Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains clarithromycin 500 mg.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

Light yellow coloured, oval shaped biconvex film coated tablets, with "C" and "2" embossed on either side of a breakline on one side and notched on both sides. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Clarithromycin is indicated for use in adults and adolescents older than 12 years for the treatment of infections caused by micro-organisms sensitive to clarithromycin. These infections include:

- Lower respiratory tract infections for example bronchitis, and pneumonia (see section 4.4 and 5.1 regarding Sensitivity Testing).
- Upper respiratory tract infections for example sinusitis and pharyngitis.

- Acute otitis media

- Skin and soft tissue infections (e.g. impetigo, folliculitis, cellulitis, abscesses) (see section 4.4 and 5.1 regarding Sensitivity Testing)
- Disseminated or localised *Mycobacterium avium* or *Mycobacterium intracellulare* infections; localised *Mycobacterium chelonae*, *Mycobacterium fortuitum* or *Mycobacterium kansasii* infections.

In HIV-infected patients (CD4 cell count ≤100 / mm^3), clarithromycin is indicated for the prevention of disseminated infections caused by the *Mycobacterium avium* (MAC) complex.

In patients with duodenal ulceration and diagnostically confirmed *Helicobacter pylori* infection, clarithromycin treatment is recommended simultaneously with preparations that suppress gastric acid secretion and other antibiotics.

4.2 Posology and method of administration

Dosage

Patients with respiratory tract, skin and soft tissue and acute otitis media infections:
Adults:

In severe infections 500 mg of clarithromycin twice a day (every 12 hours). The usual duration of treatment is 5 to 14 days, with the exception of pneumonia and sinusitis, when treatment should last 6 to 14 days.

Adolescents older than 12 years: As for adults

Children aged 12 and younger:

Use of Clarithromycin form of coated tablets has not been studied for children younger than 12 years.
Therefore, children aged 12 and younger should use clarithromycin pediatric suspension (granules for oral suspension).

Patients with renal insufficiency. In patients with renal insufficiency (creatinine clearance less than 30 ml / min) the dose of clarithromycin should be halved, i.e. administered 250 mg once daily or in severe infections, 250 mg twice daily. It is recommended to use a product containing 250 mg of clarithromycin in one tablet. Do not give the drug for more than 14 days.

Infections caused by microorganisms of the *Mycobacterium*
The recommended dose for adults is 500 mg of clarithromycin twice daily.

Treatment of the disseminated form of infection caused by the *Mycobacterium avium* (MAC) complex in AIDS patients should continue until a beneficial clinical and bacteriological effect is observed. Clarithromycin should be used in combination with other medicines acting on *Mycobacterium*.

If other, non-tuberculous infections with *Mycobacterium*-type organisms are found, treatment should be continued.

Prevention of infection caused by MAC
The recommended dosage in adults is 500 mg twice daily.

Helicobacter pylori infection
In patients with gastric or duodenal ulcer disease caused by *Helicobacter pylori* infection, clarithromycin may be administered for 7 to 14 days at a dose of 500 mg twice daily, in combination with other appropriate antibacterial and proton pump inhibitors, in accordance with national and international recommendations on *Helicobacter pylori* eradication.

4.3 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to macrolides antibiotic group or to any of the excipients listed in section 6.1.

Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see section 4.5).

Concomitant administration of clarithromycin and any of the followingdrugs is contraindicated:astemizole, cisapride, domperidone, pimozide and terfenadine, as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and ventricular arrhythmia *torsade de pointes* (see section 4.4 and 4.5).

Concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.5).

Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including *torsades de pointes* (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 4.4)

As with other strong CYP3A4 inhibitors, clarithromycin should not be used in patients taking colchicine (see sections 4.4 and 4.5).

Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).

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

Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

The use of any antibacterial drug such as clarithromycin in the treatment of *Helicobacter pylori* infection can lead to the isolation of drug-resistant microorganisms.

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

Prolonged use may, as with other antibiotics, cause the development of non-susceptible bacteria and fungi. If superinfection occurs, appropriate treatment should be started.

