APPROVED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAME (and dosage form)

KLACID P125 Granules for Reconstitution
KLACID P250 Granules for Reconstitution

COMPOSITION

Each 5 ml of **KLACID P125** contains 125 mg clarithromycin (6-0-methyl erythromycin A).
Each 5 ml of **KLACID P250** contains 250 mg clarithromycin (6-0-methyl erythromycin A).

Preservative :- Potassium sorbate 0,4% m/v. Contains sucrose.

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 508 ribosomal sub-units of susceptible bacteria and suppresses protein synthesis.

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

Streptococcus agalactiae
Streptococcus pyogenes
Streptococcus pneumoniae
Haemophilus influenzae
Legionella pneumophila
Mycoplasma pneumoniae
Chlamydia trachomatis
Moraxella (Branhamella) catarrhalis
Certain strains of *Staphylococcus aureus*

The principal metabolite of clarithromycin in man and other primates is a microbiologically active metabolite, 14-0H-clarithromycin. This metabolite is as active or 1 to 2 fold less active than the parent compound for most organisms except *H. influenzae* against which it is 1-2 log2 dilutions more active. The parent compound and the 14-0H-metabolite exert either an additive or synergistic effect on *H. influenzae in vitro* and *in vivo,* depending on bacterial strains.

Pharmacokinetics
Clarithromycin is rapidly absorbed from the gastrointestinal tract and both the onset of absorption and the formation of the antimicrobially-active metabolite, 14-0H-clarithromycin, are slightly delayed by food, but food does not affect the overall bioavailability of clarithromycin.

The comparative clarithromycin Cmax, AUC and Ty, for the paediatric formulation (non-fasted state) are 0.95 mcg/ml, 6.5 mcg.hr/ml and 3.7 hours respectively, and for the 250 mg tablet (fasted state) are 1.10 mcg/ml, 6.3 mcg.hr/ml and 3.3 hours respectively.

In a multiple dose study in which adult subjects were administered 250 mg clarithromycin every 12 hours, steady state blood levels were nearly reached by the time of the fifth dose. Pharmacokinetic parameters after the fifth dose of clarithromycin were: Cmax 1.98 mcg/ml, AUC 11.5 mcg.hr/ml, Tmax 2.8 hours and Ty, 3.2 hours for clarithromycin, and 0.67 mcg/ml, 5.33 mcg.hr/ml, 2.9 hours and 4.9 hours respectively for 14-0H-clarithromycin.

In paediatric patients, clarithromycin demonstrated good bioavailability with a pharmacokinetic profile consistent with previous results from adult subjects using the same suspension formulation. Steady-state pharmacokinetic parameters obtained after the ninth dose on treatment day 5 were as follows: Cmax 4.60 mcg/ml, AUC 15.7 mcg.hr/ml and Tmax 2.8 hours; the corresponding values for the 14-0H-metabolite were: 1.64 mcg/ml, 6.69 mcg.hr/ml and 2.7 hours, respectively.

A study to determine the penetration of clarithromycin in middle ear fluid in patients with otitis media demonstrated that approximately 2.5 hours after receiving the fifth dose (dosage was 7.5 mg/kg twice daily), the mean concentration of clarithromycin was 2.53 mcg/g of fluid in the middle ear fluid and for the 14-0H-metabolite was 1.27 mcg/g. The concentrations of parent drug and 14-0H metabolite were generally twice as high as the corresponding concentrations in serum.

INDICATIONS

KLACID P is indicated for the treatment of infections due to susceptible organisms, in the following conditions:

I. Upper respiratory tract infections, e.g. pharyngitis and tonsillitis due to *S. pyogenes.*

2. Lower respiratory tract infections, e.g. bronchitis.

3. . Mild to moderately severe acute otitis media due to *S. pneumoniae, M. catarrhalis* and *H. influenzae.*

4. Mild to moderately severe skin and skin structure infections due to *S. aureus.*

CONTRA-INDICATIONS

KLACID P is contra-indicated in patients with known hypersensitivity to macrolide antibiotics.

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

KLACID P is contra-indicated in patients receiving terfenadine therapy who have pre-existing cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischaemic heart disease, congestive heart failure, etc.) or electrolyte disturbances (see SIDE-EFFECTS AND SPECIAL PRECAUTIONS) .

Safety and efficacy in infants less than 6 months of age have not been established .

WARNINGS

KLACID P is principally excreted by the liver. Caution should be exercised in administering this antibiotic to patients with impaired hepatic function. Caution should be exercised when administering **KLACID P** to patients with moderate to severe renal failure. 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)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening.

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

INTERACTIONS

Cytochrome P450 Interactions
Data available to date indicate **KLACID P** is metabolised primarily by the hepatic cytochrome P450 3A (CYP3A) isozyme. This is an important mechanism determining many drug interactions. The metabolism of other drugs by this system may be inhibited by concomitant administration with **KLACID P** and may be associated with elevations in serum levels of these drugs.

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

Results of clinical studies indicate that there is a modest but statistically significant (p 0,05) increase in circulating theophylline and carbamazepine levels when either of these drugs was administered concomitantly with **KLACID P.** The use of **KLACID P** in patients receiving warfarin may result in a potentiation of the effects of warfarin. Prothrombin times should be monitored in these patients.

The following CYP3A based drug interactions have been observed with erythromycin products and/or with **KLACID P** in post-marketing experience.

Rhabdomyolysis co-incident with the co-admin istration of **KLACID P** and the HMG-CoA reductase inhibitors, e.g. lovastatin and simvastatin, has less frequently been reported.

