# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Clorom XL 500mg Prolonged-Release Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated prolonged-release tablet contains ;

Clarithromycin citrate equivalent to clarithromycin-500mg.

Each tablet contains 298 mg of lactose monohydrate
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged-release tablet.
Yellow coloured, film-coated, oblong shaped, biconvex tablet, with both sides plain.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Clorom XL 500mg Prolonged Release Tablets are indicated for treatment of:
Community acquired pneumonia

- Acute exacerbation of chronic bronchitis
- Acute bacterial sinusitis (adequately diagnosed)
- Skin and soft tissue infections (mild to moderate severity)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### 4.2 Posology and method of administration

Clorom XL 500mg Prolonged Release Tablets should be taken with food and must be swallowed whole and not chewed.

**Adults and Children over 12 years:**
The usual dosage is one 500 mg prolonged-release tablet daily for seven to fourteen days.
In more severe infections, the dosage can be increased to two 500 mg prolonged release tablets taken as one dose daily.
Dose must be taken at the same time every day.

**Children younger than 12 years:**
These tablets are not recommended for children under 12 years as liquid medicines are generally preferable. An alternative formulation of Clarithromycin suitable for children should be used in this patient population.

**Patients with renal impairment:**
Clorom XL 500mg Prolonged Release Tablets should not be used in patients with renal impairment (creatinine clearance less than 30 mL/min). Clarithromycin immediate release tablets may be used in this patient population. (See 4.3 Contraindications).

**Patients with hepatic impairment:**
The use of Clorom XL 500mg Prolonged Release Tablets is not recommended in patients with severe liver impairment.

## 4.3 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to clarithromycin or to any of the excipients

Clarithromycin is contra-indicated in patients with known hypersensitivity to macrolide antibiotic drugs.
Clarithromycin is contra-indicated in patients with severe liver impairment.

As the dose cannot be reduced from 500 mg daily, Clorom XL 500mg prolonged-release tablets are contra-indicated in patients with creatinine clearance less than 30 ml/min.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: ergot derivatives, cisapride, pimozide, astemizole, ergotamine dihydroergotamine and terfenadine (see section 4.5).
As the dose cannot be reduced from 500mg daily, Clarithromycin 500 mg Prolonged Release Tablets is contraindicated in patients with creatinine clearance less than 30 mL/min.

Patients with congenital or acquired hypokalaemia (QT prolongation)

## 4.4 Special warnings and precautions for use

Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic and renal function.

Prolonged or repeated used of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

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).

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

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

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.

Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If super-infections occur, appropriate therapy should be instituted.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Clarithromycin should not be given to patients with hypokalaemia (QT interval prolongation).Due to the risk of prolonged QT interval, clarithromycin should be used with caution in patients with coronary artery disease as well as patients with a history of ventricular arrhythmia, with severe cardiac insufficiency, non-compensated hypokalemia and/or hypomagnesaemia or bradycardia (pulse below 50). The use of clarithromycin is contraindicated in patients with congenital or acquired QT prolongation (see sections 4.3 and 4.5).

Caution should be exercised, if clarithromycin is indicated for patients receiving concomitant treatment with a CYP3A4 inducer, because it is possible that clarithromycin concentrations may not reach therapeutic levels (see section 4.5).

Clarithromycin is a CYP3A4 inhibitor, and its concomitant use with drugs primarily metabolised via this enzyme should be considered only when clearly necessary (see section 4.5).
Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these drugs (see section 4.5).
Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy.

## 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

Clarithromycin has been reported to elevate plasma levels of cisapride, pimozide, astemizole, and terfenadine. Increased levels of these drugs may result in increased risk of ventricular rhythm disorders, especially torsades de pointes.

Concomitant administration of clarithromycin and any of these medicinal products is contraindicated (see section 4.3).

Ergotamine/dihydroergotamine

Post-marketing reports indicate that coadministration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm, and ischemia of the extremities and other tissues including the central nervous system.

Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3).

