1.3Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) Name of the medicinal product
CLARITHROMYCIN TABLETS USP 500 MG

1.2 Strength
Each film coated tablet contains:
Clarithromycin USP……. 500 mg
Excipients Q.S.
Colour: Titanium Dioxide

1.3 Pharmaceutical Form
Oral Film Coated Tablet

2. Qualitative and Quantitative Formula

Batch Size: 1,00,000 Tablets

Sr. No.	Name of Ingredient	Label Claim (mg)	Overages	Qty./Tablet (mg)	Qty./Batch (Kg)	%	Function
MIXING							
1.	Clarithromycin USP**	500.000mg	2	510.000mg	51 kg	6.21%	Antibiotic
2.	Maize Starch BP**	--	5	89.250mg	8.925 kg	10.87%	Diluent
3.	Microcrystalline cellulose powder 101 BP**	--	5	147.000mg	14.7 kg	17.90%	Diluent
WET GRANULATION							
4.	Povidone (K-30) BP	--	--	15.000 mg	1.5 kg	1.82%	Binder
5.	Isopropyl Alcohol* BP	--	--	Q.S.	Q.S.	--	Solvent
LUBRICATION							
6.	Magnesium Stearate BP	--	--	10.000mg	1 kg	1.21%	Lubricant
7.	Purified Talc BP	--	--	5.000mg	0.5 kg	0.609%	Lubricant
8.	Cross Carmellose Sodium BP	--	--	30.000mg	3 kg	3.65%	Disintegrant
9.	Colloidal Anhydrous Silica BP	--	--	5.000mg	0.5 kg	0.609%	Disintegrant
Average Weight of Uncoated Tablet				**800.00mg**	**80.00kg**	**--**	
COATING							
10.	Hypromellose BP	--	--	11.000mg	1.1 kg	1.33%	Film Forming Agent
11.	Purified Talc BP	--	--	3.000mg	0.3 kg	0.365%	Lubricant
12.	Macrogol 4000 BP	--	--	4.000mg	0.4 kg	0.487%	Polishing

							Agent
13.	Titanium Dioxide BP	--	--	3.000mg	0.3 kg	0.365%	Colouring Agent
14.	Dichloromethane*BP	--	--	Q.S.	Q.S.	-	Solvent
15.	Isopropyl Alcohol* BP	--	--	Q.S.	Q.S.	-	Solvent
Average Weight of film coated Tablet				**821.00mg**	**82.1kg**	**100**	**-**

*This will not remain in the finished product.
**Overage is added to compensate the loss during manufacturing process.
In coating stage: Quantity of Isopropyl Alcohol 8 Liter/100000 Tablets & Quantity of Dichloromethane 12 Liter/100000 Tablets.

3. Pharmaceutical form

Oral Film coated tablet

White, capsule shaped biconvex film coated tablet, break line on one side & other side plain.

4. Clinical particulars:

4.1 Therapeutic Indication:

Clarithromycin is indicated for treatment of infections due to susceptible organisms. Such infections include.

1. Lower respiratory tract infections (e.g. bronchitis, pneumonia)
2. Upper respiratory tract infections (e.g. pharyngitis, sinusitis).
3. Skin and soft tissue infections (e.g. folliculitis, cellulitis, erysipelas)
4. Disseminated or localised mycobacterial infections due to Mycobacterium avium or Mycobacterium intracellulare. Localised infections due to Mycobacterium chelonae, Mycobacterium fortuitum or Mycobacterium kansasii.
5. Clarithromycin is indicated for the prevention of disseminated Mycobacterium avium complex infection in HIV-infected patients with CD4 lymphocyte counts less than or equal to 100/mm3.
6. Clarithromycin in the presence of acid suppression is indicated for the eradication of H. pylori, resulting in decreased recurrence of duodenal ulcer.

Consideration should be given to official guidance on the appropriate use of antibacterial agents. As with other antibiotics, it is recommended that guidelines on the prevalence of local resistance, and associated medical practice regarding the prescription of antibiotics, be consulted before prescribing Klacid Forte.

Further Information: H. pylori is strongly associated with peptic ulcer disease. Ninety to 100% of patients with duodenal ulcers are infected with this agent. Eradication of H. pylori has been shown to markedly reduce the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy.

In a well controlled double-blind study, H. pylori infected patients with duodenal ulcer received clarithromycin 500mg t.i.d for 14 days with omeprazole 40mg daily for 28 days. Clarithromycin has been used in other treatment regimens for the eradication of H. pylori. These regimens include clarithromycin plus tinidazole and omeprazole; and clarithromycin plus tetracycline, bismuth subsalicylate, and ranitidine.

