PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form)**:**

KLACID XL Modified release tablets

COMPOSITION:

KLACID XL Modified release tablets: Each tablet contains 500 mg clarithromycin (6-0-methyl erythromycin A) in a homogenous matrix, which provides sustained release during its transit through the gastrointestinal tract.

Other inactive ingredients in the tablet include: citric acid anhydrous, sodium alginate, sodium calcium alginate, lactose, povidone K30, talc, stearic acid, magnesium stearate, methylhydroxy propyl cellulose, polyethylene glycol, titanium dioxide and yellow dye E104 aluminium lake. Preservative: Sorbic acid 0,01% m/m**.**

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 - Medium and broad spectrum antibiotics

PHARMACOLOGICAL ACTION:

Clarithromycin is a macrolide antibiotic which exerts its antibacterial action by binding to the 50S ribosomal sub-units of susceptible bacteria and suppresses protein synthesis.

The *in-vitro* antibacterial spectrum of pathogens usually sensitive to clarithromycin is as follows (*in-vitro* sensitivity does not necessarily imply *in vivo* efficacy):

Streptococcus agalactiae

Streptococcus pyogenes

Streptococcus pneumoniae

Legionella pneumophila

Mycoplasma pneumoniae

Chlamydia trachomatis

Branhamella catarrhalis

Certain strains of *Staphylococcus aureus*

Haemophilus influenzae

Helicobacter (Campylobacter) pylori

Mycobacterium avium

Mycobacterium kansasii

Mycobacterium chelonae

Mycobacterium intracellulare

Clarithromycin is bactericidal to *Helicobacter pylori,* this activity being greater at neutral pH than at acid pH. The principal metabolite of clarithromycin in man and other primates is the 14(R)-hydroxy-clarithromycin metabolite, which also has antibacterial activity. This metabolite is as active or 1-to-2 fold less active than the parent compound for most organisms, except for *H. influenzae* against which it is twice as active. The parent compound and the 14-OH metabolite exert either an additive or synergistic effect on *H. influenzae, in vitro* and *in vivo*, depending on bacterial strains.

Pharmacokinetics

The kinetics of orally administered clarithromycin modified release tablets have been studied in adult humans and compared with clarithromycin 250 mg and 500 mg immediate release tablets.

The extent of absorption was found to be equivalent when equal daily doses were administered. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in humans following multiple dosing. Based upon the

finding of equivalent extent of absorption, the following *in vitro* and *in vivo* data is applicable to the modified release tablet.

In vitro studies showed the protein binding of clarithromycin in human plasma averaged about 70% at concentrations of 0.45 to 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 occurred at concentrations far in excess of the therapeutic drug levels.

Results of animal studies showed 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 fed patients given 500 mg clarithromycin modified release tablets once daily, the peak steady state plasma concentration of clarithromycin and 14-hydroxy-clarithromycin were 1.3 and 0.48 mcg/ml, respectively. Elimination half-lives of the parent drug and metabolite were approximately 5.3 hours and 7.7 hours respectively. When clarithromycin modified release tablets were administered at a dose of 1000 mg once daily (2 x 500 mg), the steady state C_{max} for clarithromycin and its hydroxylated metabolite averaged 2.4 mcg/ml and 0.67 mcg/ml, respectively. The half-life of the parent drug at the 1000 mg dose level was approximately 5.8 hours, while that of the 14-hydroxy-clarithromycin was approximately 8,9 hours. The T_{max} for both the 500 mg and 1000 mg doses was approximately 6 hours. At steady state the 14-hydroxy-clarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses.

This non-linear pharmacokinetic behaviour of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation products at the higher doses, indicates the non-linear metabolism of clarithromycin becomes more pronounced at high doses.

Urinary excretion accounts for approximately 40% of the clarithromycin dose. Faecal elimination accounts for approximately 30%.

Clarithromycin and its 14-OH-metabolite distribute readily into body tissues and fluids. Limited data from a small number of patients suggests that clarithromycin does not achieve significant levels in cerebrospinal fluid after oral doses (i.e. only 1 to 2 % of serum levels in CFS in patients with normal blood-cerebrospinal fluid barriers). Concentrations in tissues are usually several fold higher than serum concentrations.

INDICATIONS:

KLACID XL modified release tablets are indicated in the treatment of:

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

CONTRA-INDICATIONS:

KLACID XL is contra-indicated in patients with known hypersensitivity to macrolide antibiotic drugs.

As the dose of **KLACID XL** cannot be reduced from 500 mg once daily, the modified release tablets are contra-indicated in patients with a creatinine clearance of less than 30 ml/min.