Effect of other medicinal products on clarithromycin

Clarithromycin is metabolised via enzyme CYP3A4. Therefore, strong inhibitors of this enzyme may inhibit Clarithromycin metabolism, this results in increased plasma concentrations of Clarithromycin.

CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, phenobarbital, products containing St. John Wort) may induce clarithromycin metabolism. This may result in sub-therapeutic levels of clarithromycin which; decrease the product’s efficacy. If clarithromycin is clearly indicated, it may be necessary to increase the dose of clarithromycin, and closely monitor its efficacy and safety. Further monitoring of plasma levels of the CYP3A4 inducer may be necessary, because the levels may be increased due to CYP3A4 inhibition by clarithromycin (see also relevant Summary of Product Characteristics of the administered CYP3A4 inducer). Concomitant administration of rifabutin and clarithromycin has resulted in increased rifabutin levels and decreased clarithromycin levels in serum, and in an increased risk of uveitis. A 39% reduction in AUC for clarithromycin and a 34% increase in AUC for the active 14-OHhydroxy metabolite have been seen when clarithromycin was used concomitantly with the CYP3A4 inducer efavirenz. Cyclosporin, tacrolimus and sirolimus. Concomitant administration of the oral form of clarithromycin with cyclosporin or tacrolimus results in more than a two-fold increase of Cmin plasma concentrations of cyclosporin and tacrolimus. Similar effects can also be expected with sirolimus. Plasma levels of cyclosporin, tacrolimus or sirolimus should be thoroughly monitored when commencing treatment with clarithromycin in patients on any of the above-mentioned immunosuppressants, and their doses should be decreased, if necessary. Clarithromycin discontinuation in those patients also requires a thorough monitoring of cyclosporin, tacrolimus or sirolimus plasma levels to guide dose adjustment.

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

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(R)-hydroxy-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir

Coadministration of clarithromycin and ritonavir increases the area under the curve (AUC), maximum concentration (Cmax) and the minimum concentration (Cmin) of clarithromycin. 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, such as clarithromycin immediate release tablets, sachet or paediatric suspensions (not all presentations may be marketed).

Doses of clarithromycin greater than 1000 mg per day should not be coadministered with protease inhibitors.

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, bidirectional pharmacokinetic interactions).

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(R)-hydroxy-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14(R)-hydroxy-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Effect of clarithromycin on other medicinal products

CYP3A-based Interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.

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

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

Antiarrhythmics

There have been post-marketing reports of torsade de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum concentrations of these medications should also be monitored.

Carbamazepine

During therapy with clarithromycin, the metabolism of carbamazepine may be inhibited.

Consequently the serum concentrations of carbamazepine may be increased, and dose reduction may need to be considered.

HMG-CoA Reductase Inhibitors (e.g., lovastatin, simvastatin, atorvastatin)

Clarithromycin inhibits the metabolisation of a number of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. This may result in elevated plasma levels of these drugs.

In rare cases, the occurrence of rhabdomyolysis was reported with concomitant administration of clarithromycin and HMG-CoA reductase inhibitors (statins), such as lovastatin or simvastatin.

Patients should be monitored for signs and symptoms of myopathy. Adjustment of the statin dosage or use of a statin that is less dependent on CYP3A metabolism, e.g., pravastatin, should be considered.

Oral anticoagulants (e.g., warfarin, acenocoumarol)

In isolated cases, patients receiving combination therapy with clarithromycin and oral anticoagulants may experience increased pharmacologic effects and even toxic effects of these drugs.

International normalized ratio (INR) or Prothrombin times should be carefully monitored while patients are simultaneously receiving clarithromycin and oral anticoagulants.

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. Coadministration 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 coadministered with clarithromycin.

Theophylline

During therapy with clarithromycin, the metabolism of theophylline may be inhibited.

Consequently the serum concentrations of theophylline may be increased, and dose reduction may need to be considered.

Tolterodine

The primary route of metabolism for tolterodine is via the 2D6 is oform 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.

