PROFESSIONAL INFORMATION FOR CLARIBAX

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CLARIBAX 500 mg film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 500 mg clarithromycin.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

White or almost white, capsular shaped film coated tablets inscribed with “S20” on one side and blank on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Lower respiratory tract infections, e.g. bronchitis, pneumonia.
- Upper respiratory tract infections, e.g. pharyngitis, sinusitis.
- Skin and soft tissue infections, e.g. folliculitis, cellulitis, erysipelas.

- Eradication of *Helicobacter pylori (H. pylori)*, resulting in decreased recurrence of duodenal ulcer when used in combination with a proton-pump inhibitor to suppress acid secretion and another antibiotic.

  CLARIBAX has been used in treatment regimens which include CLARIBAX plus amoxicillin and omeprazole; CLARIBAX plus tinidazole and omeprazole; and CLARIBAX plus tetracycline and bismuth subsalicylate.
- There is some evidence that disseminated and localised mycobacterial infections in human immunodeficiency virus-positive (HIV-positive) adults, due to *Mycobacterium avium* or *Mycobacterium intracellulare* respond to CLARIBAX. Based on bacteriological results, CLARIBAX should be used in conjunction with other antimycobacterials.

  Localised infections due to *Mycobacterium chelonae* and *Mycobacterium kansasii* have responded to CLARIBAX to a lesser extent.

4.2 Posology and method of administration

The recommended dosage of CLARIBAX is one 250 mg tablet twice daily. In more severe infections, the dosage can be increased to 500 mg twice daily.

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

Eradication of H. pylori: To decrease recurrence of duodenal ulcer in combination with a proton-pump inhibitor and another antibiotic: CLARIBAX 500 mg twice daily in combination with amoxicillin 1 000 mg twice daily and omeprazole 20 mg daily for 7–10 days.

Dosage in HIV patients with mycobacterial infections:

The recommended treatment for adults with disseminated or localised mycobacterium infections (*M. avium*, *M. intracellulare*, *M. chelonae*, *M. kansasii*) is 500 mg twice daily.

Treatment of disseminated *Mycobacterium avium* complex infections in acquired immunodeficiency disease (AIDS) patients should continue as long as clinical and microbiological benefit is demonstrated. A decrease in efficacy has been noted in patients on treatment exceeding 12 weeks. CLARIBAX should be used in conjunction with other antimycobacterial medicines.

Treatment of other non-tuberculous mycobacterial infections should continue at the discretion of the physician.

4.3 Contraindications

- Hypersensitivity to clarithromycin, other macrolide antibacterial medicine or to any of the excipients listed in section 6.1.
- Concomitant administration of CLARIBAX and any of the following medicines is contraindicated: pimozide and ergotamine or dihydroergotamine (see section 4.5).

4.4 Special warnings and precautions for use

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

Hepatic impairment

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. Cases of fatal hepatic failure have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic 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.

Renal impairment

Caution is advised in patients with moderate to severe renal impairment taking CLARIBAX.

Pseudomembranous colitis and Clostridium difficile-associated diarrhoea

Pseudomembranous colitis has been reported and may range in severity from mild to life threatening. *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial medicines including CLARIBAX, 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 CLARIBAX 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 CLARIBAX 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 CLARIBAX and colchicine is not recommended.

Benzodiazepine medicines

Caution is advised regarding concomitant administration of CLARIBAX and triazolobenzodiazepines, such as midazolam and triazolam (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 CLARIBAX (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 pimozide (see section 4.3). The use of CLARIBAX is not recommended in patients who have hypokalaemia, in patients taking domperidone and in patients with a history of QT prolongation or ventricular cardiac dysrhythmia.

Caution is advised with the use of CLARIBAX in the following patients:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.
- Patients with hypomagnesaemia.
- Patients concomitantly taking other medicines associated with QT prolongation.

Variable results have been obtained from epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides. A rare short-term risk of dysrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides have been identified in some observational studies. These findings must be taken into consideration when prescribing CLARIBAX.

Pneumonia

Considering the emerging resistance of *Streptococcus pneumoniae* to macrolide antibiotics, sensitivity testing is essential when prescribing CLARIBAX for the treatment of community-acquired pneumonia. In hospital-acquired pneumonia, CLARIBAX should be combined with additional and appropriate antibiotics.

