SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Klarithran 500 Tablets

Klarithran Suspension 125 mg/5 ml

Klarithran Suspension 250 mg/5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Klarithran 500 Tablets

Each film coated tablet contains

Clarithromycin	500 mg

Sugar free

For full list of excipients, see section 6.1

Klarithran Suspension 125 mg/5 ml

Each 5ml of constituted suspension contains

Clarithromycin	125 mg
Sodium benzoate (as preservative)	*0,2 % m/v*

Contains Sugar:

Sucrose	2,929 g/5 ml
Contains Aspartame	20 mg

For full list of excipients, see section 6.1

Klarithran Suspension 250 mg/5 ml

Each 5 ml of constituted suspension contains

Clarithromycin	250 mg

Sodium benzoate (as preservative) 0,2 *% m/*

Contains Sugar:

Sucrose 2,508 g /5 ml

Contains Aspartame 20 mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

Klarithran 500 Tablets: Light yellow coloured, oval shaped, biconvex, film coated tablets with “C” and “2” debossed on either side of breakline on one side and notched on either sides along with the breakline.

Suspension

Klarithran Suspension 125 mg/5 ml: White to off-white granular powder forming a white to off-white suspension on constitution with water. The resulting suspension has a sweet taste and fruity flavour.

Klarithran Suspension 250 mg/5 ml: White to off-white granular powder forming a white to off-white suspension on constitution with water. The resulting suspension has a sweet taste and fruity flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- **KLARITHRAN** is indicated for the treatment of the following mild to moderately severe infections caused by susceptible organisms:
- Lower respiratory tract infections such as bronchitis and pneumonia.
- Upper respiratory tract infections such as pharyngitis and sinusitis.
- Mild to moderately severe acute otitis media due to *S. pneumoniae, M. catarrhalis* and *H. influenza.*
- Skin and soft tissue infections such as folliculitis, cellulitis or erysipelas.

- Eradication of *Helicobacter pylori* when used in combination with a proton pump inhibitor and another antibiotic to decrease recurrence of duodenal ulcer.

4.2 Posology and method of administration

Posology

Children

Safety and efficacy in infants under 6 months of age has not been established. The recommended dose for children under 6 months is based upon a 7,5 mg/kg dose administered twice daily. See dosage table below.

The usual duration of treatment is 5 to 10 days, depending on the pathogen involved and the severity of infection.

In patients with severe renal function impairment (creatinine clearance <30 ml/min), the dosage of **KLARITHRAN** should be reduced by half. Do not continue treatment in these patients for more than 14 days.

KLARITHRAN may be taken with or without meals and can be taken with milk.

Weight	**Approximate age**	**Dose in ml of 125 mg/5ml suspension**	**Dose in ml of 250 mg/5ml suspension**
8 to 11 kg	1 to 2 years	2,5 ml twice daily	-
12 to 19 kg	2 to 4 years	5 ml twice daily	2,5 ml twice daily
20 to 29 kg	4 to 8 years	7,5 ml twice daily	3,75 ml twice daily
30 to 40 kg	8 to 12 years	10 ml twice daily	5 ml twice daily

Reconstitution instructions:

The quantity of distilled water specified for the pack size in the table below should be added to the granules and the contents shaken well.

Pack size	Volume of water to be added
60 ml	34 ml
70 ml	40 ml
100 ml	55 ml

Adults: 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 **KLARITHRAN** in combination with proton-pump inhibitors other than omeprazole has not been established.

Atypical mycobacterial infections (MAC) in HIV patients

Adults: 500 mg twice daily

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

KLARITHRAN may be taken with or without meals.

Method of administration:

Administration is by the oral route.

4.3 Contraindications

Hypersensitivity to macrolide antibiotics or to any of the excipients listed in section 6.1.

• Concomitant administration of **KLARITHRAN** and ergot alkaloids (e.g. ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see sections 4.4 and 4.5).

• Concomitant administration of **KLARITHRAN** and oral midazolam is contraindicated (see section 4.5).

• Concomitant administration of **KLARITHRAN** and lomitapide is contraindicated (see section 4.5).

• Concomitant administration of **KLARITHRAN** with astemizole, cisapride, domperidone, pimozide and terfenadine as this may result in QT prolongation and cardiac dysrhythmias including ventricular tachycardia, fibrillation and torsades de pointes (see section 4.5 and 4.5).

• **KLARITHRAN** should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see sections 4.4 and 4.5).