Triazolo benzodiazepines (e.g., alprazolam, midazolam, triazolam)

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7fold after intravenous administration of midazolam and 7fold 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 metabolised by CYP3A (temazepam, nitrazepam, lorazepam) an 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.

Omeprazole

The AUC of omeprazole is increased by 89% when administered concomitantly with clarithromycin for H. pylori eradication; however the change in the mean 24-hour gastric pH value from 5.2 (omeprazole alone) to 5.7 (omeprazole + clarithromycin) is not considered clinically significant.

There are no in-vivo human data available describing an interaction between clarithromycin and the following drugs: aprepitant, eletriptan, halofantrine, and ziprasidone. However, because in vitro data suggest these drugs are CYP3A substrates, caution should be used when they are co-administered with clarithromycin.

Eletriptan should not be coadministered with CYP3A inhibitors such as clarithromycin.

There have been spontaneous or published reports of drug interactions of CYP3A inhibitors, including clarithromycin, with cyclosporine, tacrolimus, methylprednisolone, vinblastine, and cilostazol.

Ciclosporin, tacrolimus and sirolimus
Concomitant administration of the oral form of Clarithromycin with ciclosporin or tacrolimus results in a more than two-fold increase of Cmin plasma concentrations of ciclosporin and tacrolimus. Similar effects can also be expected with sirolimus.
Plasma levels of ciclosporin, tacrolimus or sirolimus should be thoroughly monitored when commencing treatment with Clarithromycin in patients on the above mentioned immunosuppressants, and their doss should be decreased if necessary.
Clarithromycin discontinuation in those patients also requires a thorough monitoring of ciclosporin, tacrolimus or sirolimus plasma levels to guide dose adjustment.

There have been spontaneous or published reports of drug interactions of CYP3A inhibitors including Clarithromycin with ciclosporin, tacrolimus, methylprednisolone, vinblastine and cilostazol.

Other Interactions

Colchicine

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

Patients should be monitored for clinical symptoms of colchicine toxicity (see section 4.4).

Digoxin

Digoxin is 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

Due to reduced gastrointestinal absorption of zidovudine in the presence of clarithromycin, reduced serum levels of zidovudine were observed in adults during concomitant therapy with clarithromycin and zidovudine.

Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, patients should observe a 4-hour interval between taking these two drugs.

This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions with CYP3A inhibitors, including clarithromycin, and drugs not thought to be metabolized by CYP3A, including phenytoin and valproate.

Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased concentrations have been reported.

Bidirectional pharmacokinetic 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(R)-hydroxy-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, such as clarithromycin immediate release tablets, sachet, paediatric suspensions (not all presentations may be marketed).

Doses of clarithromycin greater than 1000 mg per day should not be coadministered with protease inhibitors. (see also section 4.2).

Atazanavir is co-administered with ritonavir in the EU, therefore the comments for this medicinal product should also be taken into account.

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 bidirectional

drug interaction.

Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state area under the curve (AUC) and maximum concentration (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 done with unboosted saquinavir 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 above, effect of other medicinal products on clarithromycin).

## 4.6 Fertility, pregnancy and lactation

The safety of Clarithromycin during pregnancy and breast-feeding of infants has not been established. Clarithromycin should not be used during pregnancy or lactation unless the benefit outweighs the risk.

Data on the use of Clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects or adverse effects on the health of the neonate. Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of abortions. To date no other relevant epidemiological data are available.

Data from animal studies have shown reproductive toxicity (see section 5.3). The risk for humans is unknown. Clarithromycin should not be given to pregnant women unless it is clearly needed.

Lactation

Clarithromycin and its active metabolite are excreted in breast milk of lactating animals and in human breast milk. Therefore, diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

## 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. When performing these activities the possible occurrence of the adverse reactions dizziness, vertigo, confusion and disorientation should be taken into account.