Concomitant administration of **KLACID XL** and any of the following agents is contra-indicated: astemizole, cisapride, pimozide, terfenadine and ergotamine or dihydroergotamine (see INTERACTIONS).

WARNINGS:

KLACID XL is principally excreted by the liver. Caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering **KLACID XL** to patients with moderate to severe renal impairment. There have been post-marketing reports of colchicine toxicity with concomitant use of **KLACID** and colchicine,

especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients. (See INTERACTIONS: Colchicine)

Long-term use may of **KLACID XL**, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Pseudomembranous colitis has been reported with nearly all anti-bacterial agents, including macrolides, and may range in severity from mild to life-threatening.
Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including **KLACID**, 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 agent. (see SIDE EFFECTS AND SPECIAL PRECAUTIONS).

Attention should be paid to the possibility of cross-resistance between **KLACID XL** and other macrolide medicines, as well as lincomycin and clindamycin.

INTERACTIONS:

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

Elevated cisapride levels have been reported in patients receiving **KLACID XL** and cisparide 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 **KLACID XL** and pimozide concomitantly. (See CONTRA-INDICATIONS).

KLACID XL 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 (see CONTRA-INDICATIONS). In one study in 14 healthy volunteers, the concomitant administration of **KLACID** 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 **KLACID XL**.

Ergotamine/dihydroergotamine

Post-marketing reports indicate that co-administration of **KLACID** 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. Permanent tissue damage may result. Concomitant administration of **KLACID XL** and these medicinal products is contraindicated. (see CONTRAINDICATION).

Effects of Other Medicinal Products on KLACID XL

The following drugs are known or suspected to affect circulating concentrations of clarithromycin; **KLACID XL** dosage adjustment or consideration of alternative treatments may be requ ired.

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 **KLACID** 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 **KLACID XL** and enzyme inducers.

Fluconazole

Concomitant administration of fluconazole 200 mg daily and **KLACID** 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (C_{min}) 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. **KLACID XL** dose adjustment is not necessary.

Effects of KLACID XL on Other Medicinal Products

Antiarrhythmics

There have been postmarketed reports of torsades de pointes occurring with concurrent use of **KLACID** and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of **KLACID XL** with these drugs. Serum levels of these medications should be monitored during **KLACID XL** therapy

CYP3A-based Interactions

Co-administration of **KLACID XL** known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. **KLACID XL** should be used with caution in patients receiving treatment 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 **KLACID XL**.

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isoenzymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

HMG-CoA Reductase Inhibitors

As with other macrolides **KLACID** has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Omeprazole

KLACID tablets (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 (C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by the concomitant administration of KLACID. 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.

Oral anticoagulants

The use of **KLACID XL** in patients receiving warfarin may result in potentiation of the effects of warfarin. Prothrombin times should be monitored in these patients.

Sildenafil, tadalafil, and vardenafil

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

Theophylline, carbamazepine

Results of clinical studies indicate there was a modest but statistically significant ($p \leq .05$) increase of circulating theophylline or carbamazepine levels when either of these drugs was administered concomitantly with **KLACID XL.**

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 **KLACID** in the CYP2D6 poor metabolizer population.

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

When midazolam was co-administered with **KLACID** tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and **KLACID** should be avoided.

If intravenous midazolam is co-administered with **KLACID**, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolized 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 **KLACID** 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 **KLACID** and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other Drug Interactions:

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When **KLACID** and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving **KLACID** 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 **KLACID XL** simultaneously.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). **KLACID** and other macrolides are known to inhibit CYP3A and Pgp. When **KLACID** and colchicine are administered together, inhibition of Pgp and/or CYP3A by **KLACID** may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity (see WARNINGS). Deaths have been reported in elderly patients with renal insufficiency that have been receiving concomitant colchicine.

Antiretroviral Drug Interactions

Zidovudine

Simultaneous oral administration of **KLACID XL** tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because **KLACID XL** appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of **KLACID XL** and zidovudine. This interaction does not appear to occur in paediatric HIV-infected patients taking **KLACID** suspension with zidovudine or dideoxyinosine. Similar interaction studies with **KLACID XL** and zidovudine have not been conducted.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg eight hourly and **KLACID** 500 mg twelve hourly resulted in a marked inhibition of the metabolism of **KLACID**. The **KLACID** C_{max} increased by 31%, C_{min} 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 **KLACID XL**, 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 CL_{CR} 30 to 60 ml/min the dose of **KLACID XL** should be reduced by 50%, resulting in a maximum dose of one **KLACID XL** tablet per day. For patients with severe renal impairment (CL_{CR} < 30 ml/min), **KLACID XL** should not be used as appropriate **KLACID XL** dosage reduction is not possible when administering this product. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

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 **KLACID** (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 **KLACID** should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of **KLACID** should be decreased by 75% using an appropriate clarithromycin formulation. Doses of **KLACID** greater than 1000 mg per day should not be co-administered with protease inhibitors.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. **KLACID** may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and **KLACID** 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 drug interaction. Concomitant administration of **KLACID** (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state AUC and C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} 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 saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see PRECAUTIONS, DRUG INTERACTIONS)

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established. The physician should not prescribe **KLACID XL** to pregnant women without carefully weighing the benefits against the risk, particularly during the first three months of pregnancy. **KLACID XL** is excreted into human breast-milk.