4.2 Posology and method of administration:

Adults: The usual recommended dosage of clarithromycin in adults is one 250mg tablet twice daily. In more severe infections, the dosage can be increased to 500mg twice daily. The usual duration of therapy is 6 to 14 days.

Children under 12 years: The use of clarithromycin tablets has not been studied in children under 12 years. Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension (granules for oral suspension).

Children over 12 years: As for adults.

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

Dosage in patients with mycobacterial infections: The recommended dose for adults with mycobacterial infections is 500mg b.i.d. Treatment of disseminated Mycobacterium Avium Complex (MAC) infections in AIDS patients should be continued, as long as clinical microbiological benefit is demonstrated. Clarithromycin should be used in conjunction with other antimycobacterial agents.

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

Dosage for MAC prophylaxis: The recommended dosage of clarithromycin in adults is 500mg twice daily.

Eradication of H. pylori:

Triple Therapy (7 days): Clarithromycin (500mg) twice daily and a proton pump inhibitor (at the approved daily dose)* should be given with amoxycillin 1000mg twice daily for 7 days.

Triple Therapy (7 days): Clarithromycin (500mg) twice daily and a proton pump inhibitor (at the approved daily dose)* should be given with metronidazole 400mg twice daily for 7 days.

Triple Therapy (7-10 days): Clarithromycin (500mg) twice daily should be given with omeprazole 20 mg daily and amoxycillin 1000mg twice daily for 7 to 10 days.

Method of administration: Oral administration

4.3 Contraindications

Hypersensitivity to macrolide antibiotic drugs or any of the excipients. Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, domperidone, pimozide or terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.Concomitant administration with ticagrelor or ranolazine is contraindicated. Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity.Concomitant administration of clarithromycin and lomitapide is contraindicated.Clarithromycin 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. Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins), that are extensively metabolised by CYP3A4, (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.As with other strong CYP3A4 inhibitors, clarithromycin should not be used in patients taking colchicine. Concomitant administration of clarithromycin and oral midazolam is contraindicated. Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or

hypomagnesaemia due to the risk of prolongation of the QT interval). Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

4.4 Special warnings and precautions for use:

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy. Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal 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. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen. Cases of fatal hepatic failure have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. 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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. Clostridioides difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C. difficile. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

Colchicine

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

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam and intravenous or oromucosal midazolam.

Cardiovascular Events

Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in patients treated with macrolides including clarithromycin. Due to increased risk of QT prolongation and ventricular arrhythmias (including torsade de pointes), the use of clarithromycin is contraindicated: in patients taking any of astemizole, cisapride, domperidone, pimozide and terfenadine; in patients with electrolyte disturbances such as hypomagnesaemia or hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac arrhythmia.

Furthermore, clarithromycin should be used with caution in the following:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.
- Patients concomitantly taking other medicinal products associated with QT prolongation other than those which are contraindicated.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Pneumonia: In view of the emerging resistance of Streptococcus pneumoniae to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity: These infections are most often caused by Staphylococcus aureus and Streptococcus pyogenes, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where beta–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug 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 generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated. Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme.

HMG-CoA reductase inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. Caution should be exercised when prescribing clarithromycin 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 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.

Oral hypoglycaemic agents/insulin: The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended.

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

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding. Use of any antimicrobial therapy, such as clarithromycin, to treat H. pylori infection may select for drug-resistant organisms. Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occurs, appropriate therapy should be instituted.

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products 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 torsades de pointes. Similar effects have been observed in patients, taking clarithromycin and pimozide concomitantly.
Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias, such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes. In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a 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.

Ergotamine/dihydroergotamine

Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated.

Oral Midazolam

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

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment. Caution should be exercised when prescribing clarithromycin with statins. 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. Patients should be monitored for signs and symptoms of myopathy.

Effects of other Medicinal Products on Clarithromycin

Drugs 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 drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine

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

Etravirine

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

Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin
500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (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 clarithromycin dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin 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 creatinine clearance 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with creatinine clearance <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1000 mg/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 drug interactions).

Effect of clarithromycin on Other Medicinal Products

CY3A4-based interactions

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

The use of clarithromycin is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, domperidone, pimozide and terfenadine due to the risk of QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.
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.
Concomitant administration of clarithromycin with lomitapide is contraindicated due to the potential for markedly increased transaminases. Caution is required if clarithromycin is co-administered with other drugs 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 metabolized by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin. Drugs or drug classes that are known or suspected to be metabolized by the same CYP3A isozyme include (but this list is not comprehensive) alprazolam, carbamazepine, cilostazole, ciclosporin, disopyramide, ibrutinib, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine.
Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics

There have been postmarketing reports of torsades de points occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during co-administration of clarithromycin with these drugs. Serum levels of quinidine and disopyramide should be monitored during clarithromycin therapy. There have been post marketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycemic agents/Insulin

With certain hypoglycemic drugs 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.

