### 1.3.1 Summary of product characteristics (SmPC)

## 1. NAME OF THE MEDICINAL PRODUCT

**Product Name:** **VERST CLARITHROMYCIN TABLET BP 500 MG**

**Generic Name:** **Clarithromycin Tablet BP 500 mg**

**Strength:** Each Film coated Tablet Contains:

Clarithromycin BP… 500 mg

**Pharmaceutical Form:** Film coated Tablet

**Packaging:** 10 Tablets are packed in Alu-Alu Blister and 1 such blister is packed in printed inner carton along with pack insert.

## 2. QUALITY AND QUANTITATIVE COMPOSITION

**Batch size: 1,00,000 Tablets**

| Sr. No. | Ingredients | Reference | Qty./tab (mg) | Function |
|---|---|---|---|---|
| **DRY MIXING** | | | | |
| 1. | Clarithromycin | BP | *500.0 | Active |
| 2. | Di Calcium Phosphate | BP | 130.0 | Disintegrant |
| 3. | Maize Starch | BP | 288.54 | Binder |
| 4. | Colloidal Silicon dioxide (Aerosil 200) | BP | 25.8 | Disintegrant |
| 5. | Microcrystalline cellulose powder -101 | BP | 77.35 | Diluent |
| **BINDING** | | | | |
| 6. | Maize Starch | BP | 11.46 | Binder |
| 7. | PVPK 30 | BP | 25.85 | Binder |
| 8. | Sodium Methyl Paraben | BP | 2.34 | Preservative |
| 9. | Sodium Propyl Paraben | BP | 1.17 | Preservative |
| 10. | Purified Water | BP | **0.038 ml | Solvent |
| **LUBRICATION** | | | | |
| 11. | Purified Talc | BP | 41.20 | Anticaking agent |
| 12. | Magnesium Stearate | BP | 25.85 | Lubricant |

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|---|---|---|---|---|
| 13. | Croscarmellose Sodium | BP | 51.55 | Additive |
| **COATING** | | | | |
| 14. | HPMC 15 | IH | 20.0 | Binder |
| 15. | Purified Talc | BP | 1.05 | Anticaking agent |
| 16. | Titanium Dioxide | USP | 3.522 | Coating agent |
| 17. | PVPK-30 | BP | 4.14 | Binder |
| 18. | Iso propyl Alcohol | BP | ***249.15 | Coating Solvent |
| 19. | Methylene Dichloride | BP | ***228.4 | Coating Solvent |
| 20. | Colour Quinoline yellow | IH | 5.178 | Colouring agent |
| | **TOTAL WEIGHT** | | **1215.00** | |
| **Total Weight/Film coated Tablet (mg) = 1215.00 mg** | | | | |

Legend:

BP = British Pharmacopoeia

IP = Indian Pharmacopoeia

IH = In-House Specification

USP = United States Pharmacopoeia

* Assay calculated on 100% on anhydrous substance.

**Purified water is evaporated during the manufacturing process and does not exist in the final formulation.

*** Isopropyl Alcohol and Dichloromethane are coating solvents which are volatile in nature. They also evaporate during drying steps of tablet manufacturing. Thus they have negligible impact on tablet weight.

Total Weight of each tablet is 1215 mg.

## 3. PHARMACEUTICAL FORM VISUAL DESCRIPTION:

Yellow coloured, elongated, Film coated tablet having plain on both side of each tablet, 1X10 tablets ALU-ALU packed.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS:

Clarithromycin Tablet BP 500 mg 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 Tablet BP 500 mg depends on the type and severity of the infection and has to be defined in any case by the physician.

Clarithromycin Tablet BP 500 mg 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 Tablet BP 500 mg 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 pediatric 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 (eg. one gl s of water) .

Cl ithromycin Tablet BP 500 mg may be given irrespective of food int .

**4.3 Contraindications**

Cl ithromycin is contraindicated in patients with known hypersensitivity to the active subst ce cl ithromycin, to other m rolides or to of the excipients.

Concomitant administration of Claithromycin and any of the following active subst ces is contraindicated: temizole, cis ide, pimozide d terfenadine this may result in QT prolongation (congenital or documented acquired QT prolongation) d card ia arrhythmi , including ventricula tachycardia, ventricula fibrillation and Tors ade de Pointes.

Concomitant administration with ticagrelor or renolazine is contraindicated.

Concomitant administration of Cl ithromycin and ergotamine or dihydroergotami ne is contraindicated, this may result in ergot toxicity.

Concomitant administration of Claithromycin and lomitapide is c ontraindicated.

Cl ithromycin should not be given to patients with history of QT prolongation or ventricula cardia arrhythmi i ncluding torsades de pointe.

Cl ithromycin should not be used concomitantly with HMG -CoA reduct e inhibitors (st tins) that are extensively metabolized by CYP3A4 (lov tatin or simv tatin), due to the incre ed risk of myopathy, including rhabdomyolysis.