Elevated cisapride levels have been reported in patients receiving **KLACID P** and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. Similar effects have been observed in patients taking **KLACID P** and pimozide concomitantly (see CONTRA-INDICATIONS).

KLACID P may alter the metabolism of terfenadine resulting in increased levels of terfenadine which have been associated with cardiac arrhythm ias, such as QT prolongation, ventricular tachycardia, ventricular fibrillat ion and Torsades de Pointes (see CONTRA- INDICATIONS). In one study in 14 healthy volunteers, the concomitant administration of **KLACID** tablets and terfenad ine resulted in 2- to 3- fold increases 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 may be observed with concomitant administration of astemizole and **KLACID P.**

There have been post-marketing reports of Torsades de Pointes occurring with concurrent use of **KLACID P** and quinidine or disopyramide. Serum levels of these medications should be monitored during **KLACID P** therapy.

Ergotamineldihydroergotamine
Post-marketing reports indicate that co-administration of **KLACID P** with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm, and ischaemia of the extremities and other tissues induding the central nervous system. Permanent tissue damage may result.

Other Drug Interactions
Elevated digoxin serum concentrations have been reported in patients receiving **KLACID** tablets and digoxin concomitantly. Monitoring of serum digoxin levels should be considered.

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.

Co-administration of **KLACID P** and rifabutin has been reported to cause a higher incidence of uveitis compared to rifabutin alone.

Antiretroviral Drug Interactions
Simultaneous oral administrat ion of **KLACID** tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. To date, this

interaction does not appear to occur in paediatric HIV-infected patients taking **KLACID P** with zidovudine or dideoxyinosine.

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** 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-[R]-hydroxy-clarithromycin was noted. Because of the large therapeutic window for **KLACID ,** 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 **KLACID P** should be reduced by 50% . For patients with CLcR < 30 ml/min the dose of **KLACID P** should be decreased by 75%. Doses of **KLACID** greater than 1 g/day should not be co-administered with ritonavir.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established. **KLACID P** is excreted into breast milk. If **KLACID P** is considered for patients of post-pubertal age, the physician should carefully weigh the benefits against the risk when pregnancy is either suspected or confirmed.

DOSAGE AND DIRECTIONS FOR USE

The recommended daily dosage for **KLACID** P in children is given in the following table and is based on a 7,5 mg/kg twice daily regimen. (A maximum dose of 500 mg twice daily is recommended for the most severe infections) . The usual duration of treatment is 5 - 10 days depending on the pathogen involved and the severity of the condition.

Body Mass		**Dosage in medicine measuresful (ml) twice daily**			
		125 mg/5ml		**250 mg/5ml**	
8 - 11 kg	(1-2 years) *	0.5	(2.5 ml)	--	--
12 - 19 kg	(2-4 years) *	1.0	(5.0 ml)	0.5	(2.5 ml)
20 - 29 kg	(4-8 years) *	1.5	(7.5 ml)	0.75	(3.75 ml)
30 - 40 kg	(8-12 years) *	2.0	(10.0 ml)	1.0	(5.0 ml)

* Approximate ages.

Reconstitution instructions:
KLACID P125:
50 ml bottle: Add 29 ml of distilled water to reconstitute to 50 ml. Shake the bottle.
KLACID P250:
50 ml bottle: Add 29 ml of distilled water to reconstitute to 50 ml. Shake the bottle.
100 ml bottle: Add 53 ml of distilled water to reconstitute to 1OOml. Shake the bottle.

The prepared suspension can be taken with or without meals, and can be taken with milk.

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Clinical experience with oral formulations, paediatric suspensions
Adverse drug reactions reported during clinical trials with KLACID P125 & KLACID P250 (BID dosing, all indications):
The most commonly reported adverse events were diarrhoea, vomiting and 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 *		
System Organ Class (MedDRA Term)	Frequency	Adverse Drug Reactions
Gastrointestinal disorders	Common	Abdominal pain Diarrhoea Vomiting
Skin and subcutaneous tissue disorders	Common	Rash
* Reported incidence of adverse events possibly related, probably related or related in clinical studies involving 1285 patients taking KLACID P		

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 Disorientation Hallucination Insomnia Psychotic disorder
Nervous system disorders	Convulsions Dizziness 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.

Pseudomembranous colitis has been reported with **KLACID P,** 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.

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

The ingestion of large amounts of **KLACID P** can be expected to produce gastrointestinal symptoms . One patient who had a history of bipolar disorder ingested eight grams of **KLACID** and showed altered mental status, paranoic behaviour, hypokalaemia and hypoxaemia. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures. **KLACID P** serum levels are not expected to be appreciably affected by haemodialysis or dialysis.

IDENTIFICATION

KLACID P125: White to off-white granules, which when reconstituted, become a white to off-white opaque suspension, containing white suspended particles, with a fruity aroma.

KLACID P250: White to off-white granules, which when reconstituted, become a white to off-white opaque suspension, containing white suspended particles, with a fruit aroma.

PRESENTATION

KLACID P125 Granules for Reconstitution : Supplied in 50 ml bottles.
KLACID P250 Granules for Reconstitution : Supplied in 50 ml and 100 ml bottles.

STORAGE INSTRUCTIONS

Store at room temperature (below 25 °C).
After reconstitution, store at room temperature (below 25 °C) and use within 14 days.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

KLACID P125: 28/20.1.1/0035
KLACID P250: 29/20.1 .1/0190

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