**Summary of Product Characteristics**

## 1 Name of Medicinal Product

**CLARMICIN** (Clarithromycin Tablets 500 mg)

## 2 Qualitative and Quantitative Composition

Each film coated tablet contains:

Clarithromycin USP …….500 mg

Quinoline Yellow

## 3 Pharmaceutical Particulars

Oral tablet

Yellow color, caplet shaped, biconvex film coated tablet with having break line on one side and plain on other side.

## 4 Clinical Particulars

### 4.1 Therapeutic Indications

Clarithromycin is indicated for the treatment of acute and chronic bacterial infections, when caused by clarithromycin-susceptible bacteria.

- Infections of the upper respiratory tract such as pharyngitis and sinusitis.
- Infections of the lower respiratory tract, such as acute exacerbation of chronic bronchitis, and community-acquired pneumonia.
- Skin and soft tissue infections of mild to moderate severity.

In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer-healing agent for the eradication of H. pylori in patients with H. pylori associated ulcers

### 4.2 Route of Administration, Posology and Method of Administration:

**Route of Administration**: Oral Route Administration

**Method of administration and posology**

**<u>Patients with respiratory tract/skin and soft tissue infections</u>**

**Adults**: The usual dose is 250 mg twice daily for 7 days although this may be increased to 500 mg twice daily for up to 14 days in severe infections.

Children older than 12 years: As for adults.

Children younger than 12 years: Use an appropriate clarithromycin paediatric preparation.

Eradication of H. pylori in patients with duodenal ulcers (Adults)

**Triple Therapy (7 - 14 days)**

Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with amoxycillin 1000 mg twice daily for 7 - 14 days.

**Triple Therapy (7 days)**

Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with metronidazole 400 mg twice daily for 7 days.

**Triple Therapy (7 days)**

Clarithromycin 500 mg twice daily and omeprazole 40 mg daily should be given with amoxycillin 1000 mg twice daily or metronidazole 400 mg twice daily for 7 days.

**Triple Therapy (10 days)**

Clarithromycin 500 mg twice daily should be given with amoxycillin 1000 mg twice daily and omeprazole 20 mg daily for 10 days.

**Dual Therapy (14 days)**

The usual dose of clarithromycin is 500 mg three times daily for 14 days.

Clarithromycin should be administered with oral omeprazole 40 mg once daily for 14 days.

**Elderly: As for adults.**

**Renal impairment:** Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance < 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.

Clarithromycin Tablets may be given without regard to meals as food does not affect the extent of bioavailability.

**4.3 Contraindications**

Clarithromycin is contra-indicated in patients with known hypersensitivity to clarithromycin, other macrolide antibiotics or to any of the excipients in the tablet.

Clarithromycin and ergot derivatives must not be co-administered.

Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these drugs and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Clarithromycin is contra-indicated in patients with hypokaliemia. This may result in QT prolongation.

**4.4 Special Warning and Precautions for use:**

Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic or renal function. Prolong or

repeated use of clarithromycin may result in an overgrowth of non- susceptible bacteria or fungi. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted. H. pylori organisms may develop resistance to clarithromycin.

**4.5 Interaction with other medicinal products and other forms of interaction**

Contraindicated combinations

Concomitant administration of clarithromycin and terfenadine, cisapride, pimozide and ergot alkaloids is contraindicated.

The effect of other medicinal products on clarithromycin tablets

Clarithromycin is metabolised by the enzyme CYP3A4. Hence, strong inhibitors of this enzyme may inhibit the metabolism of clarithromycin, resulting in increased plasma concentrations of clarithromycin.

The effect of clarithromycin on other medicinal products

Clarithromycin is an inhibitor of the metabolising enzyme CYP3A4 and the transport protein Pglycoprotein. The degree of inhibition with different CYP3A4 substrates is difficult to predict. Hence, clarithromycin should not be used during treatment with other medicinal products that are substrates for CYP3A4, unless plasma levels, therapeutic effect or adverse events of the CYP3A4 substrate can be closely monitored. A dose reduction may be necessary for medicinal products that are substrates for CYP3A4 if co-administered with clarithromycin. Alternatively, treatment with these products may be interrupted during clarithromycin treatment.

Medicinal products with a potential to prolong QT-interval

Clarithromycin has been reported to inhibit the metabolism of cisapride and terfenadine, with a 2 to 3- fold increase in plasma levels reported for terfenadine. This has been associated with QT-prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar symptoms have been described for patients treated with pimozide when combined with clarithromycin. Concomitant administration of clarithromycin and terfenadine, cisapride of pimozide is contraindicated.

HMG-CoA reductase inhibitors

Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products. Rhabdomyolysis in association with increased plasma concentrations have in rare cases been reported in patients treated with clarithromycin and simvastatin or lovastatin. Clarithromycin may produce a similar interaction with atorvastatin and a lesser interaction with either cerivastatin. When

treatment with clarithromycin is indicated in patients receiving treatment with either simvastatin or lovastatin or atorvastatin or cerivastatin patients should be monitored for signs and symptoms of myopathy.

