December 2023

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

CLARIMYCIN - 500 (Clarithromycin 500 mg Film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet Contains 500 mg clarithromycin

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated Tablet

Yellow colored, elliptical biconvex film coated tablets with smooth surface.

4. CLINICAL PARTICULAR

4.1 Therapeutic Indications:

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

Clarithromycin is indicated in adults and children 12 years and older.

Clarithromycin is indicated for the treatment of the following infections caused by clarithromycin susceptible organisms.

- Bacterial pharyngitis
- Mild to moderate community-acquired pneumonia
- Acute bacterial sinusitis (adequately diagnosed)
- Acute exacerbation of chronic bronchitis
- Skin and soft tissue infections of mild to moderate severity.
- In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing medicinal product for the eradication of Helicobacter pylori in adult patients with Helicobacter pylori-associated ulcers.

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.

Adults:

• Standard dosage: The usual dose is 250mg 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 older than 12 years: As for adults.

Children younger than 12 years: Use of Clarithromycin 250mg Tablets are not recommended for children younger than 12 years. Use clarithromycin Paediatric Suspension.

Eradication of Helicobacter pylori in adults:

In patients with gastro-duodenal ulcers due to Helicobacter pylori infection clarithromycin is given in a dosage of 500 mg twice daily. The national recommendations for Helicobacter pylori eradication have to be considered.

Duration of therapy:

The duration of therapy with clarithromycin depends on the type and severity of the infection. The usual duration of treatment is 7 to 14 days.

Dosage in renal functional impairment:

Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance < 30 ml/min (<0.5 ml/s)). If adjustment of dose is necessary, the total daily dosage should be reduced by half. The duration of treatment should not exceed 14 days in these patients.

Patients with hepatic impairment:

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

Method of administration:

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

4.3 Contraindications

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

- Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity.
- Concomitant administration of clarithromycin and oral midazolam is contraindicated.
- Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, pimozide and terfenadine as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes.
- Clarithromycin should not be given to patients with a history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsade de pointes.
- Concomitant administration with ticagrelor or ranolazine is contraindicated.
- Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4, (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.
- As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine.
- Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).
- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Concomitant administration of clarithromycin and lomitapide is contraindicated.

4.4 Special warnings and precautions for use

Clarithromycin therapy for H. pylori may select for drug-resistant organisms.

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 this 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 diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea 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 diarrhoea 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.

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. Concomitant administration of clarithromycin and colchicine is contraindicated.

Caution is advised regarding concomitant administration of clarithromycin and triazolo benzodiazepines, such as triazolam, and intravenous or oromucosal midazolam.

Cardiovascular Events:

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades 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 torsades 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.
- 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 terfenadine is contraindicated. Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

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, severe cutaneous adverse reactions (SCAR) (e.g., Acute generalised exanthematous pustulosis (AGEP), Stevens-

Johnson Syndrome, toxic epidermal necrolysis, and DRESS, 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-CoA Reductase 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 the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g., fluvastatin) can be considered.

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

Oral anticoagulants: There is a risk of serious haemorrhage 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. Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding.

Hydroxychloroquine or chloroquine: Carefully consider the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality. Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections 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.

Contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. Contains sodium.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Cisapride, pimozide, astemizole and terfenadine:

Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly.

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias, such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes.

In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in 2- to 3-fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergot alkaloids:

Post-marketing reports indicate that co-administration 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.

Oral Midazolam:

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin is contraindicated.

HMG-CoA Reductase Inhibitors (statins):

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g., Fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

Lomitapide: Concomitant administration of clarithromycin with lomitapide is contraindicated due to the potential for markedly increased transaminases.

Hydroxychloroquine or chloroquine:

Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Because of the potential for a similar risk with other macrolides when used in combination with hydroxychloroquine or chloroquine, careful consideration should be given to the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine.

Effects of Other Medicinal Products on Clarithromycin:

Drugs that are inducers of CYP3A (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin

resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis. The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine:

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Etravirine:

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to clarithromycin should be considered for the treatment of MAC.

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 (Cmin) 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. No clarithromycin dose adjustment is necessary.

Ritonavir:

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased

182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be co-administered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, Bi-directional drug interactions).