Skin and soft tissue infections or mild to moderate severity

Staphylococcus aureus and *Staphylococcus pyogenes* are the predominant pathogens causing skin and soft tissue infections. Both of these pathogens may be resistant to macrolide antibiotics and sensitivity testing is therefore advised before prescribing CLARIBAX. In cases where beta-lactam antibiotics cannot be used (e.g., allergy), other antibiotics, such as clindamycin may be the first choice. Currently, macrolide antibiotics are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum*, acne vulgaris, erysipelas and in situations where penicillin treatment cannot be used.

Hypersensitivity reactions

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)), CLARIBAX therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Cytochrome P3A4 (CYP3A4) inducing medicines

CLARIBAX 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)

Caution is advised with the concomitant use of CLARIBAX and lovastatin, simvastatin or any of the other statins (see section 4.5). Rhabdomyolysis has been reported in patients taking CLARIBAX and statins. Patients should be monitored for signs and symptoms of myopathy.

Hypoglycaemic medicines (oral and insulin)

Clinically significant hypoglycaemia may result from the concomitant use of CLARIBAX and oral hypoglycaemic medicines (such as sulphonylureas) or insulin. Careful monitoring of glucose levels is recommended (see section 4.5).

Oral anticoagulant medicines

There is a risk of serious haemorrhage and significant elevations in International Normalised Ratio (INR) and prothrombin time when CLARIBAX is co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are

receiving CLARIBAX and oral anticoagulants concurrently.

Resistance and superinfections

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

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

4.5 Interaction with other medicines and other forms of interaction

Pimozide

Following concomitant use of CLARIBAX and pimozide, elevated levels of pimozide have been reported, which may result in QT prolongation and cardiac dysrhythmias (including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes).

Ergot alkaloids

There have been post-marketing reports indicating acute ergot toxicity characterised by vasospasm and ischaemia of the extremities and other tissues (including the central nervous system), following the concomitant use with ergotamine or dihydroergotamine. Concomitant administration of CLARIBAX and ergot alkaloids is contraindicated (see section 4.3).

Oral midazolam

A 7-fold increase in the area under the curve (AUC) of midazolam has been reported following the co-administration of CLARIBAX with oral midazolam. The concomitant use of

CLARIBAX and oral midazolam is not recommended.

HMG-CoA reductase inhibitors (statins)

Lovastatin and simvastatin undergoes extensive metabolism by CYP3A4 and concomitant treatment with CLARIBAX increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking CLARIBAX concomitantly with these statins. If treatment with CLARIBAX cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing CLARIBAX with statins. In situations where the concomitant use of CLARIBAX 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 (such as fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

Effects of other medicines on CLARIBAX

CYP3A inducing medicines:

Medicines that are inducers of CYP3A (such as rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of CLARIBAX. This may result in sub-therapeutic levels of CLARIBAX 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 CLARIBAX (see also the relevant product information for the CYP3A4 inducer administered). There are reports of an increase in rifabutin, and decrease in CLARIBAX serum levels, together with an increased risk of uveitis following the

co-administration of CLARIBAX and rifabutin.

Medicines affecting circulating concentrations of CLARIBAX

The following medicines are known or suspected to affect circulating concentrations of CLARIBAX (dosage adjustment of CLARIBAX 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 CLARIBAX and thus lower the plasma levels of CLARIBAX, while increasing those of 14-hydroxyclarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-hydroxyclarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of CLARIBAX and enzyme inducers.

Etravirine:

There have been reports of a decrease in exposure of CLARIBAX following the co-administration with etravirine, while the concentrations of the active metabolite, 14-hydroxyclarithromycin increased. 14-hydroxyclarithromycin has reduced activity against *Mycobacterium avium* complex (MAC) and overall activity against this pathogen may be altered. Alternative therapies for the treatment of MAC should be considered.

Fluconazole:

Following the co-administration of CLARIBAX 500 mg twice daily and fluconazole 200 mg daily, studies reported an increase in the mean steady-state minimum CLARIBAX concentration (C_{min}) and area under the curve (AUC). Steady-state concentrations of the active metabolite 14-hydroxyclarithromycin are not significantly affected. No CLARIBAX dose adjustment is required.

