

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

Claritek Granules 125mg/5mL

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each reconstituted 5ml granules for suspension contains:  
Clarithromycin Granules ....454.54 (Equivalent to 125mg of Clarithromycin)

### **3. PHARMACEUTICAL FORM**

White to off-white granular powder for suspension.

### **4. CLINICAL PARTICULARS**

#### **4.1. Therapeutic indications**

Claritek Granules 125mg/5mL is indicated in children 6 months to 12 years.

Claritek Granules 125mg/5mL is indicated for the treatment of infections caused by susceptible organisms. Indications include:

- Lower respiratory tract infections (e.g. bronchitis, pneumonia)
- Upper respiratory tract infections (e.g. pharyngitis, sinusitis, tonsillitis).
- Acute otitis media in Children
- Skin and soft tissue infections (e.g. folliculitis, cellulitis, erysipelas)
- Leprosy
- Disseminated or localized mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*. Localized infections due to *Mycobacterium chelonian*, *Mycobacterium fortuitum*, or *Mycobacterium kansasii*.
- It is also used in some countries as an alternative to penicillins for prophylaxis of Endocarditis.
- To eradicate *Helicobacter pylori* in treatment regimens for peptic ulcer disease. It has been tried in protozoal infections, including toxoplasmosis.
- Clarithromycin tablets and granules for oral suspension are indicated for the Prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.

#### **4.2. Posology and method of administration**

Pediatric patients under 12 years of age:

Children under 12 years of age should use Claritek Granules 125mg/5mL.

Recommended doses and dosage schedules:

The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition. The recommended daily dosage of Claritek Granules

125mg/5mL in children is given in the following table and is based on a 7.5mg/kg b.i.d. dosing regimen up to a maximum dose of 500 mg b.i.d. The prepared suspension can be taken with or without meals and can be taken with milk.

#### CLARITEK GRANULES 125mg/5ml DOSAGE IN CHILDREN

Dosage Based on Body Weight (kg)		
Weight* (kg)	Approx Age (yrs)	Dosage (ml) bid
8-11	1 - 2	2.50
12-19	3 - 6	5.00
20-29	7 - 9	7.50
30-40	10 - 12	10.00

\* Children < 8 kg should be dosed on a per kg basis (approx. 7.5 mg/kg bid)

#### *Renal Impairment*

In children with creatinine clearance less than 30 ml/min/1.73m<sup>2</sup>, the dosage of clarithromycin should be reduced by half to 7.5mg/kg per day. Dosage should not be continued beyond 14 days in these patients.

#### **4.3. Contraindications**

Hypersensitivity to macrolide antibiotic drugs 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, domperidone, pimozone and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades 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 hypokalemia (risk of prolongation of QT-time).

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

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

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

Clarithromycin is principally metabolized 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.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. 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 colchicine is contraindicated.

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

#### Cardiovascular Events:

Prolongation of the QT interval, reflecting effects on cardiac repolarization imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in patients treated with macrolides including clarithromycin. Due to increased risk of QT prolongation and ventricular arrhythmias (including *torsades de pointes*), the use of clarithromycin is contraindicated: in patients taking any of astemizole, cisapride, domperidone, pimozide and terfenadine; in patients who have hypokalemia; and in patients with a history of QT prolongation or ventricular cardiac arrhythmia.

Furthermore, clarithromycin should be used with caution in the following:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia;
- Patients with hypomagnesaemia;
- Patients concomitantly taking other medicinal products associated with QT prolongation other than those which are contraindicated

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 drug rash with eosinophilia and systemic symptoms (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 sulphonylurea) and/or insulin can result in significant hypoglycaemia. 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.

Long-term use may, as with other antibiotics, result in colonization 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.

Excipients

When prescribing to diabetic patients, the sucrose content should be taken into account.

**4.5. Interaction with other medicaments**

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

Astemizole, cisapride, domperidone, pimozone 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 pimozone 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 ergot alkaloids 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.

### 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 inducer 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 ( $C_{min}$ ) 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  $C_{max}$  increased by 31%,  $C_{min}$  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  $CL_{CR}$  30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with  $CL_{CR}$  <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, which is 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. The use of clarithromycin is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, domperidone, pimozide and terfenadine due to the risk of QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazolam, HMG CoA reductase inhibitors metabolized mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor and ranolazine.

