PACKAGE INSERT OF CLARIFIC

For the use of Registered Medical Practitioner or a Hospital or a Laboratory

CLARIFIC

Clarithromycin Lyophilized Powder for Solution for Infusion 500mg

Rx

For Single Use Only, Lyophilized Powder for Solution for Infusion, For I.V. Infusion after Dilution

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Clarithromycin Ph. Eur. …… 500mg
Excipients …….. q.s.

PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off white lyophilized powder or cake in colourless glass vial Type I (20 ml)

Description after reconstitution/dilution: clear and colourless solution.

CLINICAL PARTICULARS

Therapeutic indications

Clarithromycin I.V. is indicated whenever parenteral therapy is required for treatment of sensitive microorganisms in the following conditions:

1. Upper respiratory tract infections
2. Lower respiratory tract infections
3. Skin and soft tissue infections
4. Disseminated or localized mycobacterial infections due to Mycobacterium avium or Mycobacterium intracellulare. Localized infections due to Mycobacterium chelonae, Mycobacterium fortuitum, or Mycobacterium kansasii.

Posology and method of administration

Method of administration: For intravenous administration only.

The recommended dosage of clarithromycin I.V. in adults 18 years of age or older is 1.0 g daily, divided into two equal doses, each infused after further dilution with an appropriate I.V. diluent, over a 60-minute time period. At the present time, there are no data supporting intravenous use of clarithromycin in children. Clarithromycin should not be given as a bolus or an intramuscular injection.

Dosage in Patients With Mycobacterial Infections

Although there currently is no data regarding use of clarithromycin I.V. in immunocompromised patients, data are available regarding the use of oral clarithromycin in HIV-infected patients. In disseminated or localized infections (M. avium, M. intracellulare, M. chelonae, M.fortuitum, M. kansasii), the recommended treatment, in adults, is 1000 mg/day in two divided doses.

Intravenous therapy may be limited for up to two to five days in the very ill patient and should be changed to oral therapy whenever possible as determined by the physician.

In patients with renal impairment who have creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced to one half of the normal recommended dose.

The final solution for infusion is prepared as follows:

1. Prepare the initial solution of clarithromycin I.V. by adding 10 mL of Sterile Water for Injection to the 500 mg vial. Use only Sterile Water for Injection, as other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts. Note: When the product is reconstituted as directed above, the resulting solution contains an effective antimicrobial preservative; each mL contains 50 mg of clarithromycin I.V.

2. The reconstituted product (500 mg in 10 mL Water for Injection) should be added to a minimum of 250 mL of one of the following diluents before administration: 5% dextrose in Lactated Ringer's Solution, 5% dextrose, Lactated Ringer's, 5% dextrose in 0.3% sodium chloride, Normosol-M in 5% dextrose, Normosol-R in 5% dextrose, 5% dextrose in 0.45% sodium chloride, and 0.9% sodium chloride.

No drug or chemical agent should be added to a clarithromycin I.V. fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.

Pediatric

There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.

Contraindications

Hypersensitivity to macrolide antibiotic drugs or to any of the excipients.

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

Concomitant administration of clarithromycin and oral midazolam is contraindicated.

Concomitant administration of clarithromycin and lomitapide is contraindicated.

Concomitant administration of Clarithromycin and the following drugs is contraindicated: Domperidone as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (See Section Interactions).

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

Concomitant administration with ticagrelor or ranolazine is contraindicated. Clarithromycin should not be used concomitantly with HMGCoA reductase inhibitors (statins) that are extensively metabolized byCYP3A4, (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

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

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.

Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function.

Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including

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

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam.

Cardiovascular Events

Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in patients treated with macrolides including clarithromycin. Due to increased risk of QT prolongation and ventricular arrhythmias (including torsades de pointes), the use of clarithromycin is contraindicated: in patients taking any of astemizole, cisapride, domperidone, pimozide and terfenadine; in patients with electrolyte disturbances such as hypomagnesaemia or hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac arrhythmia.

Carefully consider the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality.

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

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

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

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

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

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], CLARIFIC Clarithromycin Lyophilized Powder for Solution for Infusion 500mg 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.