Digoxin

The concentration of digoxin may be increased when co-administered with clarithromycin. Monitoring of plasma levels of digoxin should be considered when co-treatment with clarithromycin is initiated or terminated since a dose adjustment may be warranted.

Theophylline

The administration of clarithromycin to patients who are receiving theophylline has been associated with an increase in serum theophylline levels and potential theophylline toxicity.

Warfarin

The use of clarithromycin in patients receiving warfarin may result in potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine levels. This can be largely avoided by staggering the doses of clarithromycin and zidovudine by 1-2 hours. No such reaction has been reported in children.

**4.6 Pregnancy and Lactation**

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin Tablets should thus not be used during pregnancy or lactation unless the benefit is considered to outweigh the risk. Some animal studies have suggested an embryotoxic effect, but only at dose levels which are clearly toxic to mothers. Clarithromycin has been found in the milk of lactating animals and in human breast milk.

**4.7 Effects on ability to drive and use machines**

Although clarithromycin is not expected to affect driving ability directly, side effects such as dizziness and vertigo may interfere with driving.

**4.8 Undesirable Effects**

Infections and infestations:

Oral monilla, genital candidiasis

Blood and lymphatic system disorders:

Isolated cases of leukopenia and thrombocytopenia have been reported.

Immune system disorders:

Allergic reactions ranging from urticaria, mild skin eruptions and angioedema to anaphylaxis and rarely Stevens-Johnson syndrome / toxic epidermal necrolysis.

Metabolic disorders:

There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.

Sense organs disorders (Eye disorders, Ear and labyrinth disorders, taste):

Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received. There have been reports of hearing loss with clarithromycin which is usually reversible on withdrawal of therapy. Tinnitus. There have been very rare reports of uveitis mainly in patients treated with concomitant rifabutin, most of these were reversible.

Psychiatric and nervous system disorders:

There have been reports of transient central nervous system side-effects including headache, dizziness, vertigo, anxiety, insomnia, bad dreams, confusion, disorientation, hallucinations, psychosis and depersonalisation. Convulsions have been reported rarely.

Cardiac disorders:

As with other macrolides, QT prolongation, ventricular tachycardia and Torsade de Pointes have been rarely reported with clarithromycin.

Gastrointestinal disorders:

Nausea, dyspepsia, diarrhoea, vomiting, abdominal pain, paraesthesia, glossitis and tongue discolouration. There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning. Stomatitis has been reported.

Pseudomembranous colitis has been reported rarely with clarithromycin, and may range in severity from mild to life threatening. Pancreatitis has been reported rarely.

Hepatobiliary disorders:

As with other macrolides, hepatic dysfunction (which is usually reversible) including altered liver function tests, hepatitis and cholestasis with or without jaundice, has been reported. Dysfunction may be severe and very rarely fatal hepatic failure has been reported.

Musculoskeletal and connective tissue disorders:

Arthralgia, myalgia.

Rhabodomyolysis can occur in rare cases during concomitant administration of clarithromycin and HMG-CoA reductase inhibitor, lovastatin and simvastatin.

Specific side effects have been observed in HIV patients treated for mycobacterial infections.

Renal and urinary disorders:

Cases of interstitial nephritis and renal failure have been reported rarely.

Increased investigations:

Increased serum creatinine, altered liver function tests.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients.

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**

Symptoms of intoxication:

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Symptoms of overdose may largely correspond to the profile of adverse reactions. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokaliaemia and hypoxaemia.

Therapy of intoxication:

There is no specific antidote on overdose. Serum levels of clarithromycin can not be reduced by haemodialysis or peritoneal dialysis.

Adverse reactions accompanying overdosage should be treated by gastric lavage and supportive measures. Severe acute allergic reactions may be seen very rarely, e.g. anaphylactic shock. At the first signs of hypersensitivity reactions therapy with clarithromycin must be discontinued and the required measures should be initiated immediately.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamics properties**

Pharmacotherapeutic group: macrolides

ATC-Code: J01FA09

Mechanism of action:

Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein

synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound, except for H. influenzae where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Mechanisms of resistance

Resistance of gram-positive organisms to the macrolides usually involves an alteration of the antimicrobial binding site. The MLSB type of resistance, which may be constitutive or induced by exposure to certain macrolides in staphylococci and which is inducible in streptococci, is mediated by a variety of acquired genes (erm family) encoding methylases targeted at the peptidyl transferase centre of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides and type B streptogramins but not to type A streptogramins. Less frequent mechanisms of resistance include antimicrobial degradation by inactivating enzymes such as esterase and active efflux of the antimicrobial from the bacteria.

