**1.6 Product Information**

**1.6.1 Prescribing Information (Summary of Product Characteristics)**

**1. Name of the Medicinal Product**

**1.1 Trade Name** : CLARIZIM 500 (Clarithromycin Tablets USP 500 mg)

**1.2 Strength** : 500 mg

**1.3 Pharmaceutical Form** : Film Coated Tablets

**2. Qualitative and Quantitative Composition**

| S. No | Name of Ingredients | Quantity/ Tablets (mg) |
|---|---|---|
| **Active Substance** | | |
| 1 | Clarithromycin | 500.00 |
| **Inactive Substance** | | |
| 2 | Microcrystalline Cellulose | 257.00 |
| 3 | Maize Starch | 65.00 |
| 4 | Colloidal Anhydrous Silica | 14.00 |
| 5 | Polyethylene Glycol | 2.00 |
| 6 | Povidone | 10.00 |
| 7 | Pregelatinised Starch | 67.00 |
| 8 | Sodium Stearyl Fumarate | 10.00 |
| 9 | Purified Talc | 30.00 |
| 10 | Croscarmellose Sodium | 45.00 |
| 11 | Colorezy White | 25.00 |
| 12 | Purified Water | Q.S. |
| | **Total** | **1025.00 mg** |

**3. Pharmaceutical Form**

*"Film Coated Tablet"*

White, caplet shaped, film coated tablets, having breakline on one side and plain on other side.

**4. Clinical Particulars**

**4.1 Therapeutic indications**

Clarithromycin tablets are indicated for the treatment of the following bacterial infections, when caused by clarithromycin-susceptible bacteria.

• Bacterial pharyngitis
• Mild to moderate community acquired pneumonia
• Acute bacterial sinusitis (adequately diagnosed)
• Acute exacerbation of chronic bronchitis
• Skin infections 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 Helicobacter pylori in patients with Helicobacter pylori associated ulcers.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

**4.2 Posology and method of administration**

**Posology**

The dosage of Clarithromycin film-coated tablets depends on the type and severity of the infection and has to be defined in any case by the physician.

*Clarithromycin 500 mg film-coated tablet is not suitable for doses below 500 mg. There are other options for this strength available on the market.*

*Adults and adolescents (12 years and older)*

• Standard dosage: The usual dose is 250 mg twice daily (in the morning and in the evening)
• High dosage treatment (severe infections): The usual dose may be increased to 500 mg twice daily in severe infections.

*Children younger than 12 years:*

Use of Clarithromycin film-coated tablets is not recommended for children younger than 12 years with a body weight less than 30 kg. Clinical trials have been conducted using clarithromycin pediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension.

For children with a body weight of more than 30kg, the dose for adults apply.

*Dosage in renal functional impairment:*

In patients with renal impairment with creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced by one-half, i.e. 250 mg once daily, or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients.

*Patients with hepatic impairment:*

Caution should be exercised when administrating clarithromycin in patients with hepatic impairment.

*H. pylori eradication in peptic ulcer disease*

For the eradication of *H. pylori* the selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.

Usually clarithromycin is administered in combination with another antibiotic and a proton-pump inhibitor for one week.

The therapy may be repeated if the patient is still H. pylori-positive

*Duration of therapy:*

The duration of therapy with Clarithromycin film-coated tablets depends on the type and severity of the infection and has to be defined in any case by the physician.

• The usual duration of treatment is 7 to 14 days.

• Therapy should be continued at least for 2 days after symptoms have subsided.

• In Streptococcus pyogenes (group A beta-haemolytic streptococcus) infections the duration of therapy should be at least 10 days.

• Combination therapy for the eradication of H. pylori infection should be continued for 7 days.

**Method of administration**

The tablet should be swallowed whole with a sufficient amount of fluid (e.g. one glass of water). Clarithromycin film-coated tablets may be given irrespective of food intake.

**4.3 Contraindication**

Clarithromycin is contraindicated in patients with known hypersensitivity to the active substance clarithromycin, to other macrolides or to any of the excipients used in the formulation.

