.

Adverse Reactions Occurring In More Than 1% of Patients

Skin:

Pigmentation from pink to brownish-black in 75%-100% of the patients within a few weeks of treatment; ichthyosis and dryness (8%-28%); rash and pruritus (1%-5%).

Gastrointestinal:

Abdominal and epigastric pain, diarrhea, nausea, vomiting, gastrointestinal intolerance (40%-50%).

Ocular:

Conjunctival and corneal pigmentation due to clofazimine crystal deposits; dryness; burning; itching; irritation.

Other:

Discoloration of urine, feces, sputum, sweat; elevated blood sugar; elevated ESR.

Adverse Reactions Occurring In Less Than 1% of Patients

Skin:

Phototoxicity, erythroderma, acneiform eruptions, monilial cheilosis.

Gastrointestinal:

Bowel obstruction, gastrointestinal bleeding, anorexia, constipation, weight loss, hepatitis, jaundice, eosinophilic enteritis, enlarged liver.

Ocular:

Diminished vision.

Nervous:

Dizziness, drowsiness, fatigue, headache, giddiness, neuralgia, taste disorder.

Psychiatric:

Depression secondary to skin discoloration; two suicides have been reported.

Laboratory:

Elevated levels of albumin, serum bilirubin, and AST (SGOT);eosinophilia; hypokalemia.

Other:

Splenic infarction, thromboembolism, anemia, cystitis, bone pain, edema, fever, lymphadenopathy, vascular pain, may cause stomach upset and diarrhoea.

4.9 Overdose

No specific data are available on the treatment of overdosage with clofazimine. However, in case of overdose, the stomach should be emptied by inducing vomiting or by gastric lavage, and supportive symptomatic treatment should be employed.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Mechanism of Action

Clofazimine exerts a slow bactericidal effect on *Mycobacterium leprae* (Hansen's bacillus). Clofazimine inhibits mycobacterial growth and binds preferentially to mycobacterial DNA. Clofazimine also exerts anti-inflammatory properties in controlling erythema nodosum leprosum reactions. However, its precise mechanisms of action are unknown.

5.2 Pharmacokinetic properties

Absorption

Clofazimine is absorbed relatively slowly. After administration of a single oral dose of 200 mg clofazimine with breakfast, mean (±SD) peak plasma concentrations of 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 morning trough concentrations of 580pmol/g and 910 pmol/g, respectively, were measured after 42 consecutive days. Steady-state concentrations were not reached within this time period.

Clofazimine has a variable absorption rate in leprosy patients, ranging from 45% to 62% after oral administration. The average serum concentrations of clofazimine in leprosy patients treated with Clofazimine Tablet 100 mg and 300 mg daily were 0.7 mcg/mL and 1

mcg/mL, respectively. Time to reach peak plasma concentration (median Tmax) of clofazimine decreases from 12 hours to 8 hours under fed conditions relative to the fasted state.

Distribution

Clofazimine is strongly lipophilic and accumulates mainly in fatty tissue and in macrophages of the reticuloendothelial system. After longterm treatment, clofazimine has been detected in the following organs and tissues and body fluids: subcutaneous fat, mesenteric lymph nodes, bile and gall bladder, adrenals, spleen, small intestine, liver, muscle tissue, bones, and skin, but never in the brain. Clofazimine does not appear to cross the intact blood-brain barrier. Clofazimine crosses the placenta and passes into the breast milk in sufficient quantities to colour the milk.

Clofazimine is highly lipophilic and tends to be deposited predominantly in fatty tissue and in cells of the reticuloendothelial system. It is taken up by macrophages throughout the body. In autopsies performed on leprosy patients who had received clofazimine, clofazimine crystals were found predominantly in the mesenteric lymph nodes, adrenals, subcutaneous fat, liver, bile, gall bladder, spleen, small intestine, muscles, bones, and skin.

Clofazimine is bound to alpha-and beta-lipoproteins in serum, particularly the beta-lipoproteins, and the binding was saturable at plasma concentrations of approximately 10 mcg/mL. Binding to gamma-globulin and albumin was negligible.

Metabolism

Information on the metabolism of clofazimine is limited. Three metabolites, two glucuronides, have been identified in urine.

Elimination

Clofazimine is eliminated slowly from the plasma. The mean elimination half-life of the unchanged substance following a single dose of 200 mg was 10.6 (±4.0) days. After repeated administration of 50 mg and 100 mg daily to leprosy patients, the elimination half-life was about 25 days. Unchanged clofazimine is excreted via the bile mainly in the faeces. Within 3 days on average, 35% of the dose is recovered. No more than 0.4% of the dose is found in the urine as unchanged clofazimine after 24 hours. The urinary metabolites account for about 0.6% of the daily dose

After ingestion of a single 300 mg dose of Clofazimine, elimination of unchanged clofazimine and its metabolites in a 24-hour urine collection was negligible. 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. The elimination half-life of clofazimine following repeated oral doses of 50 or 100 mg Clofazimine Tablet in leprosy patients was highly variable with estimates ranging from 6.5 to 160 days. The overall mean half-life of clofazimine in these leprosy patients was approximately 25 days.

