PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

CLARIHEXAL 500 XL (Modified Release Film-coated Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CLARIHEXAL 500 XL film-coated tablet contains: 500 mg Clarithromycin.

Sugar free.

3. PHARMACEUTICAL FORM

Light ochre – yellow, oval, biconvex film-coated tablet with debossing “500” on one side and “CXL” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLARIHEXAL 500 XL is indicated in the treatment of infections with micro-organisms sensitive to CLARIHEXAL 500 XL

- Lower respiratory tract infections such as bronchitis and pneumonia.
- Upper respiratory tract infections such as pharyngitis and sinusitis.
- Skin and soft tissue infections such as folliculitis, cellulitis or erysipelas.

4.2 Posology and method of administration

Adults:

500 mg once daily with food.

In more severe infections, the dosage may be increased to 1000 mg (2 x 500 mg) once daily.

Tablets should be swallowed whole.

The usual duration of treatment is 7 to 14 days.

CLARIHEXAL 500 XL should not be used in patients with severe renal function impairment (creatinine clearance < 30 ml/min). CLARIHEXAL 500 XL is not suitable for patients with creatinine clearance less than 50 ml/min.

4.3 Contraindications

- Hypersensitivity to macrolide antibiotics or to any of the excipients listed in section 6.1.
- As the dose cannot be reduced from 500 mg daily, CLARIHEXAL 500 XL is contraindicated in patients with creatinine clearance < 30 ml/min.
- Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see sections 4.4 and 4.5).
- Concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.5).
- Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).
- Concomitant administration of clarithromycin and any of the following medicine is contraindicated: astemizole, cisapride, domperidone, pimozide and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see section 4.4 and 4.5).
- Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see sections 4.4 and 4.5).
- Concomitant administration with ticagrelor or ranolazine is contraindicated.

- Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4, (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see section 4.5).
- As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine (see sections 4.4 and 4.5).
- Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).
- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Porphyria.
- Safety in pregnancy and lactation has not been established.

4.4 Special warnings and precautions for use

CLARIHEXAL 500 XL should be used with caution in:

- 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 (see section 4.2).
- Treatment with CLARIHEXAL 500 XL should be discontinued if any signs of hepatic dysfunction develop. Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. Hepatic dysfunction is usually reversible but may be severe. However, hepatic failure with fatal outcome has been reported, usually associated with other serious underlying diseases and/or concomitant medicines. Cases of increased serum creatinine have been reported but an association with CLARIHEXAL 500 XL has not been established. Some patients may have had pre-existing hepatic disease

or may have been taking other hepatotoxic medicines. 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.

- Rhabdomyolysis has been reported with concomitant use of CLARIHEXAL 500 XL and the HMG-CoA reductase inhibitors e.g. simvastatin (see section 4.5).
- Rifabutin and rifampicin: may decrease serum concentration of CLARIHEXAL 500 XL by > 50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone (see section 4.5).
- Theophylline – the area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended (see section 4.5).
- Cross-resistance between CLARIHEXAL 500 XL and other macrolides, lincomycin and clindamycin has been reported.
- Pseudomembranous colitis has been reported with nearly all antibacterial medicines, 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 medicines including clarithromycin and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial medicines 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 medicines.

  Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Medicines inhibiting peristalsis should be avoided.
- Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam (see section 4.5).

Cardiovascular Events:

- Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac dysrhythmia and torsades de pointes, have been seen in patients treated with macrolides including clarithromycin (see section 4.8). Due to increased risk of QT prolongation and ventricular dysrhythmias (including torsades de pointes), the use of clarithromycin is contraindicated: in patients taking any of astemizole, cisapride, domperidone, pimozide and terfenadine; in patients who have electrolyte disturbances such as hypomagnesaemia or hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac dysrhythmia (see section 4.3).
- Furthermore, clarithromycin should be used with caution in the following:
    - Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
    - Patients concomitantly taking other medicines 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 dysrhythmia, 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 (SJS), 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 hypoglycaemic medicines/Insulin:

- There have been less frequent reports of hypoglycaemia, some of which occurred in patients on concomitant oral hypoglycaemics (such as sulphonylurias) or insulin. Careful monitoring of glucose is recommended (see section 4.5).

Oral anticoagulants:

- There is a risk of serious haemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.
- Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding (see section 4.5).
- 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.
- Cross-resistance between CLARIHEXAL 500 XL and other macrolides, lincomycin and clindamycin has been reported.
- Adverse effects in immunocompromised patients treated with higher doses of CLARIHEXAL 500 XL over long periods include nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, hearing disturbance, AST and ALT elevations, elevated blood urea levels and abnormally low white blood cell and platelet counts. Additional low-frequency events included dyspnoea, insomnia and dry mouth.