Ritonavir:

A pharmacokinetic study has reported a marked inhibition of CLARIBAX metabolism following the concomitant use of CLARIBAX and ritonavir 200 mg, resulting in increased CLARIBAX C_{max}, C_{min} and AUC. The formation of 14-hydroxyclarithromycin is essentially completely inhibited. Due to the large therapeutic window for CLARIBAX, no dosage reduction is required in patients with normal renal function. The following dosage adjustments must be considered for patients with renal impairment:

For patients with a creatinine clearance of 30–60 mL/min, a dose reduction of 50 % CLARIBAX is required. For patients with a creatinine clearance of < 30 mL/min, the CLARIBAX dose should be decreased by 75 %. When using concomitantly with ritonavir, doses >1 g/day of CLARIBAX should not be used.

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 4.5, ***Bi-directional interactions***).

Effects of CLARIBAX on other medicines

CYP3A-based interactions:

Co-administration of CLARIBAX, which is 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 CLARIBAX is contraindicated in patients receiving the CYP3A substrate pimozide and caution is advised in patients receiving domperidone 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).

Caution is required if CLARIBAX is co-administered with other medicines known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (such as 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 CLARIBAX. Medicines or medicine classes that are known or suspected to be metabolised by the same CYP3A isozyme include (but this list is not comprehensive) alprazolam, carbamazepine, cilostazol, ciclosporin, disopyramide, ibrutinib, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine.

Medicines interacting by similar mechanisms through other isozymes within the CYP450 system include phenytoin, theophylline and valproate.

Anti-dysrhythmic medicines:

There have been post-marketed reports of Torsades de Pointes occurring with the concurrent use of CLARIBAX and quinidine or disopyramide.

Electrocardiograms should be monitored for QT prolongation during co-administration of CLARIBAX with these medicines. Serum levels of quinidine and disopyramide should be monitored during CLARIBAX therapy.

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

Hypoglycaemic medicines (oral and insulin):

Hypoglycaemia may result due to the CYP3A inhibiting effects of CLARIBAX when used concomitantly with certain hypoglycaemic medicines, such as nateglinide and repaglinide. Careful monitoring of blood glucose levels is advised.

Omeprazole:

Studies show that following co-administration of CLARIBAX (500 mg every 8 hours) and omeprazole (40 mg daily), the steady-state plasma concentrations of omeprazole are increased. When omeprazole is administered alone, the mean 24-hour gastric pH value is 5,2 and when co-administered with CLARIBAX, 5,7.

Sildenafil, tadalafil and vardenafil:

Sildenafil, tadalafil and vardenafil are at least partially metabolised by CYP3A, and CYP3A may be inhibited by concomitantly administered CLARIBAX. Co-administration of CLARIBAX

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 CLARIBAX.

Theophylline and carbamazepine:

A modest, yet statistically significant increase of circulating theophylline or carbamazepine can result from the co-administration with CLARIBAX and a dose reduction may therefore be considered during concomitant use.

Tolterodine:

Tolterodine is primarily metabolised via CYP2D6, the 2D6 isoform of CYP450. 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 CLARIBAX in the CYP2D6 poor metaboliser population.

Triazolobenzodiazepines (such as aprazolam, midazolam and triazolam):

Following co-administration of CLARIBAX and midazolam, a 2,7-fold and a 7-fold increase of the midazolam AUC have been reported following intravenous (IV) and oral midazolam administration respectively. The concomitant use of oral midazolam and CLARIBAX should be avoided. If intravenous midazolam is co-administered with CLARIBAX, the patient must be closely monitored to allow dose adjustment. Administration of oromucosal midazolam will likely result in a similar interaction as seen with IV administration, due to the bypass of the pre-systemic elimination. The same precautions should 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 CLARIBAX is unlikely.

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

Other interactions

Colchicine:

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

Digoxin:

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

Zidovudine:

Simultaneous oral administration of CLARIBAX and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because CLARIBAX appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of CLARIBAX and zidovudine to allow for a 4-hour interval between each medication.

Phenytoin and valproate:

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including CLARIBAX with medicines not thought to be metabolised by CYP3A (such as phenytoin and valproate). Serum level determinations are recommended for these medicines when administered concomitantly with CLARIBAX. Increased serum levels have been reported.

Bi-directional interactions

Atazanavir:

CLARIBAX and atazanavir are both substrates and inhibitors of CYP3A and there is evidence of a bi-directional interaction. When co-administered, a 2-fold increase in exposure of CLARIBAX, 70 % decrease in exposure of 14-hydroxyclarithromycin and 28 % increase in the AUC of atazanavir have been reported. Because of the large therapeutic window for CLARIBAX, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30–60 mL/min), the dose of CLARIBAX should be decreased by 50 %. For patients with creatinine clearance of <30 mL/min, the dose should be decreased by 75 %. Doses of CLARIBAX greater than 1 000 mg

daily should not be co-administered with protease inhibitors.