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5.3 Preclinical safety data

Long-term carcinogenicity studies in animals have not been conducted with Clofazimine (clofazimine). Results of mutagenicity studies (Ames test) were negative. There was some evidence of impaired fertility in one study in rats treated at a dose 25 times the usual human dose; the number of offspring was reduced and there was a lower proportion of implantations.

Long-term carcinogenicity studies in animals have not been conducted with clofazimine. Results of mutagenicity studies (Ames test) were negative. There is some evidence of clastogenic potential in mice.

Impaired female fertility (reduced number of offspring and lower proportion of implantations) was observed in one study in rats receiving Clofazimine Tablet (from 9 weeks before mating until weaning) at 50 mg/kg/day, equivalent to about 2.4 times the maximum recommended clinical dose. No non-clinical data on male fertility are available.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sr. No	Ingredients	Reference to Quality Standards	Qty mg/tablet		Qty / Batch (kg)	
			50 mg	100 mg	50 mg	100 mg
					Batch Size: 600,000 Tablets	Batch Size: 300,000 Tablets
1.0	Polyoxyl 40 hydrogenated castor oil (Kolliphor RH 40)	USP-NF	12.5	25.0	7.50	7.50
2.0	Povidone (Plasdone K-25)	USP-NF / Ph.Eur	1.5	3.0	0.90	0.90
3.0	Polysorbate 80 [Tween 80 (HP-LQ-(MH)]	USP-NF / Ph.Eur	2.5	5.0	1.50	1.50
4.0	Purified Water***	USP	125.0	250.0	75.0	75.0
5.0	Betadex	BP	48.5	97.0	29.10	29.10
6.0	Microcrystalline Cellulose (Comprecel M101 D+)#	USP-NF / Ph.Eur	116.0	232.0	69.60	69.60
7.0	Colloidal silicon dioxide (Aerosil 200)	USP-NF / Ph.Eur	16.0	32.0	9.60	9.60
8.0	Crospovidone Type A (Polyplasdone XL)	USP-NF / Ph.Eur	20.0	40.0	12.00	12.00
9.0	Crospovidone Type A (Polyplasdone XL)	USP-NF / Ph.Eur	20.0	40.0	12.00	12.00

SUMMARY OF PRODUCT CHARACTERISTIC

Sr. No	Ingredients	Reference to Quality Standards	Qty mg/tablet		Qty / Batch (kg)	
			50 mg	100 mg	50 mg	100 mg
					Batch Size: 600,000 Tablets	Batch Size: 300,000 Tablets
10.0	Microcrystalline Cellulose (Comprecel M102 D+)	USP-NF / Ph.Eur	5.0	10.0	3.00	3.00
11.0	Sodium stearyl fumarate	USP-NF / Ph.Eur	6.0	12.0	2.40	2.40
12.0	Instacoat Universal Brown (A05G11412)	IHS	11.7	23.4	7.020	7.00
13.0	Isopropyl alcohol***	USP-NF / Ph.Eur	110.0	220.0	66.00	66.00
14.0	Methylene Chloride***	USP-NF / Ph.Eur	73.5	147.0	44.10	44.10

#: The quantity of Microcrystalline Cellulose (Comprecel M 101 D+) is to be adjusted to keep the core tablet weight as 298/598 mg for Clofazimine 50 mg and 100 mg respectively.
##: Coating composition includes 30% overages to compensate losses during processing.
***: Not considered in final weight of tablet.

6.2 Incompatibilities

None

6.3 Shelf life

24 months from the manufacturing date.

Never use after the expiry date clearly indicated on the outer packaging.

6.4 Special precautions for storage

Store below 30°C (86°F). Protect from moisture.

Keep out of the reach and sight of children.

6.5 Nature and contents of container

Clofazimine Tablets 50 mg

Blister Pack - Plain 25µ Aluminium foil/ 6- 8 gsm HSL (width-137 mm) with Clear PVC/PVDC film 250/60 gsm (Width – 141 mm)

Blister Pack of 28 tablets, such 10 blisters in a box.

Strip Pack - Plain 40u micron Aluminium foil (soft tempered) laminated with 150 gauge polyethylene film (Width- 255mm)

Strip Pack of 10 tablets, such 10 Strips in a box.

Container Pack:

100's Tablet packed in a round, white 60CC HDPE Container with CR closure along with pack insert.

"Use within 30days of opening"

SUMMARY OF PRODUCT CHARACTERISTIC

Clofazimine Tablets 100 mg

Blister Pack - Plain 25µ Aluminium foil/ 6- 8 gsm HSL (width-222 mm) with Clear PVC/PVDC film 250/60 gsm (Width – 226 mm)

Blister Pack of 28 tablets, such 10 blisters in a box.

Strip Pack -

Plain 40u micron Aluminium foil (soft tempered) laminated with 150 gauge polyethylene film (Width- 210 mm) Strip Pack of 6 tablets, such 8 Strips in a box.

Container Pack:

100's Tablet packed in a round, white 120CC HDPE Container with CR closure along with pack insert.

"Use within 30days of opening"

6.6 Special Precaution for disposal

No special requirements.

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 (Prequalification Programme)

TB361-Clofazimine Tablets 50mg

TB362-Clofazimine Tablets 100mg

9. Date of Prequalification/ Renewal of Prequalification

10. Date of Revision of the Text:

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