Approved Professional Information for Medicines for Human Use:

CLARITHROMYCIN 250 mg / 500 mg AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CLARITHROMYCIN 250 mg AUSTELL film-coated tablets

CLARITHROMYCIN 500 mg AUSTELL film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CLARITHROMYCIN 250 mg AUSTELL film-coated tablet

Each film-coated tablet contains 257 mg clarithromycin (6-0 methyl erythromycin A) equivalent to 250 mg anhydrous clarithromycin.

Preservative: Sorbic acid 0,063 % *m/m.*

Sugar free.

CLARITHROMYCIN 500 mg AUSTELL film-coated tablet

Each film-coated tablet contains 515,5 mg clarithromycin (6-0 methyl erythromycin A) equivalent to 500 mg anhydrous clarithromycin.

Preservative: Sorbic acid 0,063 % *m/m.*

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

CLARITHROMYCIN 250 mg AUSTELL film-coated tablets

Yellow, oval- shaped, convex tablets, scored on one side, film-coated, 14 x 8 mm.

CLARITHROMYCIN 500 mg AUSTELL film-coated tablets

Yellow, oval- shaped, convex tablets, scored on one side, film coated, 19 x 10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLARITHROMYCIN 250 mg AUSTELL tablets and CLARITHROMYCIN 500 mg AUSTELL tablets is indicated for the treatment of the following mild to moderate severe infections caused by susceptible organisms:

- Lower respiratory tract infections such as bronchitis and pneumonia-caused by *S. pneumonia, M. pneumonia, M. catarrhalis, or H. influenzae*.
- Upper respiratory tract infections such as pharyngitis and sinusitis due to *S. pyogenes*.
- Mild to moderately severe acute otitis media due to *S. pneumoniae, M. catarrhalis and H. influenza*.
- Skin and soft tissue infections such as folliculitis, cellulitis or erysipelas due to *S. aureus*.
- Eradication of *Helicobacter pylori* when used in combination with a proton pump inhibitor and another antibiotic to decrease recurrence of duodenal ulcer.

4.2 Posology and method of administration

Posology

DOSAGE AND DIRECTIONS FOR USE

Adults and children older than 12 years: 250 mg twice daily.

In more severe infections, the dosage may be increased to 500 mg twice daily.

Eradication of *H. pylori:*

Adults: 500 mg twice daily, in combination with an appropriate antibiotic and an acid lowering agent, for 7 to 10 days.

The safety and efficacy of CLARITHROMYCIN AUSTELL tablets in combination with proton-pump inhibitors other than omeprazole has not been established.

Concomitant use of ritonavir

The metabolism of CLARITHROMYCIN AUSTELL is inhibited. No dosage reduction of CLARITHROMYCIN AUSTELL is needed in patients with normal renal function. Patients with renal function impairment require a reduction in the dosage of CLARITHROMYCIN AUSTELL as follows:

- Creatinine clearance 30 to 60 mL/min – Reduce dose by 50 %
- Creatinine clearance < 30 mL/min – Reduce dose by 75 %.

Do not exceed a dose of 1 g/day during concurrent administration of CLARITHROMYCIN AUSTELL with ritonavir.

It has been suggested that other HIV-protease inhibitors and non-nucleotide reverse transcriptase inhibitors may have a similar effect on CLARITHROMYCIN AUSTELL.

Atypical mycobacterial infections (MAC) in HIV patients:

Adults: 500 mg twice daily.

Treatment of disseminated MAC infections in AIDS patients should continue as long as clinical and microbiological benefit is demonstrated. A decrease in efficacy has been noted in patients taking CLARITHROMYCIN AUSTELL tablets for more than 12 weeks. CLARITHROMYCIN AUSTELL tablets should be used in conjunction with other antimycobacterial agents.

CLARITHROMYCIN AUSTELL tablets may be taken with or without meals.

Special populations

Renal impairment

Creatinine clearance (< 30 mL/min): Reduce dose by half i.e. 250 mg once daily or 250 mg twice daily for severe infections. Limit the duration of treatment to 14 days.

Paediatric population

The safety and efficacy in infants under 6 months have not been established.

This formulation is not suitable for use in children less than 12 years of age.

Method of administration

CLARITHROMYCIN AUSTELL tablets is for oral use.