The effect of clarithromycin on other medicinal products:

CYP3A-based interactions:

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively metabolized by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban, atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine but this list is not exhaustive. Drugs interacting by similar mechanisms

through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics:

There have been post-marketed reports of torsades de pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during co-administration of clarithromycin with these drugs. Serum levels of quinidine and disopyramide should be monitored during clarithromycin therapy.

There have been post marketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore, blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycemic agents/Insulin:

With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

Omeprazole:

Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (Cmax, AUC0-24, and t1/2 increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

Sildenafil, tadalafil and vardenafil:

Each of these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

Theophylline, carbamazepine:

Results of clinical studies indicate that there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin. Dose reduction may need to be considered.

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.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam):

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam.

For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Direct acting oral anticoagulants (DOACs):

The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolized via CYP3A4 and are also substrates for P-gp. Caution should be exercised when

clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding.

4.6 Fertility, Pregnancy and Lactation

Pregnancy:

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofoetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks.

Breast-feeding:

The safety of clarithromycin for using during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin.

4.7 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive or 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

a. Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without pre-existing mycobacterial infections.

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended-release tablets and modified-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10, common (≥1/100 to < 1/10), uncommon (≥1/1,000 to<1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

Infections and infestations: Uncommon -Cellulitis, candidiasis, gastroenteritis, infection, vaginal infection; Not Known – Pseudomembranous colitis, erysipelas; **Blood and lymphatic system:** Uncommon-Leukopenia, neutropenia, thrombocythaemia, eosinophilia; Not Known-Agranulocytosis, thrombocytopenia; **Immune system disorders:** Anaphylactoid reaction, hypersensitivity; Not Known-Anaphylactic reaction, Angioedema; **Metabolism and nutrition disorders, Psychiatric disorders:** Common-Insomnia; Uncommon- Anorexia, decreased, appetite, Anxiety, nervousness; Not known- Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania; **Nervous system disorders:** Common- Dysgeusia, headache, taste perversion; Uncommon- Loss of consciousness, dyskinesia1, dizziness, somnolence, tremor, Vertigo, hearing impaired, tinnitus; Not Known- Convulsion, ageusia, parosmia, anosmia, paraesthesia, Deafness; **Cardiac disorders, Vascular disorders, Respiratory, thoracic and mediastinal disorder:** Common-Vasodilation; Uncommon- Cardiac arrest, atrial, fibrillation, electrocardiogram QT prolonged, extrasystoles, palpitations, Asthma, epistaxis, pulmonary embolism; **Not Known:** Torsades de pointes, ventricular, tachycardia, Ventricular fibrillation, Haemorrhage; **Gastrointestinal disorders:** Common- Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain, Uncommon-

Oesophagitis, gastrooesophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis, abdominal distension, constipation, dry mouth, eructation, flatulence; Not known: Pancreatitis acute, tongue discolouration, tooth discolouration; **Hepatobiliary disorders:** Liver function test, abnormal; Uncommon- Cholestasis, hepatitis, alanine aminotransferase, increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased,Not Known- Hepatic failure, jaundice, hepatocellular; **Skin and subcutaneous tissue disorders:** Common- Rash, hyperhidrosis; Uncommon- Dermatitis bullous, pruritus, urticaria, rash maculo-papular; Not known- Stevens-Johnson, syndrome, toxic, epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, acute generalised exanthematous pustolosis (AGEP); **Musculoskeletal and connective tissue disorders, Renal and urinary disorders:** Muscle spasms, musculoskeletal stiffness, myalgia, Blood creatinine increased, blood urea increased; Not Known- Rhabdomyolysis, myopathy, Renal failure, nephritis interstitial; **General disorders and administration site conditions:** Very Common- Injection site, phlebitis; Common- Injection site pain1, injection site inflammation; Uncommon- Malaise, pyrexia, asthenia, chest pain, chills, fatigue; **Investigations:** Uncommon- Albumin globulin ratio, abnormal, blood alkaline phosphatase increased, blood lactate dehydrogenase increased; Not known- International normalised ratio increased, prothrombin time, prolonged, urine, colour abnormal.