Concomitant administration of clarithromycin and any of the following active substances is contraindicated: Astemizole, cisapride, pimozide and terfenadine as this may result in QT prolongation (congenital or documented acquired QT prolongation) and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes.

Concomitant administration with ticagrelor or renolazine is contraindicated.

Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity.

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointe.

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolised by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time).

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine.

**4.4 Special warnings and special precautions for use**

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy.

Caution is advised in patients with severe renal insufficiency.

Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

Cases of fatal hepatic failure have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C. difficile. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

The colchicine shows the toxicity with concomitant use of clarithromycin, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients. Concomitant administration of clarithromycin and colchicines is contraindicated.

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam.

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.

Prolongation of the QT Interval

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides including clarithromycin. Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes), clarithromycin should be used with caution in the following patients;

• Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia

• Patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia.
• Patients concomitantly taking other medicinal products associated with QT prolongation.
• Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfendine is contraindicated.
• Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia.

*Pneumonia:* In view of the emerging resistance of Streptococcus pneumoniae to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

*Skin and soft tissue infections of mild to moderate severity:* These infections are most often caused by Staphylococcus aureus and Streptococcus pyogenes, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where beta–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by Corynebacterium minutissimum, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens - Johnson syndrome, and toxic epidermal necrolysis, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme.

*HMG-CoARreductase Inhibitors (statins*): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.

*Oral hypoglycemic agents/Insulin:* The concomitant use of clarithromycin and oral hypoglycemic agents (such as sulfonylurias) and/or insulin can result in significant hypoglycemia. Careful monitoring of glucose is recommended.

*Oral anticoagulants:* There is a risk of serious hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Use of any antimicrobial therapy, such as clarithromycin, to treat H. pylori infection may select for drug-resistant organisms.

Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If super-infection occur, appropriate therapy should be instituted.
Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

**4.5 Interaction with other medicinal products and other forms of interaction**
*Cisapride, pimozide, terfenadine and astemizole:*
Clarithromycin has been reported to elevate plasma levels of cisapride, pimozide, astemizole, and terfenadine. Increased levels of these drugs may result in increased risk of ventricular rhythm disorders, especially Torsades de Pointes.
Concomitant administration of clarithromycin and any of these medicinal products is contraindicated.
*Ergotamine/ dihydroergotamine:*
Post-marketing reports indicate that coadministration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system.
Concomitant administration of clarithromycin and these medicinal products is contraindicated.
*CYP3A-based interactions:*
The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.
**The effect of other medicinal products on clarithromycin:**
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.
Concomitant administration of clarithromycin and antimycotics of the azole class (fluconazol, itraconazol, ketoconazol) increases the risk of cardial toxicity (prolonged QT-interval, Torsades des Pointes, cardiac arrest).
*Fluconazole:* Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration ($C_{min}$) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14(R)-hydroxy-clarithromycin were not significantly affected by concomitant administration of fluconazole.
*Ritonavir:* Ritonavir (200 mg three times daily) have been shown to inhibit the metabolism of clarithromycin (500 mg twice daily.), with an increase in $C_{max}$, $C_{min}$ and AUC of 31, 182 and 77%, respectively, when co-administered with ritonavir. Formation of the active 14-OH-

hydroxy metabolite was almost completely inhibited. A general dose reduction is probably not required in patients with normal renal function, but the daily dose of clarithromycin should not exceed 1g. Dose reduction should be considered in patients with renal impairment. For patients with a creatinine clearance of 30 to 60 ml/min (0.5 - 1 ml/s), the clarithromycin dose should be reduced with 50%, and at a creatinine clearance of < 30 ml/min (<0.5 ml/s) the dose should be reduced with 75%.

Medicinal Products that are inducers of CYP3A4 (e.g. efavirenz, nevirapine, rifampicin, phenytoin, carbamazepine, phenobarbital, St. Johns wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to a reduced efficacy.

Concomitant administration of rifabutin and clarithromycin resulted in an increase and decrease, respectively, in serum levels, followed by an increased risk of uveitis.

