SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Clarithromycin 500 mg film-coated tablets
Clarigen 500

2. Qualitative and quantitative composition
Each tablet contains 500 mg of clarithromycin.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablet.

Yellow-coloured, capsule-shaped, concave, film-coated tablets, with a breakline on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications
Clarithromycin is indicated for the treatment of the following bacterial infections in adults and children 12 years and older when caused by clarithromycin-susceptible bacteria (see sections 4.4 and 5.1).

- *Bacterial pharyngitis*.
- Mild to moderate community-acquired pneumonia.
- Acute bacterial sinusitis (adequately diagnosed).
- Acute exacerbation of chronic bronchitis.
- Skin infections and soft tissue infections of mild to moderate severity.

Clarithromycin film-coated tablets are also indicated for the eradication of *Helicobacter pylori* in adult patients with *Helicobacter pylori*-associated ulcers, in appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing agent (see section 4.2). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
The dosage of clarithromycin film-coated tablets depends on the clinical condition of the patient and has to be defined in any case by the physician.

Children older than 12 years and adults

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

Clinical trials have been conducted using clarithromycin pediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin pediatric suspension (granules for oral suspension).

Eradication of H. pylori in patients with duodenal ulcers (Adults)
The usual duration of treatment is 6 to 14 days.

Triple Therapy
Clarithromycin (500 mg) twice daily and lansoprazole 30 mg twice daily should be given with amoxicillin 1000 mg twice daily.

Triple Therapy
Clarithromycin (500 mg) twice daily and lansoprazole 30 mg twice daily should be given with metronidazole 400 mg twice daily.

Triple Therapy
Clarithromycin (500 mg) twice daily and omeprazole 40 mg daily should be given with amoxicillin 1000 mg twice daily or metronidazole 400 mg twice daily for 7 days.

Triple Therapy
Clarithromycin (500 mg) twice daily should be given with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily.

Dual Therapy
The usual dose of clarithromycin is 500 mg three times daily. Clarithromycin should be administered with oral omeprazole 40 mg once daily. The pivotal study was conducted with omeprazole 40 mg once daily for 28 days. Supportive studies have been conducted with omeprazole 40 mg once daily for 14 days.

Dosage in patients with renal impairment
The maximum recommended dosages should be reduced proportionately to renal impairment. In patients with renal impairment with creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be reduced by one-half, i.e., 250 mg once daily, or 250 mg twice daily. Treatment should not be continued beyond 14 days in these patients.

Duration of therapy
The duration of therapy with Clarithromycin film-coated Tablets depends on the clinical condition of the patient. The duration of therapy has in any case to be determined by the physician.

- The usual duration of treatment is 6 to 14 days.
- In *Streptococcus pyogenes* (as a beta-haemolytic streptococcal) infections the duration of therapy should be at least 10 days.
- Combination therapy for the eradication of *H. pylori* infection, e.g., clarithromycin 500 mg twice daily in combination with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily should be continued for 7 days.

Method of administration
Oral use.

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

4.3 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs or to any of its excipients.

In the case of Clarigen, as the dose cannot be reduced from 500 mg daily, it is contraindicated in patients with creatinine clearance less than 30 mL/min. All other formulations may be used in this patient population.

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

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, pimozide and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see section 4.5).

Clarithromycin should not be given to patients with a history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes (see sections 4.4 and 4.5).

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. (See section 4.5).

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

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

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

4.4 Special warnings and 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 (see section 4.6).

Caution is advised in patients with severe renal insufficiency (see section 4.2). 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 (see section 4.8) 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 the use of nearly all antibacterial agents including clarithromycin and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. CDAD must be considered in all patients who present with diarrhoea following antibiotic use.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated.

Drugs inhibiting peristalsis should be avoided.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5). Concomitant administration of clarithromycin and colchicine is contraindicated (see section 4.3).

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam (see section 4.5).
Caution is advised regarding the concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.

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 (see section 4.5).

Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or a history of ventricular arrhythmia (see section 4.3).

Pneumonia
Given 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, maybe 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, DRESS and Henoch-Schonlein purpura, 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 (see section 4.5).

HMG-CoA Reductase Inhibitors (statins)
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). 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. The use of a statin that is not dependent on CYP3A metabolism (e.g., fluvastatin) can be considered (see section 4.5).

Oral hypoglycaemic agents/Insulin
The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylureas) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended (see section 4.5).

Oral anticoagulants
There is a risk of serious haemorrhage and significant elevations in the International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin (see section 4.5). 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 be selected 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 macrolide drugs, as well as lincomycin and clindamycin.

4.5 Interaction with other medicinal products and other forms of interaction

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

Cisapride, pimozide, astemizole and terfenadine
Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes.
Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly (see section 4.3).

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 (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a 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 clinical detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergotamine/dihydroergotamine
Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3).