HMG-CoA reductase inhibitors (statins):
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated

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

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

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

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk

of bleeding.

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

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

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.

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. In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in 2- to 3-fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergot alkaloids:
Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated

Oral Midazolam
When midazolam was co-administered with clarithromycin tablets (500mg 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 as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking

clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

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

Effects of Other Medicinal Products on Clarithromycin

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

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

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine

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

Etravirine

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

Fluconazole

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

Ritonavir

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

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

Effect of Clarithromycin on Other Medicinal Products

CY3A4-based interactions

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

The following drugs or drug classes are known or suspected to be metabolized by CYP3A isozyme: Domperidone

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

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.

Concomitant administration of clarithromycin with lomitapide is contraindicated due to the potential for markedly increased transaminases.

Caution is required if clarithromycin is co-administered 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. Drugs or drug classes that are known or suspected to be metabolized by the same CYP3A isozyme include (but this list is not comprehensive) alprazolam, carbamazepine,

cilostazole, ciclosporin, disopyramide, ibrutinib, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine.

Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

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.

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

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

Oral hypoglycemic agents/Insulin
With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia 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

Direct acting oral anticoagulants (DOACs)
The DOACs dabigatran and edoxaban are substrates 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.

Sildenafil, tadalafil and vardenafil
Each of these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of

clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

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

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

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

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

Other drug interactions

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

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 metabolised by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

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.

Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Because of the potential for a similar risk with other macrolides when used in combination with hydroxychloroquine or chloroquine, careful consideration should be given to the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine.

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 bi-directional 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.

Patients taking oral contraceptives should be warned that if diarrhoea, vomiting or breakthrough bleeding occur there is a possibility of contraceptive failure.

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.

Patients taking oral contraceptives should be warned that if diarrhoea, vomiting or breakthrough bleeding occur there is a possibility of contraceptive failure.

Fertility, pregnancy and lactation

Pregnancy
The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embyofoetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the

same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Breast-feeding

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

Fertility

In the rat, fertility studies have not shown any evidence of harmful effects

Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

Undesirable effects

a. Summary of the safety profile

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

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

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, granules for oral suspension, powder for solution for injection, extended-release tablets and modified-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-

marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System Organ Class	**Very common ≥1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥1/1,000 to < 1/100**	**Not Known* (cannot be estimated from the available data)**
Infections and infestations			Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia, neutropenia[4], thrombocythemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3]	Psychotic disorder, confusional state[5], depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations	Torsades de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders		Vasodilation[1]		Haemorrhage

Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Oesophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discolouration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gammaglutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3]	severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP).
Musculoskeletal and connective tissue disorders			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2,6], myopathy
Renal and urinary disorders			Blood creatinine increased[1], blood urea increased[1]	Renal failure, nephritis interstitial
General disorders and administration	Injection site phlebitis[1]	Injection site pain[1], injection site	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	

site conditions		inflammation[1]		
Investigations			Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased, prothrombin time prolonged, urine color abnormal

[1] ADRs reported only for the powder for solution for infusion

[2]ADRs reported only for the extended-release tablets formulation

[3]ADRs reported only for the granules for oral suspension formulation

[4]ADRs reported only for the immediate-release tablets formulation

[5,6] See section c)

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

c. Description of selected adverse reactions

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

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol

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

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients (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.

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 events by patients treated with total daily doses of 1000mg and 2000mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations.

Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1000mg and 2000mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000mg of clarithromycin.

In these immunocompromised patients evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1000mg or 2000mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4000mg daily for all parameters except White Blood Cell.

Overdose

Reports indicate that the ingestion of large amounts of clarithromycin orally 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 the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels

are not expected to be appreciably affected by haemodialysis or peritoneal dialysis. In the case of overdosage, Clarithromycin Powder for Solution for Infusion 500 mg should be discontinued and all other appropriate supportive measures should be instituted.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

ATC Classification:

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC-Code: J01FA09

Mode of Action:

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal sub-unit of susceptible bacteria preventing translocation of activated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria.