Caution is required if clarithromycin is co-administered 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. Drugs or drug classes that are known or suspected to be metabolized by the same CYP3A isozyme include (but this list is not comprehensive) alprazolam, carbamazepine, cilostazole, ciclosporin, disopyramide, ibrutinib, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine.

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 hypoglycemia 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 ( $C_{max}$ ,  $AUC_{0-24}$ , and  $t_{1/2}$  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 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 metaboliser 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.

#### Other drug interactions

##### 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 pediatric 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.

### Bi-directional drug interactions

#### Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

#### Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g. verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, Brady arrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

#### Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

#### Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and C<sub>max</sub> values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C<sub>max</sub> values were approximately 40% higher than those seen with clarithromycin alone.

No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin.

Patients taking oral contraceptives should be warned that if diarrhea, vomiting or breakthrough bleeding occur there is a possibility of contraceptive failure.

#### 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 studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

##### Breastfeeding

The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

#### 4.7. Effects on ability to drive and use machine

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 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 preexisting 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.

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 <sup>1</sup> , candidiasis, gastroenteritis <sup>2</sup> , infection <sup>3</sup> , vaginal infection	Pseudomembranous colitis, erysipelas,
Blood and lymphatic system			Leukopenia, neutropenia <sup>4</sup> , thrombocythaemia <sup>3</sup> , eosinophilia <sup>4</sup>	Agranulocytosis, thrombocytopenia
Immune system disorders			Anaphylactoid reaction <sup>1</sup> , hypersensitivity	Anaphylactic reaction. angioedema

<b>Metabolism</b>			Anorexia, decreased	
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<b>and nutrition disorders</b>			appetite	
<b>Psychiatric disorders</b>		Insomnia	Anxiety, nervousness <sup>3</sup> ,	Psychotic disorder, confusional state <sup>5</sup> , depersonalization, depression, disorientation, hallucination, abnormal dreams, mania
<b>Nervous system disorders</b>		Dysgeusia, headache	Loss of consciousness <sup>1</sup> , dyskinesia <sup>1</sup> , dizziness, somnolence <sup>5</sup> , tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
<b>Ear and labyrinth disorders</b>			Vertigo, hearing impaired, tinnitus	Deafness
<b>Cardiac disorders</b>			Cardiac arrest <sup>1</sup> , atrial fibrillation <sup>1</sup> , electrocardiogram QT prolonged, extrasystoles <sup>1</sup> , palpitations	Torsades de pointes, ventricular tachycardia, ventricular fibrillation
<b>Vascular disorders</b>		Vasodilation <sup>1</sup>		Hemorrhage
<b>Respiratory, thoracic and mediastinal disorder</b>			Asthma <sup>1</sup> , epistaxis <sup>2</sup> , pulmonary embolism <sup>1</sup>	
<b>Gastrointestinal disorders</b>		Diarrhea, vomiting, dyspepsia, nausea, abdominal pain	Oesophagitis <sup>1</sup> , gastroesophageal reflux disease <sup>2</sup> , gastritis, proctalgia <sup>2</sup> , stomatitis, glossitis, abdominal distension <sup>4</sup> , constipation, dry mouth, eructation, flatulence,	Pancreatitis acute, tongue discoloration, tooth discoloration

<p><b>Hepatobiliary disorders</b></p>		<p>Liver function test abnormal</p>	<p>Cholestasis<sup>4</sup>, hepatitis<sup>4</sup>, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased<sup>4</sup></p>	<p>Hepatic failure, jaundice hepatocellular</p>
<p><b>Skin and subcutaneous tissue disorders</b></p>		<p>Rash, hyperhidrosis</p>	<p>Dermatitis bullous<sup>1</sup>, pruritus, urticaria, rash maculopapular<sup>3</sup></p>	<p>Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson</p>

				syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne
<b>Musculoskeletal and connective tissue disorders</b>			Muscle spasms <sup>3</sup> , musculoskeletal stiffness <sup>1</sup> , myalgia <sup>2</sup>	Rhabdomyolysis <sup>2</sup> , myopathy
<b>Renal and urinary disorders</b>			Blood creatinine increased <sup>1</sup> , blood urea increased <sup>1</sup>	Renal failure, nephritis interstitial
<b>General disorders and administration site conditions</b>	Injection site phlebitis <sup>1</sup>	Injection site pain <sup>1</sup> , injection site inflammation <sup>1</sup>	Malaise <sup>4</sup> , pyrexia <sup>3</sup> , asthenia, chest pain <sup>4</sup> , chills <sup>4</sup> , fatigue <sup>4</sup>	
<b>Investigations</b>			Albumin globulin ratio abnormal <sup>1</sup> , blood alkaline phosphatase increased <sup>4</sup> , blood lactate dehydrogenase increased <sup>4</sup>	International normalized ratio increased, prothrombin time prolonged, urine color abnormal

<sup>1</sup> ADRs reported only for the Powder for Solution for Injection formulation

<sup>2</sup> ADRs reported only for the Extended-Release Tablets formulation

<sup>3</sup> ADRs reported only for the Granules for Oral Suspension formulation

<sup>4</sup> ADRs reported only for the Immediate-Release Tablets formulation

<sup>5, 6</sup> 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 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 granules 125mg/5ml in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin granules 125mg/5ml. 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 dyspnea, 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.

#### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

### **4.9. Over dosage**

#### 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 behavior, hypokalemia and hypoxemia.

#### Therapy of intoxication:

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Macrolides (Antibacterial for systemic use) ATC code: J01FA09

Mode of action:

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

The 14-hydroxy metabolite of clarithromycin, a product of parent drug metabolism also has anti-microbial 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 also bactericidal against several bacterial strains.

Clarithromycin is usually active against the following organisms in vitro:-

*Gram-positive Bacteria*:

Staphylococcus aureus (methicillin susceptible); Streptococcus pyogenes (Group A beta-haemolytic streptococci); alpha-haemolytic streptococci (viridans group); Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes.

*Gram-negative Bacteria*:

Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae; Legionella pneumophila, Bordetella pertussis, Helicobacter pylori; Campylobacter jejuni.

*Mycoplasma*:

Mycoplasma pneumoniae; Ureaplasma urealyticum.

*Other Organisms*:

Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae; Chlamydia pneumoniae.

*Anaerobes*:

Macrolide-susceptible Bacteroides fragilis; Clostridium perfringens; Peptococcus species; Peptostreptococcus species; Propionibacterium acnes.

Clarithromycin also has bactericidal activity against several bacterial strains. These organisms include H. influenza, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Moraxella (Brahamella) catarrhalis, Neisseria gonorrhoeae, Helicobacter pylori and Campylobacter species.

## 5.2. Pharmacokinetic properties

### *Absorption*

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration. The microbiologically active 14(R)-hydroxyclearithromycin is formed by first pass metabolism. Clarithromycin, may be given without regard to meals as food does not affect the extent of bioavailability. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxy metabolite. Although the pharmacokinetics of clarithromycin are non linear, steady state is attained within 2 days of dosing.

### *Distribution*

Clarithromycin provides tissue concentrations that are several times higher than circulating drug level. Increased levels of clarithromycin have been found in both tonsillar and lung tissue. Clarithromycin penetrates into the middle ear fluid at concentrations greater than in the serum. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

### *Metabolism*

14-Hydroxyclearithromycin is the major urinary metabolite and accounts for 10-15% of the dose.

### *Elimination*

Most of the remainder of the dose is eliminated in the feces, primarily via the bile. 5-10% of the parent drug is recovered from the feces.

## 5.3. Preclinical safety data

The acute oral LD<sub>50</sub> values for a clarithromycin suspension administered to 3-day old mice were 1290 mg/kg for males and 1230 mg/kg for females. The LD<sub>50</sub> values in 3-day old rats were 1330 mg/kg for males and 1270 mg/kg for females. For comparison, the LD<sub>50</sub> of orally-administered clarithromycin is about 2700 mg/kg for adult mice and about 3000 mg/kg for adult rats. These results are consistent with other antibiotics of the penicillin group, cephalosporin group and macrolide group in that the LD<sub>50</sub> is generally lower in juvenile animals than in adults.