Concomitant administration with ticagrelor, **i**vabradine or ranolazine is contraindicated.

• **KLARITHRAN** should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4, (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see section 4.5).

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

• As with other strong CYP3A4 inhibitors, **KLARITHRAN** should not be used in patients taking colchicine (see sections 4.4 and 4.5).

• **KLARITHRAN** should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).

• **KLARITHRAN** should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

- Porphyria.

4.4 Special warnings and precautions for use

KLARITHRAN should be used with caution in:

- **KLARITHRAN** is principally metabolised by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function.
- Caution should also be exercised when administering **KLARITHRAN** to patients with moderate to severe renal impairment (see section 4.2).
- Renal function impairment (severe) – The elimination of **KLARITHRAN** is reduced in patients with renal function impairment, especially those with a creatinine clearance of < 30 ml/min. The dose of **KLARITHRAN** should be halved or the dosing interval doubled in patients with a creatinine clearance of < 30 ml/min.
- Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. Treatment with **KLARITHRAN** 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. 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. Isolated cases of increased serum creatinine have been reported.
- Rifabutin and rifampicin – May decrease serum concentration of **KLARITHRAN** by

>50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone (see section 4.5).

- Theophylline – The area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended (see section 4.5).
- Pseudomembranous colitis has been reported with nearly all antibacterial medicines, including macrolides, and may range in severity from mild to life-threatening. *Clostridioides difficile*- associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial medicines including clarithromycin and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial medicines alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicines. Therefore, discontinuation of **KLARITHRAN** therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Medicines inhibiting peristalsis should be avoided.
- There have been reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5). Concomitant administration of **KLARITHRAN** and colchicine is contraindicated (see section 4.3).
- Caution is advised regarding concomitant administration of **KLARITHRAN** and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam (see section 4.5).
- ***Cardiovascular Events*****:** Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac dysrhythmia and torsades de

pointes, have been seen in patients treated with macrolides including clarithromycin (see section 4.8). Due to increased risk of QT prolongation and ventricular dysrhythmias (including torsades de pointes), the use of **KLARITHRAN i**s contraindicated: in patients taking any of astemizole, cisapride, domperidone, pimozide and terfenadine; in patients who have electrolyte disturbances such as hypomagnesaemia or hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac dysrhythmia (see section 4.3).

Furthermore, **KLARITHRAN** should be used with caution in the following: Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.

- Patients concomitantly taking other medicines associated with QT prolongation other than those which are contraindicated.
- Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of dysrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing **KLARITHRAN**.

- ***Pneumonia:*** In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing **KLARITHRAN** for community-acquired pneumonia. In hospital-acquired pneumonia, **KLARITHRAN** should be used in combination with additional appropriate antibiotics.
- ***Skin and soft tissue infections of mild to moderate severity:*** These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that

sensitivity testing be performed. In cases where beta–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the medicine of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum*, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

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

• **KLARITHRAN** 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 **KLARITHRAN** with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing **KLARITHRAN** with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy.

In situations where the concomitant use of **KLARITHRAN** with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see section 4.5).

• ***Oral hypoglycaemic medicines/Insulin***: There have been less frequent reports of hypoglycaemia, some of which occurred in patients on concomitant oral hypoglycaemics

(such as sulphonylureas) or insulin. Careful monitoring of glucose is recommended (see section 4.5).

- ***Oral anticoagulants***: There is a risk of serious haemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving **KLARITHRAN** and oral anticoagulants concurrently.

  Caution should be exercised when **KLARITHRAN** is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban, apixaban **and edoxaban**, particularly to patients at high risk of bleeding (see section 4.5).
- Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.
- Cross-resistance between **KLARITHRAN** and other macrolides, lincomycin and clindamycin have been reported.
- Adverse effects in immunocompromised patients treated with higher doses of **KLARITHRAN** 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.

KLARITHRAN contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Aspartame

KLARITHRAN contains 20 mg Aspartame in each 5 ml which is equivalent 4 mg/ml. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Sodium

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

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of KLARITHRAN with:

Astemizole, cisapride, domperidone, pimozide and terfenadine:

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

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac dysrhythmias, such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes (see section 4.3). 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:

Co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of **KLARITHR**AN and ergot alkaloids is contraindicated (see section 4.3).

Oral Midazolam:

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and **KLARITHRAN** is contraindicated (see section 4.3).

HMG-CoA Reductase Inhibitors (statins):

Concomitant use of **KLARITHRAN** with lovastatin or simvastatin is contraindicated (see section 4.3) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with **KLARITHRAN** increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with **KLARITHRAN** cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing **KLARITHRAN** with statins.