A 39% reduction in AUC for clarithromycin and a 34% increase in AUC for the active 14-OH-hydroxy metabolite have been seen when clarithromycin was used concomitantly with the CYP3A4 inducer efavirenz.

*The effect of clarithromycin on other medicinal products:*

Clarithromycin is an inhibitor of the metabolizing enzyme CYP3A4 and the transport protein P-glycoprotein. 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.

*Sildenafil, tadalafil, and vardenafil:* Each of these phosphodiesterase inhibitors is metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Coadministration of clarithromycin with sildenafil, tadalafil or vardenafil may result in increased phosphodiesterase inhibitor exposure.

Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when coadministered with clarithromycin.

*Co-administration with medicinal products with a potential to prolong QT-interval:* Cases of *torsades de pointes* has been reported in patients where clarithromycin has been co-administered with quinidine or disopyramide. These combinations should therefore be avoided, or plasma levels of quinidine or disopyramide closely monitored to allow dose adjustment.

*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 cerivastatin. When treatment with clarithromycin is indicated in patients receiving statin treatment, therapy with statins should be suspended during the course of treatment.

*Tolterodine:* The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A.

In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

*Benzodiazepines:* When midazolam was co-administered with clarithromycin tablets (250mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A4, especially triazolam but also alprazolam. For benzodiazepines which are not metabolised by CYP3A4 (temazepam, nitrazepam, lorazepam) an interaction with clarithromycin is unlikely.

*Omeprazole:* The AUC of omeprazole is increased by 89% when administered concomitantly with clarithromycin for H. pylori eradication; however the change in the mean 24-hour gastric pH value from 5.2 (omeprazole alone) to 5.7 (omeprazole + clarithromycin) is not considered clinically significant.

There are no in-vivo human data available describing an interaction between clarithromycin and the following drugs: aprepitant, eletriptan, halofantrine, and ziprasidone. However, because in vitro data suggest these drugs are CYP3A substrates, caution should be used when they are co-administered with clarithromycin.

Eletriptan should not be co-administered with CYP3A inhibitors such as clarithromycin.

There have been spontaneous or published reports of drug interactions of CYP3A inhibitors, including clarithromycin, with cyclosporine, tacrolimus, methylprednisolone, vinblastine, and cilostazol.

*Cyclosporin, tacrolimus and sirolimus:* Concomitant use of oral clarithromycin has resulted in more than a 2-fold increase of the $C_{min}$ levels of both cyclosporin and tacrolimus. Similar effects are also expected for sirolimus. When initiating treatment with clarithromycin in patients already receiving any of these immunosuppressive agents, cyclosporin, tacrolimus or sirolimus plasma levels must be closely monitored and their doses decreased as necessary. When clarithromycin is discontinued in these patients, close monitoring of plasma levels of cyclosporine, tacrolimus or sirolimus, is again necessary to guide dose adjustment.

*Digoxin and other active substances transported by P-glycoprotein:* The concentration of the Pgp substrate 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.

*Anti-diabetic products:* After concomitant administration of Clarithromycin with insulin and other anti-diabetic medicinal products Hypoglycaemia has been observed.

The mechanism for this phenomenon is not fully understood, though it may be related to pharmacokinetic interaction between clarithromycin and some oral antidiabetics. In healthy subjects, the use of clarithromycin 250 mg twice daily for two days increased glibenclamide plasma levels (0.875 mg single dose) with 1.3 fold, possibly by inhibiting P-glycoprotein in

the intestinal wall. In a study in healthy volunteers, clarithromycin use (250 mg twice daily for 5 days) increases the plasma levels of repaglinide (0.25 mg single dose) with 40%, possibly by inhibiting CYP3A4 enzymes by clarithromycin.

*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.

*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.

*Zidovudine:* Simultaneous oral administration of clarithromycin 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.

*Colchicine:* Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine.

*Phenytoin and valproate:* There have been spontaneous or published reports of interactions with CYP3A inhibitors, including clarithromycin, and drugs not thought to be metabolised by CYP3A, including phenytoin and valproate.

Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased concentrations have been reported.

***Bidirectional pharmacokinetic interactions***

*Atazanavir:* Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14(R)-hydroxyclarithromycin, with a 28% increase in the AUC of atazanavir.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function.

For patients with moderate renal function (creatinine clearance 30 to 60 ml/min), the dose of clarithromycin should be decreased by 50%.

For patients with creatinine clearance <30 ml/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation, such as immediate-release tablets, sachet, or paediatric suspensions (not all presentations may be marketed).

Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

*Itraconazole:* Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction: Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin.

Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

*Saquinavir:* Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bidirectional drug interaction.
Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatine capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state area under the curve (AUC) and maximum concentration (Cmax) values of saquinavir, which were 177% and 187% higher than those seen with saquinavir alone.
Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone.
No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied.
Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule.
Observations from drug interaction studies done with unboosted saquinavir may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin.

**4.6 Pregnancy and lactation**
*Pregnancy:* The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.
*Breast-feeding:* The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

**4.7 Effects on ability to drive and use machines**
The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

**4.8 Undesirable effects**
The majority of side effects observed were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections and fewer than 2% of pediatric patients without mycobacterial infections discontinued therapy because of drug-related side effects. Fewer than 2% of adult patients taking Clarithromycin tablets discontinued therapy because of drug-related side effects.
The most frequently reported events in adults taking Clarithromycin tablets were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). In pediatric patients, the most frequently reported events were diarrhea (6%), vomiting (6%), abdominal pain (3%), rash (3%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

In the acute exacerbation of chronic bronchitis and acute maxillary sinusitis studies overall gastrointestinal adverse events were reported by a similar proportion of patients taking Clarithromycin Tablet.

In community-acquired pneumonia studies conducted in adults comparing clarithromycin to erythromycin base or erythromycin stearate, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to erythromycin-treated patients (13% vs 32%; $p < 0.01$). Twenty percent of erythromycin-treated patients discontinued therapy due to adverse events compared to 4% of clarithromycin-treated patients.

In two U.S. studies of acute otitis media comparing clarithromycin to amoxicillin/potassium clavulanate in pediatric patients, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to amoxicillin/potassium clavulanate-treated patients (21% vs. 40%, $p < 0.001$). One-third as many clarithromycin-treated patients reported diarrhea as did amoxicillin/potassium clavulanate-treated patients.

**Post-Marketing Experience**

Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, anorexia, vomiting, pancreatitis, tongue discoloration, thrombocytopenia, leukopenia, neutropenia, and dizziness. There have been reports of tooth discoloration in patients treated with Clarithromycin. Tooth discoloration is usually reversible with professional dental cleaning. There have been isolated reports of hearing loss, which is usually reversible, occurring chiefly in elderly women. Reports of alterations of the sense of smell including smell loss, usually in conjunction with taste perversion or taste loss, have also been reported.

Transient CNS events including anxiety, behavioral changes, confusional states, convulsions, depersonalization, disorientation, hallucinations, insomnia, depression, manic behavior, nightmares, psychosis, tinnitus, tremor, and vertigo have been reported during post-marketing surveillance. Events usually resolve with discontinuation of the drug.

Adverse reactions related to hepatic dysfunction have been reported in postmarketing experience with clarithromycin.

There have been rare reports of hypoglycemia, some of which have occurred in patients taking oral hypoglycemic agents or insulin.

As with other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

There have been reports of interstitial nephritis coincident with clarithromycin use.

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.

**Changes in Laboratory Values**

Changes in laboratory values with possible clinical significance were as follows:

**Hepatic**
Elevated SGPT (ALT) < 1%; SGOT (AST) < 1%; GGT < 1%; alkaline phosphatase < 1%; LDH < 1%; total bilirubin < 1%
**Hematologic**
Decreased WBC < 1%; elevated prothrombin time 1%
**Renal**
Elevated BUN 4%; elevated serum creatinine < 1% GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

**4.9 Overdose**
*Symptoms of intoxication:* Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxemia.
*Therapy of intoxication:* Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.
In the case of Overdosage, clarithromycin IV (powder for solution for injection) should be discontinued and all other appropriate supportive measures should be instituted.