Clarithromycin is mainly metabolised by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.
During Clarithromycin use it has been reported impaired hepatic function, including increased liver enzymes and parenchymal and / or cholestatic hepatitis with or without jaundice. Such liver dysfunction may be severe and it is generally transient. In some cases, hepatic failure leading to death was reported. In general, it was associated with serious underlying diseases and / or concomitant medications. Patients should be advised to stop treatment immediately 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.

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 (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 for intravenous and oral mucosal administration (see section 4.5).

Cardiovascular Events
Prolongation of the QT interval, reflecting effects on cardiac repolarisation, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in patient treatment with macrolides including clarithromycin (see section 4.8). Due to increased risk of QT prolongation and ventricular arrhythmias (including *torsade de pointes*), the use of clarithromycin is contraindicated: in patients taking any of astemizole, cisapride, domperidone, pimozide and terfenadine; in patients who have hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac arrhythmia (see section 4.3).

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

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

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

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

Skin and soft tissue infections of mild to moderate severity: These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed.
In cases where *beta*–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum*, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) [e.g. acute generalised exanthematous pustulosis (AGEP), Stevens - Johnson syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)], clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

Bacteria resistant to clarithromycin may also show resistance to other macrolide antibiotics, lincomycin and clindamycin (so-called cross-resistance).

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. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see section 4.5).

Oral hypoglycemic agents and/or 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 hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.
Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding (see section 4.5).

Excipients
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

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

Cisapride, pimozide, domperidone, astemizole and terfenadine
Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This can cause ECG changes - 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 two to three fold increase in the serum level of the acid metabolite of terfenadine

and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergot alkaloids

Postmarketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated (see section 4.3).

Midazolam administered orally
When clarithromycin tablets (500 mg twice daily) were co-administered with oral midazolam, the area under the curve (AUC) of midazolam increased 7-fold. Concomitant oral administration of midazolam and clarithromycin 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 isoenzyme metabolism (e.g.fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

Concomitant administration of clarithromycin with lomitapide is contraindicated due the potential for markedly increased transaminases (see section 4.3).

Effects of other medicinal products on clarithromycin

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

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

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

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

Fluconazole

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

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31%, C_{min} increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (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 metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.

The use of clarithromycin is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, domperidone, pimozide and terfenadine due to the risk of QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and *torsades de pointes* (see sections 4.3 and 4.4).

The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazolam, HMG CoA reductase inhibitors metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor and ranolazine (see section 4.3).

Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolized by this enzyme.

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

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme (but this list is not comprehensive): alprazolam, carbamazepine, cilostazole, ciclosporin, disopyramide, ibrutinib, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics

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

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

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

Omeprazole
Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

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

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

Tolterodine
The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

Triazolobenzodiazepines (e.g. alprazolam, midazolam, triazolam)
When midazolam was co-administered with clarithromycin tablets (500 mgtwice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

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

Direct acting oral anticoagulants (DOACs)
The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

Other drug interactions

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. When clarithromycin and colchicine are administered together, inhibition of P-gp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine (see section 4.3 and 4.4).

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (P-gp). Clarithromycin is known to inhibit P-gp. When clarithromycin and digoxin are administered together, inhibition of P-gp 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 appearsto interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

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

Interactions between clarithromycin and other drugs

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) to 12 healthy volunteers 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 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 above - Ritonavir).

4.6 Fertility, pregnancy and lactation

Pregnancy:
The safety of clarithromycin for use during pregnancy has not been established. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks.

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

Fertility
In fertility studies in rats, no adverse effects have been demonstrated (see section 5.3).

4.7 Effects on ability to drive and use machines

There are no data available 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

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

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

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, 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; frequency 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			Leukopenia,	Agranulocytosis, thrombocytopenia

lymphatic system			neutropenia[4], thrombocythemia[3], eosinophilia[4]	
Immune system disorders[5]			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3]	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache,	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence, tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations	Torsade de pointes, ventricular tachycardia ventricular fibrillation
Vascular disorders		Vasodilation[1]		Hemorrhage
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhoea[9], vomiting, dyspepsia, nausea, abdominal pain	Oesophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence,	Pancreatitis acute, tongue discolouration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3]	Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, Severe cutaneous adverse reactions (SCAR)

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

[1] ADRs reported only for the Powder for Solution for Injection formulation
[2]ADRs reported only for the Modified-Release Tablets formulation
[3] ADRs reported only for the Granules for Oral Suspension formulation
[4] ADRs reported only for the Immediate-Release Tablets formulation

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

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

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 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.

