**APPROVED PACKAGE INSERT**

**SCHEDULING STATUS:** S4

**PROPRIETARY NAME (and dosage form)**

**KLACID I.V. Lyophilised Powder for Injection**

**COMPOSITION**

Each vial contains clarithromycin 500 mg and lactobionic acid as a solubilising agent.

**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 thereby suppressing 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*
*Mycobacterium avium*
*Mycobacterium kansasii*
*Mycobacterium chelonae*
*Mycobacterium intracellulare*

The 14-hydroxy-clarithromycin metabolite also has antibacterial activity. The minimum inhibitory concentrations for this metabolite were found to be equal to or 1 $\log_2$ dilution more than the parent compound, except for *H. influenzae* where the metabolite was 1 $\log_2$ dilution more active.

**Pharmacokinetics**

In the pharmacokinetics of orally administered clarithromycin it was shown that clarithromycin is readily and rapidly absorbed, with a bioavailability of approximately 50%. The major metabolite in human plasma was the 14-hydroxy(R) epimer of clarithromycin, with peak levels of 0.5 mcg/ml and 1.2 mcg/ml after oral doses of 250 mg and 1 200 mg,

respectively. In humans given single oral doses of 250 mg or 1 200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46% of the higher dose. Faecal elimination accounted for 40.2% and 29.1% of these respective doses.

With twice-daily oral dosing at 250 mg, the peak steady state plasma concentrations averaged about 1 mcg/ml for clarithromycin and 0,6 mcg/ml for 14-hydroxy-clarithromycin, while the elimination half-lives of the parent drug and metabolite were 3-4 hours and 5-6 hours respectively. With twice-daily oral dosing at 500 mg, the steady state $C_{max}$ for clarithromycin and its hydroxylated metabolite averaged 2.7 – 2.9 mcg/ml and 0.83 – 0.88 mcg/ml respectively. The half-life of the parent drug at the 500 mg dose level was 4.5 – 4.8 hours, while that of 14-hydroxy-clarithromycin was 6.9 – 8.7 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. The 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 that metabolism of clarithromycin approaches saturation at high doses.

*Pharmacokinetics in Patients with Mycobacterial Infections*

Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following oral 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 1 000 and 2 000 mg/day in two divided doses, steady-state clarithromycin $C_{max}$ values ranged from 2 - 4 mcg/ml and 5 -10 mcg/ml respectively. Elimination half-lives appeared to be lengthened at these higher doses as compared with those seen with usual doses in normal subjects. The higher clarithromycin concentrations and longer elimination half-lives observed at these doses are consistent with the known non-linearity in clarithromycin pharmacokinetics.

## INDICATIONS

**KLACID I.V.** is indicated in the treatment of infections due to susceptible organisms in the following conditions whenever parenteral therapy is required:

- Lower respiratory tract infections, e.g. bronchitis, pneumonia
- Upper respiratory tract infections, e.g. pharyngitis and tonsillitis due to *S. pyogenes,* sinusitis
- Skin and soft tissue infections due to *S. aureus*
- There is some evidence that disseminated and localised infections in HIV-positive adults, due to *Mycobacterium avium* or *Mycobacterium intracellulare* respond to clarithromycin. Based on bacteriological results, **KLACID I.V.** should be used in conjunction with other antimycobacterials. To a lesser extent localised infections due to *Mycobacterium kansasii* have responded to **KLACID I.V.**

## CONTRA-INDICATIONS

**KLACID I.V.** is contra-indicated in patients with a known hypersensitivity to macrolide antibiotic drugs. Allergic or hypersensitive reactions should be managed by prompt supportive measures.

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

## WARNINGS

**KLACID** 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** 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).

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

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

## INTERACTIONS

*Cytochrome P450 Interactions*
Data available to date indicate **KLACID I.V.** 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 I.V.** 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, methyl prednisolone, midazolam, omeprazole, oral 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 was a modest but statistically significant ($p \leq 0,05$) increase of circulating theophylline or carbamazepine levels when either of these drugs was administered concomitantly with orally administered **KLACID.** The use of **KLACID I.V.** in patients receiving warfarin may result in the potentiation of the effects of warfarin. Prothrombin times in these patients should be monitored.

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

Rhabdomyolysis co-incident with the co-administration of **KLACID** 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** 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 **KLACID** and pimozide concomitantly (see **CONTRA-INDICATIONS**).

**KLACID** may 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** (tablets) and terfenadine resulted in a two or three 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 may be observed with concomitant administration of astemizole and **KLACID**.

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 clarithromycin therapy.

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 extremeties and other tissues including the central nervous system. Permanent tissue damage has been reported.

*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 administration of **KLACID** tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because **KLACID** appears to interfere with the absorption of simultaneously-administered oral zidovudine, this interaction would most likely not be a problem when **KLACID** is administered intravenously. This interaction does not appear to occur in paediatric HIV-infected patients taking **KLACID** suspension with zidovudine or dideoxyinosine.

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every 8 hours and **KLACID** 500 mg every 12 hours resulted in a marked inhibition of the metabolism of **KLACID**. The **KLACID** $C_{max}$ increased by 31%, $C_{min}$ 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 I.V.**, 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 I.V.** should be reduced by 50%. For patients with $CL_{CR}$ < 30 ml/min the dose of **KLACID I.V.** should be decreased by 75%. Doses of **KLACID I.V.** greater than 1 g/day should not be co-administered with ritonavir.

