

### D3 Proposed package insert

#### PRODUCT NAME

Clarithromycin HEC 500 mg Prolonged-release Tablets

#### NAME & STRENGTH OF ACTIVE INGREDIENT AND EXCIPIENT

Each prolonged-release tablet contains clarithromycin 500 mg.

List of excipients

##### *Tablet core:*

Lactose monohydrate  
Hypromellose  
Glycerol dibehenate  
Magnesium Stearate

##### *Tablet coating:*

Lactose monohydrate  
Macrogol 6000  
Hypromellose  
Titanium Dioxide (E171)  
Macrogol 400

#### DOSAGE FORM

Prolonged-release tablet

#### PRODUCT DESCRIPTION

White or almost white, capsular shaped film-coated tablets, debossed with "S57" on one side and blank on the other side.

#### PHARMACODYNAMICS

Pharmacological-therapeutical group: Macrolides

ATC Code: J01FA09

Clarithromycin is a semi-synthetic derivative of erythromycin. It exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria. It selectively binds to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

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

Clarithromycin is usually active against the following organisms in vitro:

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

Gram-negative Bacteria: *Haemophilus influenza*; *Haemophilus parainfluenza*; *Moraxella (Branhamella) catarrhalis*; *Neisseria gonorrhoeae*; *Legionella pneumophila*; *Bordetella pertussis*; *Campylobacter jejuni*.

Mycoplasma: *Mycoplasma pneumoniae*; *Ureaplasma urealyticum*.

Other Organisms: *Chlamydia trachomatis*; *Mycobacterium avium*; *Mycobacterium leprae*; *Mycobacterium kansasii*; *Mycobacterium chelonae*; *Mycobacterium fortuitum*; *Mycobacterium intracellulare*; *Chlamydia pneumoniae*.

Anaerobes: *Clostridium perfringens*; *Peptococcus* species; *Peptostreptococcus* species; *Propionibacterium acnes*.

Clarithromycin has bactericidal activity against several bacterial strains. The organisms include *Haemophilus influenzae*; *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Streptococcus agalactiae*; *Moraxella (Branhamella) catarrhalis*; *Neisseria gonorrhoeae* and *Campylobacter* spp.

### Pharmacokinetics

The kinetics of orally administered modified-release clarithromycin have been studied in adult humans and compared with clarithromycin 250mg and 500mg immediate release tablets. The extent of absorption was found to be equivalent when equal total daily doses were administered. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Based upon the finding of equivalent absorption the following in vitro and in vivo data are applicable to the modified-release formulation.

**In vitro:** Results of in vitro studies showed that the protein binding of clarithromycin in human plasma averaged about 70 % at concentrations of 0.45 - 4.5µg/mL. A decrease in binding to 41% at 45.0µg/mL suggested that the binding sites might become saturated, but this only occurred at concentrations far in excess of therapeutic drug levels.

**In vivo:** Clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were found in the liver and lung tissue, where the tissue to plasma ratios reached 10 to 20.

The pharmacokinetic behaviour of clarithromycin is non-linear. In fed patients given 500mg clarithromycin modified-release daily, the peak steady state plasma concentration of clarithromycin and 14 hydroxy clarithromycin were 1.3 and 0.48µg/mL, respectively. When the dosage was increased to 1000mg daily, these steady-state values were 2.4µg/mL and 0.67µg/mL respectively. Elimination half-lives of the parent drug and metabolite were approximately 5.3 and 7.7 hours respectively. The apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at higher doses.

Urinary excretion accounted for approximately 40% of the clarithromycin dose. Faecal elimination accounts for approximately 30%.

### Indications

Clarithromycin is indicated for treatment of infections due to susceptible organisms. Such infections include:

1. Lower respiratory tract infections (e.g., bronchitis, pneumonia)
2. Upper respiratory tract infections (e.g., pharyngitis, sinusitis)
3. Skin and soft tissue infections (e.g., folliculitis, cellulitis, erysipelas)

### Dosage and Administration

The usual recommended dosage of Clarithromycin-HEC tablets in adults 12 years old of age or older is 500 mg once daily with food.

In more severe infections, the dosage may be increased to 1000 mg once daily (2 x 500 mg).

The usual duration of therapy is 5 - 14 days for all indications except for sinusitis and community-acquired pneumonia which need 6 to 14 days of treatment.

Clarithromycin-HEC should not be used in patients with significant renal impairment (creatinine clearance less than 30 mL/min). Clarithromycin 250 mg and 500 mg immediate release tablets may be utilized in this patient population.

Do not crush or chew clarithromycin modified release tablets.

### Pediatric

The use of Clarithromycin-HEC has not been studied in children less than 12 years of age.

### **Contraindications**

Hypersensitivity to the active substance, to other macrolide antibiotics or to any of the excipients.