## 4.8 Undesirable effects

The following undesirable effects may occur under treatment with clarithromycin
Frequencies are defined as follows:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

**Clinical experience**

| System Organ Class | Frequency | Adverse Drug Reactions |
|---|---|---|
| **Infections and infestations** | Uncommon | Gastroenteritis<br>Oral candidiasis<br>Rash pustular<br>Rhinitis<br>Vaginal candidiasis<br>Vaginal infection |
| **Blood and lymphatic system disorders** | Uncommon | Anaemia<br>Eosinophilia<br>Hypochromic anaemia<br>Leukopenia<br>Thrombocythaemia<br>White blood cell disorders |
| **Metabolism and nutrition disorders** | Uncommon | Anorexia<br>Hyperchloraemia<br>Hyperuricaemia<br>Hypocalcaemia<br>Increased appetite |
| **Psychiatric disorders** | Uncommon | Depression<br>Insomnia<br>Nervousness<br>Somnolence |
| **Nervous System disorders** | Common | Dysgeusia |
| | Uncommon | Dizziness<br>Headache<br>Tremor |
| | Very rare | Paraesthesia |
| **Eye disorders** | Uncommon | Conjunctivitis<br>Visual disturbance |
| **Ear and labyrinth disorders** | Uncommon | Ear disorder<br>Tinnitus<br>Vertigo |
| **Vascular disorders** | Uncommon | Vasodilation |
| **Respiratory, thoracic and mediastinal disorders** | Uncommon | Asthma<br>Dyspnoea<br>Lung disorder |
| **Gastrointestinal disorders** | Common | Abdominal pain<br>Diarrhoea<br>Dyspepsia<br>Nausea |
| | Uncommon | Abdominal distension<br>Constipation<br>Dry mouth<br>Eructation<br>Flatulence<br>Gastrointestinal disorder<br>Gastrointestinal haemorrhage<br>Stomatitis<br>Tongue discolouration<br>Vomiting |

| | | |
|---|---|---|
| **Hepato-biliary disorders** | Uncommon | Hyperbilirubinaemia |
| **Skin and subcutaneous tissue disorders** | Uncommon | Dry skin<br>Eczema<br>Hyperhidrosis<br>Pruritus<br>Rash<br>Rash macula-papular<br>Urticaria |
| **Musculoskeletal and connective tissue disorders** | Uncommon | Arthralgia<br>Back pain<br>Myalgia |
| **Renal and urinary disorders** | Uncommon | Albuminuria<br>Haematuria<br>Pyuria |
| **Reproductive system and breast disorders** | Uncommon | Genital discharge |
| **General disorders and administration site conditions** | Uncommon | Asthenia<br>Chest pain<br>Drug interaction<br>Face oedema<br>Malaise<br>Pain<br>Thirst |
| **Investigations** | Uncommon | Alanine aminotransferase increased<br>Alkaline phosphate increased<br>Aspartate aminotransferase increased<br>Blood creatinine increased<br>Blood lactate dehydrogenase increased<br>Blood urea increased<br>Laboratory test abnormal<br>Liver function test abnormal<br>Prothrombin decreased<br>Prothrombin time prolongation |

**Post-marketing experience**

The ADRs reported are consistent with those observed in clinical studies. 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 treatments days for clarithromycin.

| System Organ Class | Adverse Drug Reactions |
|---|---|
| **Infection and infestations** | Oral Candidiasis |
| **Blood and lymphatic system disorders** | Leukopenia<br>Thrombocytopenia |
| **Immune system disorders** | Anaphylactic reaction<br>Hypersensitivity |
| **Metabolism and nutrition disorders** | Hypoglycaemia |
| **Psychiatric disorders** | Abnormal dreams<br>Anxiety<br>Confusional state<br>Depersonalisation<br>Disorientation<br>Hallucination |

