APPROVED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAME (and dosage form)

CLACEE 250 mg Tablets
CLACEE 500 mg Tablets

COMPOSITION

CLACEE 250 mg Tablets: Each tablet contains 250 mg clarithromycin (6-0-methyl erythromycin A)
CLACEE 500 mg Tablets: Each tablet contains 500 mg clarithromycin (6-0-methyl erythromycin A)
Preservative: sorbic acid 0,1% 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, 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
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 a microbiologically active metabolite, 14-hydroxyclarithromycin . 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.

Absorption:
Mean peak plasma levels after a single oral dose of clarithromycin occurred approximately 2 hours after administration and ranged from 0,35 mcg/ml after a 100 mg dose to 3,97 mcg/ml after a 1200 mg dose.

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Mean half-life appeared to be dose dependent and ranged from 2,27 hours after a 100 mg dose to 5,98 hours after the 1 200 mg dose.

Pharmacokinetic data from a multidose study aga in indicated that the half-life ranged from 2,6 hours after doses of 100 mg b.d. to 4,9 hours following doses of 800 mg b.d. Mean peak plasma concentrations ranged from 0,37 mcg/ml at doses of 100 mg b.d. to 3,73 mcg/ml at doses of 800 mg b.d.

Results of a study of the effects of food on absorption indicated that food taken shortly before dosing somewhat delayed the onset of absorption of clarithromycin . However, food intake did not affect the overall bioavailability of the drug.

Protein binding decreased with increasing drug concentration in plasma. The average percentage binding of clarithromycin was 70 % for plasma concentrations of 0,45 - 4,5 mcg/ml and 41 % for plasma concentrations of 45 mcg/ml.

Thus ^{14}C-clarithromycin is not extensively bound to plasma proteins and its binding sites appeared to be readily saturated at high drug concentrations.

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 cerebrosp inal fluid after oral doses (i.e. only 1 to 2 % of serum levels in CSF in patients with normal blood-cerebrospinal fluid barriers). Concentrations in tissues are higher than serum concentrations . There are no data available on penetration into cerebrospinal fluid . Examples from tissue and serum concentrations are presented below.

	Concentration (after 250 mg every 12 hours	
	Tissue meg/g)	**Serum (mcg/ml**
Tonsil	1,6	0,8

Lung	8,8	1,7

Metabolism:
A metabolism study in human males given ^{14}C-clarithromycin showed peak plasma levels of radioactivity and parent drug occurred 2-4 hours after administration of a 200 mg or 1 200 mg total dose. The major metabolite in plasma after either dose was the 14-hydroxy (R) epimer of clarithromycin, with peak levels of 0,5 mcg/ml and 1,2 mcg/ml after doses of 250 mg and 1200 mg respectively.

Low levels of descladinosyl-clarithromycin were seen in the plasma only after the 1200 mg dose. 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, indicate that metabolism of clarithromycin approaches saturation at high doses.

Excretion:
With single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37,9 % of the lower dose and 46,0 % of the higher dose. Parent drug and 14-hydroxyclarithromycin accounted for most of the urinary radioactivity after doses of 250 mg and 1 200 mg (18,4 % and 29,4 % respectively).

Faecal elimination accounted for 40,2 % of the 250 mg dose and 29,1 % of the 1 200 mg dose. Parent drug represented 4,4 % of the low dose and 10,6 % of the high dose.

Comparison of metabolic profiles in urine and faeces indicated that the products of secondary metabolism were excreted primarily in the faeces.

A pharmacokinetic study conducted with clarithromycin 500 mg three times daily and omeprazole 40 mg once daily, showed that:

1. When 500 mg clarithromycin was given alone every 8 hours, the mean steady state value was approximately 31 % higher compared to a previous study where 500 mg clarithromycin was administered every 12 hours.
2. When clarithromycin was administered with omeprazole, increases in omeprazole half-life and AUCo-24 were observed. For all subjects combined, mean omeprazole AUCo-24 was 89 % greater and the harmonic mean for omeprazole h was 34 % greater when omeprazole was administered concomitantly with clarithromycin than when omeprazole was administered alone.
3. When clarithromycin was administered with omeprazole, the steady state Cmax, Cmin, and AUCo-s of clarithromycin were increased by 10 %, 27 % and 15 % respectively, compared with values achieved when clarithromycin was administered with placebo.
4. At 6 hours post-dosing, clarithromycin gastric mucous concentrations were approximately 25 times higher steady-state in the clarithromycin/omeprazole group compared with the clarithromycin-only group.

5. Six hours post-dosing, mean clarithromycin gastric tissue concentrations were approximately twice as high in the clarithromycin/omeprazole group compared with the clarithromycin/placebo group.

Pharmacokinetics in Patients with *Mycobacterium avium* Infections:
Steady-state concentrations of clarithromycin and 14-0H-clarithromycin observed following administration of 500 mg doses of clarithromycin every 12 hours 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 *Mycobacterium avium* infections, clarithromycin concentrations were much higher than those observed at the usual doses . In adult HIV-infected patients taking 1000 and 2000 mg/day in two divided doses, steady-state clarithromycin Cmax 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 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 non-linearity in clarithromycin pharmacokinetics.