In situations where the concomitant use of **KLARITHRA**N with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

Effects of other medicines on KLARITHRAN:

Medicines that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inducer administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin and decrease in clarithromycin serum levels together with an increased risk of uveitis.

The following medicines are known or suspected to affect circulating concentrations of clarithromycin; **KLARITHRAN** dosage adjustment or consideration of alternative treatments may be required:

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine:

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of **KLARITHRAN** and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of **KLARITHRAN** and enzyme inducers.

Etravirine:

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH- clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to **KLARITHRAN** should be considered for the treatment of MAC.

Fluconazole:

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33 % and 18 % respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No **KLARITHRAN** dose adjustment is necessary.

Ritonavir:

Marked inhibition of the metabolism of clarithromycin has been demonstrated during concomitant administration of ritonavir 200 mg every 8 hours and clarithromycin 500 mg every 12 hours. The clarithromycin Cmax increased by 31 %, Cmin increased 182 % and AUC increased by 77 % with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 ml/min the dose of **KLARITHRAN** should be reduced by 50 %. For patients with CLCR < 30 ml/min the dose of **KLARITHRAN** should be decreased by 75 %. Doses of **KLARITHRAN** greater than 1 g/day should not be co-administered with ritonavir

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

Effect of KLARITHRAN on other medicines:

CYP3A-based interactions:

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

The use of **KLARITHRAN** is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, domperidone, pimozide and terfenadine due to the risk of QT prolongation and cardiac dysrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see sections 4.3 and 4.4).

The use of **KLARITHRAN** is also contraindicated with ergot alkaloids, oral midazolam, HMG CoA reductase inhibitors metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor, ivabradine and ranolazine (see section 4.3).

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

Caution is required if **KLARITHRAN** is co-administered with other medicines known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolised by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of medicines primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving **KLARITHRAN**. Medicine 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, cilostazole, ciclosporin, disopyramide, ibrutinib, methadone, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine.

Concomitant administration of **KLARITHRAN** and atypical antipsychotics that are predominantly metabolised through the CYP3A4 pathway, for example quetiapine,

cariprazine, and aripiprazole may result in an increase of the antipsychotics as a result of inhibition which may present a potential for serious adverse reactions.

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

Antidysrhythmics:

There have been reports of torsades de pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during co-administration of **KLARITHRAN** with these medicines. Serum levels of quinidine and disopyramide should be monitored during **KLARITHRAN** therapy. There have been reports of hypoglycaemia with the concomitant administration of clarithromycin and disopyramide. Therefore, blood glucose levels should be monitored during concomitant administration of **KLARITHRAN** and disopyramide.

Oral hypoglycaemic medicines/Insulin:

With certain hypoglycaemic medicines such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended.

Omeprazole:

Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (Cmax, AUC0-24, and t1/2 increased by 30 %, 89 %, and 34 %, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5,2 when omeprazole was administered alone and 5,7 when omeprazole was co-administered with clarithromycin.

Direct acting oral anticoagulants (DOACs):

The DOAC dabigatran **and edoxaban** are substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp.

Caution should be exercised when **KLARITHRAN** is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

Sildenafil, tadalafil and vardenafil:

Each of these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of **KLARITHRAN** 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 **KLARITHRAN.**

Theophylline, carbamazepine:

A modest but statistically significant (p≤0,05) increase of circulating theophylline or carbamazepine levels occurred when either of these medicines were administered concomitantly with **KLARITHRAN**. Dose reduction may need to be considered.

Tolterodine:

The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as **KLARITHRAN** in the

CYP2D6 poor metaboliser population.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam):

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2,7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with **KLARITHRAN**, the patient must be closely monitored to allow dose adjustment. Medicine delivery of midazolam via oromucosal route,

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

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

Other medicine interactions:

Colchicine:

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

Digoxin:

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

Zidovudine:

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of **KLARITHRAN** and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate:

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

Bi-directional medicine interactions:

Atazanavir:

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional medicine interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2- fold increase in exposure to clarithromycin and a 70 % decrease in exposure to 14-OH-clarithromycin, with a 28 % increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 ml/min), the dose of **KLARITHRAN** should be decreased by 50 %. For patients with creatinine clearance < 30 ml/min, the dose of **KLARITHRAN** should be decreased by 75 % using an

appropriate clarithromycin formulation. Doses of **KLARITHRAN** greater than 1000 mg per day should not be co-administered with protease inhibitors.