| | |
|---|---|
| | Insomnia<br>Psychotic disorder |
| **Nervous system disorders** | Convulsions<br>Dizziness<br>Dysgeusia<br>Parosmia |
| **Ear and labyrinth disorders** | Deafness<br>Tinnitus<br>Vertigo |
| **Cardiac disorders** | Electrocardiogram QT prolonged<br>Torsades de Pointes<br>Ventricular tachycardia |
| **Gastrointestinal disorders** | Glossitis<br>Pancreatitis acute<br>Stomatitis<br>Tongue discolouration<br>Tooth discolouration |
| **Hepatobiliary disorders** | Hepatic failure<br>Hepatic function abnormal<br>Hepatitis<br>Hepatitis cholestatic<br>Jaundice cholestatic<br>Jaundice hepatocellular |
| **Skin and subcutaneous tissue disorders** | Rash<br>Stevens-Johnson syndrome<br>Toxic epidermal necrolysis<br>Urticaria |
| **Renal and urinary disorders** | Interstitial nephritis |
| **Investigations** | Blood creatinine increased<br>Hepatic enzyme increased |

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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with fatal outcome (see sections 4.5 and 4.4).

## 4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia. Adverse reactions accompanying overdosage should be treated by gastric lavage 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

Pharmacotherapeutic group: Macrolide Antibiotic,
ATC code: J01FA09

Mode of Action

Clarithromycin is an antibiotic belonging to the macrolide antibiotics group. It exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria. It selectively binds to the 50S subunit of bacterial ribosomes and thus prevents the translocation of activated amino acids.

Clarithromycin has relevant bactericidal activity against several bacterial strains.

The organisms include *H. influenzae, S. pneumoniae, S. pyogenes, S. aureus, M. catarrhalis, H. pylori, C. pneumoniae, M. pneumoniae, L. pneumophila, M. avium*, and *M. intracellulare*.

The 14(R)-hydroxy metabolite of clarithromycin, a product of parent drug metabolism in humans, also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including Mycobacterium spp. An exception is *Haemophilus influenzae* against which the metabolite is 1 to 2 times more active than the parent compound. Clarithromycin combined with the metabolite showed a strain-dependent additive or synergistic effect both *in vitro* and *in vivo*.

PK/PD Relationship
Clarithromycin is extensively distributed in body tissues and fluids. Because of high tissue penetration, intracellular concentrations are higher than serum concentrations.
Clarithromycin concentrations in tonsil and whole lung tissue are 2 - to 6 - fold higher than those observed in the serum. Tissue and serum concentrations observed in Abbott studies with immediate-release (IR) tablets are presented below.

| Mean Clarithromycin Concentration [250mg BID] | | |
|---|---|---|
| Tissue Type | Tissue | Serum |
| Tonsil | 1.6 µg/g | 0.8 µg/ml |
| Lung | 8.8 µg/g | 1.7 µg/ml |

The pharmacokinetics of orally administered modified-release (MR) clarithromycin tablets have been studied in adult humans (refer to section 5.2) and compared with clarithromycin 250 mg and 500 mg IR tablets. The extent of absorption – area under curve (AUC) – was found to be equivalent when equal total daily doses were administered. The equivalent AUCs would be expected to drive tissue levels equivalent to those observed for clarithromycin IR tablets.

***Mechanism of Resistance***
Acquired macrolide resistance in *S. pneumoniae, S. pyogenes*, and *S. aureus* is mediated primarily by the presence of one of two mechanisms (i.e. *erm* and *mef* or *msr*).
Ribosomal binding of the antimicrobial is prevented through methylation of the ribosome by an enzyme (*erm*). Alternatively an efflux mechanism (*mef* or *msr*) can prevent the antimicrobial from reaching its ribosomal target by pumping the antimicrobial out of the cell. No acquired resistance mechanisms have been identified in Moraxella or Haemophilus spp. Macrolide resistance mechanisms are equally effective against 14- and 15-membered macrolides including erythromycin, clarithromycin, roxithromycin, and azithromycin. The mechanisms for penicillin resistance and macrolide resistance are unrelated.