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 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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
Reports indicate the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Symptoms of overdose may largely correspond to the profile of adverse reactions. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxaemia

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharamacotherapeutic group: Antibacterial for systemic use, macrolides
ATC Code: J01FA09
Mechanismof action:
Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50S ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis

Clarithromycin demonstrates excellent *in vitro* activity against standard strains of clinical isolates. 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.

In vitro studies also indicate very strong activity of clarithromycin on Legionella pneumophila and Mycoplasma pneumoniae. Clarithromycin has a bactericidal effect on Helicobacter pylori, the effect being stronger in an inert environment than in an acidic environment.
Data from in vitro and in vivo studies show that this antibiotic works on clinically relevant microorganisms of the Mycobacterium genus. In in vitro studies, lack of sensitivity to clarithromycin of Enterobacteriaceae and the Pseudomonas genus and other Gram-negative bacilli that did not cause lactose fermentation was demonstrated.

The micro-organisms sensitive to clarithromycin in vitro and in vivo are listed below.

Aerobic Gram-positive Bacteria
Staphylococcus aureus,Streptococcus pneumoniae, Streptococcus pyogenes; Listeria monocytogenes.

Aerobic Gram-negative Bacteria
Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella catarrhalis, Neisseria gonorrhoeae; Legionella pneumophila.

Other microorganisms
Mycoplasma pneumoniae, Chlamydia pneumoniae.

Mycobacteria
Mycobacterium leprae, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium fortuitum, Mycobacterium avium complex (MAC), which includes Mycobacterium avium and Mycobacterium intracellulare.

The production of beta-lactamase usually does not affect the activity of clarithromycin.

Note. Most methicillin and oxacillin-resistant *Staphylococci* strains are also resistant to clarithromycin.

Micro-aerophilic bacteria
Helicobacter pylori.

Studies have shown that the following microorganisms are sensitive to clarithromycin *in vitro*, but the clinical relevance of these studies has not been confirmed by properly documented clinical trials:

Aerobic Gram-positive Bacteria
*Streptococcus agalactiae, Streptococcus (*group C, F, G*), Streptococcus viridans.*

Aerobic Gram-negative Bacteria
Bordetella pertussis, Pasteurella multocida.

Anaerobic Gram-positive bacteria
Bacteroides melaninogenicus.

AnaerobicGram-positive Bacteria
Borrelia burgdorferi, Treponema pallidum, Campylobacter jejuni.

The microbiologically active metabolite of clarithromycin in humans is 14-OH-clarithromycin. This metabolite acts on most bacteria with the same strength as the parent compound or up to 2 times less; only on *H. influenzae* works twice as strongly. The parent compound and 14-OH-clarithromycin have an *in vitro* and *in vivo* additive or synergistic activity with *H. influenzae*, depending on the type of strain.

In several experimental animal models of infection, clarithromycin was found to work 2 to 10 times more potent than erythromycin. For example, in mice, clarithromycin was found to be more effective than erythromycin in systemic infection, subcutaneous abscess and respiratory infections caused by *S. pneumoniae, S. aureus, S. pyogenes and H. influenzae.*
In guinea pigs infected with *Legionella*, this effect was more pronounced - the clarithromycin at the dose of 1.6 mg / kg / day given by the intraperitoneal route was more effective than erythromycin 50 mg / kg / day.

Mechanism of resistance
Acquired resistance to macrolides in *S. pneumoniae, S. pyogenes and S. aureus* arises mainly through one of two mechanisms (i.e. *erm* and *mef* or *msr*). Binding of the antibacterial drug to the ribosomes prevents the enzyme methylation of the ribosome (*erm*). Alternatively, the mechanism of active transport outside the cell (*mef* or *msr*) can interfere with the antibacterial agent in achieving the goal, which is the ribosome, by pumping the antibacterial agent from the cell. The acquired resistance mechanisms have not been identified in *Moraxella* or *Haemophilus spp*. Mechanisms of resistance to macrolides are equally effective against macrolides with 14 and 15 carbonaceous lactone rings, such as erythromycin, clarithromycin, roxithromycin and azithromycin. Mechanisms of resistance to penicillin and resistance to macrolides are not related.