4.5 Interaction with other medicines and other forms of interaction

Clarithromycin is metabolised in the liver where it inhibits the actions of some cytochrome P-450 enzymes. *In vitro* studies have demonstrated that cytochrome P450 (CYP) 3A isoenzyme is involved in 14-hydroxylation and N-demethylation of clarithromycin.

In concomitant administration of clarithromycin and ranitidine bismuth citrate, concentration of ranitidine is increased. This interaction is important in patients with porphyria and renal insufficiency.

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 dysrhythmias 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 dysrhythmias, 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 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 characterized by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids 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 (see section 4.3).

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.

Effects of Other medicines on Clarithromycin

Medicines 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 medicines 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 CLCR 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 ml/min the dose of clarithromycin should be decreased by 75 %. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

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

Effect of Clarithromycin on Other medicines

CYP3A-based interactions:

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

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 dysrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see sections 4.3 and 4.4).

The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazolam, HMG CoA reductase inhibitors metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor and ranolazine (see section 4.3).
Concomitant administration of clarithromycin with lomitapide is contraindicated due to the potential for markedly increased transaminases (see section 4.3).
Caution is required if clarithromycin is co-administered with other medicines known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolised by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of medicines primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving clarithromycin. Drugs or drug classes that are known or suspected to be metabolised by the same CYP3A isozyme include (but this list is not comprehensive) alprazolam, carbamazepine, cilostazole, ciclosporin, disopyramide, ibrutinib, methadone, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine.

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

Antidysrhythmics:

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 medicines/Insulin:

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

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 (P-gp). Clarithromycin and other macrolides are known to inhibit CYP3A and P-gp. When clarithromycin and colchicine are administered together, inhibition of P-gp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine (see section 4.3 and 4.4). In a patient with end-stage renal disease, but no hepatic impairment, fatal colchicine toxicity developed after 4 days of clarithromycin therapy. A patient with moderate chronic renal impairment developed acute but non-fatal colchicine intoxication on day 4 of a 7-day *Helicobacter pylori* treatment course containing clarithromycin. A retrospective study in 116 patients given both medicines concluded that clarithromycin increased the risk of colchicine toxicity, especially in those patients with renal impairment, and that CLARIHEXAL 500 XL should not be used concomitantly with colchicine.

Digoxin:

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (P-gp). Clarithromycin is known to inhibit P-gp. When clarithromycin and digoxin are administered together, inhibition of P-gp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin

concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine:

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin 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 medicines not thought to be metabolised by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

Bi-directional medicine 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, bradydysrhythmias 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 medicine interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and C_{max} values of saquinavir which were 177 % and 187 % higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40% higher than those seen with clarithromycin alone. No dose

adjustment is required when the two drugs are co- administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section 4.5: Ritonavir).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of CLARIHEXAL 500 XL 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 embryofoetal 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.

Breastfeeding

The safety of CLARIHEXAL 500 XL for use during breastfeeding of infants has not been established. CLARIHEXAL 500 XL is excreted in the 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 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.

Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Infections and Infestations:

Less frequent: Cellulitis[1], oral candidiasis, gastroenteritis[2], infection[3], vaginal infection.

Frequency unknown*: Pseudomembranous colitis, erysipelas.

Blood and lymphatic system disorders:

***Less frequent*:** Leucopenia, neutropenia[4], thrombocythaemia[3], eosinophilia[4].

Frequency unknown*: Agranulocytosis, thrombocytopenia.

Immune system disorders:

Less frequent: Hypersensitivity, anaphylactoid reaction[1].

Frequency unknown*: Anaphylactoid reaction**,** angioedema.

Metabolism and nutrition disorders:

***Less frequent*:** Anorexia, decreased appetite.

Psychiatric disorders:

Frequent: Insomnia.

Less frequent: Anxiety, nervousness[3].

Frequency unknown*: Psychotic disorder, confusional state[5], depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania.

Nervous system disorders:

Frequent: Dysgeusia, headache.

Less frequent: Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor.

Frequency unknown*: Convulsion, ageusia, parosmia, anosmia, paraesthesia.

Ear and labyrinth disorders:

Less frequent: Vertigo, tinnitus, hearing impaired.

Frequency unknown*: Deafness.

Cardiac disorders:

Less frequent: Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations.

Frequency unknown*: Ventricular fibrillation, ventricular tachycardia, torsades de pointes.

Vascular disorders:

Frequent: Vasodilation[1].

Frequency unknown*: Haemorrhage.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Asthma[1], epistaxis[2], pulmonary embolism[1].

Gastrointestinal disorders:

Frequent: Nausea, vomiting, abdominal pain, diarrhoea, dyspepsia.

Less frequent: Oesophagitis[1], gastroesophageal reflux disease[2], gastritis, proctalgia[2], glossitis, stomatitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence.

Frequency unknown: Tongue discolouration, tooth discolouration, pancreatitis acute.