In both mice and rats, body weight was reduced or its increase suppressed and suckling behavior and spontaneous movements were depressed for the first few days following drug administration. Necropsy of animals that died disclosed dark-reddish lungs in mice and about 25% of the rats; rats treated with 2197 mg/kg or more of a clarithromycin suspension were also noted to have a reddish - black substance in the intestines, probably because of bleeding. Deaths of these animals were considered due to debilitation resulting from depressed suckling behavior or bleeding from the intestines.

Pre-weaning rats (5 days old) were administered a clarithromycin suspension formulation for two weeks at doses of 0, 15, 55 and 200 mg/kg/day. Animals from the 200 mg/kg/day group had decreased body-weight gains, decreased mean hemoglobin and hematocrit values, and increased mean relative kidney weights compared to animals from the control group. Treatment-related minimal to mild multifocal vacuolar degeneration of the intrahepatic bile duct epithelium and an increased incidence of nephritic lesions were also observed in animals from this treatment group. The "no-toxic effect" dosage for this study was 55 mg/kg/day.

An oral toxicity study was conducted in which immature rats were administered a clarithromycin suspension (granules for suspension) for 6 weeks at daily dosages of 0, 15, 50 and 150 mg base/kg/day. No deaths occurred and the only clinical sign observed was excessive salivation for some of the animals at the highest dosage from 1 to 2 hours after administration during the last 3 weeks of treatment. Rats from the 150 mg/kg dose group had lower mean body weights during the first three weeks, and were observed to have decreased mean serum albumin values and increased mean relative liver weight compared to the controls. No treatment-related gross or microscopic histopathological changes were found. A dosage of 150 mg/kg/day produced slight toxicity in the treated rats and the "no effect dosage" was considered to be 50 mg/kg/day.

Juvenile beagle dogs, 3 weeks of age, were treated orally daily for four weeks with 0, 30, 100, or 300 mg/kg of clarithromycin, followed by a 4-week recovery period. No deaths occurred and no change in the general condition of the animals was observed. Necropsy revealed no abnormalities. Upon histological examination, fatty deposition of centrilobular hepatocytes and cell infiltration of portal areas were observed by light microscopy and an increase in hepatocellular fat droplets was noted by electron microscopy in the 300 mg/kg dose group. The toxic dose in juvenile beagle dogs was considered to be greater than 300 mg/kg and the "no effect dose" 100 mg/kg.

#### Fertility, Reproduction and Teratogenicity

Fertility and reproduction studies have shown daily dosages of 150-160 mg/kg/day to male and female rats caused no adverse effects on the oestrus cycle, fertility, parturition and number and viability of offspring. Two teratogenicity studies in both Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.) rats, one study in New Zealand white rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

- Sucrose
- Titanium Dioxide
- Colloidal Anhydrous Silica (Aerosil 200)
- Xanthan Gum
- Methyl paraben
- Trusil Powder Orange Flavor

### **6.2. Incompatibilities**

None

### **6.3. Shelf-life**

2 Years

Once reconstituted, Claritek Granules 125mg/5ml should be used within 14 days. The expiration dates refer to the product correctly stored in the required conditions.

#### **6.4.Special precautions for storage**

Do not store above 30°C.  
Protect from sunlight & moisture.

#### **6.5.Nature and contents of container**

Claritek (Clarithromycin) Granules 125mg/5mL are available in HDPE Plastic bottle (1x50 ml) in a unit carton, along with package insert.

#### **6.6.Special precautions for disposal and other handling**

- To be sold on prescription of a registered medical practitioner only.
- Keep out of the reach of children.
- Fill drinking water up to the line mark and shake well.

##### 50ml bottle:

Water should be added to the granules in the bottle and shaken until all of the particles are suspended. Avoid vigorous and/ or lengthy shaking. Shake prior to each subsequent use to ensure re-suspension. The concentration of clarithromycin in the reconstituted suspension is 125mg per 5ml.

#### **7. MARKETING AUTHORISATION HOLDER**

Getz Pharma (Private) Limited  
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan  
Tel: (92-21) 111 111 511  
Fax: (92-21) 505 7592

#### **8. MARKETING AUTHORIZATION NUMBER**

TAN 22 HM 0204

#### **9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**

04<sup>th</sup> May, 2022

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