Cl ithromycin should not be given to patients with electrolyte disturbances (hypokalaemi or hypom nesaemi due to the risk of prolongation of the QT interval).

Cl ithromycin should not be used in patients who suffe from sere hepatic failure in combination with renal impairment.

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

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

The physician should not prescribe Claithromycin to pregnant women without carefully weighing the benefits inst risk, particulaly during the first three months of pregnancy.

Caion 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.

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 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.

**Cardiovascular Events**

Prolonged cardiac repolarization 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.

• 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.

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 generalized exanthematous pustulosis (AGEP), 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.

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.

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

**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 a two to three 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.

Ergotamine/dihydroergotamine

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.

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.

**Effects of other medicinal products on clarithromycin**

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carabamazepin, phenobarbital, St. Johns wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of Clarithromycin leading to a 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-OH-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 g/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.

**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 metabolized by CYP3A should be monitored closely in patients concurrently receiving Clarithromycin.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, 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 comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

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.

Antiarrhythmics

There have been post marketing reports of torsades de pointes occurring with 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 metabolized, 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 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 Tablet BP 500 mg (500 mg 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 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.

**Other drug interactions**

Aminoglycosides

Caution is advised regarding concomitant administration of Clarithromycin with other ototoxic drugs, especially with aminoglycosides.

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.

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When Clarithromycin and digoxin are administered together, inhibition of Pgp by Clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving Clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and Clarithromycin simultaneously.

Zidovudine

Simultaneous oral administration of Clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because Clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of Clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking Clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when Clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including Clarithromycin with drugs not thought to be metabolized by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with Clarithromycin. Increased serum levels have been reported

Concomitant administration of Clarithromycin with lomitapide is contraindicated due the potential for markedly increased transaminases.

## 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 embryo 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 use 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.

**Fertility**

There is no data available on the effect of Clarithromycin on fertility in humans. In rats, the limited data available do not indicate any effects on fertility.

**4.7Effects 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.

**4.8Undesirable / side effects**

**a. Summary of the safety profile**

The most frequent and common adverse reactions related to Clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, 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.

| System Organ Class | Very common (≥1/10 | Common ≥ 1/100 to < 1/10 | Uncommon ≥1/1,000 to < 1/100 | Not Known (cannot be estimated from the available data) |
|---|---|---|---|---|
| **Infections and infestations** | | | Cellulitis[1], candidiasis, | Pseudomembranous colitis, erysipelas |

| | | | | |
|---|---|---|---|---|
| | | | gastroenteritis[2], infection[3], vaginal infection | |
| **Blood and lymphatic system** | | | Leukopenia, neutropenia[4], thrombocythemia[3], eosinophilia[4] | Agranulocytosis, thrombocytopenia |
| **Immune system disorders[5]** | | | Anaphylactoid reaction[1], Hypersensitivity | Anaphylactic reaction, angioedema |
| **Metabolism and nutrition disorders** | | | Anorexia, decreased appetite | |
| **Psychiatric disorders** | | Insomnia | Anxiety, nervousness[3], | Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania |
| **Nervous system disorders** | | Dysgeusia, headache, taste perversion | Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[6], tremor | Convulsion, ageusia, parosmia, anosmia, paraesthesia |
| **Ear and labyrinth disorders** | | | Vertigo, hearing, impaired, tinnitus | Deafness |
| **Cardiac disorders** | | | Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged[7], | Torsade de pointes[7], ventricular tachycardia[7] ventricular |

| | | | | |
|---|---|---|---|---|
| | | | extrasystoles[1], palpitations | fibrillation |
| **Vascular disorders** | | Vasodilation[1] | | Hemorrhage[8] |
| **Respiratory, thoracic and mediastinal disorder** | | | Asthma[1], epistaxis[2], pulmonary embolism[1] | |
| **Gastrointestinal disorders** | | Diarrhea[9], vomiting, dyspepsia, nausea, abdominal pain | Esophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence | Pancreatitis acute, tongue discolouration, tooth discoloration |
| **Hepatobiliary disorders** | | Liver function test abnormal | Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased | Hepatic failure[10], jaundice hepatocellular |
| **Skin and subcutaneous tissue disorders** | | Rash, hyperhidrosis | Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3] | Stevens-Johnson syndrome[5], toxic epidermal necrolysis[5], drug rash with eosinophilia and systemic symptoms |

| | | | | |
|---|---|---|---|---|
| | | | | (DRESS), acne, acute generalised exanthematous pustulosis (AGEP) |
| **Musculoskeletal and connective tissue disorders** | | | Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2] | Rhabdomyolysis[2,11], myopathy |
| **Renal and urinary disorders** | | | Blood creatinine increased[1], blood urea increased[1] | Renal failure, nephritis interstitial |
| **General disorders and administration site conditions** | Injection site phlebitis[1] | Injection site pain[1], injection site inflammation[1] | Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4] | |
| **Investigations** | | | Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4] | International normalised ratio increased[8], prothrombin time prolonged[8], urine color abnormal |