HMG-CoA Reductase Inhibitors (statins)
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see 4.3) 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 inhibitor administered). Concomitant administration of rifabutin and clarithromycin increased rifabutin and decreased clarithromycin serum levels together with an increased risk of uveitis.

The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

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

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

Fluconazole
Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady-state concentrations of the active metabolite 14- OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir
A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased by 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 for 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 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 drug primarily metabolised by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively metabolised by this enzyme.

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

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g., warfarin, see 4.4), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus,

terfenadine, 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 the CYP3A enzyme by clarithromycin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

Omeprazole

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

Sildenafil, tadalafil and vardenafil

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

Theophylline, carbamazepine

Results of clinical studies indicate that there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs was 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

Aminoglycosides

Caution is advised regarding the concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. See section 4.4.

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 (see section 4.4).

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 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 metabolised 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 for 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) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies 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 (see section 4.5: Ritonavir). Clarithromycin has been shown not to interact with oral contraceptives.

4.6 Pregnancy and lactation

Pregnancy
There is no or limited amount of data on the use of clarithromycin in pregnant women. Animal studies are insufficient concerning reproductive toxicity (see section 5.3). Clarithromycin is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding
Clarithromycin/metabolites have been identified in breastfed newborns/infants of treated women. The effect of clarithromycin on newborns/infants is unknown.

Fertility
Data from animal studies has shown no adverse effects on fertility. The risk for humans is unknown (see section 5.3).

4.7 Effects on the ability to drive and use machines
There is 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

Summary of the safety profile
The most frequent and common adverse reactions related to clarithromycin therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics (see section b of section 4.8).

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

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

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

System Organ Class	Very common ≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥1/1,000 to < 1/100	Not Known* (cannot be estimated from the available data)

Infections and infestations			Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection	Pseudomembranous colitis, erysipelas,
Blood and lymphatic system			Leukopenia, neutropenia[4], thrombocythaemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders[5]			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction. angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3], screaming[3]	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams
Nervous system disorders		Dysgeusia, headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[6], tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest1, atrial fibrillation1, electrocardiogram QT prolonged7, extrasystoles1, palpitations	Torsades de pointes7, ventricular tachycardia7
Vascular disorders		Vasodilation1		Haemorrhage8
Respiratory, thoracic and mediastinal disorder			Asthma1, epistaxis2, pulmonary embolism1	
Gastrointestinal disorders		Diarrhoea9, vomiting, dyspepsia,	Oesophagitis1, gastrooesophageal reflux disease2,	Pancreatitis acute, tongue discolouration, tooth discolouration

		nausea, abdominal pain	gastritis, proctalgia2, stomatitis, glossitis, abdominal distension4, constipation, dry mouth, eructation, flatulence,	
Hepatobiliary disorders		Liver function test abnormal	Cholestasis4, hepatitis4, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased4	Hepatic failure10, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous1, pruritus, urticaria, rash maculo- papular3	Stevens-Johnson syndrome5, toxic epidermal necrolysis5, drug rash with eosinophilia and systemic symptoms (DRESS), acne, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders			Muscle spasms3, musculoskeletal stiffness1, myalgia2	Rhabdomyolysis2,11**, myopathy
Renal and urinary disorders			Blood creatinine increased1, blood urea increased1	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain1, injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal1, blood alkaline phosphatase increased4, blood lactate dehydrogenase increased4	International normalised ratio increased8, prothrombin time prolonged8, urine colour abnormal

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

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

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

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

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

[6, 8, 11] See section c)

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

***In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with other drugs known to be associated with rhabdomyolysis (such as statins, fibrates, colchicine or allopurinol).*

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 (see sections 4.3 and 4.4).

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 (see section 4.5). 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.

Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There is insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age. The frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Other special populations

Immunocompromised patients

In AIDS and other immunocompromised patients treated with higher doses of clarithromycin over long periods 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 2000 mg 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 1000 mg and 2000 mg but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000 mg 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. Based on these criteria, about 2% to 3% of those patients who received 1000 mg or 2000 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 4000 mg daily for all parameters except White Blood Cells.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose
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 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drugs and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 7.2.5 Other antibacterials.

Mechanism of action
Clarithromycin exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.
The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound, except for H influenzae where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Breakpoints
The following breakpoints have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

Breakpoints (MIC, mg/L)		
Microorganism	Susceptible (≤)	Resistant (>)
Staphylococcus spp.	1 mg/L	2 mg/L
Streptococcus A, B, C and G	0.25 mg/L	0.5 mg/L
Streptococcus pneumonia	0.25 mg/L	0.5 mg/L
Viridans group streptococcus	IE	IE
Haemophilus spp.	1 mg/L	32 mg/L
Moraxella catarrhalis	0.25 mg/L	0.5 mg/L[1]
Helicobacter pylori	0.25 mg/L1	0.5 mg/L

[1] The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.
"IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug.

