APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAME (and dosage form)

KLARIBIN TABLETS 250 mg (Tablet)

KLARIBIN TABLETS 500 mg (Tablet)

COMPOSITION

KLARIBIN TABLETS 250 mg: Each film-coated tablet contains 250 mg clarithromycin.

KLARIBIN TABLETS 500 mg: Each film-coated tablet contains 500 mg clarithromycin.

The other ingredients of the formulation are microcrystalline cellulose, croscarmellose sodium, povidone, colloidal anhydrous silica, and magnesium stearate. **KLARIBIN TABLETS 250 mg** and **KLARIBIN TABLETS 500 mg** are coated with Opadry yellow which is composed of hypromellose, propylene glycol, titanium dioxide, hydroxypropylcellulose, vanillin, sorbic acid and iron oxide yellow.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION

Pharmacodynamics:

Clarithromycin is a macrolide antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of sensitive micro organisms, thereby inhibiting bacterial RNA-dependant protein synthesis.

Clarithromycin has activity against gram +ve and some gram –ve organisms. The following are resistant:

- Erythromycin-resistant isolates of *Streptococcus pneumonia.*
- Incidence of resistance is higher among penicillin-resistant strains.
- Clarithromycin-resistant isolates of *H. pylori* have emerged.

- Resistance develops rapidly in *Mycobacterium avium* when clarithromycin is used as monotherapy.

Pharmacokinetics:

Clarithromycin is absorbed rapidly from the gastro-intestinal 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. The extent of absorption is relatively unaffected by food. Clarithromycin may therefore be given with or without food. Clarithromycin is metabolised by the liver to the active metabolite, 14-hydroxyclarithromycin, as well as to several other metabolites. Both clarithromycin and 14-hydroxyclarithromycin are distributed widely throughout the body and achieve high intracellular concentrations. Clarithromycin does not achieve significant levels in the cerebrospinal fluid. Protein binding of clarithromycin ranges from 40 % to 70 % and is concentration-dependent. 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 non-renal 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 is 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). The elimination half-lives also appear to be lengthened.

INDICATIONS

KLARIBIN is indicated for the treatment of the following mild to moderately severe bacterial 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. influenzae.*
- 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.

CONTRA-INDICATIONS

- Hypersensitivity to clarithromycin or other macrolide antibiotics or to any component of **KLARIBIN**.
- Concomitant administration of **KLARIBIN** with astemizole, cisapride and pimozide as this may result in QT prolongation and cardiac dysrhythmias including ventricular tachycardia, fibrillation and torsades de pointes (See **"INTERACTIONS"**).
- Porphyria.
- Pregnancy (see **"PREGNANCY AND LACTATION")**
- Concomitant administration of **KLARIBIN** 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 **KLARIBIN** treatment (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"INTERACTIONS"**).
- Colchicine is contraindicated in patients on **KLARIBIN** with renal or hepatic impairment who are taking P-glycoprotein inhibitors or a strong CYP34A inhibitor (see **"INTERACTIONS"**).

WARNINGS AND SPECIAL PRECAUTIONS:

- **KLARIBIN** is metabolised by the liver and excreted in faeces via the bile. Caution should be exercised in patients with impaired hepatic function. Hepatic dysfunction, including increased liver enzymes and hepato-cellular and/or cholestatic hepatitis, with or without jaundice, has been reported with **KLARIBIN**. This hepatic dysfunction may be severe and is usually reversible. In some instances hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying and/or concomitant medications. Discontinue **KLARIBIN** immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus or tender abdomen.
- Renal function impairment (severe) - The elimination of **KLARIBIN** is reduced in patients with renal

function impairment, especially those with a creatinine clearance of <30 mL/min. The dose of **KLARIBIN** should be halved or the dosing interval doubled in patients with a creatinine clearance of <30 mL/min.

- Rhabdomyolysis has been reported with concomitant use of **KLARIBIN** and the HMGCoA reductase inhibitors e.g. simvastatin, atorvastatin, rosuvastatin and lovastatin. Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (See **"INTERACTIONS"** and **"CONTRAINDICATIONS"**).
- Rifabutin and rifampicin - May decrease serum concentration of **KLARIBIN** by >50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone (See **"INTERACTIONS"**).
- Theophylline - The area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended (See **"INTERACTIONS"**).
- Cross-resistance between **KLARIBIN** and other macrolides, lincomycin and clindamycin have been reported.
- Long term use of **KLARIBIN** may result in colonisation with increased numbers of non-susceptible bacteria and fungi. If super-infections occur, appropriate therapy should be instituted.
- Pseudomembranous colitis has been reported with macrolides such as **KLARIBIN** and may range in severity from mild to life threatening. Treatment with antibacterial medicines alters the normal flora of the colon, which may lead to overgrowth of *Clostridium difficile. Clostridium difficile* associated diarrhoea (CDAD) has been reported with the use of **KLARIBIN** and may range in severity from mild to fatal colitis. CDAD must be considered as diagnosis in all patients who present with diarrhoea during or subsequent to the administration of **KLARIBIN**. Careful medical history is necessary since CDAD has been reported to occur two months after the administration of an antibacterial agent (see **"SIDE EFFECTS"**).
- Should CDAD occur, **KLARIBIN** should immediately be discontinued, a medical practitioner be consulted and an appropriate therapy initiated. Antiperistaltic medicines are contra-indicated in this situation.
- Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving **KLARIBIN** therapy.

- Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines such as alprazolam, midazolam and triazolam (see **"INTERACTIONS"**).
- In view of the emerging resistance of *Streptococcus pneumonia* to macrolides, it is important that sensitivity testing be performed when prescribing **KLARIBIN** for community acquired pneumonia. In hospital-acquired pneumonia, **KLARIBIN** should be used in combination with additional appropriate antibiotics.
- Skin and soft tissue infections are most often caused by *S. aureus* and *S. pyogenes*, both of which may be resistant to macrolides.
- **KLARIBIN** should be used with caution when administered concurrently with medicines that induce the cytochrome CYP3A4 enzyme (see "**INTERACTIONS"**)
- The concomitant use of **KLARIBIN** and oral hypoglycaemic agents and/or insulin can result in significant hypoglycaemia. With certain hypoglycaemic medicines such as nateglinide, pioglitazone and repaglinide, inhibition of CYP3A4 by **KLARIBIN** may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended.
- There is a risk of serious haemorrhage and significant elevations in INR and prothrombin time when **KLARIBIN** is co-administered with warfarin. INR and prothrombin times should be monitored frequently.
- Treatment with **KLARIBIN** should be discontinued if any signs of hepatic dysfunction develop. 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 **KLARIBIN** has not been established.
- There have been reports of hypoglycaemia, some of which occurred in patients on concomitant oral hypoglycaemics or insulin.
- Adverse effects in immunocompromised patients treated with higher doses of **KLARIBIN** 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.

Effects on the ability to drive and use machinery

The potential for dizziness, vertigo, confusion and disorientation should be taken into account before patients on **KLARIBIN** drive or use machinery.

INTERACTIONS

- Concomitant use of **KLARIBIN** with the following medicines are contraindicated: colchicine, HMGCoA reductase inhibitors and ergot alkaloids (see **"CONTRAINDICATIONS"**).
- Astemizole, cisapride and pimozide has resulted in cardiac dysrhythmias, including QTc-interval prolongation, ventricular dysrhythmia, ventricular tachycardia, ventricular fibrillation and torsade de pointes. Fatalities have occurred. The most likely cause is the inhibition of metabolism of these medicines by **KLARIBIN** (see "**CONTRAINDICATIONS"**).
- Inducers of cytochrome P450 which may affect the concentration of clarithromycin – Inducers of CYP3A4 (such as rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort) may increase the metabolism of **KLARIBIN** and may result in sub-therapeutic levels of **KLARIBIN**, leading to reduced efficacy.
- The following medicines may affect the circulating concentrations of clarithromycin. **KLARIBIN** dosage adjustment or consideration of alternative treatments may be required:
    - Strong inducers of cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin and rifapentine may accelerate the metabolism of **KLARIBIN** and thus lower the plasma levels of clarithromycin, while increase ing the levels of the active metabolite, 14-OH-clarithromycin. 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 **KLARIBIN** and enzyme inducers.
    - **KLARIBIN** exposure may be 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.
- Inhibitors of cytochrome P450 which may affect the concentration of clarithromycin:

- Concomitant administration of fluconazole and **KLARIBIN** may lead to increases in the mean steady-state minimum clarithromycin concentration and area under the curve. Steady state concentrations of the active metabolite, 14-OH-clarithromycin are not significantly increased. **KLARIBIN** dose adjustment is not necessary.
- Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A and there is evidence of a bidirectional interaction. Co-administration of **KLARIBIN** with atazanavir and saquinavir may result in a large increase to the exposure to clarithromycin and increases in the plasma concentrations of atazanavir and saquinavir. For patients on atazanavir with renal impairment, the same dose reductions should be followed as with ritonavir.
- Co-administration of **KLARIBIN** and itraconazole may increase each other's plasma levels. Patients on both these medicines should be monitored for signs or symptoms of increased or prolonged pharmacological effect.

