SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Claricide® (Clarithromycin) 500mg Film Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

500 mg Clarithromycin, Sorbic acid as preservative agent, Titanium Dioxide (E171) and Quinoline yellow (E104) as coloring agents.

3. PHARMACEUTICAL FORM

Film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Claricide® is used to treat the below listed infections caused by the susceptible microorganisms.

- Upper respiratory tract infections: pharyngitis, tonsillitis, sinusitis, acute otitis media.
- Lower respiratory tract infections: acute and chronic bronchitis, pneumoniae.
- Soft tissue and dermal infections: pyodermi impetigo, ecthyma, erysipelas, lymphangitis, cellulitis, infected dermal lesions.
- Claricide® in the presence of acid suppression is also indicated for the eradication of Helicobacter pylori in patients with duodenal ulcers.

4.2 Posology and method of administration

The usual adult dosage of clarithromycin tablets is 250 mg every 12 hours. In severe infections dosage can be increased to 500 mg twice daily. Unless the physician dictates otherwise, the usual duration of clarithromycin therapy is 7-14 days. Acute sinusitis should be treated for 14 days and pharyngitis and tonsillitis for at least 10 days.

Eradication of H. pylori in patients with duodenal ulcers. The usual dose of clarithromycin is 500 mg three times daily for 14 days with an oral antiulcer drug. Mycobacterium avium complex disease in adults, the recommended dose of Claricide® is 500 mg. b.i.d.Children older than 12 years: Same as adults.

Mycobacterium avium complex disease in adults, the recommended dose of Claricide® is 500 mg bid.

Children younger than 12 years: The recommended dose of Claricide® is 15 mg/kg every 12 hours for 5-10 days. There is no clinical safety evidence for use children younger than 6 months.

Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearence <30 ml/min). If adjustment is necessary, the total daily dosage should be reduced by half e.g. 250 mg once daily or 250 mg twice daily in more severe infections

4.3 Contraindications

Claricide® is contraindicated in patients with a known hypersensitivity to clarithromycin or any of the macrolide antibiotics.

When clarithromycin is co-administered with terfenadine, resulting in arrhythmia, bradycardia, QT prolongation and cardiac abnormalities such as ischemic heart disease and congestive heart failure. Concomitant administration of Clarithromycin with terfenadine is contraindicated.

4.4 Special warnings and precautions for use

Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

The possibility of cross resistance with other macrolide antibiotics should be considered.

The possibility of superinfection should be kept in mind during therapy. If superinfections occur, the drug should be discontinued and appropriate therapy instituted.

Pediatric Use: Safety and effectiveness of clarithromycin in children under 6 months of age have not been established.

Geriatric Use: Dosage adjustment should be considered in elderly patients with severe renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of ritonavir with clarithromycin results in increased plasma concentration and adverse effect of clarithromycin. When clarithromycin is used in patients receiving ritonavir, usual clarithromycin dosage modification generally is not necessary in

those with normal renal function; however, the clarithromycin dosage should be reduced by 50% in patients with creatinine clearances of 30-60 mL/minute and reduced by 75% in patients with creatinine clearances less than 30 mL/minute. Claritromycin doses more than 1g/day must not be used with Ritonavir.

Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations.

Spontaneous reports in the post-marketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported.

When clarithromycin and terfenadine were coadministered, plasma concentrations of the active acid metabolite of terfenadine were threefold higher on average, than the values observed when terfenadine administered alone. The pharmacokinetics of clarithromycin and the 14-hydroxy-clarithromycin were not significantly affected after reaching steady state concentration by coadministration of terfenadine. Concomitant administration of clarithromycin with terfenadine is contraindicated.

When Clarithromycin was given concomitantly with omeprazole, the steady-state plasma concentrations of omeprazole and the mean 24-hour gastric pH value was increased.

Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine.

Simultaneous oral administration of Claricide® tablets and zidovudine to HIV infected adult patients resulted in decreased steady-state zidovudine concentrations.

The use of erythromycin and clarithromycin in patients concurrently taking drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of the other drugs. There have been reports of interactions of erythromycin and/or clarithromycin with carbamazepine, cyclosporine, tacrolimus, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin, bromocriptine, valproate, terfenadine, cisapride, pimozide, and

astemizole. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving these drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy Category: B There are no adequate and well-controlled studies in pregnant women. Clarithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing woman: Caution should be exercised when clarithromycin is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive and use machines. The potential for dizziness, vertigo, confusion, and disorientation with the drug should be considered before patients drive or operate machinery.

4.8 Undesirable effects

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides.

- In AIDS patients treated with clarithromycin over long periods of time for prophylaxis against M. avium, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying HIV disease or intercurrent illness.
- There have been reports of tongue discoloration in patients treated with clarithromycin and omeprazole.
- Claricide® is generally well tolerated Gastrointestinal adverse effects with oral clarithromycin therapy is lower than that of conventional macrolides. Nausea, vomiting, dyspepsia, diarrhea, abdominal discomfort, abnormal taste, headache, skin rash were reported.
- Allergic reactions ranging from mild urticaria and mild skin eruptions to rare cases of anaphylaxis and Stevens-Jonhson syndrome have occured. Glossitis, stomatitis, oral moniliasis, vomiting, dizziness, reversible hearing loss, behavioral changes, confusional states, depersonalization, disorientation, hallucinations, insomnia,

nightmares, tinnitus and vertigo have been reported during post-marketing surveillance. Events usually resolve with discontinuation of the drug.

- Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In very rare instances, hepatic failure has been reported and generally has been associated with serious underlying diseases and/or concominant medications.
- Rarely, erythromycin and clarithromycin have been associated with veritricular arrhythmias including ventricular tachycardia and torsades de pointes in individuals with prolonged QT intervals.

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. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. Allergic reactions accompanying over dosage should be treated by gastric lavage and supportive measures.As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clarithromycin is a semi-synthetic macrolide antibiotic.

Mechanism of Action: Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis. Clarithromycin is active in vitro against a variety of aerobic and anaerobic gram positive and gram-negative microorganisms. Clarithromycin also has bactericidal activity against Helicobacter pylori in the presence of acid suppression. Additionally, its metabolite 14-OH clarithromycin has clinically significant antimicrobial activity, as well.

Microbiology: In vitro studies have demonstrated the susceptibility of the following microorganisms to clarithromycin. Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Listeria monocytogenes, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Legionella pneumophilia, Bordetella pertussis, Helicobacter pylori, Mycoplasma pneumoniae, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium leprae, Chlamydia pneumoniae, Chlamydia trachomatis, Ureaplasma urealyticum, Bacterioides fragilis, Clostridium perfiringens, Propionibacterium acnes, Peptococcus and peptostreptococcus species.

5.2 Pharmacokinetic properties

Clarithromycin is a semi-synthetic macrolide antibiotic. Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. Claricide® tablets may be given with food. The absolute bioavailability is approximately 50%. Clarithromycin undergoes extensive first-pass metabolism and transform to the antimicrobially active metabolite, 14-OH clarithromycin in the liver. Peak serum concentrations are attained within 2 hours after oral dosing. Clarithromycin is 80% bound to plasma proteins at therapeutic levels. Clarithromycin distributes tissues and hummers well. Clarithromycin also penetrates to the gastric mucosa. Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels.

If the tissue concentrations and circulating drug levels given as 500 mg/day, it shows below:

Tissue Type	**Tissue (μg/g)**	**Serum (μg/mL)**
Tonsil	1.6	0.8
Lung	8.8	1.7

Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

Metabolization: Clarithromycin undergoes extensive first-pass metabolism and transform to the antimicrobially active metabolite, 14-OH clarithromycin in the liver. After a 500mg tablet administered orally every 12 hours, the elimination half-life of clarithromycin and 14-OH clarithromycin is about 5 to 7 hours.

Excretion: Clarithromycin is mainly excreted in the urine and the remainder of the dose is eliminated in the faeces. After a 500 mg tablet administered orally every 12 hours, approximately 36% of the dose is excreted in the urine as clarithromycin and 10-15% of the dose is excreted in the urine as 14-OH clarithromycin.

5.3 Preclinical safety data

In repeat-dose studies, clarithromycin toxicity was related to the dose and duration of treatment. The primary target organ in all species is the liver, and hepatic lesions were observed after 14 days in dogs and monkeys. The systemic exposure levels associated with this toxicity are unknown, but toxic mg/kg doses were higher than those recommended for patient treatment.

No evidence of the mutagenic potential of clarithromycin was observed in in vitro and in vivo tests.

Fertility, Reproduction and Teratogenicity

Studies in rats at oral doses up to 500 mg/kg/day (the highest dose associated with overt renal toxicity) showed no evidence of clarithromycin-related adverse effects on male fertility. This dose corresponds to a human equivalent dose of approximately 5 times the maximum recommended human dose on a mg/m2 basis for a 60 kg individual.

Fertility and reproductive studies in female rats showed that a daily dose of 150 mg/kg/day (the highest dose tested) caused no adverse effects on the oestrus cycle, fertility, number and viability of offspring, and birth. Rats (Wistar and Sprague-Dawley), rabbits (New Zealand White), and cynomolgous monkeys did not show any teratogenicity from clarithromycin at the highest doses tested up to 1.5, 2.4, and 1.5 times the maximum recommended human dose on a mg/m2 basis.

However, a similar study in Sprague-Dawley rats showed a low (6%) incidence of cardiovascular abnormalities, which appears to be due to spontaneous expression of genetic changes. Two studies in mice showed a variable incidence (3% to 30%) of cleft palate and embryonic loss in monkeys at use close to 5 times the maximum recommended human dose for a 60 kg individual; but these doses

at doses that are clearly toxic to

Another toxicological finding that is thought to be at the doses recommended for patient treatment not reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose Sodium

Pregelatinised Starch (Starch 1500)
Microcrystalline Cellulose(101(120 mg) and 102(52 mg))
Quinoline Yellow lake 30 E104
Colloidal Anhydrous Silica (Aerosil 200)
Povidone K-30
Stearic Acid
Magnesium Stearate
Purified Talc (Talc)
Hydroxy propyl cellulose
Vanilin (Vanilya)
Sorbic acid
titanium dioxide
Propylene Glycol
Hydroxypropyl Methyl cellulose
Ethanol
Purified Water
sorbitan oleate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C at room temperature.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

14 Film coated tablets in Al/PVC/PVDC blister packaging in a carton box with a leaflet

6.6 Special precautions for disposal <and other handling>

Any unused medicinal product or waste material should be disposed of in accordance with "Regulation on Control of Medical Waste" and "Regulation on Control of Packaging and Packaging Wastes".

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Certificate No: 05290/07380/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Aug 27, 2020

10. DATE OF REVISION OF THE TEXT

September 2023