4.3 Contraindications

- Hypersensitivity to clarithromycin, other macrolide antibiotics or to any of the excipients listed in section 6.1.
- Concomitant administration of CLARITHROMYCIN AUSTELL tablets with astemizole, cisapride, pimozide and terfenadine as this may result in QT prolongation and cardiac dysrhythmias including ventricular tachycardia, fibrillation and torsades de pointes (see section 4.5).
- Clarithromycin should not be given to patients with a history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointe (see sections 4.4 and 4.5).
- Porphyria.
- Pregnancy (see section 4.6)
- Concomitant administration of CLARITHROMYCIN AUSTELL tablets with ergotamine or dihydroergotamine as this may result in ergot toxicity characterised by vasospasm and ischaemia of the extremities and central nervous system resulting in permanent tissue damage.
- HMG-CoA reductase inhibitors (statins) such as lovastatin or simvastatin taken with clarithromycin may increase the risk of rhabdomyolysis. Treatment with statins should be discontinued during CLARITHROMYCIN AUSTELL treatment (see section 4.4 and 4.5).
- Colchicine is contraindicated in patients on CLARITHROMYCIN AUSTELL with renal or hepatic impairment who are taking P-glycoprotein inhibitors or a strong CYP34A inhibitor (see section 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 with ticagrelor or ranolazine is contraindicated.
- Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).
- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Concomitant administration with atypical antipsychotics that are predominantly metabolised through the CYP3A4 pathway, for example quetiapine, cariprazine and aripiprazole is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

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

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

Liver function impairment

Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function. No dosage adjustment is required in patients with hepatic function impairment unless there is also concurrent severe renal function impairment.

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. In rare instances, hepatic failure with fatal outcome has been reported, usually associated with other serious underlying diseases and/or concomitant medicines. Isolated cases of increased serum creatinine have been reported but an association with CLARITHROMYCIN AUSTELL tablets has not been established. Treatment with CLARITHROMYCIN AUSTELL tablets should be discontinued if any signs of hepatic dysfunction develop, such as anorexia, jaundice, dark urine, pruritus,

or tender abdomen.

Renal function impairment

Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment (see section 4.2).

The elimination of CLARITHROMYCIN 250 mg AUSTELL tablets and CLARITHROMYCIN 500 mg AUSTELL tablets is reduced in patients with renal function impairment, especially those with a creatinine clearance of < 30 mL/min.

The dose of CLARITHROMYCIN 250 mg AUSTELL tablets and CLARITHROMYCIN 500 mg AUSTELL tablets should be halved, or the dosing interval doubled in patients with creatinine clearance of < 30 mL/min.

Clostridioides difficile-associated diarrhoea (CDAD)

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. Medicines inhibiting peristalsis should be avoided.

Colchicine

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

clarithromycin and colchicine is contraindicated (see section 4.3).

Triazolobenzodiazepines

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such astriazolam, and intravenous or oromucosal-midazolam (see section 4.5).

Concomitant administration of clarithromycin and oral midazolam is contraindicated.

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 treatment with macrolides including clarithromycin (see section 4.8). 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 who have electrolyte disturbances such as hypomagnesaemia or hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac arrhythmia (see section 4.3).

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 (see section 4.5).

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 medicine 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, and toxic epidermal necrolysis and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), treatment with clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Atypical antipsychotics

Concomitant administration of clarithromycin and atypical antipsychotics that are metabolised through the CYP3A4 pathway, for example quetiapine, cariprazine and aripiprazole are contraindicated (see section 4.3 and 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 with concomitant use of CLARITHROMYCIN AUSTELL tablets and the HMGCoA reductase inhibitors e.g. simvastatin (see section 4.5).

Patients should be monitored for signs and symptoms of myopathy.

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

Oral hypoglycemic agents/Insulin

There have been less frequent reports of hypoglycaemia, some of which occurred in patients on concomitant oral hypoglycaemics (such as sulfonylureas) or insulin which can result in significant hypoglycaemia. 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).

Superinfections

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.

Rifabutin and rifampicin

May decrease serum concentration of CLARITHROMYCIN AUSTELL tablets 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 the theophylline serum concentrations is recommended (see section 4.5).

Cross-resistance between CLARITHROMYCIN AUSTELL tablets and other macrolides, lincomycin and clindamycin has been reported.

Adverse effects in immunocompromised patients treated with higher doses of CLARITHROMYCIN AUSTELL tablets over long periods include nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, hearing disturbance, AST and ALT elevations, elevated BUN levels and abnormally low white blood cell and platelet counts. Additional low-frequency events included dyspnoea, insomnia and dry mouth.

Excipient sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

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

Astemizole, cisapride, pimozide, domperidone 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 arrhythmia, ventricular tachycardia, ventricular fibrillation and torsade de pointes. Fatalities have occurred. The most likely cause is the inhibition of metabolism of these medicines by

CLARITHROMYCIN AUSTELL tablets.

Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly (see section 4.3).

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two-to-three-fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergot alkaloids

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 these ergot alkaloids is contraindicated (see section 4.3).

Oral midazolam

When midazolam was co-administered together with clarithromycin tablets (500 mg twice per day), the AUC of midazolam increased 7-fold following the administration of oral midazolam. The concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.3).

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see 4.3) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis.

Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin

must be suspended during the course of treatment.

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.

Atypical antipsychotics

Concomitant administration of clarithromycin and atypical antipsychotics that are predominantly metabolised through the CYP3A4 pathway, for example quetiapine, cariprazine, and aripiprazole may result in an increase in plasma levels of these antipsychotics as a result of inhibition which may present a potential for serious adverse reactions.

Lomitapide

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

Colchicine

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

Effects of other medicinal products 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 a 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 CYP3A4inducer 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.

Rifabutin and rifampicin – May decrease serum concentration of CLARITHROMYCIN AUSTELL tablets by > 50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone (see section 4.4).

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 of CLARITHROMYCIN AUSTELL tablets is needed in patients with normal renal function. Patients with renal function impairment require a reduction in the dose of CLARITHROMYCIN AUSTELL tablets as follows:

- Creatinine clearance 30 to 60 mL/min - Reduce dose by 50 %.
- Creatinine clearance of 30 mL/min - Reduce dose by 75 %.

Do not exceed a dose of 1g/day during concurrent administration of CLARITHROMYCIN AUSTELL tablets with ritonavir.

It has been suggested that other HIV-protease inhibitors and non-nucleoside revered transcriptase inhibitors may have a similar effect on CLARITHROMYCIN AUSTELL tablets.

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).

Effects of clarithromycin on other medicinal products

CYP3A-based interactions

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

The use of clarithromycin should be used with caution and is contraindicated in patients receiving CYP3A substrates, astemizole, cisapride, domperidone, pimozide and terfenadine due to the risk of QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and

torsades de pointes (see sections 4.3 and 4.4).

The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazolam, HMG-CoA reductase inhibitors mainly metabolised 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. Medicines or medicines 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), 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.

Antiarrhythmics

There have been post-marketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during co-administration of clarithromycin with these medicines. 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 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 viaCYP3A4 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).

Anticoagulants such as warfarin

CLARITHROMYCIN AUSTELL tablets may result in the potentiation of the effects of warfarin. Prothrombin time should be monitored closely.

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 medicines 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 medicines 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. Medicine delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the medicine, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

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

Other medicine interactions

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 medicines not thought to be metabolised by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these medicines when administered concomitantly with clarithromycin. Increased serum levels have been reported.

Hydroxychloroquine and Chloroquine

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., vardenafil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged

pharmacologic effect.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1 200 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 medicines 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).

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

Safety and efficacy in 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. Therefore, use during pregnancy is

not advised without carefully weighing the benefits against risks

Breastfeeding

Safety and efficacy in lactation has not been established.

CLARITHROMYCIN AUSTELL tablets is excreted in the 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.

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.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and 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 (see section b of section 4.8).
There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without preexisting mycobacterial infections.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with clarithromycin.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system disorders		Leukopenia, neutropenia[4], thrombocythemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system		Anaphylactoid reaction[1], Hypersensitivity	Anaphylactic reaction, angioedema

disorders[5]			
Metabolism and nutrition disorders		Anorexia, decreased appetite, hypoglycaemia	
Psychiatric disorders	Insomnia	Anxiety, nervousness[3]	Psychotic disorder, confusional state[5], depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders	Dysgeusia,headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor, convulsions.	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders		Vertigo, hearing loss, tinnitus	Deafness
Cardiac disorders		Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolongation, extrasystoles[1], palpitations	Torsades de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders	Vasodilation[1]		Haemorrhage
Respiratory, thoracic and mediastinal disorders		Asthma[1], epistaxis[2], pulmonary embolism[1]	

Gastrointestinal disorders	Nausea, vomiting, abdominal pain, abnormal taste, diarrhoea, dyspepsia	Oesophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], glossitis, stomatitis, oral candidiasis, pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea which may also be bloody, fever), 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, gamma-glutamyl transferase increased[4], increase in liver enzymes	Hepatitis (with or without jaundice), hepatocellular and/or cholestatic, pancreatitis
Skin and subcutaneous tissue disorders	Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rashmaculo-papular[3]	Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with

			eosinophilia and systemic symptoms (DRESS)), acne
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 site conditions	Injection sitephlebitis[1], injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations		Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased, prothrombin time prolonged, urine colour abnormal
Other			Allergic reactions, anaphylaxis