Hepatobiliary disorders:

Frequent: Abnormal liver function test.

***Less frequent*:** Cholestasis[4], hepatitis[4], increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma glutamyltransferase [4].

Frequency unknown*: Hepatic failure, jaundice hepatocellular.

Skin and subcutaneous tissue disorders:

Frequent: Rash, hyperhidrosis.

Less frequent: Dermatitis bullous[1], pruritus, rash maculo-papular[3], urticaria.

Frequency unknown*: Stevens-Johnson syndrome, toxic epidermal necrolysis, severe cutaneous adverse reactions (SCAR) (e.g. acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS), acne.

Musculoskeletal and connective tissue disorders:

Less frequent: Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2].

Frequency unknown*: Rhabdomyolysis[2, 6], myopathy.

Renal and urinary disorders:

Less frequent: Increased blood creatinine [1], increased blood urea [1].

Frequency unknown*: Nephritis interstitial, renal failure.

General disorders and administration site conditions:

Frequent: Injection site phlebitis[1], injection site pain[1], injection site inflammation[1].

Less frequent: Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4].

Investigations:

Less frequent: Albumin globulin ratio abnormal[1], increased blood alkaline phosphatase [4], increased blood lactate dehydrogenase [4].

Frequency unknown*: Increased international normalised ratio, prothrombin time prolonged, abnormal urine colour.

[1] Undesirable effects reported only for the powder for solution for injection formulation.

[2] Undesirable effects reported only for the extended-release tablets formulation.

[3] Undesirable effects reported only for the granules for oral suspension formulation.

[4] Undesirable effects reported only for the immediate-release tablets formulation.

[5,6] 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.

Description of selected adverse reactions

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 medicine 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 Extended Release (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 Other special populations).

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.

Other special populations

Immunocompromised patients

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

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1000 mg and 2000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1000 mg and 2000 mg but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000 mg of clarithromycin.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

(See section 4.4).

Symptoms of overdose:

Ingestion of large amounts of CLARIHEXAL 500 XL can be expected to produce gastrointestinal symptoms.

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

Treatment of overdose:

Treatment is symptomatic and supportive. As with other macrolides, CLARIHEXAL 500 XL is not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics

ATC Classification: Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC-Code: J01FA09

5.1 Pharmacodynamic properties

Mechanism of action

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

The 14-(R)-hydroxy metabolite of clarithromycin, a product of parent drug metabolism also has antimicrobial 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.

Resistance

Erythromycin-resistant isolates of Streptococcus pneumoniae are commonly cross-resistant to clarithromycin. The incidence of resistance to clarithromycin and other macrolides is higher among penicillin-resistant strains than among penicillin sensitive strains. Clarithromycin-resistant isolates of *Helicobacter pylori* have also emerged. Genetic mutations responsible for clarithromycin resistance have been identified in H. pylori and in Mycobacterium spp. Since resistance develops rapidly in M. avium during clarithromycin monotherapy, combination therapy is usually recommended. However, resistance to clarithromycin in an AIDS patient

with systemic M. avium complex infection, despite combined treatment with clofazimine, has been described.

When equal daily doses were administered the extent of absorption of clarithromycin from modified release tablets is the same as with usual clarithromycin immediate release tablets. The absolute bioavailability is approximately 50 %. Clarithromycin is stable in the presence of gastric acid and is readily absorbed. Food increases the extent of its absorption; therefore, clarithromycin tablets should be taken with food.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core excipients:

Calcium stearate, cellulose microcrystalline, glycerol dibehenate, hypromellose (Methocel E-50), polysorbate 80, povidone K-25, silica colloidal anhydrous, stearic acid, talc.

Coating Excipients:

Ferric oxide (E 172) yellow, hypromellose (Pharmacoat 606), hypromellose (Methocel E-15), hydroxypropylcellulose, macrogol 400, talc, titanium dioxide, vanilla cream flavour.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ˚C.

6.5 Nature and contents of container

Alu/Alu blisters in packs of 5 or 10 tablets packed into carton boxes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER

43/20.1.1/0859

9. DATE OF FIRST AUTHORISATION

27 July 2012

10. DATE OF REVISION OF THE TEXT

26 July 2022

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Clarihexal 500 XL (5 tablets)	S2	BOT1402655A

	Clarihexal 500 XL (10 tablets)	S2	BOT14022655B
Namibia	Clarihexal 500 XL	NS2	13/20.1.1/0125

ATC Code: J01FA09 - Macrolides

Name and address of manufacturer:

Lek Pharmaceuticals D.D
Verovškova 57
1526 Ljubljana
Slovenia

or

S.C. Sandoz S.R.L.
7A Livezeni Street,
540472 Targu Mures,
Romania

[1]Company Reg. No.: 1990/001979/07