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

No clinically relevant studies addressing physical compatibility of **KLACID I.V.** with other intravenous admixtures have been performed at this time.

## PREGNANCY AND LACTATION

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

## DOSAGE AND DIRECTIONS FOR USE

The recommended dosage of **KLACID I.V.** is 1.0 gram daily, divided into 2 equal doses, each infused, after further dilution with an appropriate I.V. diluent, over a 60 minute period. **KLACID I.V.** should not be given as a bolus or an intra-muscular injection.

Intravenous therapy may be limited for up to 2 to 5 days in the very ill patient and should be changed to oral therapy whenever possible as determined by the physician.

In patients with renal impairment who have creatinine clearance of less than 30 ml/min, the dosage of **KLACID I.V.** should be reduced to one-half of the normal recommended dose.

***Dosage in Patients with Mycobacterial Infections:***
Although there currently are no data regarding use of **KLACID I.V.** in immunocompromised patients, data are available regarding the use of oral clarithromycin in HIV-infected patients. In disseminated or localised mycobacterium infections (*M. avium, M. intracellulare, M. chelonae, M. kansasii)* the recommended treatment in adults is 1000 mg/day in two divided doses. Treatment of disseminated MAC infections in AIDS patients should continue as long as clinical and microbiological benefit is demonstrated. A decrease in efficacy has been noted in patients on treatment exceeding 12 weeks. **KLACID** should be used in conjunction with other antimycobacterial agents.

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

The final solution for infusion is prepared as follows:

1. Prepare the initial solution of **KLACID I.V.** by adding 10 ml of sterile Water for Injection to the 500 mg vial and shake vigorously until the entire contents are dissolved. Use only sterile Water for Injection, as other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts. Note: When the product is reconstituted as directed above, each ml contains 50 mg of clarithromycin.

   The reconstituted product should be used within 24 hours if stored at room temperature (25° C) or within 48 hours if stored at 5° C.

2. The reconstituted product (500 mg in 10 ml Water for Injection) should be added to a minimum of 250 ml of one of the following diluents before administration.

5% dextrose in Lactated Ringer's Solution, 5% dextrose, Lactated Ringer's, 5% dextrose in 0,3% sodium chloride, Normosol-M in 5% dextrose, Normosol-R in 5% dextrose, 5% dextrose in 0,45 % sodium chloride, and 0,9 % sodium chloride.

The final diluted product should be used within 6 hours if stored at room temperature (25° C) or within 48 hours if stored at 5° C.

No medicine or chemical agent should be added to **KLACID I.V.** fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.

The safety of **KLACID I.V.** for use in children has not been established.

## SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Clinical experience with the intravenous formulation:
Adverse drug reactions reported during clinical trials with **KLACID I.V.** 500 mg (lower respiratory tract infections):
The most commonly reported adverse reactions were phlebitis and injection site phlebitis.

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

| Intravenous Formulation - Summary of Adverse Drug Reactions Reported During Clinical Trials | | |
|---|---|---|
| System organ class (MedDRA Term) | Frequency * | Adverse Drug Reactions |
| Psychiatric disorders | Common | Insomnia |
| Nervous system disorders | Common | Headache<br>Taste perversion ** |
| Vascular disorders | Very common<br>Common | Phlebitis<br>Thrombophlebitis<br>Vasodilatation |
| Gastrointestinal disorders | Common | Diarrhoea<br>Gastrointestinal upset **<br>Nausea |
| Hepatobiliary disorders | Common | Hepatic function abnormal |
| Skin and subcutaneous tissue disorders | Common | Sweating** |
| General disorders and administration site conditions | Very common<br>Common | Injection site phlebitis<br>Injection site inflammation<br>Injection site pain<br>Venipuncture site pain |
| * Reported incidence of adverse events possibly related, probably related or related in clinical studies involving 312 patients taking **KLACID I.V.**<br>** Terms listed as MedDRA lower level terms rather than the preferred terms to accurately reflect the term reported in the clinical source documentation | | |

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 |

| | |
|---|---|
| | 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<br>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>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**, 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

In the case of overdosage, **KLACID I.V.** should be discontinued and all other appropriate supportive measures should be instituted.

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

## IDENTIFICATION

A white to off-white caked, lyophilised powder which, on reconstitution with Water for Injection, produces a clear, colourless solution free of particulate matter.

## PRESENTATION

**KLACID I.V.** Lyophilised Powder for Injection is supplied in clear glass vials with a capacity of 15 ml.

## STORAGE INSTRUCTIONS

Store at room temperature (below 30 °C) and protect from light. The reconstituted product can be stored at 25 °C for 24 hours or at 5 °C for 48 hours.

Keep out of reach of children.

## REGISTRATION NUMBER

28/20.1.1/0264

## NAME AND BUSINESS ADDRESS OF THE APPLICANT

Abbott Laboratories S.A. (Pty) Limited
Abbott Place
219 Golf Club Terrace
Constantia Kloof
1709
South Africa

## DATE OF PUBLICATION OF THIS PACKAGE INSERT

1 December 2006