Calcium channel blockers:

Caution is advised regarding the concomitant administration of CLARIBAX and calcium channel blockers metabolised by CYP3A4 (such as verapamil, amlodipine and diltiazem) due to the risk of hypotension. Plasma concentrations of CLARIBAX as well as calcium channel blockers may increase due to the interaction. Hypotension, bradydysrhythmias and lactic acidosis have been observed in patients taking CLARIBAX and verapamil concomitantly.

Itraconazole:

Both CLARIBAX and itraconazole are substrates and inhibitors of CYP3A, leading to a bi-directional drug interaction. CLARIBAX may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of CLARIBAX. Patients taking itraconazole and CLARIBAX concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir:

Both CLARIBAX and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional medicine interaction. Steady-state AUC and C_{max} values of saquinavir, 177 % and 178 % higher than that obtained with saquinavir alone, have been reported following co-administration of CLARIBAX (500 mg twice daily) and saquinavir (1 200 mg three times daily). CLARIBAX AUC and C_{max} values were approximately 40 % higher than that obtained with CLARIBAX alone. No dose adjustment is required when the two medicines are co-administered for a limited time at the doses/formulations studied.

Reports from interaction studies using the soft gelatine capsule formulation of saquinavir may not be representative of the effects seen with hard gelatin capsules. Observations from interaction studies alone may not be representative of the effects seen with saquinavir and ritonavir combination therapy. When saquinavir is administered in combination with ritonavir, the potential effects of ritonavir on CLARIBAX needs to be taken into consideration.

Oral contraceptives

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 CLARIBAX during pregnancy has not been established and the use of CLARIBAX during pregnancy is therefore not advised. Based on various animal studies, including mice, rats, rabbits and monkeys, the possibility of embryofoetal development cannot be excluded.

Breastfeeding

CLARIBAX is excreted into breast milk and should not be used during breastfeeding.

Fertility

No data are available on the effects of CLARIBAX on human fertility.

4.7 Effects on ability to drive and use machines

Side effects such as dizziness, vertigo, confusion and disorientation may occur and impair the ability to drive or operate machines. Caution is advised before driving a vehicle or operating machinery until the effects of CLARIBAX are known.

4.8 Undesirable effects

Summary of safety profile

The most frequent adverse reactions reported are abdominal pain, diarrhoea, nausea, vomiting, dyspepsia and taste perversion. These adverse reactions are generally mild to moderate in severity and are consistant with the known safety profile of macrolide antibiotics. Clinical trials have reported no significant difference in the incidence of these gastrointestinal effects between patients with or without preexisting mycobacterial infections.

The following adverse reactions were reported during clinical trials and post-marketing experience:

Infections and infestations

Frequent: Infection.

Less frequent: Candidiasis, vaginal infection.

Frequency unknown: Pseudomembranous colitis, erysipelas.

Blood and lymphatic system disorders

Less frequent: Leukopenia, neutropenia, eosinophilia.

Frequency unknown: Agranulocytosis, thrombocytopenia.

Immune system disorders

Less frequent: Hypersensitivity.

Frequency unknown: Anaphylactic reaction, angioedoema.

Metabolism and nutrition disorders

Less frequent: Anorexia, decreased appetite.

Frequency unknown: Hypoglycaemia.

Psychiatric disorders

Frequent: Insomnia.

Less frequent: Anxiety.

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

Nervous system disorders

Frequent: Dysgeusia, headache, dizziness.

Less frequent: Somnolence, tremor.

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

Ear and labyrinth disorders

Less frequent: Vertigo, hearing impairment, tinnitus.

Frequency unknown: Deafness.

Cardiac disorders

Less frequent: Electrocardiogram QT prolongation, palpitations.

Frequency unknown: Torsades de Pointes, ventricular tachycardia, ventricular fibrillation.

Vascular disorders

Frequency unknown: Haemorrhage.

Gastrointestinal disorders

Frequent: Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain.

Less frequent: Gastritis, stomatitis, glossitis, abdominal distension, constipation, dry mouth, eructation, flatulence.

Frequency unknown: Acute pancreatitis, tongue discolouration, tooth discolouration.