Attention should be paid to cross-reactive mediators that develop via *erm* between macrolides, such as clarithromycin, and lincosamides, such as lincomycin and clindamycin.

Breakpoints:

According to the EUCAST (European Committee on Antimicrobial Susceptibility Testing) the following breakpoints have been established for clarithromycin:

Breakpoints (MIC, mcg/ml)		
Microorganism	Susceptible (£)	Resistant (>)
Streptococcus spp.	0.25 mcg/ml	0.5 mcg/ml
Staphylococcus spp.	1 mcg/ml	2 mcg/ml
Haemophilus spp.	1 mcg/ml	32 mcg/ml
Moraxella catarrhalis	0.25 mcg/ml	0.5 mcg/ml
Clarithromycin is used for the eradication of *H. pylori*; minimum inhibitory concentration (MIC) ≤ 0.25 mcg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).		

The rates of occurrence of acquired resistance of selected species may be different in different geographic regions and at different time periods and it is advisable to obtain information on resistance in a given area, especially when treating severe infections. If necessary, ask the experts whether the presence of resistance in a given region is so high that the usefulness of the drug in at least some types of infections is questionable.

5.2 Pharmacokinetic properties

Absorption:
The pharmacokinetic properties of clarithromycin administered orally have been evaluated in a number of studies conducted on many animal species and in adult humans. These studies have shown that clarithromycin is well and rapidly absorbed from the gastrointestinal tract, and its bioavailability is about 50%. There was no accumulation of the drug or it was small. The consumption of food immediately before the dose administration increases the bioavailability of clarithromycin by an average of 25%, which is of little clinical relevance when used at the recommended dosage. Clarithromycin can therefore be administered with food or on an empty stomach.

Distribution, biotransformation, elimination:
In vitro
In vitro, clarithromycin was shown to bind to human plasma proteins at approximately 70% when its concentration is between 0.45 and 4.5 µg/ml. A reduction in the percentage of antibiotic associated with proteins to 41% was observed when its concentration was 45.0 µg/ml, indicating that all binding sites of the drug are likely to be saturated. However, this occurs only when the concentration of antibiotic is significantly higher than the therapeutic concentration.

In vivo
The results of animal studies showed that the concentration of clarithromycin in all tissues, with the exception of the central nervous system, was several times higher than in the blood concentration. The highest concentrations were usually found in the liver and lungs, where the ratio of drug concentrations in tissue to plasma concentrations ranged from 10 to 20.

Healthy persons
After an oral dose of 250 mg twice daily, steady-state is achieved after 2-3 days. At steady-state the mean maximum plasma clarithromycin concentration is approximately 1 µg/ml, and the concentration of 14-OH-clarithromycin 0.6 µg/ml. The half-lives of the parent compound and the active metabolite are 3-4 hours and 5-6 hours, respectively. Oral administration of clarithromycin 500 mg twice daily resulted in the maximum steady-state drug and active metabolite (C_{max}) concentrations achieved after the fifth dose. After the fifth and seventh doses, the mean clarithromycin Cmax values were 2.7 and 2.9 µg / ml, respectively, and 14-OH-clarithromycin 0.88 and 0.83 µg/ml. After administration of 500 mg, the half-life of clarithromycin was 4.5-4.8 hours, and 14-hydroxymetabolite was 6.9-8.7 hours. It has been shown that after reaching steady state, increasing the dose does not increase the concentration of 14-OH-clarithromycin, while the half-life of clarithromycin and its metabolite is prolonged. These non-linear changes in the pharmacokinetic parameters of clarithromycin in combination with the formation of 14-hydroxylation and N-demethylation products limitation indicate that the non-linear course of the drug metabolism is more pronounced at high doses.