The 14-hydroxy metabolite of clarithromycin, a product of parent drug metabolism also has anti-microbial activity. The metabolite is less active than the parent compound for most organisms, including mycobacterium spp. An exception is Haemophilus influenza where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Clarithromycin Powder for Solution for Infusion 500 mg is usually active against the following organisms in vitro:

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

Gram-negative Bacteria: *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae; Legionella pneumophila, Bordetella pertussis, Helicobacter pylori; Campylobacter jejuni.*

Mycoplasma: *Mycoplasma pneumoniae; Ureaplasma urealyticum.*

Other Organisms: *Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae; Chlamydia pneumoniae.*

Anaerobes: Macrolide-susceptible *Bacteriodes fragilis; Clostridium perfringens; Peptococcus* species; *Peptostreptococcus* species; *Propionibacterium acnes.*

Clarithromycin has bactericidal activity against several bacterial strains. These organisms include *H.influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Morazella (Brahamella) catarrhalis, Neisseria gonorrhoeae, Helicobacter pylori* and *Campylobacter spp*.

The activity of clarithromycin against *H. pylori* is greater at neutral pH than at acid pH.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for clarithromycin and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-micbreakpoints_en.xlsx

Pharmacokinetic properties

The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism as indicated by lower bioavailability of the metabolite following IV administration. Following IV administration the blood levels of clarithromycin achieved are well in excess of the MIC_{90}s for the common pathogens and the levels of 14-hydroxyclarithromycin exceed the necessary concentrations for important pathogens, e.g. *H. influenzae*.

The pharmacokinetics of clarithromycin and the 14-hydroxy metabolite are nonlinear; steady state is achieved by day 3 of IV dosing. Following a single 500mg IV dose over 60 minutes, about 33% clarithromycin and 11% 14-hydroxyclarithromycin is excreted in the urine at 24 hours.

Clarithromycin Powder for Solution for Infusion 500 mg does not contain tartrazine or other azodyes, lactose or gluten.

PHARMACEUTICAL PARTICULARS

List of excipients

Lactobionic acid

Incompatibilities

None known.

This medicinal product must not be mixed with other medicinal products except excipients.

Shelf life

Unopened: refer to label or carton

After reconstitution with 10 ml Water for Injection, the solution remains stable for 48 hours at 2-8˚C.

Further dilution of reconstituted solution in 240 ml diluent, the solution remains stable for 48 hours at 2- 8˚C and 6 hours at 25˚C.

Special precautions for storage

Store below 30°C. Protect from light.

Nature and contents of container

20ml clear, tubular glass USP-I vial is stoppered with 20 mm full slotted grey bromobutyl "RFU" rubber stopper and sealed with 20 mm aluminum flip-off tear-off seal cap.
The glass vial affixed with sticker label and then placed in a plastic tray.
One plastic tray with labelled vial is packed in a carton along with pack insert (leaflet).

OR

Ten labelled vials are packed in a monocarton with honeycomb separator along with pack insert (leaflet).

Special precautions for disposal and other handling

Clarithromycin Powder for Solution for Infusion 500mg should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a solution concentration of about 2mg/ml. Clarithromycin should not be given as a bolus or an intramuscular injection.

Preparation for Use

Reconstitution (Step 1)

Prepare the initial solution of Clarithromycin Powder for Solution for Infusion 500mg by adding 10 ml of Water for Injection to the vial. Shake until the vial contents have dissolved. Use only Water for Injection, as other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts. Each ml contains 50 mg clarithromycin.

Dilution (Step 2)

The reconstituted product (500 mg in 10 ml Water for Injection) should be added to a minimum of 250 ml of one of the following diluents before administration: Sodium chloride injection (0.9 % w/v), Dextrose injection (5% w/v), Ringer lactate Solution for Injection, 5% Dextrose in Ringer Lactate Solution for Injection, 5% Dextrose in 0.3% w/v Sodium chloride injection, 5% Dextrose in 0.45% w/v Sodium chloride injection, Normosol- M in Dextrose injection (5% w/v), Normosol-R in Dextrose injection (5% w/v).

IMPORTANT: BOTH DILUENT STEPS (1 and 2) SHOULD BE COMPLETED BEFORE USE. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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