DOSAGE AND DIRECTIONS FOR USE:

The recommended dosage of **KLACID XL** modified release tablets in adults is 500 mg once daily with food. In more severe infections, the dosage can be increased to 1000 mg once daily (2 x 500 mg). Tablets should be swallowed whole.

KLACID XL modified release tablets should not be used in patients with significant renal impairment (creatinine clearance less than 30 ml/min) as appropriate clarithromycin dosage reduction is not possible when administering this product. For patients with moderate renal function (creatinine clearance 30 to 60 ml/min, a 50% dosage reduction should be implemented resulting in a maximum dose of one **KLACID XL** tablet per day.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Clinical experience with **KLACID XL**:

Adverse drug events reported during clinical trials with **KLACID XL** tablets, 500 mg:

The most commonly reported adverse drug reaction was abdominal pain.

Adverse events are displayed in the following tables by System Organ Class and frequency, according to the following convention: Common (>1/100 ≤ 1/10).

Summary of Adverse Drug Reactions Reported During Clinical Trials with **KLACID XL** Tablets once daily, 500 mg (lower respiratory tract infections)*		
System Organ Class	Frequency	Adverse Drug Reactions
Infections and infestations	Common	Oral candidiasis
Gastrointestinal disorders	Common	Abdominal pain Nausea Diarrhoea
Nervous system disorders	Common	Dizziness Disgeusia Headache
Investigations	Common	Alanine aminotransferase increased
* Reported incidence of adverse events possibly related, probably related or related in phase III clinical studies on KLACID treatment of lower respiratory tract infections involving 376 patients taking **KLACID XL**.		

Post-Marketing Experience

The adverse reactions reported are consistent with those observed in clinical studies.

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 for all **KLACID** formulations.

System organ class (MedDRA) term)	Adverse Drug Reactions
Infections and infestations	Oral candidiasis
Blood and lymphatic system disorders	Leukopenia Thrombocytopenia

Immune system disorders	Anaphylactic reaction Hypersensitivity
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Anxiety Abnormal dreams Confusional state Depersonalisation Depression Disorientation Hallucination Insomnia Psychotic disorder
Nervous system disorders	Convulsions Dizziness Ageusia Anosmia Dysgeusia Parosmia
Ear and labyrinth disorders	Deafness Tinnitus Vertigo
Cardiac disorders	Electrocardiogram QT prolonged Torsade de Pointes Ventricular tachycardia
Gastrointestinal disorders	Glossitis Pancreatitis acute

	Stomatitis Tongue discolouration Tooth discolouration
Hepatobiliary disorders	Hepatic failure Hepatic function abnormal Hepatitis Hepatitis cholestatic Jaundice cholestatic Jaundice hepatocellular
Skin and subcutaneous tissue disorders	Rash Stevens-Johnson syndrome Toxic epidermal necrolysis Urticaria
Renal and urinary disorders	Interstitial nephritis
Investigations	Blood creatinine increased Heptic enzymes increased

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

Exacerbation of symptoms of myaesthenia gravis has been reported in patients receiving clarithromycin therapy.

Pseudomembranous colitis has been reported with **KLACID XL**, and may range in severity from mild to life threatening. Therefore it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents. (see WARNINGS)

There have been post-marketing reports of colchicine toxicity with concomitant use of **KLACID** and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients. (See INTERACTIONS: Colchicine, and WARNINGS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Reports indicate that the ingestion of large amounts of **KLACID XL** can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested 8 g of **KLACID** and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. **KLACID XL** serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

IDENTIFICATION:

KLACID XL Modified release tablets: Yellow, ovaloid film-coated tablets which are either plain or have the Abbott logo imprinted on one side.

PRESENTATION:

KLACID XL is supplied in blister packs of 5 and 10 tablets.

STORAGE INSTRUCTIONS:

Store at room temperature (below 30 ºC) in a well-closed container. Protect from light. Keep out of reach of children.

REGISTRATION NUMBER:

KLACID XL Modified release tablets: 31/20.1.1/0379

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

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