Attention should be paid to the erm-mediated cross-resistance between macrolides such as clarithromycin and lincosamides such as lincomycin and clindamycin.
Clarithromycin antagonises the bacterial effects of beta-lactam antibiotics. Also the effects of lincomycin and clindamycin are antagonised, at least *in vitro*.

***Breakpoints***
The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

| Breakpoints (MIC, µg/ml) | | |
|---|---|---|
| Microorganism | Susceptible (≤) | Resistant (>) |
| *Streptococcus spp.* | 0.25 µg/ml | 0.5 µg/ml |
| *Staphylococcus spp.* | 1 µg/ml | 2µg/ml |
| *Haemophilus spp.** | 1 µg/ml | 32 µg/ml |
| *Moraxella catarrhalis* | 0.25 µg/ml | 0.5 µg/ml |

Clarithromycin is used for the eradication of *H. pylori*; minimum inhibitory concentration (MIC) ≤ 0.25 µg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).
*The correlation between H. Influenzae macrolides MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorise wild type H. Influenzae as intermediate.

The activity of 14(R) hydroxyl clarithromycin is greater than that of clarithromycin against *Haemophilus influenzae*. Studies done *in vitro* have suggested an additive activity of the 14(R)-hydroxy-clarithromycin and the parent molecule against *H. influenzae*.

Susceptibility

The prevalence of acquired resistance rates may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of an agent in at least some types of infections is questionable.

| **Commonly susceptible species** |
|---|
| **Aerobic Gram-positive micro-organisms**<br>Streptococcus group F<br><br>**Aerobic Gram-negative micro-organisms**<br>Legionella pneumophila<br>Moraxella catarrhalis<br>Legionella spp<br><br>**Anaerobic micro-organisms**<br>Clostridium perfringens<br><br>**"Other"**<br>Chlamydia pneumoniae<br>Chlamydia trachomatis<br>Mycoplasma pneumoniae |
| **Species for which acquired resistance may be a problem#**<br>**Aerobic Gram-positive micro-organisms**<br>Staphylococcus aureus (resistant or susceptible* to methicillin)+<br>staphylococcus coagulase negative +<br>Streptococcus group B, C, G<br>Streptococcus pneumoniae* +<br>Streptococcus pyogenes*<br>Streptococcus spp<br><br>**Aerobic Gram-negative micro-organisms**<br>H. Influenzae§ |
| **Inherently resistant organisms** |

| |
|---|
| **Aerobic Gram-positive micro-organisms**<br>Enterococcus spp<br><br>**Aerobic Gram-negative micro-organisms**<br>Enterobacteriaceae<br>Pseudomonas aeruginosa |

* Species against which efficacy has been demonstrated in clinical investigations (if susceptible)

+ Indicates species for which a high rate of resistance (i.e. greater than 50%) has been observed in one or more area/country/regions(s) of the EU

§species with intermediate natural susceptibility

# ≥10% resistance in at least one country of the European Union

## 5.2 Pharmacokinetic properties

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

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

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

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

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

## 5.3 Preclinical safety data

In acute toxicity studies in mouse and rat, 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 included 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 Sprague-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 rats 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 in monkeys embryonic loss was seen but only at dose levels which were clearly toxic to the mothers.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Tablet core
- Lactose Monohydrate
- Hypromellose
- Hypromellose Phthalate
- Talc
- Magnesium Stearate

Film Coat
- Hypromellose
- Lactose Monohydrate
- Macrogol
- Quinoline Yellow Aluminium Lake (E104)
- Talc
- Titanium Dioxide (E171)

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf Life

3 years

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

## 6.5 Nature and contents of container

Blister pack of Clear PVC/PVDC lidded with aluminium foil for blister pack of 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, 100 and 112 film coated tablets.

Not all pack sizes may be marketed

## 6.6 Special precautions for disposal and other handling

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd
115 Narborough Road
Leicester
LE3 0PA
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER

PA 1333/10/1

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 15th April 2011

## 10 DATE OF REVISION OF THE TEXT