Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 500 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg Clarithromycin

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Clarithromycin 500mg tablets are white oblong, biconvex film-coated tablets with a break-line on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The treatment of infections due to susceptible organisms. Such infections include:

1. Lower respiratory tract infections (e.g. bronchitis, pneumonia).

2. Upper respiratory tract infections (e.g. pharyngitis, sinusitis).

3. Skin and soft tissue infections (e.g. folliculitis, cellulitis, erysipelas).

4. Disseminated or localised mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*. Localised infections due to *Mycobacterium chelonae*, *Mycobacterium fortuitum* or *Mycobacterium kansasii*.

5. The prevention of disseminated *Mycobacterium avium* complex infection in HIV infected patients with CD4 lymphocyte counts less than or equal to 100/mm^3.

6. Clarithromycin in the presence of acid suppression is indicated for the eradication of *Helicobacter pylori*, resulting in decreased recurrence of duodenal ulcer. (See further information.)

As with other antibiotics, it is recommended that guidelines on the prevalence of local resistance, and associated medical practice regarding the prescription of antibiotics be consulted before prescribing Clarithromycin.

Further information: Helicobacter pylori is strongly associated with peptic ulcer disease. Ninety to 100% of patients with duodenal ulcers are infected with this agent. Eradication of *Helicobacter pylori* has been shown to markedly reduce the need for maintenance anti-secretory therapy.
In a well controlled double-blind study, *Helicobacter pylori* infected patients with duodenal ulcer received clarithromycin 500mg TID for 14 days with omeprazole 40mg daily for 28 days.

Clarithromycin has been used in other treatment regimens for the eradication of *Helicobacter pylori*. These regimens include: clarithromycin plus tinidazole and omeprazole: and clarithromycin plus tetracycline, bismuth salicylate and ranitidine.

4.2 Posology and method of administration

The usual recommended dosage of clarithromycin in adults is 250mg twice daily. In more severe infections, the dosage can be increased to 500mg twice daily. The usual duration of therapy is 6 to 14 days.

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

Treatment of mycobacterial (MAC) infections: The recommended starting dose is 500mg twice daily. If no clinical or bacteriologic response is observed in 3 to 4 weeks, the dose may be increased to 1000mg twice daily. Treatment of disseminated MAC infections in AIDS patients should be continued, as long as clinical microbiological benefit is demonstrated. Clarithromycin should be used in conjunction with other antimycobacterial agents.

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

Dosage for MAC prophylaxis: The recommended dosage of Clarithromycin in adults is 500mg twice daily.

Eradication of Helicobacter pylori:
Dual therapy (14 days): The recommended dose of clarithromycin is 500mg three times daily for 14 days (see Further information).
Triple therapy (7 days): Clarithromycin (500mg) twice daily and a proton pump inhibitor (at the approved daily dose)* should be given with amoxicillin 1000mg or metronidazole 400mg twice daily for 7 days.
Triple therapy (7 – 10 days): Clarithromycin (500mg) twice daily should be given with amoxicillin 1000mg twice daily and Omeprazole 20mg daily for 7 – 10 days.
* see individual Summaries of Product Characteristics for the dose recommendations for *Helicobacter pylori* eradication.

4.3 Contraindications

Use in patients with known hypersensitivity to Clarithromycin, other macrolide antibiotic drugs or to any of the excipients.

Clarithromycin and ergot derivatives should not be co-administered.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these drugs and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular fibrillation and torsades de pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

4.4 Special warnings and precautions for use

Clarithromycin should not be prescribed to pregnant women without carefully weighing the benefits against the risks, particularly during the first 3 months of pregnancy.

Clarithromycin is principally excreted by the liver and kidney so that caution must be exercised in its use in patients with impaired hepatic or renal function or in those concomitantly receiving potentially hepatotoxic drugs.

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

Prolonged or repeated use of clarithromycin may result in overgrowth of non-susceptible bacteria. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions: 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 were co-administered with clarithromycin.

As with other macrolide antibiotics the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system (e.g. warfarin, ergot alkaloids, triazolam, midazolam, disopyramide, lovastatin, phenytoin, ciclosporin, tacrolimus and rifabutin) may be associated with elevations in serum levels of these other drugs. (See also section 4.3, Contraindications.)

The effect of digoxin may be potentiated with concomitant administration of clarithromycin. Monitoring of serum digoxin levels should be considered.

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

Ritonavir increases the area under the curve (AUC), C_{max} and C_{min} of clarithromycin when administered concurrently. Because of the large therapeutic window for clarithromycin, 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 clarithromycin should be reduced by 50%. For patients with CL_{CR} < 30 ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1g/day should not be coadministered with ritonavir.