Concomitant administration of clarithromycin and any of the following active substances is contraindicated: astemizole, cisapride, pimozone and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

Concomitant administration with ticagrelor or ranolazine is contraindicated.

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

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

Clarithromycin must 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.

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

### ***Patients with renal impairment***

As the dose cannot be reduced from 500mg daily, Clarithromycin-HEC is contraindicated in patients with creatinine clearance less than 30 ml/min. All other formulations may be used in this patient population.

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

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

### **Warnings and precautions**

#### ***Pregnant***

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

#### ***Renal impairment***

Caution is advised in patients with severe renal insufficiency.

#### ***Hepatic impairment***

Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment. Cases of fatal hepatic failure have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

***Pseudomembranous colitis:*** has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening.

***Clostridium difficile- associated diarrhoea (CDAD)*** has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*.

CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Medicinal products inhibiting peristalsis should be avoided.

**Colchicine:**

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 in patients with renal or hepatic impairment.

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

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

**QT prolongation**

Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesaemia, bradycardia (<50 bpm), or when co-administered with other medicinal products associated with QT prolongation. Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia.

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

**Skin and soft tissue infections of mild to moderate severity:** These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where beta-lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the medicinal product 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.

**Hypersensitivity reactions**

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [eg: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], Clarithromycin HEC 500 mg Prolonged-release should be discontinued immediately and appropriate treatment should be urgently initiated

**Medications induce cytochrome CYP3A4 enzyme:**

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 possible dose of the statin. Use of a statin that is not dependent on CYP3A4 metabolism (e.g. fluvastatin) can be considered.

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

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

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 colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolides, as well as lincomycin and clindamycin.

The medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### **Driving and using machines**

Clarithromycin HEC may make you feel dizzy or drowsy. If affected you should not drive, operate machinery or do anything that requires you to be alert.

#### **Interaction with other medicaments**

**The use of the following active substance 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. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergotamine/dihydroergotamine:

Co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischaemia 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***

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

The following medicinal products 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 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

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%. These patients have other clarithromycin formulations with lower content of active substance. Doses of clarithromycin greater than 1 gm/day should not be co-administered with ritonavir.

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

### ***Effect of Clarithromycin on Other Medicinal Products***

#### CYP3A-based interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a medicinal product primarily metabolised by CYP3A may be associated with elevations in active substance concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant medicinal product. Clarithromycin should be used with caution in patients receiving treatment with other medicinal products 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 metabolised by this enzyme.

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

The following active substances or active substance classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine. Active substances 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 torsade de points occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these active substances. 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 active substances 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

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

#### Theophylline, carbamazepine

There was a modest but statistically significant ( $p \leq 0.05$ ) increase of circulating theophylline or carbamazepine levels when either of these medicinal products 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 and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolised by 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. Patients should be monitored for clinical symptoms of colchicine toxicity.

#### 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 active substances not thought to be metabolised by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these active substances 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, bradyarrhythmias 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) resulted in steady-state AUC and  $C_{max}$  values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and  $C_{max}$  values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two medicinal products 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.

### **Pregnancy and lactation**

#### Pregnancy

Data on the use of clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects, or of adverse effects on the health of the neonate. Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of abortions. To date no other relevant epidemiological data are available. Clarithromycin should only be used during pregnancy after a careful benefit/risk assessment.

#### Breast-feeding

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

### **Side Effects**

#### **Summary of the safety profile**

The most frequent and common adverse reactions related to clarithromycin for both adult and paediatric populations are abdominal pain, 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 between the patient population with or without pre-existing mycobacterial infections.

