# 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

**Adults and children older than 12 years**

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.

**Renal impairment**

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.

**Paediatric population**

CLARIBAX should not be used in children younger than 12 years.

**Method of administration**

Oral.

**4.3 Contraindications**

- Hypersensitivity to clarithromycin, other macrolide antibacterial medicine or to any of the excipients listed in section 6.1.
- Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine), as this may result in ergot toxicity (see section 4.5).
- Concomitant administration of clarithromycin and oral midazolam (see section 4.5).
- Concomitant administration of clarithromycin and any of the following drugs: astemizole, cisapride, domperidone, pimozide and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsade's de pointes (see section 4.4 and 4.5).

- Concomitant administration with ticagrelor or ranolazine
- Concomitant administration 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 history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsade's de pointes (see sections 4.4 and 4.5).
- Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time).
- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Concomitant administration of CLARIBAX and atypical antipsychotics that are predominantly metabolised through the CYP3A4: quetiapine, cariprazine and aripiprazole.

## 4.4 Special warnings and precautions for use

***Helicobacter pylori* infections**

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 toxicity**

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 contraindicated.

**Benzodiazepine medicines**

Caution is advised regarding concomitant administration of CLARIBAX 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 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 any of astemizole, cisapride, domperidone, pimozide and terfenadine; in patients who have hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac arrhythmia (see section 4.3).

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 other than those which are contraindicated.

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)**

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 CLARIBAX 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).

**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:*

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

**Cross resistance**

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**

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

**Astemizole, cisapride, domperidone, pimozide, and terfenadine**

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

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias, such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsade's 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**

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 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 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 s 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 astemizole, cisapride, 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 metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor and ranolazine (see section 4.3).

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.

***Atypical antipsychotics (such as quetiapine, cariprazine and aripiprazole):***

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. The administration of clarithromycin with atypical antipsychotics such a quetiapine, cariprazine and aripiprazole is therefore contraindicated (see section 4.3).

**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. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine.

***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 187 % 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**

**Women of childbearing potential / Contraception in males and females**

Concurrent use of CLARIBAX and oral contraceptives decreases the efficacy of the oral contraceptive. Patients should be strongly advised to use an alternative or additional method of contraception while taking this medicine (see section 4.5).

**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, 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:***

| **System Organ Class** | **Frequency** | **Adverse reaction** |
|---|---|---|
| Infections and infestations | Less frequent<br><br>Frequency unknown | Candidiasis, gastroenteritis, vaginal infection<br><br>Pseudomembranous colitis, erysipelas |
| Blood and lymphatic system disorders | Less frequent<br><br>Frequency unknown | Leukopenia,neutropenia, eosinophilia<br><br>Agranulocytosis, thrombocytopenia |
| Immune system disorders | Less frequent<br><br>Frequency unknown | Hypersensitivity<br><br>Anaphylactic reaction, angioedoema |
| Metabolism and nutrition disorders | Less frequent | Anorexia, decreased |
| Psychiatric disorders | Frequent<br><br>Less frequent<br><br>Frequency unknown | Insomnia<br><br>Anxiety, nervousness<br><br>Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania |
| Nervous system | Frequent | Dysgeusia, headache, |

| | | |
|---|---|---|
| disorders | Less frequent<br><br>Frequency unknown | Somnolence, dizziness, tremor<br><br>Convulsion, ageusia, parosmia, anosmia, paraesthesia |
| Ear and labyrinth disorders | Less frequent<br><br>Frequency unknown | Vertigo, hearing impairment, tinnitus<br><br>Deafness |
| Cardiac disorders | Less frequent<br><br>Frequency unknown | Electrocardiogram QT prolongation, palpitations<br><br>Torsades de Pointes, ventricular tachycardia, ventricular fibrillation |
| Vascular disorders | Frequency unknown | Haemorrhage |
| Respiratory, thoracic and mediastinal disorder | Less frequent | Epistaxis |
| Gastrointestinal disorders | Frequent<br><br>Less frequent | Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain<br><br>Gastritis, gastroesophageal reflux disease, proctalgia, 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 |
| | Less frequent | Cholestasis, hepatitis, increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyl transferase |
| | Frequency unknown | Hepatic failure, jaundice hepatocellular |
| Skin and subcutaneous tissue disorders | Frequent | Rash, hyperhidrosis |
| | Less frequent | Urticaria, pruritis, rash maculo-papular |
| | 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 | Less frequent<br><br>Frequency unknown | Muscle spasms, myalgia<br><br>Rhabdomyolysis, myopathy |
| Renal and urinary disorders | Frequency unknown | Renal failure, nephritis interstitial |
| General disorders and administration site conditions | Less frequent | Malaise, pyrexia, asthenia, chest pain, chills, fatigue |
| Investigations | Less frequent<br><br><br><br><br><br>Frequency unknown | Increased blood alkaline phosphatase, increased blood lactate dehydrogenase<br><br><br>Increased international normalised ratio, abnormal prothrombin time prolonged, abnormal urine colour |

**Description of selected adverse events**

***Paediatric population***

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

**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.<br>"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

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, 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

Lamar International (Pty) Ltd

2 Waterford Mews

Waterford Place

Century City

7441

Cape Town

South Africa

## 8. REGISTRATION NUMBER

51/20.1.1/0193

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

Registration date: 20 July 2021

## 10. DATE OF REVISION OF THE TEXT

10 January 2025