Susceptibility
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only appropriate guidance on the probabilities of whether microorganisms will be susceptible to clarithromycin or not.

Commonly susceptible species
Aerobic Gram-positive microorganisms
Streptococcus agalactiae
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus viridans
Streptococcus (Diplococcus) pneumoniae
Staphylococcus aureus (methicillin-susceptible)
Listeria monocytogenes
Aerobic Gram-negative microorganisms
Bordetella pertussis
Haemophilus influenzae
Haemophilus parainfluenzae
Helicobacter pylori
Campylobacter jejuni

Moraxella (Branhamella) catarrhalis
Neisseria gonorrhoeae
Legionella spp.
Anaerobic microorganisms
Clostridium perfrigens
Bacterioides fragilis
Peptococcus/Peptostreptococcus spp.
Propionibacterium acnes
Other microorganisms
Mycoplasma pneumoniae
Chlamydia trachomatis
Ureaplasma urealyticum
Mycobacterium spp.

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

Other information
Susceptibility and resistance of *Streptococcus pneumoniae* and *Streptococcus spp*. to clarithromycin can be predicted by testing erythromycin.

The mechanisms of acquired resistance in macrolides are efflux of the drug by an active pump mechanism, inducible or constitutive production of a methylase enzyme that modifies the ribosomal target, hydrolysis of macrolides by esterases, chromosomal mutations that alter a 50 S ribosomal protein. Cross-resistance between clarithromycin and other macrolides and clindamycin and lincomycin may therefore occur. Methicillin-resistant and oxacillin-resistant staphylococci (MRSA) and penicillin-resistant *Streptococcus pneumoniae* are resistant to all currently available beta-lactam antibiotics and macrolides such as clarithromycin.

Most available clinical experience from controlled randomised clinical trials indicates that clarithromycin 500 mg twice daily in combination with another antibiotic e.g., amoxicillin or metronidazole e.g., omeprazole (given at approved levels) for 7 days achieves >80% *H. pylori* eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant *H. pylori* isolates. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken into account in the choice of an appropriate combination regimen for *H. pylori* eradication therapy. Furthermore, in patients with persistent infection, the potential development of secondary resistance (in patients with primary susceptible strains) to an antimicrobial agent should be taken into consideration for a new treatment regimen.

5.2 Pharmacokinetic properties

Absorption
Clarithromycin is rapidly and well absorbed from the gastrointestinal tract - primarily in the jejunum - after oral administration. Due to its chemical structure (6-0- Methylerythromycin), clarithromycin is quite resistant to degradation by stomach acid. Serum levels of 1 - 2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily serum levels of 2, 8 µg/ml were obtained. After administration of 250 mg clarithromycin twice daily the pharmacologically active 14-hydroxy metabolite attains peak plasma concentrations of 0, 6 µg/ml.

Distribution
Clarithromycin gives good penetration into different compartments. Therapeutic drug levels exceeding the minimum inhibitory levels for common pathogens can be rapidly achieved. Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin also penetrates the gastric mucus. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

Serum half-life
The serum half-life of the active 14-(R)-hydroxy metabolite ranges between 5 to 6 hours.

Biotransformation and elimination
Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism involves mainly N-dealkylation, oxidation and stereospecific hydroxylation at position C 14.

After oral administration of radioactive clarithromycin, 70 - 80% of the radioactivity was found in the faeces. Approximately 20 -30% of clarithromycin is collected as the unchanged parent molecule in the urine. This proportion is increased when the dose is increased. Renal insufficiency increases clarithromycin levels in plasma if the dose is not decreased.

The pharmacokinetics of clarithromycin are non-linear. This is an indication of the saturation of hepatic metabolism at high doses. However, a steady state is attained within 2 days of dosing.

5.3 Preclinical safety data
In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5g/kg).

In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species, the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected include the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats [Wistar (p.o.) and Spraque-Dawley (p.o. and i.v.)], New Zealand White rabbits and cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. However, a further similar study in Sprague-Dawley rates indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels which were toxic to the mothers.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Sodium starch glycolate
Maize starch
Magnesium stearate
Croscarmellose sodium
Colloidal anhydrous silica

Tablet coat
Yellow colourcoat FC4WQ 260109
Isopropyl alcohol
Methylene chloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of the container

The tablets are packed in Alu-PVC blister packs.

Pack size: 2 x 7 tablets.

6.6 Special precautions for disposal and handling

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

7. APPLICANT

Cospharm Investments (Pty) Limited
ERF 492 Dante Street, Prosperita
Windhoek
Namibia

8. MANUFACTURER

Celogen Pharma Pvt. Limited
Plot no.: 646/1&2 Agrawal Industrial Somnath Road
Dabhel, Daman (UT)-396210
India

9. REGISTRATION DETAILS

Zimbabwe registration number: 2023/7.2.5/6434
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF TEXT

October 2023