**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 twofold 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.
*PK/PD relationship:* Clarithromycin is extensively distributed into body tissues and fluids. Due to the high tissue penetration, intracellular concentrations higher than serum concentrations.
*Mechanisms of resistance:* Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic or are based on modification and/or the active efflux of the antibiotic. Resistance development can be mediated via chromosomes or plasmids, be induced or exist constitutively. Macrolide resistant bacteria generate enzymes which lead to methylation of residual adenine at ribosomal RNA and consequently to inhibition of the

antibiotic binding to the ribosome. Macrolide-resistant organisms are generally cross-resistant to lincosamides and streptogramine B based on methylation of the ribosomal binding site.

**5.2 Pharmacokinetic Properties**

*Absorption:* Clarithromycin is rapidly and well absorbed from the gastrointestinal tract – primarily in the jejunum – but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250-mg clarithromycin tablet is approximately 50%. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to food. Due to its chemical structure (6-O-Methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of 1 – 2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 µg/ml. After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of 0.6 µg/ml. Steady state is attained within 2 days of dosing.

*Distribution:* Clarithromycin penetrates well into different compartments with an estimated volume of distribution of 200-400 l. Clarithromycin provides concentrations in some tissues that are several times higher than the circulating drug levels. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus.

Clarithromycin is approximately 70% bound to plasma proteins at therapeutic levels.

*Biotransformation and elimination:* Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism is in the liver involving the P450 cytochrome system. Three metabolites are described: N-demethyl clarithromycin, decladinosyl clarithromycin and 14-hydroxy clarithromycin. The pharmacokinetics of clarithromycin is non-linear due to saturation of hepatic metabolism at high doses. Elimination half-life increased from 2-4 hours following administration of 250 mg clarithromycin twice daily to 5 hours following administration of 500 mg clarithromycin twice daily. The half-life of the active 14-hydroxy metabolite ranges between 5 to 6 hours following administration of 250 mg clarithromycin twice daily.

Approximately 20 -40% of clarithromycin is excreted as the unchanged active substance in the urine. This proportion is increased when the dose is increased. An additional 10% to 15% is excreted in the urine as 14-hydroxy metabolite. The rest is excreted in the faeces. Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased. Total plasma clearance has been estimated to approximately 700 mL/min (11,7 mL/s), with a renal clearance of approximately 170 mL/min (2,8 mL/s).

**Special populations:**

*Renal impairment:* Reduced renal insufficiency function results in increased plasma levels of clarithromycin and the active metabolite levels in plasma.

**5.3 Preclinical safety data**

The clarithromycin toxicity was found to be related to the dose and to the 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. Other tissues affected included the stomach, thymus and other lymphoid tissues as well as the kidneys.
No mutagenic effects were found in *in vitro*- and *in vivo* -studies with clarithromycin

## 6. Pharmaceutical Particulars

### 6.1 List of excipients

Microcrystalline cellulose (E460)
Maize starch (E1442)
Colloidal anhydrous silica (E551)
Polyethylene glycol (1521)
Povidone (E1201)
Pregelatinised starch (E1400)
Sodium Stearyl fumarate (E485)
Purified talc (E553b)
Croscarmellose sodium (E468)
Colorezy white

### 6.2 Incompatibilities

None

### 6.3 Shelf life

3 years from the date of manufacture

### 6.4 Special precautions for storage

Store at temperature not exceeding 30°C, protect from light and moisture.

### 6.5 Nature and contents of container

10 × 1 x 4 Film coated tablets in Alu-PVC Blister Pack.

### 6.6 Special precautions for disposal and other handling

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

## 7. Marketing Authorization Holder

ZIM Laboratories Limited
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441501
Maharashtra State,
India.

## 8. Number(S) In the National Register of Finished pharmaceutical products

NA

## 9. Date of First Authorization/Renewal of the Authorization

NA

**10. Date of Revision of the Text**
01 April 2019