[1] ADRs reported only for the Powder for Solution for Injection formulation

[2]ADRs reported only for the Extended-Release Tablets formulation

[3] ADRs reported only for the Granules for Oral Suspension formulation

[4] ADRs reported only for the Immediate-Release Tablets formulation

[5], [7, 9, 10,] See section a)

[6, 8, 11] See section c)

**c. Description of selected adverse reactions**

Injection site phlebitis, injection site pain, vessel puncture 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 colchicine toxicity with concomitant use of Clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome.

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 diarrhea. 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 (see section e).

**d. Pediatric populations**

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 pediatric suspension. There are insufficient data to recommend a dosage regimen for use of the Clarithromycin IV formulation in patients less than 18 years of age.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

**e. Other special populations**

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of Clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with Clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1,000 mg and 2,000 mg of Clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT)

elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1,000 mg and 2,000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4,000 mg of Clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1,000 mg or 2,000 mg of Clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4,000 mg daily for all parameters except White Blood Cell.

**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 over dosage 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 over dosage, Clarithromycin IV (powder for solution for injection) should be discontinued and all other appropriate supportive measures should be instituted.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group**: Macrolides

**ATC code** J01FA09.

**Mode 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. The main pharmacodynamic parameters to predict macrolidenactiviteit are unconvincing established. The time above the MIC (T / MIC) is the best determinant for the efficacy of Clarithromycin. Because the concentrations of Clarithromycin in the lung tissues and epithelial tissue fluid reaches the plasma concentrations exceed, the use of plasma concentrations based parameters are insufficient to accurately predict response for respiratory infections.

**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. Clarithromycin ranks among the strong inducers of this enzyme as well. Furthermore, macrolides have a bacteriostatic action by inhibiting the peptidyl transferase of ribosomes. A complete cross-resistance exists among Clarithromycin,

erythromycin and azithromycin. Methicillin-resistant staphylococci and penicillin-resistant *Streptococcus pneumoniae* are resistant to macrolides such as Clarithromycin.

**Breakpoints:**

The following breakpoints for Clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) 2010-04-27 (v 1.1)

| | | Species-related break points (S</R>) | | | | | | | | | | | | | | Non species related break points S</R> |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Enterobacteriaceae* | *Pseudomonas* | *Acinetobacter* | *Staphylococcus* | *Enterococcus* | *Streptococcus A,B,C,G* | *S.pneumoniae* | Other streptococci | *H.influenzae* | *M.catarr-halis* | *N.gonorrhoeae* | *N.meningitidis* | *Gram –negative anaerobes* | *Gram-positive anaerobes* | |
| **Clarithromycin**[B,C] | | | | | | | | | | | | | | | | IE |
| | | | | | | | | | | | | | | | | |

[A] Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes However, pharmacodynamic data for calculation of macrolide, lincosamines and streptogramins non-species related breakpoints are not robust, hence IE.

[B] Erythromycin can be used to determine the susceptibility of the listed bacteria to the other macrolides (Azithromycin, Clarithromycin and Roxithromycin).

[C] Clarithromycin is used for the eradication of *H. pylori* (MIC ≤0.25 mg/l for wild type isolates).

[D] The correlation between *H. influenzae* macrolide MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorize wild type *H. influenzae* as intermediate.

Clarithromycin is used for the eradication of *H. pylori*; minimum inhibitory concentration (MIC) ≤ 0.25 μg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).

**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 prevalance of resistance is such that the utility of the agent in at least some types of infections is questionable.

**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 metabolized 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 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. 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 400 mg/kg/day some dogs and monkeys developed corneal opacities and/or oedema.

No mutagenic effects were found in in vitro- and in vivo -studies with Clarithromycin.

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

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**

NA

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

### 6.5 Nature and contents of container

Clarithromycin Tablets BP 500 mg is available in packing of 10 Tablets are packed in Alu-Alu Blister and 1 such blister is packed in printed inner carton along with pack insert.

### 6.6 Special precautions for disposal and other handling

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

**7. MANUFACTURER:**

**WINTECH PHARMACEUTICALS LTD.**

**Address:** Office No. 2 & 3, 3rd floor, Broadway Shopping Centre, Dr. Ambedkar Road, Dadar T.T. Mumbai- 400014, India. Tel: (+ 9122) 42123456 (100 lines).

**8. DISTRIBUTED BY:**

**LIFE VERST GLOBAL PHARMACY LTD**

**Address:** 42, Ajidola Crescent, Alapere Ketu, Lagos, Nigeria.

**9. DOSIMETRY (IF APPLICABLE)**

Not Applicable