

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 250 mg film-coated tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of clarithromycin  
For the full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Film-coated tablet.

dark yellow, film-coated, capsule shaped tablets.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Clarithromycin film-coated tablets is indicated in adults and adolescents 12 years and older for the treatment of the following bacterial infections, when caused by clarithromycin-susceptible bacteria (see section 4.4 and 5.1).

- Acute bacterial exacerbation of chronic bronchitis
- Mild to moderate community acquired pneumonia
- Acute bacterial sinusitis
- Bacterial pharyngitis
- Skin infections and soft tissue infections of mild to moderate severity, such as folliculitis, cellulitis and erysipelas

Clarithromycin film-coated tablets can also be used in appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing agent for the eradication of *Helicobacter pylori* in patients with *Helicobacter pylori* associated ulcers (see section 4.2).

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

#### 4.2 Posology and method of administration

The dosage of Clarithromycin film-coated Tablets depends on the clinical condition of the patient and has to be defined in any case by the physician.

Children older than 12 years and adults:

- Standard dosage: The usual dose is 250 mg twice daily.
- High dosage treatment (severe infections): The usual dose may be increased to 500 mg twice daily in severe infections.
- Clinical trials have been conducted using clarithromycin pediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin pediatric suspension (granules for oral suspension).

Elimination of *Helicobacter pylori* in adults:

In patients with gastro-duodenal ulcers due to *H. pylori* infection clarithromycin can be used in a dose of 500 mg twice daily during the eradication therapy in combination with amoxicillin 1000 mg twice daily and omeprazole 20 mg twice daily\*.

Dosage in patients with renal impairment:

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

Duration of therapy:

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

- The usual duration of treatment is 6 to 14 days.
- In *streptococcus pyogenes* (as a beta-haemolytic streptococcal) infections the duration of therapy should be at least 10 days.
- Combination therapy for the eradication of *H. pylori* infection, e.g. clarithromycin 500 mg (two 250 mg tablets or one 500 mg tablet) twice daily in combination with amoxicillin 1000 mg twice daily and omeprazole 20 mg twice daily should be continued for 7 days\*.

Method of administration:

Clarithromycin film-coated tablets may be given irrespective of food intake. Food does not affect the extent of bioavailability. Food does only slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxy metabolite.

### 4.3 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to the active substance, macrolide antibiotic drugs or to any of the excipients listed in section 6.1.

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\* according to the publication in Gastroenterology. 1999 Feb; 116(2): 248-53

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

Concomitant administration with ticagrelor, ivabradine or ranolazine is contraindicated.

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

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 pointe (see sections 4.4 and 4.5).

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 and 4.5).

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

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

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

Concomitant administration of clarithromycin and ivabradine is contraindicated, as this may result in increased plasma exposure of ivabradine (see section 4.5).

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

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy (see section 4.6).

Caution is advised in patients with severe renal insufficiency (see section 4.2).

Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Cases of fatal hepatic failure (see section 4.8) have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (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 intravenous or oromucosal midazolam (see section 4.5).

#### Cardiovascular events

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in

treatment with macrolides including clarithromycin (see section 4.8). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes), clarithromycin should be used with caution in the following patients:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia,
- Patients with electrolyte disturbances. Clarithromycin must not be given to patients with hypokalaemia (see section 4.3).
- Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.5).
- Concomitant administration of clarithromycin with astemizole, cisapride, pimozone and terfenadine is contraindicated (see section 4.3).
- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

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).

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/Insulin: The concomitant use of clarithromycin and oral hypoglycemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycemia. Careful monitoring of blood glucose is recommended (see section 4.5).

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 (see section 4.5). Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban, apixaban and edoxaban, particularly to patients at high risk of bleeding (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori* infection may select for drug-resistant organisms.

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

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

Clarithromycin contains sodium

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

#### **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:**

Astemizole, cisapride, domperidone, pimozide, and terfenadine

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

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a 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.