Hepato-biliary disorders

Frequent: Abnormal liver function test, increased alanine aminotransferase, increased aspartate aminotransferase.

Less frequent: Cholestasis, hepatitis, increased gamma-glutamyl transferase.

Frequency unknown: Hepatic failure, jaundice hepatocellular, abnormal hepatic function,

hepatitis cholestatic, cholestatic jaundice.

Skin and subcutaneous tissue disorders

Frequent: Rash, hyperhidrosis, pruritis.

Less frequent: Urticaria.

Frequency unknown: Severe cutaneous adverse reactions (SCAR); such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, medicine rash with eosinophilia and systemic symptoms (DRESS), acne.

Musculoskeletal and connective tissue disorders

Frequency unknown: Rhabdomyolysis, myopathy.

Renal and urinary disorders

Frequency unknown: Renal failure, nephritis interstitial.

General disorders and administration site conditions

Frequent: Asthenia.

Less frequent: Malaise, chest pain, chills, fatigue.

Investigations

Less frequent: Increased blood alkaline phosphatase, increased blood lactate

dehydrogenase.

Frequency unknown: Increased international normalised ratio, abnormal prothrombin time prolonged, abnormal urine colour, increased blood creatinine, increased hepatic enzymes.

Description of selected adverse events

Some of the reports of rhabdomyolysis followed simultaneous use with statins, fibrates, colchicine or allopurinol (see sections 4.3 and 4.4).

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

Other special populations

Immunocompromised patients:

When studying treatment in AIDS and other immunocompromised patients treated with higher doses over long periods of time for mycobacterial infections, it is often difficult to distinguish adverse events possibly associated with CLARIBAX 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 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 events, such as dyspnoea, insomnia and dry mouth occurred at a low frequency. The incidences were comparable for patients treated with 1 000 mg and 2 000 mg, but were generally about 3–4 times as frequent for those patients who received total daily doses of 4 000 mg.

Evaluations of laboratory values were made by analysing values outside the seriously abnormal level (the extreme high or low limit) for the specified test. Based on these criteria, an estimated 2 %–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. Elevated blood urea nitrogen levels were also observed in a lower percentage of patients in these two dosage groups. In patients receiving 4 000 mg daily, slightly higher incidences of abnormal values were noted for all parameters except white blood cell.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms of overdose

Following ingestion of large amounts of CLARIBAX, it is anticipated that gastrointestinal

symptoms may occur. The consumption of 8 g clarithromycin in a patient with a history of bipolar disorder resulted in altered mental status, paranoid behaviour, hypokalaemia and hypoxemia.

Management of overdose

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures. CLARIBAX serum levels are not expected to be appreciably affected by haemodialysis or peritoneal 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, macrolides

ATC code: J01FA09.

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 activitated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria.

The 14-hydroxy metabolite of clarithromycin, a product of parent 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 2-fold more active than the parent compound.

Breakpoints

The following breakpoints have been established for clarithromycin by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

Breakpoints (MIC, mg/L)		
Microorganism	Susceptible (≤)	Resistant (>)
Staphylococcus spp.	1 mg/L	2 mg/L
Streptococcus A, B, C, G	0,25 mg/L	0,5 mg/L
Streptococcus pneumoniae	0,25 mg/L	0,5 mg/L
Viridans group streptococcus	IE	IE
Haemophilus spp.	1 mg/L	32 mg/L
Moraxella catarrhalis	0,25 mg/L	0,5 mg/L[1]
Helicobacter pylori	0,25 mg/L[1]	0,5 mg/L
[1] The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility. "IE" indicates that there are insufficient evidence that the species in question are a good target for therapy with the medicine.		

5.2 Pharmacokinetic properties

H. pylori is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95 % and 80 % of patients respectively are infected with the agent. *H. pylori* is also implicated as a major contribution factor in the development of gastritis and ulcer recurrence in such patients.

Clarithromycin has been used in small numbers of patients in other treatment regimens. Possible kinetic interactions have not been fully investigated. These regimens include:

Clarithromycin plus tinidazole and omeprazole; clarithromycin plus tetracycline, bismuth subsalicylate and ranitidine; clarithromycin plus ranitidine alone.

Clinical studies using various different eradication regimens have shown that eradication of *H. pylori* prevents ulcer recurrence.