Direct acting oral anticoagulants (DOACs)

The DOAC dabigatran is a 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 clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

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.

Sildenafil, tadalafil and vardenafil

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

administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

Theophylline and carbamazepine

Results of clinical studies indicate that there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin. Dose reduction may need to be considered.

Tolterodine

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

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

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. A drug-drug interaction study between oromucosal midazolam and clarithromycin has not been conducted. However drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, 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 post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other drug 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 clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Concomitant use of clarithromycin and colchicine is contraindicated.

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

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously

administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV- infected patientstaking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

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

Bi- directional drug interactions

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Calcium Channel Blockers Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g. 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, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

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

Saquinavir Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 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 drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavi r is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embyofoetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Breast-feeding

The safety of clarithromycin use during breast-feeding of infants has not beenestablished. Clarithromycin is excreted into human breast milkin small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight -adjusted dose of clarithromycin.

Fertility

There is no data available on the effect of clarithromycin on fertility in humans. In the rat, fertility studies have not shown any evidence of harmful effects.

4.7 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be takeninto account before patients drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics. There was no significant difference in the incidenceof these gas trointestinal adverse reactions during clinical trials between the patient population with or without preexisting mycobacterial infections.

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended-release tablets and modified-release tablets.The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System Organ Class	Very common (≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥1/1,000 to < 1/100	Not Known (*cannot be Estimate available data)
Infections and infestations			Cellulitis[1],candidiasis , Gastroenteritis [2]	Pseudomembranous colitis, erysipelas

			,infection[3], vaginal infection	
Blood and Lymphatic system			Leukopenia, neutropenia[4], thrombocythemia[3],eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and Nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3],	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination,abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache	Loss of consciousness[1], dyskinesia[1], dizziness,somnolence, tremor	Convulsion, ageusia parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged,extrasystoles[1],palpitations	Torsades de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders		Vasodilation[1]		Haemorrhage
Respiratory,thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhoea, vomiting, dyspepsia, nausea, abdomina[1] pain	Oesophagitis[1], gastrooesophageal reflux disease[2], gastritis,proctalgia[2], stomatitis, glossitis,abdomina[1] distension[4], constipation, dry mouth, eructation,	Pancreatitis acute, tongue discolouration, tooth discolouration

			flatulence	
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4] , hepatitis[4], Alanine amino transferase increased,aspartate amino transferase increased, gamma-glutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1],pruritus, urticaria, rash maculo-papular[3]	Severe cutaneous adverse reactions (SCAR) (e.g acute generalised exanthematous pustulosis, Stevens-johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS)),acne
Musculoskeletal and connective tissue disorders			Muscle spasms [3],musculoskeletal stiffness[1],myalgia [2]	Rhabdomyolysis 2,** ,myopathy
Renal and urinary disorders			Blood creatinine increased[1], blood urea increased[1]	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1],injection Site inflammation[1]	Malaise[4],pyrexia[3] , asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal[1] , blood alkaline phosphatise increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased, prothrombin prolonged, urine colour abnormal

* 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 drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.

** In some reports of rhabdomyolysis, clarithromycin was administered concomitantly with other drugs known to be associated with rhabdomyolysis (such as statins, fibrates, colchicine or allopurinol).

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

[2]ADRs reported only for the Extended-Release Tablets formulation
[3] ADRs reported only for theGranules for Oral Suspension form ulation
[4] ADRs reported only for the Immediate-Release Tablets formulation

c. Description of se lected adverse reactions Injection site phlebitis, injection site pain, vessel puncture site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation. In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol There have been post-marketing reports of drug interactions and central

d. Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

e. Other special populations

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

4.9 Overdose:

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia, and hypoxa emia. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacotherapeutic Group

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC code: J01FA09

Clarithromycin is a semi-synthetic macrolide antibiotic obtained by substitution of the hydroxyl group in position 6 by a CH_3O group in the erythromycin lactonic ring. Specifically, clarithromycin is 6-O-methyl erythromycin A. Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible bacteria and suppressing protein synthesis.