Calcium Channel Blockers:

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

Itraconazole:

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

Saquinavir:

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional medicine interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were

177 % and 187 % higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40 % higher than those seen with clarithromycin alone. No dose adjustment is required when the two medicines are co-administered for a limited time at the doses/formulations studied. Observations from medicine interaction studies

using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from medicine interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section 4.5: Ritonavir).

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

Hydroxychloroquine and chloroquine:

Clarithromycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

Corticosteroids

Caution should be exercised in concomitant use of clarithromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely

monitored for systemic corticosteroid undesirable effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy and lactation have not been established.

Breastfeeding

KLARITHRAN is excreted in the breast milk.

Fertility

In the rat, fertility studies have not shown any evidence of harmful effects.

4.7 Effects on ability to drive and use machines

There are no data on the effect of **KLARITHRAN** on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation should be taken into account before patients on **KLARITHRAN** drive or use machinery

4.8 Undesirable effects

Table 1: Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency not known***
Infections and infestations		Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection.	Pseudomembranous colitis, erysipelas.
Blood and lymphatic system disorders		Leucopoenia, neutropenia[4], thrombocythaemia[3], eosinophilia[4].	Agranulocytosis, thrombocytopenia.
Immune system disorders		Hypersensitivity reactions, anaphylaxis anaphylactoid reaction[1].	Anaphylactoid reaction, angioedema.
Metabolism and nutrition disorders		Anorexia, decreased appetite.	
Psychiatric disorders	Insomnia.	Anxiety, nervousness[3]	Psychotic disorder, confusional state[5], depersonalisation, depression, disorientation,

			hallucination, abnormal dreams, mania.
Nervous system disorders	Dysgeusia, headache.	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor.	Convulsions, ageusia, parosmia, anosmia, paraesthesia.
Ear and labyrinth disorders		Vertigo, tinnitus, impaired hearing.	Deafness.
Cardiac disorders		Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations.	Ventricular fibrillation, torsades de pointes, ventricular tachycardia.
Vascular disorders	.	Vasodilation[1]	Haemorrhage.
Respiratory, thoracic and mediastinal disorders		Asthma[1], epistaxis[2], pulmonary embolism[1].	
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhoea, dyspepsia.	Oesophagitis[1], gastroesophageal reflux disease[2], gastritis, proctalgia[2], glossitis, stomatitis, abdominal distension[4],	Tongue discolouration, tooth discolouration, pancreatitis acute.

		constipation, dry mouth, eructation, flatulence.	
Hepato-biliary disorders	Abnormal liver function test.	Cholestasis[4], hepatitis[4], increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma glutamyltransferase[4].	Hepatic failure, jaundice hepatocellular.
Skin disorders	Rash, hyperhidrosis.	Dermatitis bullous[1], pruritus, rash maculo-papular[3], urticaria.	Stevens-Johnson syndrome, toxic epidermal necrolysis, Severe cutaneous adverse reactions (SCAR) (e.g. acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) acne'
Musculoskeletal and connective tissue disorders		Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2,6], myopathy.
Renal and urinary disorders		increased blood creatinine [1], increased blood	Nephritis interstitial, renal failure.

		urea [1].	
General disorders	Injection site phlebitis[1], injection site pain[1], injection site inflammation[1].	Malaise[4], pyrexia [3], asthenia, chest pain [4], asthenia, chest pain[4], chills [4], fatigue [4].	
Investigations		Albumin globulin ratio abnormal[1], increased blood alkaline normalised ratio, phosphatase [4], increased blood lactate dehydrogenase [4].	Increased International normalised ratio, prothrombin time prolonged, abnormal urine colour.

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

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

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

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

[5,6] see Description of selected adverse reactions.

* Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to medicinal product exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.

Description of selected adverse reactions

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see section 4.3 and 4.4).

There have been reports of medicine interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested (see section 4.5).

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

Special population:

Adverse Reactions in Immunocompromised patients (see section Other special populations).

Other special populations

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to

distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **KLARITHRAN** is important. It allows continued monitoring of the benefit/risk balance of **KLARITHRAN**. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: Suspected adverse reactions can also be reported directly to the Holder of Certificate of Registration via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000

4.9 Overdose

(See section 4.4)

Symptoms of overdose:

Ingestion of large amounts of **KLARITHRAN** can be expected to produce gastrointestinal 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. **KLARITHRAN** is not expected to be appreciably affected by haemodialysis or dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC code: J01FA09

Category and Class: A.20.1.1 Broad and medium spectrum antibiotics.