Absorption

Following oral administration, clarithromycin is rapidly and well absorbed. After a single oral dose of 100 mg or 1 200 mg clarithromycin, mean peak plasma levels occurred approximately two hours after administration and ranged from 0,35 micrograms/mL to 3,97 micrograms/mL respectively. The mean half-life appears to be dose-dependant and ranges from 2,27–5,98 hours following a 100 mg and 1 200 mg dose respectively.

Based on pharmacokinetic data reported by a multidose study, the half-life and mean peak plasma concentrations of clarithromycin ranged from 2,6 hours and 0,37 micrograms/mL following a dose of 100 mg twice daily, to 4,9 hours and 3,73 micrograms/mL following a dose of 800 mg twice daily.

Clarithromycin can be given without regards to meals. Although food slighty delays the onset absorption and formation of the 14-hydroxy metabolite, the extent of bioavailability of clarithromycin remains unaffected.

Distribution

Clarithromycin and the 14-hydroxy metabolite are extensively distributed in the body tissues

and fluids, resulting in tissue concentrations several times higher than the circulating concentrations. Increased levels have been found in both tonsillar and lung tissue. At therapeutic levels, clarithromycin is 80 % bound to plasma proteins. Protein binding however decreases with an increase in clarithromycin plasma concentration.

When clarithromycin 500 mg is given three times daily, the plasma concentrations are increased when compared to a dose of 500 mg twice daily. Therefore, ^{14}C-clarithromycin is not extensively bound to plasma proteins and its binding sites appear to be readily saturated at high clarithromycin concentrations.

Clarithromycin also penetrates the gastric mucus. Higher levels of clarithromycin are observed in the gastric mucus and gastric tissue when clarithromycin is co-administered with omeprazole, in comparison to treatment with clarithromycin alone.

Biotransformation

The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. Based on reports from a metabolism study, peak plasma levels of radioactivity and parent compound occurred 2–4 hours following administration of a 200 mg or 1 200 mg total dose of ^{14}C-clarithromycin. Following either dose of 250 mg or 1 200 mg, the main metabolite observed was the 14-hydroxy (R) epimer of clarithromycin, with peak levels of 0,5 micrograms/mL and 1,2 micrograms/mL respectively. Only after a 1 200 mg dose were low levels of descladinosyl-clarithromycin seen in the plasma.

Elimination and linearity

The pharmacokinetics of clarithromycin are non-linear, however a steady-state is obtained within 2 days of dosing. At 250 mg twice daily, 15–20 % of unchanged clarithromycin is

excreted in the urine. With 500 mg twice daily dosing, urinary excretion is greater (approximately 36 %). 14-hydroxyclarithromycin is the major urinary metabolite and accounts for 10–15 % of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile and 5–10 % of the parent drug is recovered from the faeces.

Special populations

Pharmacokinetics in patients with Mycobacterium avium infections:

Following administration of 500 mg doses of clarithromycin every 12 hours to adult patients with HIV infection, studies reported steady-state concentrations of clarithromycin and 14-hydroxyclarithromycin similar to that observed in normal subjects. Hoewever, at higher doses which may be required to treat *Mycobacterium avium* infections, clarithromycin concentrations were much higher than those observed at the usual doses. Steady-state clarithromycin C_{max} values ranged from 2–4 micrograms/mL and 5–10 micrograms/mL in adult HIV-infected patients taking 1 000 and 2 000 mg daily in two divided doses, respectively. Elimination half-lives appeared to be lengthened at these higher doses as compared to those seen with usual doses in normal subjects. The higher plasma concentrations and longer elimination half-lives observed with these doses are consistent with the known non-linearity in clarithromycin pharmacokinetics.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal anhydrous silica

Croscarmellose sodium (E468)

Magnesium stearate (E572)

Microcrystalline cellulose (E460)

Polyvinylpyrrolidone (E1201)

Tablet coating:

Opadry Y-1-7000 (containing hypromellose (E464), polyethylene glycol (E1521) and titanium dioxide (E171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blister strip(s) in the outer carton until required for use.

6.5 Nature and contents of container

White opaque PVC/PVdC and silver aluminium push through blister strip(s) packed in an outer cardboard carton.

CLARIBAX is available in pack sizes of 5 or 10 film coated tablets.

CLARIBAX 250 mg is not registered and marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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Waterford Place

Century City

7441

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8. REGISTRATION NUMBER

51/20.1.1/0193

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 20 July 2021