***Microbiology*:** Clarithromycin has demonstrated excellent *in vitro* activity against standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobicand anaerobic Gram -positive and Gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally one log2 dilution more potent than the MICs of erythromycin. *In vitro* data also indicate clarithromycin has excellent activity against *Legionella pneumophila*, and *Mycoplasma pneumoniae*. It is bactericidal to *Helicobacter pylori*; this activity of clarithromycin is greater at neutral pH than at acid pH. *In vitro*and *in-vivo*data show that this antibiotic has activity against clinically significant mycobacterial species.

Usually sensitive Bacteria : Streptococcus agalactiae, Streptococcus pyogenes,Streptococcus viridans ,Streptococcus pneumoniae ,Haemophilus influenzae ,

Haemophilus parainfluenzae ,Neisseria gonorrhoea ,Listeria monocytogene

Non- sensitive Bacteria : Enterobacteriacae, Pseudomonas species

5.2 Pharmacokinetic properties

The non-linear kinetics of orally administered clarithromycin have been studied extensively in a number of animal species and adult humans. These studies have shown that clarithromycin is readily and rapidly absorbed with an absolute bioavailability of approximately 50%. No accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Results of these animal studies showed that clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were usually found in the liver and lung where the tissue to plasma (T/P) ratios reached 10 to 20.

In vitro studies showed that the protein binding of clarithromycin in human plasma averaged about 70% at concentrations of 0.45 - 4.5 mcg/ml. A decrease in binding to 41% at 45.0 mcg/ml suggested that the binding sites might become saturated, but this only occurred at concentrations far in excess of the therapeutic drug levels.

Pharmacokinetics in elderly subjects: A study was also conducted to evaluate and compare the safety and pharmacokinetic profiles of multiple 500 mg oral doses of clarithromycin in healthy elderly male and female subjects to those in healthy young adult male subjects. In the elderly group, circulating plasma levels were higher and elimination slower than in the younger group for both parent drug and the 14-OH metabolite. However, there was no difference between the two groups when renal clearance was correlated with creatinine clearance. It is concluded from those results that any effect on the handling of clarithromycin is related to renal function and not to age *per se*.

Pharmacokinetics in patients with mycobacterial infections: Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following administration of usual doses to adult patients with HIV infection were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations were much higher than those observed at the usual doses. In adult HIV-infected patients taking 2000 mg/day in two divided doses, steady-state clarithromycin C*max* values ranged from 5-10 mcg/ml. C*max* values as high as 27 mcg/ml have been observed in HIV-infected adult patients taking 4000 mg/day in two divided doses. 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 at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

5.4 Preclinical safety data

Acute, subchronic and Chronic Toxicity: Studies were conducted in mice, rats, dogs and/or monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for 6 consecutive months.In acute mouse and rat studies, 1 rat, but no mice, died following a single gavage of 5g/kg body weight. The median lethal dose, therefore, was greater than 5g/kg, the highest feasible dose for administration.

Fertility, Reproduction, and Teratogenicity: Fertility and reproduction studies have shown daily dosages of 150-160 mg/kg/day to male and female rats caused no adverse effects on the oestrous cycle, fertility, parturition and a number of viability of offspring. Two teratogenicity studies in both Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.) rats,

1 study in New Zealand White rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague- Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony.

Mutagenicity: Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagagenic potential at drug concentrations of 25 mcg/petri plate or less. At a concentration of 50 mcg, the drug was toxic for all strains tested.

6. Pharmaceutical particulars

6.1 List of Excipients

Name of Material	Specification
Maize Starch	BP
Microcrystalline cellulose powder 101	BP
Povidone	BP
Isopropyl Alcohol	BP
Magnesium Stearate	BP
Purified Talc	BP
Cross Carmellose Sodium	BP
Colloidal Anhydrous Silica	BP
Hypromellose	BP
Titanium Dioxide	BP
Macrogol 4000	BP
Dichloromethane	BP

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
36 months from the date of manufacturing.

6.4 Special precautions for storage
Store below 30°C. Keep medicines out of reach of children.

6.5 Nature and contents of container
1 X 10Tablets in Alu-Alu Blister is packed in Printed Carton along with printed insert.

6.6 Special precautions for disposal
No special requirements.

7. REGISTRANT
KESSINGTON GLOBAL SYNERGY LTD.
Governors Way, Maple Wood Estate,

Oko-Oba, Lagos Agege,
Lagos, Nigeria

8. DATE OF REVISION OF THE TEXT

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9. NAME AND ADDRESS OF MANUFACTURER

SWISS PHARMA PVT. LTD.
Manufacturing At: Plot No. - 3709, GIDC,
Phase-IV, Vatva, Dist-Ahmedabad-382 445,
Gujarat, Country: India.