#### *Ergotamine/dihydroergotamine*

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 these medicinal products is contraindicated (see section 4.3).

#### *Oral midazolam*

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin is contraindicated.

#### *HMG-CoA reductase inhibitors (statins)*

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

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

#### Hydroxychloroquine and chloroquine

Clarithromycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

#### **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 active substances are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dose 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 gm/day should not be coadministered 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).

#### Ivabradine

Clarithromycin is considered to be a strong cytochrome P450 3A4 inhibitor which is the primary enzyme for Ivabradine metabolism. This may result in increased Ivabradine plasma exposure, hence concomitant administration of Clarithromycin and Ivabradine is contraindicated (see section 4.3).

### **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 medicinal product. The use of clarithromycin is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, domperidone, pimozone 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, ivabradine 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: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, ergot alkaloids, ibrutinib, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban, see section 4.4), atypical antipsychotics (e.g. quetiapine), pimozone, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

#### Direct acting oral anticoagulants (DOACs)

The DOACs dabigatran and edoxaban are 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).

#### 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/Insulin

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

#### Omeprazole

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

#### Sildenafil, tadalafil, and vardenafil

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

#### Theophylline, carbamazepine

Results of clinical studies indicate 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 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Active substance delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the active substance, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

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

### **Other drug interactions**

### Colchicine

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

### Corticosteroids

Caution should be exercised in concomitant use of clarithromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

### Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

### Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

### Phenytoin and Valproate

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

## **Bi-directional drug interactions**

### Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir

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

#### Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, 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.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

### Breast-feeding

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

### Fertility

There is no data available on the effect of clarithromycin on fertility in humans. In the rat, fertility studies have not shown any evidence of harmful effects.

## 4.7 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive and use machines. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (see section 4.8). The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

## 4.8 Undesirable effects

### *a. Summary of the safety profile*

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

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

### *b. Tabulated summary of adverse reactions*

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon

(≥1/1,000 to <1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

Infections and infestations

Uncommon: Cellulitis<sup>1</sup>, candidiasis, gastroenteritis<sup>2</sup>, infection<sup>3</sup>, vaginal infection

Not known: Pseudomembranous colitis, erysipelas

Blood and the lymphatic system disorders

Uncommon: Leukopenia, neutropenia<sup>4</sup>, eosinophilia<sup>4</sup>

Not known: Agranulocytosis, thrombocytopenia

Immune system disorders\*

Uncommon: Anaphylactoid reaction<sup>1</sup>, hypersensitivity

Not known: Anaphylactic reaction, angioedema

Metabolism and nutrition disorders

Uncommon: Anorexia, decreased appetite

Psychiatric disorders

Common: Insomnia

Uncommon: Anxiety, nervousness<sup>3</sup>

Not known: Psychotic disorder, confusional state<sup>5</sup>, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania

Nervous system disorders

Common: Dysgeusia, headache, taste perversion

Uncommon: Loss of consciousness<sup>1</sup>, dyskinesia<sup>1</sup>, dizziness, somnolence<sup>5</sup>, tremor

Not known\*: Convulsion, ageusia, parosmia, anosmia, paraesthesia

Ear and labyrinth disorders

Uncommon: Vertigo, impaired hearing, tinnitus

Not known\*: deafness

Cardiac disorders

Uncommon: Cardiac arrest<sup>1</sup>, atrial fibrillation<sup>1</sup>, electrocardiogram QT prolonged

Not known: Torsade de Pointes\*, ventricular tachycardia\*, ventricular fibrillation

Vascular disorders

Common: Vasodilation<sup>1</sup>

Not known\*: Hemorrhage<sup>#</sup>

Respiratory, thoracic and mediastinal disorders

Uncommon: Asthma<sup>1</sup>, epistaxis<sup>2</sup>, pulmonary embolism<sup>1</sup>