Clarithromycin is metabolised in the liver. After a single oral administration of 250 mg or 1.2 g of clarithromycin in urine, 37.9% or 46% of the administered dose is excreted, respectively, and 40.2% or 29.1% in faeces.

Patients
Clarithromycin and its metabolite, 14-OH-clarithromycin, penetrate rapidly into tissues and body fluids. Limited data from a small number of patients indicate that clarithromycin does not reach significant concentrations in the cerebrospinal fluid after oral administration. (In patients with normal blood-cerebrospinal fluid barrier, the clarithromycin concentration in the cerebrospinal fluid is only 1 to 2% of the concentration found in the serum). The concentration in tissues is usually several times higher than in serum concentration. Examples of concentrations in tissues and serum are given below.

CONCENTRATION (after 250 mg every 12 h)		
Type of tissue	Tissue (µg/g)	Serum (µg/ml)
Palatine tonsil	1,6	0,8
Lung	8,8	1,7

Liver failure
In a trial comparing healthy adults to a group of patients with liver failure, 250 mg of clarithromycin twice daily for two days and a single dose of 250 mg on the third day were administered. There were no significant differences between plasma clarithromycin at steady state and total drug clearance in both groups. In contrast, steady state concentrations of 14-hydroxymetabolite were significantly lower in the group of patients with liver failure. The reduction in the formation of 14-OH-clarithromycin in the liver was partially compensated for by increasing the renal clearance, thanks to which the steady state concentrations of the drug were comparable in patients with liver failure and in healthy subjects. This study shows that there is no need to change the dosage in patients with moderate or severe liver failure, but normal renal function.

Renal failure
The pharmacokinetic parameters of clarithromycin after multiple oral doses of 500 mg to patients with normal renal function and renal failure were compared. In patients with renal failure there was an increase in plasma concentration, half-life, C_{max} and C_{min}, and AUC of clarithromycin and its 14-hydroxymethabolite. The K_{-elim} value and urinary excretion were reduced. The difference between these parameters correlated with the degree of renal failure, i.e. the more severe renal failure, the more significant the difference (see section 4.2).

Elderly patients
A study was conducted to compare the safety and pharmacokinetic profile of clarithromycin after repeated oral administration of doses of 500 mg to healthy elderly men and women and healthy young men. In the elderly group, plasma concentrations of the drug and its metabolite were higher, and the excretion was slower than in the group of young people. There were, however, no differences between the two groups when renal clearance was correlated with creatinine clearance. The research shows that all changes in the metabolism of clarithromycin in the body depend on kidney function, not on age.

Infections caused by Mycobacterium avium
The concentration of clarithromycin and its metabolite at steady-state in adult patients infected with human immunodeficiency virus (HIV), treated with clarithromycin given every 12 hours at a dose of 500 mg, were similar to those found in healthy subjects. However, the administration of higher doses necessary to treat infections caused by *Mycobacterium avium* causes plasma clarithromycin concentrations to be much greater than those observed after administration of the usual doses. In adult patients infected with HIV receiving 1 gram and 2 grams of clarithromycin per day in two divided doses, steady-state C_{max} was 2-4 µg/ml and 5-10 µg/ml, respectively. The elimination half-life was longer after the administration of these higher doses compared to the usual doses in healthy subjects. Elevated plasma concentrations and a longer half-life result from the non-linear course of clarithromycin pharmacokinetics.

Combination therapy with omeprazole
The pharmacokinetics of clarithromycin, given three times daily at a dose of 500 mg and omeprazole 40 mg once a day, were analysed. When clarithromycin was given every 8 hours, the mean steady-state C_{max} was around 3.8 µg/ml, and C_{min} around 1.8 µg/ml. The clarithromycin AUC0-8 value was 22.9 µg*h/ml. T_{max} and half-life were 2.1 hours and 5.3 hours, respectively.

In the same study, when clarithromycin was given with omeprazole, it increased the AUC_{0-24} value and the half-life of omeprazole. The mean omeprazole AUC_{0-24} was 89% higher and the mean $T_{1/2}$ harmonic value was 34% higher when omeprazole was co-administered with clarithromycin compared to omeprazole only. In contrast, C_{max}, C_{min} and AUC_{0-8} at steady-state were 10%, 27% and 15% higher, respectively, compared to values obtained from the administration of clarithromycin with placebo.