Gram negative organisms may be intrinsically resistant to the macrolides because of the inability of the macrolide to effectively penetrate the outer cell membrane; macrolides having a better penetration may have activity against some gram-negative organisms.

Gram-negative organisms may also produce ribosomal methylase

Breakpoints

Breakpoint Concentrations

According to BSAC (January 2005) the following breakpoints have been defined for clarithromycin:

| Organism | MIC Breakpoint Concentration (mg/L) | |
|---|---|---|
| | Susceptible ≤ | Resistant > |
| Staphylococci | 0.5 | 0.5 |
| ß-Haemolytic Streptococci* | 0.5 | 0.5 |
| *S.pneumoniae* | 0.5 | 0.5 |
| *M. catarrhalis** | 0.5 | 0.5 |
| *H. influenzae** | 0.5 | 16** |

***** Active metabolite not taken into consideration

****** Breakpoints for H. influenzae; strains with MICs below the low breakpoint are susceptible, those with MICs above the high breakpoint are resistant, others are intermediate

The following tentative MIC breakpoints have been defined for clarithromycin:

H. Pylori < 1 mg/L susceptible, > 2 mg/L resistant.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

**The susceptibility pattern of various micro-organisms to clarithromycin is presented below:**

| |
|---|
| ***Commonly susceptible species*** |
| ***Aerobic Gram-negative microorganisms***<br>Moraxella catarrhalis |
| ***Anaerobic microorganisms***<br>Peptococcus *species*<br>Peptostreptococcus *species*<br>Propionibacterium acnes<br>Clostridium perfringens |
| ***Other microorganisms***<br>Chlamydia pneumoniae<br>Legionella pneumophila<br>Mycoplasma pneumoniae |
| ***Species for which acquired resistance may be a problem*** |
| ***Aerobic Gram-positive microorganisms***<br>Staphylococcus aureus<br>Staphylococcus aureus *(methicillin-resistant)**<br>Streptococcus agalactiae<br>Streptococcus pneumoniae<br>Streptococcus pyogenes |
| ***Aerobic Gram-negative microorganisms***<br>Haemophilus influenzae |

*** Resistance to macrolides among MRSA is commonly more than 50% in the EU and affects nearly all strains in some areas.**

**5.2 Pharmacokinetic properties**

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Clarithromycin Tablets. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. Clarithromycin Tablets may be

given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin Tablets. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxymetabolite. The pharmacokinetics of clarithromycin are non linear; however, steady-state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclarithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.

When clarithromycin 500 mg are given three times daily, the clarithromycin plasma concentrations are increased with respect to the 500 mg twice daily dosage.

Clarithromycin 250 mg Film Coated Tablets provide tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

Clarithromycin Tablets also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with omeprazole than when clarithromycin is administered alone.

**5.3 Preclinical Safety Data**

In 4-week studies in animals, the toxicity of clarithromycin was found to be related to the dose and duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The systemic levels of exposure related to this toxicity are not known in detail, but toxic doses were clearly higher than the therapeutic doses recommended for humans.

No mutagenic effects were found in in vitro or in vivo studies with clarithromycin.

Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (iv) and x10 the clinical dose in monkey (po) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryotoxicity or teratogenicity was noted in rat studies. However, cardiovascular malformations were observed in rats treated with doses of 150 mg/kg/day. In mouse at doses x70 the clinical dose cleft palate occurred at varying incidence (3-30%).

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of Excipients**

- Microcrystalline cellulose
- Maize Starch
- Croscarmellose sodium
- Polyvinyl Pyrrolidone (PVP K-30)
- Tween- 80 (Polysorbate 80)

- Aerosil
- Talcum Powder (Purified talc)
- Hydroxyl propyl methyl cellulose 15 CPS
- Magnesium Stearate
- Cross povidone
- Isopropyl alcohol
- Titanium dioxide
- Polyethylene glycol 6000 (PEG-6000)
- Ethyl cellulose
- Quinoline yellow lake

**1.8.1.6.2. Incompatibilities**

None Known

**6.3. Shelf Life**

36 Months from the date of manufacture.

**6.4. Special precautions for Storage**

Keep out of the sight and reach of children.

Do not store above 30°C.

Keep in a dry place in the original package.

**6.5 Nature and content of Container**

1 x10 tablets in ALU-PVC Blister pack.

**6.6 Special precaution for disposal and other handling**

No Special Requirements

**7. MARKETING AUTHORISATION HOLDER**

**BDA HEALTHCARE PVT. LTD.,**

Plot No.: B-1, 2, 3, Near Gov. ITI MIDC, Parseoni – 441105,

Taluka: Parseoni, District: Nagpur, M.S., India.

**8. MARKETING AUTHORISATION NUMBER(S)**

07182/08817/NMR/2021

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

07.03.2022

**10. DATE OF REVISION OF THE TEXT**

02 July 2023