INDICATIONS

- 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
- Eradication of *H.pylori,* resulting in decreased recurrence of duodenal ulcer when used in combination with a proton-pump inhibitor to suppress acid secretion and another antibiotic . **CLACEE** has been used in treatment regimens which include **CLACEE** plus amoxycillin and omeprazole; **CLACEE** plus tinidazole and omeprazole; and **CLACEE** plus tetracycline and bismuth subsalicylate .
- There is some evidence that disseminated and localised mycobacterial infections in HIV-positive adults, due to *Mycobacterium avium* or *Mycobacterium intrace //u /are* respond to **CLACEE .** Based on bacteriological results, **CLACEE** should be used in conjunction with other antimycobacterials. Localised infections due to *Mycobacterium chelonae* and *Mycobacterium kansasii* have responded to **CLACEE** to a lesser extent.

CONTRA-INDICATIONS

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

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

WARNINGS

CLACEE 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 **CLACEE** to patients with moderate to severe renal impairment.

There have been post-marketing reports of colchicine toxicity with concomitant use of **CLACEE** 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-res istance between **CLACEE** and other macrolide medicines, as well as lincomycin and clindamycin .

INTERACTIONS

Cytochrome P450 Interactions
Data available to date indicate **CLACEE** 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 **CLACEE** 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. 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.

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 **CLACEE.** The use of **CLACEE** in patients receiving warfarin may result in 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 **CLACEE** in post-marketing experience:

Rhabdomyolysis co-incident with the co-administration of **CLACEE** 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 **CLACEE** and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillat ion and Torsades de Pointes. Similar effects have been observed in patients taking **CLACEE** and pimozide concomitantly (see CONTRA-INDICATIONS) .

CLACEE 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 **CLACEE** 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 **CLACEE.**

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

Ergotamine/dihydroergotamine :
Post-marketing reports indicate that co-administration of **CLACEE** with ergotamine or dihydroe rgotamine 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 has been reported.

Other Drug Interactions
Elevated digoxin serum concentrations have been reported in patients rece1v1ng **CLACEE** 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-glycoprote in (Pgp). **CLACEE** and other macrolides are known to inhibit CYP3A and Pgp. When **CLACEE** and colchicine are administered together, inhibition of Pgp and/or CYP3A by **CLACEE** 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 **CLACEE** and rifabutin has been reported to cause a higher incidence of uveitis compared with rifabutin alone.

Antiretroviral Drug Interactions

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

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and **CLACEE** 500 mg every twelve hours resulted in a marked inhibition of the metabolism of **CLACEE .** The **CLACEE** 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]-hydroxyclarithromycin was noted. Because of the large therapeutic window for **CLACEE,** 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 **CLACEE** should be reduced by 50%. For patients with CLcR <30 ml/min the dose of **CLACEE** should be decreased by 75% . Doses of **CLACEE** 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 **CLACEE** to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy . **CLACEE** is excreted into human breast-milk.

DOSAGE AND DIRECTIONS FOR USE

The recommended dosage of **CLACEE** is one 250 mg tablet twice daily. In more severe infections, the dosage can be increased to 500 mg twice daily.

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

Eradication of *H. pylori:* to decrease recurrence of duodenal ulcer in combination with a proton-pump inhibitor and another antibiotic: **CLACEE** 500 mg twice daily in combination with amoxycillin 1000 mg twice daily and omeprazole 20 mg daily for 7 - 10 days.

Dosage in HIV patients with mycobacterial infections: The recommended treatment for adults with disseminated or localised mycobacterium infections (M. *avium, M. intrace/lulare, M. chelonae, M. kansasii)* is 500 mg b.d.

Treatment of disseminated MAC infections in Al OS patients should continue as long as clinica l and microbiological benefit is demonstrated . A decrease in efficacy has been noted in patients on treatment exceeding 12 weeks . CLACEE should be used in conjunction with other antimycobacterial agents.

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Adverse drug events reported during clinical trials with CLACEE 250 mg and 500 mg tablets (BID dosing, all indications):
The most commonly reported adverse events were nausea, diarrhoea and dyspepsia.

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 events reported during clinical trials (BID dosing, all indications)*

System organ class (MedDRA Term)	Frequency *	Adverse Events
Infections and infestations	Common	Infection
Nervous system disorders	Common	Dizziness Dysgeusia Headache
Gastrointestinal disorders	Common	Abdominal pain Diarrhoea Dyspepsia Nausea Vomiting
Skin and subcutaneous tissue disorders	Common	Pruritus
General disorders and administration site conditions	Common	Asthenia
Investigations	Common	Alanine aminotransferase increased Aspartate aminotransferase increased

* Reported incidence of adverse events in clinical studies involving 3437 patients taking CLACEE

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.

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 **CLACEE** , 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 administrat ion of antibacterial agents.

There have been post-marketing reports of colchicine toxicity with concomitant use of **CLACEE** 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 **CLACEE** can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of **CLACEE** and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxemia . Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. **CLACEE** serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

IDENTIFICATION

CLACEE 250 mg Tablets: Yellow, ovaloid tablets.
CLACEE 500 mg Tablets: Pale yellow, ovaloid tablets.

PRESENTATION

CLACEE 250 mg is supplied in packs of 1O tablets.
CLACEE 500 mg is supplied in packs of 10 and 14 tablets.

STORAGE INSTRUCTIONS

Store below 25 °C and protect from light. Keep out of reach of children.

REGISTRATION NUMBER

CLACEE 250mg Tablets: X/20.1.1/229
CLACEE 500 mg Tablets: 29/20.1.1/0163

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Marketed and distributed by:
Aspen Pharmacare (Pty) Ltd

DATE OF PUBLICATION OF THIS PACKAGE INSERT

7 July 2006