**APPROVED PACKAGE INSERT (Approved 01.12.2006)**

**SCHEDULING STATUS** 84

**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 SOS 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 intracel/ulare*

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-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 14-0H 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 follow ing 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 Cmax 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 Tmax for both the 500 mg and 1000 mg doses was approx imately 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 14-0H-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 funct ion. 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)

Pseudomembranous colitis has been reported with nearly all anti-bacter ial 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 XL** and other macrolide medicines , as well as lincomycin and clindamycin.

**INTERACTIONS**

***Cytochrome P450 Interactions***

Data available to date indicate **KLACID XL** 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 XL** and may be associated with elevations in serum levels of these other 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 , disopyramide, ergot alkaloids , lovastatin, methylprednisolone , midazolam , omeprazole, oral anticoagulants (e.g. warfar in), 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.

Results of clinical studies indicate that there was a modest but statistically significant (p 0,05) increase of circulating theophylline or carbamazepine levels when either of these drugs was administered concomitantly with **KLACID XL.** 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.

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

Rhabdomyolysis co-incident with the co-administration of **KLACID XL** and the HMG-CoA reductase inhibitors, lovastatin and simvastatin, has less frequently been reported.

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

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 (see CONTRA-INDICATIONS). In one study in 14 healthy volunteers, the concomitant administration of **KLACID** and terfenad ine 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 astemizo le and other macrolides.

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

Ergotamine/dihydroergotamine :

Post-marketing reports indicate that co-admin istration 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.

*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.

*Antiretroviral Drug Interactions*

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.

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 by 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 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 CLcR 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 (CLcR < 30 ml/min), **KLACID XL** should not be used as appropriate **KLACID** dosage reduction is not possible when administering this product. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

**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 , accordinQ to the followinQ 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<br>Nausea<br>Diarrhoea |
| Nervous system disorders | Common | Dizziness<br>Dysgeusia<br>Headache |
| Investigations | Common | Alanine aminotransferase increased |

* Reported incidence of adverse events possibly related, probably related or related in phase Ill 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<br>Thrombocytopenia |
| Immune system disorders | Anaphylactic reaction<br>Hypersensitivity |
| Metabolism and nutrition disorders | Hypoglycaemia |
| Psychiatric disorders | Anxiety<br>Abnormal dreams<br>Confusional state<br>Depersonalisation<br>Disorientation<br>Hallucination<br>Insomnia<br>Psychotic disorder |
| Nervous system disorders | Convulsions<br>Dizziness<br>Dysgeusia<br>Parosmia |
| Ear and labyrinth disorders | Deafness<br>Tinnitus<br>Vertigo |
| Cardiac disorders | Electrocardiogram QT prolonged |

| | |
|---|---|
| | Torsade de Pointes<br>Ventricular tachycardia |
| Gastrointestinal disorders | Glossitis<br>Pancreatitis acute<br>Stomatitis<br>Tongue discolouration<br>Tooth discolouration |
| Hepatobiliary disorders | Hepatic failure<br>Hepatic function abnormal<br>Hepatitis<br>Hepatitis cholestatic<br>Jaundice cholestatic<br>Jaundice hepatocellular |
| Skin and subcutaneous tissue disorders | Rash<br>Stevens-Johnson syndrome<br>Toxic epidermal necrolysis<br>Urticaria |
| Renal and urinary disorders | Interstitial nephritis |
| Investigations | Blood creatinine increased<br>Hepatic 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 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.

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 over-dosage 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.

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## PRESENTATION

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

## STORAGE INSTRUCTIONS

Store at room temperature (below 30 °C) 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

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

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## DATE OF PUBLICATION OF THIS PACKAGE INSERT

01 December 2006