[1] ADRs reported only for the Concentrate for Solution for Infusion formulation

[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* medicine *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 (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 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 population

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 reactions by patients treated with total daily doses of 1 000 mg and 2 000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, 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 1 000 mg and 2 000 mg but were generally about 3 to4 times as frequent for those patients who received total daily doses of 4 000 mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2 % to 3 % of those patients who received 1 000 mg or 2 000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted

for patients who received 4 000 mg daily for all parameters except White Blood Cell.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Symptoms of overdose:

Ingestion of large amounts of CLARITHROMYCIN AUSTELL tablets can be expected to produce gastrointestinal 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. Allergic reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures.

Treatment of overdosage:

Treatment is symptomatic and supportive. CLARITHROMYCIN AUSTELL tablets is not expected to be appreciably affected by haemodialysis or dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.1 – Medium and broad-spectrum antibiotics

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC Code: J01FA09

Mechanism of action

Clarithromycin is a macrolide antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of sensitive microorganisms, thereby inhibiting bacterial RNA-dependant protein synthesis. The in vitro antibacterial spectrum of pathogens sensitive to Clarithromycin includes:

(in vitro sensitivity does not necessarily imply in vivo efficacy)

Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus pneumoniae

Legionelle pneumophilia

Mycoplasma pneumoniae

Chlamydia trachomatis

Moraxella (Branhamella) catarrhalis

Haemophilus influenzae

Staphylococcus aureas (methicillin sensitive)

Helicobacter pylori

Mycobacterium avium, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium intracellulare

5.2 Pharmacokinetic properties

Absorption

Clarithromycin is absorbed rapidly from the gastrointestinal tract after oral administration, but its bioavailability is reduced to 50 to 55 % because of rapid first-pass metabolism. Peak plasma concentration occurs approximately 2 hours after administration. Clarithromycin may be given with or without food.

Distribution

Both clarithromycin and 14-hydroxyclarithromycin distribute widely throughout the body and achieve higher intracellular concentrations. Tissue concentrations generally exceed serum concentrations. Clarithromycin does not achieve significant levels in the cerebrospinal fluid. Protein binding of Clarithromycin ranges from 40 – 70 % and is concentration-dependant.

Biotransformation

Clarithromycin is metabolised by the liver to the active metabolite, 14-hydroxyclarithromycin, as well as to several other metabolites.

Elimination

The elimination half-lives of clarithromycin and 14-hydroxyclarithromycin are approximately 3 to 7 and 5 to 9 hours respectively. Longer half-lives are observed after larger doses. Clarithromycin is eliminated by renal and nonrenal routes. The amount of clarithromycin excreted unchanged in the urine ranges from 20

to 40 %, depending on the dose administered and the formulation. Between 10 and 15 % of the dose is excreted in the urine as the 14-hydroxy metabolite. Although the pharmacokinetics of clarithromycin are altered in patients with hepatic or renal dysfunction, dosage adjustment is not necessary unless a patient has severe renal dysfunction (creatinine clearance of < 30 mL/minute). At higher doses in HIV-infected patients clarithromycin and 14-hydroxyclarithromycin concentrations are much higher when compared with usual doses in non-infected patients. The elimination half-lives also appear to be lengthened.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal anhydrous silica

Microcrystalline cellulose (Avicel 101)

Croscarmellose sodium (Acdisol)

Povidone (K25)

Stearic acid

Purified talc

Magnesium stearate

Film-coating

Hypromellose (methocel)

Propylene glycol

Sorbitan monooleate

Vanilla dry flavour

Quinoline yellow lake (E104) C.I No. 47005

Titanium dioxide

Hydroxypropyl cellulose

Sorbic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store in well closed container at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

CLARITHROMYCIN 250 mg AUSTELL film-coated tablets:

Packed in clear PVC/PVDC-Aluminium blister packs of 10 or 14 tablets.

CLARITHROMYCIN 500 mg AUSTELL film-coated tablets:

Packed in clear PVC/PVDC-Aluminium blister packs of 10 or 14 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd.

1 Sherborne Road,

Parktown

Johannesburg, 2193

South Africa

Tel: +27 11 611 1400 or +27 860 287 835

8. REGISTRATION NUMBERS

CLARITHROMYCIN 250 mg AUSTELL film-coated tablets: A38/20.1.1/0475

CLARITHROMYCIN 500 mg AUSTELL film-coated tablets: A38/20.1.1/0476

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 August 2006

10. DATE OF REVISION OF THE TEXT

15 October 2024