- Medicines metabolised by the cytochrome P450 enzyme system (CYP3A4) may be affected by **KLARIBIN** as an enzyme inhibitor for example: alprazolam, ciclosporin, disopyramide, ergot alkaloids, carbamazepine, methylprednisolone, midazolam, omeprazole, quinidine, sildenafil, simvastatin, tacrolimus, triazolam, vinblastine, phenytoin, and valproate –**KLARIBIN** may therefore be associated with increased levels of these medicines. Serum concentrations of these medicines may require monitoring especially medicines with a narrow safety margin such as theophylline and carbamazepine. Rhabdomyolysis has been reported with concomitant use of **KLARIBIN** and the HMGCoA reductase inhibitors e.g. simvastatin and lovastatin (See **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"CONTRAINDICATIONS"**).
- Concurrent use of **KLARIBIN** and medicines causing QT prolongation, cardiac dysrhythmias or torsades de pointes should be used with caution. Quinidine or disopyramide serum levels and ECGs should be monitored during therapy with **KLARIBIN**.
- Concomitant administration of clarithromycin and oral or IV administration of midazolam increases the midazolam AUC 7 and 2,7 fold respectively. Therefore concomitant administration of **KLARIBIN** with oral midazolam should be avoided and with IV midazolam the patient should be closely monitored. The same precautions should apply to other benzodiazepines metabolised by CYP3A4 including alprazolam and triazolam. CNS adverse effects such as somnolence and

confusion have occurred.

- Concomitant use of **KLARIBIN** and colchicine especially in the elderly, some of which occurred in patients with renal insufficiency may cause colchicine toxicity. Deaths have been reported in some such patients (see **"CONTRAINDICATIONS"**).
- Co-administration of clarithromycin and phosphodiesterase type 5 (PDE5) inhibitors may result in increased (PDE5) inhibitor exposure. Reduction of the dosages of sildenafil, tadalafil and vardenafil should be considered when these medicines are co-administered with **KLARIBIN**.
- A reduction in tolterodine dosage may be necessary in the presence of CYP3A4 inhibitors such as **KLARIBIN** in the subset of patients who are devoid of the CYP2D6 enzyme.
- Concomitant administration of omeprazole and **KLARIBIN** led to increases in the mean steady-state concentration and area under the curve of omeprazole. The gastric pH increases. The concentration of clarithromycin (such as in **KLARIBIN**) also increased in gastric tissue and mucus, and to a lesser extent in plasma during the use of omeprazole.
- As increased serum levels have been reported with phenytoin and valproate in combination with CYP3A4 inhibitors including clarithromycin, serum level determinations are recommended for these medicines when administered concomitantly with **KLARIBIN**.
- Hypotension bradydysrhythmias and lactic acidosis have been observed in patients taking clarithromycin (such as in **KLARIBIN**) and verapamil concomitantly.
- Rifabutin and rifampicin - May decrease serum concentration of **KLARIBIN** by > 50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone (See **"WARNINGS AND SPECIAL PRECAUTIONS"**).
- Theophylline and carbamazepine - The area under the plasma concentration-time curves is increased with concomitant use with **KLARIBIN**. Monitoring of the serum concentrations of these medicines is recommended (See **"WARNINGS AND SPECIAL PRECAUTIONS"**)
- Anticoagulants such as warfarin - **KLARIBIN** may result in the potentiation of the effects of warfarin. Prothrombin time or INR should be monitored closely.
- Digoxin –**KLARIBIN** has been shown to increase serum digoxin concentrations and lead to digoxin toxicity including fatal dysrhythmias. Monitoring of digoxin serum concentrations is recommended.
- Zidovudine - A decrease in the steady-state concentration of zidovudine may occur. Doses of

zidovudine and **KLARIBIN** should be taken at least 4 hours apart.

PREGNANCY AND LACTATION

Safety and efficacy in pregnancy and lactation have not been established. **KLARIBIN** is excreted in the breast milk.

KLARIBIN should not be used during pregnancy as its use has been associated with embryo toxicity in animals.

DOSAGE AND DIRECTIONS FOR USE

Children

Safety and efficacy in infants under 6 months of age has not been established.

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

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.

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.

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 **KLARIBIN** in combination with proton-pump inhibitors other than omeprazole have not been established.

Concomitant use of ritonavir

The metabolism of **KLARIBIN** is inhibited. No dosage reduction of **KLARIBIN** is needed in patients with normal renal function. Patients with renal function impairment require a reduction in the dosage of **KLARIBIN** 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 1 g/day during concurrent administration of **KLARIBIN** with ritonavir.

It has been suggested that other HIV-protease inhibitors and non-nucleoside reverse transcriptase inhibitors may have a similar effect on **KLARIBIN.**

KLARIBIN may be taken with or without meals.