Mechanism of action

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

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

Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus pneumoniae,

Legionella pneumophilia

Mycoplasma pneumoniae

Chlamydia trachomatis

Moraxella (Branhamella) catarrhalis

Haemophilus influenzae

Staphylococcus aureus (methicillin sensitive)

Helicobacter pylori

Mycobacterium avium, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium intracellulare

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.

5.2 Pharmacokinetic properties

Clarithromycin is absorbed rapidly from the gastro-intestinal tract after oral administration, but its bioavailability is reduced to 50 % from 55 % because of rapid first-pass metabolism. Peak plasma concentration occurs approximately 5 to 7 hours after administration. Clarithromycin may 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 distribute widely throughout the body and achieve high intracellular concentrations. Tissue concentrations generally exceed serum concentrations. Clarithromycin does not achieve significant levels in the cerebrospinal fluid. Protein binding of clarithromycin ranges from 40 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 are altered in patients with hepatic or renal dysfunction, dosage adjustment is not necessary unless a patient has severe renal dysfunction (creatinine clearance of <30 ml/minute). At higher doses in HIV-infected patients clarithromycin and 14-hydroxyclarithromycin concentrations are much higher when compared with usual doses in non-infected patients. The elimination half-lives also appear to be lengthened.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

KLARITHRAN 500 TABLETS

Intragranular ingredients

- Croscarmellose sodium
- Microcrystaliine cellulose
- Povidone
- Purified water

Extragranular ingredients

- Colloidal anhydrous silica
- Croscarmellose sodium
- Magnesium stearate
- Purified talc
- Stearic acid

Film Coating Ingredients

- Opadry 20H 52875(Yellow)

- Purified water

KLARITHRAN 125 mg and 250 mg SUSPENSION

- Alginic acid
- Aspartame
- Carbomer (Carbopol 974 P)
- Colloidal anhydrous silica
- Croscarmellose sodium
- Flavour Peppermint
- Flavour Tutti Frutti 051880 AP0551
- Hypromellose
- Hydroxypropyl cellulose
- Isopropyl alcohol
- Macrogol 1500 (polyethylene glycol)
- Methacrylic acid -ethyl acrylate copolymer (1:1) Dispersion 30 %
- Microcrystalline cellulose
- Monosodium citrate
- Purified water
- Sodium benzoate
- Sodium chloride
- Sucrose
- Titanium dioxide
- Talc
- Xanthan Gum

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 °C in the original container protected from moisture.

6.5 Nature and contents of container

Klarithran 500 Tablets: Blister strips comprising of clear PVC film (coated uniformly with PVdC on inner side) with a backing of aluminium foil (coated with heat seal lacquer) containing 10 or 14 tablets.

Klarithran Suspension 125 mg/5ml: Natural translucent HDPE bottle pack of 60 ml, 70 ml and 100 ml.

Klarithran Suspension 250 mg/5ml: Natural translucent HDPE bottle pack of 60 ml, 70 ml and 100 ml.

6.6 Special precautions for disposal and other handling

Klarithran Suspension 125 and 250 mg/5ml:

Reconstitution instructions:

The quantity of distilled water specified for the pack size in the table below should be added to the granules and the contents shaken well.

Pack size	**Volume of water to be added**
60 ml	34 ml
70 ml	40 ml
100 ml	55 ml

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7 HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

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8 REGISTRATION NUMBER(S)

KLARITHRAN 500 TABLETS: 37/20.1.1/0437 (South Africa)

KLARITHRAN SUSPENSION 125 mg/5ml: 38/20.1.1/0174 (South Africa)

KLARITHRAN SUSPENSION 250 mg/5ml: 38/20.1.1/0175 (South Africa)

NS2 Klarithran 500 Tablets: 06/20.1.1/0058 (Namibia)

NS2 Klarithran Suspension 125 mg/5 ml: 06/20.1.1/0059 (Namibia)

NS2 Klarithran Suspension 250 mg/5 ml: 06/20.1.1/0060 (Namibia)

S2 Klarithran 500 Tablets: BOT 0500780 (Botswana)

S2 Klarithran Suspension 125 mg/5 ml: BOT 0801266 (Botswana)

S2 Klarithran Suspension 250 mg/5 ml: BOT 0801265 (Botswana)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 March 2005

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