ADRs reported only for the Powder for Solution for Injection formulation. ADRs reported only for the Extended-Release Tablets formulation. ADRs reported only for the Granules for Oral Suspension formulation. ADRs reported only for the Immediate-Release Tablets formulation.

**** Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.***

c. Description of selected adverse reactions

Injection site phlebitis, injection site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation. In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g., suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients.

d. Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

4.9 Over Dosage:

Symptoms of intoxification: Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. 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 intoxification: 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 haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharamacotherapeutic group: Macrolides; **ATC Code:** J01FA09

Mechanism of action:

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal sub-unit of susceptible bacteria preventing translocation of activitate amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria.

The 14-(R)-hydroxy metabolite of clarithromycin also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including mycobacterium spp. An exception is Haemophilus influenza where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Clarithromycin is usually active against the following organisms in vitro:

Gram-positive Bacteria: Staphylococcus aureus (methicillin susceptible); Streptococcus pyogenes (Group A beta-hemolytic streptococci); alpha-hemolytic streptococci (viridans group); Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes.

Gram-negative Bacteria: Haemophilus influenza; Haemophilus parainfluenza; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae; Legionella, pneumophila; Bordetella pertussis; Campylobacter jejuni. Mycoplasma: Mycoplasma pneumoniae; Ureaplasma urealyticum.

Other Organisms: Chlamydia trachomatis; Mycobacterium avium; Mycobacterium, leprae; Mycobacterium kansasii; Mycobacterium chelonae; Mycobacterium, fortuitum; Mycobacterium intracellularis; Chlamydia pneumoniae. Anaerobes: Clostridium perfringens; Peptococcus species; Peptostreptococcus, species; Propionibacterium acnes.

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 level of the active substance. 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

In 4-week-studies in animals, toxicity of clarithromycin 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. The levels of systemic exposure at which this toxicity occurred are not known in detail, but toxic doses (300 mg/kg/day) were clearly higher than the therapeutic doses recommended for humans. Other tissues affected included the stomach, thymus and other lymphoid tissues as well as the kidneys. At near therapeutic doses conjunctival injection and lacrimation occurred only in dogs. At a dose of 400mg/kg/day some dogs and monkeys developed corneal opacities and/or oedema. In vitro and in vivo studies showed that clarithromycin did not have genotoxic potential.

Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (iv) and 10x 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 generally noted in rat studies. However, cardiovascular malformations were observed in two studies in rats treated with doses of 150 mg/kg/d. In mice at doses 70x the clinical dose, cleft palate occurred at varying incidences (3-30%).

Fertility and reproduction studies have shown that daily doses of 150 to 160mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats at 150mg/kg/day were 2-fold higher than that observed in humans. Clarithromycin has been found in the milk of lactating animals.

In 3-day old mice and rats, the LD50 values were approximately half those in adult animals. Juvenile animals presented similar toxicity profiles to mature animals although enhanced nephrotoxicity in neonatal rats has been reported in some studies. Slight reductions in erythrocytes, platelets and leukocytes have also been found in juvenile animals.

Clarithromycin has not been tested for carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose (PH 102)

Pregelatinized starch (starch 1500)

Croscarmellose Sodium (Ac-di-sol SD -711)

Colloidal Anhydrous Silica BP, Povidone (K-30)

Isopropyl Alcohol

Purified Talc

Magnesium Stearate

Stearic Acid (50) (Powder grade)

Opadry OY – S32924

Propylene Glycol

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in the original package in order to protect from moisture.

6.5 Nature and Contents of Container

Printed Aluminum Foil/Clear PVC Film

Blister Pack:1 x 14 Tablets

6.6 Special precautions for disposal and other handling

No Special Requirements

7. MARKETING AUTHORIZATION HOLDER

M/S BAFNA PHARMACEUTICALS LTD
Bafna Towers,
299, Thambu Chetty Street,
Chennai – 600001, India.
Tel No:044-25267517/25270992/42677555

8. MARKETING AUTHORIZATION NUMBER(S)

07202/07076/REN/2019

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of latest renewal: 17/03/2022

10. DATE OF REVISION OF THE TEXT

13/07/2023

11. REFERENCES