SIDE EFFECTS:

Infections and infestations:

Less frequent: Oral candidiasis, gastroenteritis, vaginal infection, pseudomembranous colitis, erysipelas, erythrasma.

Blood and the lymphatic system disorders:

Less frequent: Leucopenia, thrombocytopenia, agranulocytosis.

Immune system disorders:

Less frequent: Allergic reactions, anaphylaxis.

Endocrine disorders:

Less frequent: Hypoglycaemia.

Metabolism and nutrition disorders:

Less frequent: Anorexia, decreased appetite, hypoglycaemia.

Psychiatric disorders:

The following side effects have been reported and frequencies are unknown:

Anxiety, insomnia, hallucinations, bad dreams, depersonalisation, psychotic disorder, depression.

Nervous system disorders:

Frequent: Headache

The following side effects have been reported and frequencies are unknown: Dizziness, vertigo,

disorientation, confusion, convulsions, tremor, parosmia, anosmia, disgeusia and ageusia.

Ear and labyrinth disorders:

Less frequent: Hearing loss, vertigo and tinnitus.

Cardiac disorders:

Less frequent: QT prolongation, ventricular tachycardia, torsades de pointes and palpitations.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Epistaxis.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, abdominal pain, abnormal taste, diarrhoea.

Less frequent: Glossitis, stomatitis, oral candidiasis, tongue discolouration, tooth discolouration, pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea which may also be bloody, fever), dyspepsia, gastrointestinal reflux, gastritis, proctalgia, constipation, dry mouth, eructation and acute pancreatitis.

Hepato-biliary disorders:

Less frequent: Increase in liver enzymes, hepatocellular and/or cholestatic hepatitis (with or without jaundice), and hepatic failure.

Skin and subcutaneous tissue disorders:

The following side effects have been reported and frequencies are unknown: Hyperhidrosis, pruritus, mild skin eruptions, acne, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS) and Henoch-Schonlein purpura.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Myalgia, rhabdomyolysis and myopathy.

Renal and urinary disorders:

The following side effects have been reported and frequencies are unknown: Interstitial nephritis and renal failure.

General disorders and administration site conditions:

Less frequent: Asthenia.

Investigations:

The following side effects have been reported and frequencies are unknown: Increased INR and prolonged prothrombin time, abnormal globulin ratio.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See **"SIDE EFFECTS AND SPECIAL PRECAUTIONS"**

Symptoms of overdose

Ingestion of large amounts of **KLARIBIN** can be expected to produce gastro-intestinal symptoms. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures. Altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia may occur.

Treatment of overdose

Treatment is symptomatic and supportive. **KLARIBIN** is not expected to be appreciably affected by haemodialysis or dialysis.

IDENTIFICATION

KLARIBIN TABLETS 250 mg: Light yellow coloured, oval shaped, biconvex film-coated tablets, with 'D' debossed on one side and '62' on the other side.

KLARIBIN TABLETS 500 mg: Light yellow coloured, oval shaped, biconvex film-coated tablets, with 'D' debossed on one side and '63' on the other side.

PRESENTATION

KLARIBIN TABLETS 250 mg:

1. PVC / PVdC Blister Pack:

Tablets are packed in clear 250 micron PVC film coated with 60 gsm PVdC and printed aluminium foil with 6-8 gsm Heat seal Lacquer.

Pack size: 10's – Each carton contains 1 blister of 10 tablets.

14's - Each carton contains 1 blister of 14 tablets.

2. HDPE Container Pack:

Tablets are packed in 100 ml white HDPE container of 38 mm neck finish (OFC 113 ml) with 38mm-400RS white closure with induction seal wad.

Pack size: 100's: One HDPE container of 100 tablets.

KLARIBIN TABLETS 500 mg:

1) PVC / PVdC Blister Pack:

Tablets are packed in clear 250 micron PVC film coated with 60 gsm PVdC and printed aluminium foil with 6-8 gsm Heat seal Lacquer.

Pack size: 10's – Each carton contains 1 blister of 10 tablets.

14's - Each carton contains 1 blister of 14 tablets.

2) HDPE Container Pack:

Tablets are packed in 120 ml white HDPE container of 38 mm neck finish (OFC 138 ml) with 38mm-400RS white closure with induction seal wad. Each container contains 100 tablets.

Pack size: 100's: One HDPE container of 100 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from moisture.

Keep HDPE containers tightly closed.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

KLARIBIN TABLETS 250 mg: 42/20.1.1/0852

KLARIBIN TABLETS 500 mg: 42/20.1.1/0853

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

Date of registration:

31 July 2014

Date of revision:

31 January 2023