Gastrointestinal disorders

Common: Diarrhea\*, vomiting, abdominal pain, nausea, dyspepsia,

Uncommon: Oesophagitis<sup>1</sup>, gastroesophageal reflux disease<sup>2</sup>, gastritis, stomatitis, glossitis, abdominal distension<sup>4</sup>, abdominal distension, constipation, dry mouth, eructation, flatulence,

Not known\*: Pancreatitis, tongue discolouration, tooth discoloration

Hepato-biliary disorders

Common: Liver function test abnormal

Uncommon: Cholestasis<sup>4</sup>, hepatitis<sup>4</sup>, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased<sup>4</sup>

Not known: Hepatic failure\*, jaundice hepatocellular

*Skin and subcutaneous tissue disorders*

Common: Rash, hyperhidrosis

Uncommon: Dermatitis bullous<sup>1</sup>, pruritus, urticaria, rash maculo-papular<sup>3</sup>

Not known: Stevens-Johnson syndrome\*, toxic epidermal necrolysis\*, drug rash with eosinophilia and systemic symptoms (DRESS), acne, severe cutaneous adverse reactions (SCAR) (eg: acute generalised exanthematous pustulosis (AGEP))

*Musculoskeletal, connective tissue and bone disorders*

Uncommon: Muscle spasms<sup>3</sup>, musculoskeletal stiffness<sup>1</sup>, myalgia<sup>2</sup>

Not known\*: Rhabdomyolysis<sup>2,6</sup>, myopathy

*Renal and urinary disorders*

Uncommon: Blood creatinine increased<sup>1</sup>, blood urea increased<sup>1</sup>

Not known: Renal failure, interstitial nephritis

*General disorders and administration site conditions*

Very common: Injection site phlebitis<sup>1</sup>

Common: Injection site pain<sup>1</sup>, injection site inflammation<sup>1</sup>

Uncommon: Malaise<sup>4</sup>, Pyrexia<sup>3</sup>, asthenia, chest pain<sup>4</sup>, chills<sup>4</sup>, fatigue<sup>4</sup>

*Investigations*

Uncommon: Albumin globulin ratio abnormal<sup>1</sup>, blood alkaline phosphatase increased<sup>4</sup>, blood lactate dehydrogenase increased<sup>4</sup>

Not known: International normalised ratio increased<sup>#</sup>, prolongation of prothrombin time<sup>#</sup>, urine color abnormal

<sup>1</sup> ADRs reported only for the powder for solution for injection formulation

<sup>2</sup> ADRs reported only for the extended-release tablets formulation

<sup>3</sup> ADRs reported only for the granules for oral suspension formulation

<sup>4</sup> ADRs reported only for the immediate-release tablets formulation

<sup>5,6</sup> see Description of selected adverse reactions

\* 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 medicinal product exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.

***c. Description of selected adverse reactions***

Injection site phlebitis, injection site pain, vessel puncture site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see section 4.3 and 4.4).

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested (see section 4.5).

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit

times. In several reports, tablet residues have occurred in the context of diarrhea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients (see section e)

***d. Paediatric populations***

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.

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

***e. Other special populations***

***Immunocompromised patients***

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1,000 mg and 2,000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1,000 mg and 2,000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4,000 mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by 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 1,000 mg or 2,000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4,000 mg daily for all parameters except White Blood Cell.

**Reporting of suspected adverse reactions**

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

([www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Reports indicate the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures.

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group:  
ATC Code J01FA09.

Clarithromycin is a semi-synthetic derivative of erythromycin A.