#### **Tabulated summary of adverse reactions**

The following table displays adverse reactions of 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, common, uncommon 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                           | Common                                                                      | Uncommon                                                                                                                                   | Not known (cannot be estimated from the available data)                                                                              |
|------------------------------------------------------|---------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Infections and infestations                          |                                       |                                                                             | cellulitis <sup>1</sup> , gastroenteritis <sup>2</sup> , candidiasis, infection <sup>3</sup> , vaginal infection                           | pseudomembranous colitis, erysipelas, erythrasma                                                                                     |
| Blood and the lymphatic system disorders             |                                       |                                                                             | leukopenia, neutropenia <sup>4</sup> , eosinophilia <sup>4</sup> , thrombocythaemia                                                        | agranulocytosis, thrombocytopenia                                                                                                    |
| Immune system disorders                              |                                       |                                                                             | anaphylactoid reaction <sup>1</sup> , hypersensitivity                                                                                     | anaphylactic reaction                                                                                                                |
| Psychiatric disorders                                |                                       | insomnia                                                                    | Anxiety, nervousness <sup>3</sup> , screaming                                                                                              | psychiatric disorder, confusional state, depression, hallucination, disorientation, depersonalisation, abnormal dreams and confusion |
| Metabolism and nutrition disorders                   |                                       |                                                                             | anorexia, decreased appetite                                                                                                               | hypoglycaemia                                                                                                                        |
| Vascular disorders                                   |                                       |                                                                             | vasodilation                                                                                                                               | hemorrhage                                                                                                                           |
| Respiratory, thoracic and mediastinal disorders      |                                       |                                                                             | asthma <sup>1</sup> , epistaxis <sup>2</sup> , pulmonary embolism <sup>1</sup>                                                             |                                                                                                                                      |
| General disorders and administration site conditions | Injection site phlebitis <sup>1</sup> | injection site pain <sup>1</sup> , injection site inflammation <sup>1</sup> | pyrexia <sup>3</sup> , asthenia, chest pain <sup>4</sup> , chills <sup>4</sup> , malaise <sup>4</sup> , fatigue, thirst                    |                                                                                                                                      |
| Nervous system disorders                             |                                       | dysgeusia, headache, taste perversion                                       | loss of consciousness <sup>1</sup> , dyskinesia <sup>1</sup> , tremor, dizziness, somnolence                                               | convulsions, aguesia, parosmia, anosmia                                                                                              |
| Ear and labyrinth disorders                          |                                       |                                                                             | vertigo, hearing impaired, tinnitus                                                                                                        | deafness                                                                                                                             |
| Cardiac disorders                                    |                                       |                                                                             | cardiac arrest <sup>1</sup> , atrial fibrillation <sup>1</sup> , electrocardiogram QT prolonged, extrasystoles <sup>1</sup> , palpitations | ventricular tachycardia, torsade de pointes                                                                                          |
| Gastrointestinal disorders                           |                                       | nausea, diarrhoea, vomiting,                                                | esophagitis <sup>1</sup> , gastroesophageal                                                                                                | pancreatitis acute; tongue discolouration,                                                                                           |

|                                                       |  |                                                                                                                                                 |                                                                                                                                                                                               |                                                                                                                                                                                                                                           |
|-------------------------------------------------------|--|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                       |  | abdominal pain, dyspepsia                                                                                                                       | reflux disease <sup>2</sup> , gastritis, proctalgia, stomatitis, glossitis, abdominal distention <sup>4</sup> , constipation, dry mouth, eructation, flatulence, gastrointestinal haemorrhage | tooth discolouration                                                                                                                                                                                                                      |
| Hepato-biliary disorders                              |  | liver function test abnormal                                                                                                                    | hepatitis <sup>4</sup> , cholestasis <sup>4</sup> , alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased <sup>4</sup>                | fatal hepatic failure has been reported particularly in patients with pre-existing liver disease or taking other hepatotoxic drugs                                                                                                        |
| Skin and subcutaneous tissue disorders                |  | rash, hyperhidrosis                                                                                                                             | dermatitis bullous <sup>1</sup> , dry skin, pruritus, urticaria, rash maculopapular <sup>3</sup>                                                                                              | severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). |
| Musculoskeletal, connective tissue and bone disorders |  |                                                                                                                                                 | muscle spasms <sup>3</sup> , musculoskeletal stiffness <sup>1</sup> , myalgia <sup>2</sup>                                                                                                    | Rhabdomyolysis, myopathy, exacerbation of symptoms of myasthenia gravis                                                                                                                                                                   |
| Renal and urinary disorders                           |  |                                                                                                                                                 | blood creatinine increased <sup>1</sup> , blood urea increased <sup>1</sup>                                                                                                                   |                                                                                                                                                                                                                                           |
| Investigations                                        |  | albumin globulin ratio abnormal <sup>1</sup> , alkaline phosphatase increased <sup>4</sup> , blood lactate dehydrogenase increased <sup>4</sup> |                                                                                                                                                                                               | international normalised ration increased, increased prothrombin time, urine colour 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

#### 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 diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients.

### ***Paediatric populations***

Adolescents under 12 years of age should use clarithromycin paediatric suspension.

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

### ***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 1000 mg and 2000mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, 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 1000mg and 2000mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analysing 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 1000mg or 2000mg 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 4000mg daily for all parameters except White Blood Cell.

## **14 Symptoms and Treatment of Overdose**

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxemia.

Adverse reactions accompanying overdose should be treated by the prompt elimination of unabsorbed active substance and supportive measures, such as emptying the stomach content and use of activated charcoal.

As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

#### **15 Storage condition**

Do not store above 30°C.

#### **16 Shelf life**

3 years

#### **17 pack size**

10 tabs/blister/carton

#### **18. Manufacturer**

**Sunshine Lake Pharma Co., Ltd.**

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