At steady-state, 6 hours after administration, the clarithromycin concentration in the gastric mucosa was approximately 25-fold higher in the clarithromycin and omeprazole group than in the clarithromycin-only group. Six hours after dosing, the average clarithromycin concentration in the gastric tissue was approximately 2-fold higher in the case of clarithromycin with omeprazole than with clarithromycin with placebo.

5.3 Preclinical safety data

Acute, subchronic and chronic toxicity studies
Studies were conducted in mice, rats, dogs and monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for 6 consecutive months.

In acute mouse and rat studies, 1 rat, but no mice, died following a single gavage of 5 g/kg body weight. The median lethal dose was greater than the highest feasible dose for administration (5g/kg).

No adverse effects were attributed to clarithromycin in primates exposed to 100 mg/kg/day for 14 consecutive days or to 35 mg/kg/day for 1 month. Similarly, no adverse effects were seen in rats exposed to 75 mg/kg/day for 1 month, to 35 mg/kg/day for 3 months, or to 8 mg/kg/day for 6 months. Dogs were more sensitive to clarithromycin, tolerating 50 mg/kg/day for 14 days, 10 mg/kg/day for 1 and 3 months, and 4 mg/kg/day for 6 months without adverse effects.

The major clinical signs at toxic doses in these studies described above included emesis, weakness, reduced food consumption and reduced weight gain, salivation, dehydration, and hyperactivity. Two of 10 monkeys receiving 400 mg/kg/day for 28 days died on treatment day 8. Yellow discoloured faeces were passed on a few isolated occasions by some surviving monkeys. The primary target organ at toxic dosages in all species was the liver. The development of hepatotoxicity in all species was detectable by early elevation of serum concentrations of alkaline phosphatase, alanine and aspartate aminotransferase, gamma-glutamyl transferase, and/or lactic dehydrogenase. Discontinuation of the medicine generally resulted in a return to or toward normal concentrations of these specific parameters.

Additional tissues less commonly affected in the various studies included the stomach, thymus and other lymphoid tissues, and the kidneys. Conjunctival injection and lacrimation, following near therapeutic dosages, occurred in dogs only. At a massive dosage (400 mg/kg/day), some dogs and monkeys developed corneal opacities and/or edema.

Fertility, reproduction, mutagenicity and teratogenicity
Fertility and reproduction studies have shown daily dosages of 150 to 160 mg/kg/day to male and female rats caused no adverse effects on the oestrous cycle, fertility, parturition, and number and viability of offspring. Two teratogenicity studies in both Wistar (po) and Sprague-Dawley (po and i.v) rats, one study in New Zealand White rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony. Two studies in mice also revealed a variable incidence of cleft palate (3 to 30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg b.i.d), suggesting maternal and foetal toxicity but not teratogenicity.

Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately 10 times the upper range of the usual daily human dose (500 mg b.i.d), starting at gestation day 20. This effect has been attributed to maternal toxicity of the medicine at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage produced no unique hazard to the conceptus.

A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose) was clearly negative for any mutagenic activity, and, in a study of rats treated with up to 500 mg/kg/day (approximately 35 times the maximal daily human clinical dose), no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.

Mutagenicity
In mutagenic studies (Ames Test) the potential for mutagenicity of clarithromycin at drug cocnetrations of 25 mcg/petri plate or less was not demonstrated. At a concentration of 50 mcg, the drug was toxic for all strains tested.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Povidone
Magnesium stearate
Talc
Colloidal anhydrous silica
Stearic acid

Coating Material: Opadry 20H 52875 containing:
Hypromellose
Hydroxypropylcellulose
Propylene glycol
Vanillin
Titanium dioxide

Talc
Quinoline yellow lake (E 104).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The film-coated tablets are packed in blister strips (PVC PVdC) with aluminium foil backing.
The blisters are inserted into cardboard carton boxes.

Pack sizes:
Packs of 1, 10, 14, 20, 21, 30, 42, 50 or 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132JH Hoofddorp
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2050/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th October 2006
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10 DATE OF REVISION OF THE TEXT

January 2022