#### Mechanism of action:

Clarithromycin exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

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

#### Breakpoints

	NCCLS*		BSAC**	
	susceptible (µg/ml)	resistant (µg/ml)	susceptible (µg/ml)	resistant (µg/ml)
Staphylococcus spp.	≤ 2	≥ 8	≤ 0.5	≥ 1
Haemophilus spp.	≤ 8	≥ 32	≤ 0.5	≥ 32
Streptococcus pneumoniae	≤ 0.25	≥ 1	≤ 0.5	≥ 1
Streptococcus spp. other than S.	≤ 0.25	≥ 1	≤ 0.5	≥ 1

pneumoniae				
<i>Helicobacter pylori</i>	≤ 0.25	≥ 1	≤ 1	≥ 2

\* National Committee on Clinical Laboratory Standards, in 2001

\*\* British Society for Antimicrobial Chemotherapy

### Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an appropriate guidance on the probabilities whether micro-organisms will be susceptible to clarithromycin or not. As far as applicable the information on the European range of acquired resistance for the individual micro-organism is indicated in brackets.

<i>Species</i>	Frequency of resistance ranges in EU (if > 10%) (extreme values) <sup>1)</sup>
<b>Susceptible</b>	
Gram-positive aerobes	
<i>Staphylococcus aureus</i> (methicillin-susceptible)	(18.1%)
<i>Streptococcus pyogenes</i>	
<i>Streptococcus agalactiae</i>	
Group C, F, G <i>Streptococci</i>	
<i>Streptococcus pneumoniae</i>	(37.8%)
Gram-negative aerobes	
<i>Haemophilus influenzae</i>	(13.4%)
<i>Helicobacter pylori</i>	(14%)
<i>Legionella</i> spp.	
<i>Moraxella catarrhalis</i>	
<i>Neisseria gonorrhoeae</i>	
Anaerobes	
<i>Bacteroides</i> spp.	
<i>Clostridium</i> spp. other than <i>C. difficile</i>	
<i>Fusobacterium</i> spp.	
<i>Peptococcus/Peptostreptococcus</i> spp.	
Others	
<i>Chlamydia trachomatis</i>	
<i>Chlamydia pneumoniae</i>	
<i>Mycoplasma pneumoniae</i>	
<b>Insusceptible</b>	
Gram-positive aerobes	
<i>Enterococcus</i> spp.	
<i>Staphylococcus aureus</i> (Erythromycin resistant or MRSA)	
Others	
<i>Mycobacterium tuberculosis</i>	

MRSA - methicillin resistant *Staphylococcus aureus*

<sup>1)</sup> Frequencies of resistance ranges calculated on NCCLS breakpoints

### Other information

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

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

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

## **5.2 Pharmacokinetic properties**

### Absorption:

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

After administration of 250 mg clarithromycin twice daily the pharmacological active 14-hydroxy metabolite attains peak plasma concentrations of 0,6 µg/ml.

### Distribution:

Clarithromycin gives good penetration into different compartments. Therapeutic drug levels exceeding the minimum inhibitory levels for common pathogens can be rapidly achieved. Clarithromycin provides tissue

concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin also penetrates the gastric mucus.

Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

Serum half-life:

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

Biotransformation and elimination:

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

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

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

### **5.3 Preclinical safety data**

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5 g/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 400 mg/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 rates indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels which were clearly toxic to the mothers.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

*Core:* Croscarmellose sodium, Microcrystalline cellulose, Povidone, Magnesium stearate, Colloidal anhydrous silica, Talc.

*Film-Coat:* Hypromellose, Propylene glycol, Titanium dioxide (E171), Hydroxypropylcellulose, Sorbitan monooleate, Quinolin yellow (E104), Vanillin.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

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

Store in the original package in order to protect from moisture.

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

PVC/PVDC aluminium blister

Pack sizes:

Clarithromycin 250 mg film-coated Tablets: 8, 10, 12, 14, 15, 16, 20, 21, 24, 49, 50, 100, 100x1.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

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

## **7 MARKETING AUTHORISATION HOLDER**

Sandoz Limited  
Park View, Riverside Way  
Watchmoor Park  
Camberley, Surrey  
GU15 3YL  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 04416/0641

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

22/11/2009

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

22/03/2024