Rhabdomyolysis coincident with the co-administration of clarithromycin and HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, has rarely been reported.

There are no known clinically significant interactions between clarithromycin and proton pump inhibitors.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicines, especially in the elderly, some of which occurred in patients with renal insufficiency.

4.6 Pregnancy and lactation

The safety of clarithromycin in during pregnancy or breastfeeding of infants has not been established. Clarithromycin is excreted into human breast milk.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The most frequently reported side-effects of clarithromycin in clinical studies were gastrointestinal related complaints,

i.e. nausea, dyspepsia, abdominal pain, vomiting and diarrhoea. Other side effects included headache, altered taste, and transient elevations of liver enzymes.

Stomatitis, glossitis, oral monilia and tongue discolouration have been reported. Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis and Stevens - Johnson syndrome have occurred with orally administered clarithromycin. There have been reports of transient central nervous system side-effects including dizziness, vertigo, anxiety, insomnia, bad dreams, tinnitus, confusion, disorientation, hallucinations, psychosis and depersonalization, however, a cause and effect relationship has not been established.

As with other macrolides, hepatic dysfunction (which is usually reversible), including altered liver function tests, hepatitis and cholestasis with or without jaundice, has been reported. Dysfunction may be severe and very rarely fatal hepatic failure has been reported.

Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received. There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning.

Reversible cases of hearing loss have been reported with clarithromycin. There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin. Isolated cases of thrombocytopenia have been reported.

Pseudomembraneous colitis has been reported rarely with clarithromycin and may range in severity from mild to life threatening.

Isolated cases of increased serum creatinine have been reported but an association has not been established.

As with other macrolides, QT prolongation, ventricular tachycardia and Torsades de Pointes have been rarely reported with clarithromycin.

Adverse events in immunocompromised patients: In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness.

In adult patients, the most frequently reported adverse events by patients treated with total daily doses of 1000 mg and 2000 mg were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, SGOT and SGPT elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1000 mg and 2000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000 mg of clarithromycin.

In these immunocompromised patients evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2 to 3% of those patients who received 1000 mg or 2000 mg of clarithromycin daily had seriously abnormally elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two groups also had elevated Blood Urea Nitrogen (BUN) levels. Slightly higher incidences of abnormal values were noted for patients who received 4000 mg daily for all parameters except WBC.

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin orally can be expected to produce gastrointestinal symptoms. One patient who has a history of bipolar disorder ingested 8000 mg of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxemia. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clarithromycin is a semi-synthetic macrolide antibiotic obtained by substitution of the hydroxyl group in position 6 by a CH_3O group in the erythromycin lactonic ring. Specifically, Clarithromycin is 6-0-Methyl Erythromycin A.

Clarithromycin exerts its antibacterial action by binding to the 50s ribosomal subunits of susceptible bacteria and suppressing protein synthesis.

Microbiology: Clarithromycin has demonstrated excellent *in vitro* activity against standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally one $\log^2$ dilution more potent than the MICs of erythromycin.

In vitro data also indicate clarithromycin has excellent activity against *Legionella pneumophila*, and *Mycoplasma pneumoniae*. It is bactericidal to *Helicobacter pylori*; this activity of Clarithromycin is greater at neutral pH than at acid pH. *In vitro* and *in vivo* data show that this antibiotic has activity against clinically significant mycobacterial species. The *in vitro* antibacterial spectrum of clarithromycin is as follows:

USUALLY SENSITIVE BACTERIA	*NON-SENSITIVE BACTERIA*
Streptococcus agalactiae	*Enterobacteriacae*
Streptococcus pyogenes	*Pseudomonas* species
Streptococcus viridans	
Streptococcus pneumoniae	
Haemophilus influenzae	
Haemophilus parainfluenzae	
Neisseria gonorrhoeae	
Listeria monocytogenes	
Legionella pneumophila	
Pasteurella multocida	
Mycoplasma pneumoniae	
Helicobacter (Campylobacter) pylori	
Campylobacter jejuni	
Chlamydia pneumoniae (TWAR)	
Chlamydia trachomatis	
Moraxella (Branhamella) catarrhalis	
Bordetella pertussis	
Borrelia burgdorferi	
Staphylococcus aureus	
Clostridium perfringens	
Peptococcus niger	
Propionibacterium acnes	
Bacteroides melaninogenicus	
Mycobacterium avium	
Mycobacterium leprae	
Mycobacterium kansasii	
Mycobacterium chelonae	
Mycobacterium fortuitum	
Mycobacterium intracellulare	

The principal metabolite of clarithromycin in man and primates is a microbiologically-active metabolite, 14-OH-clarithromycin. The metabolite is as active or 1 to 2 fold less active than the parent compound for most organisms, except for *Haemophilus influenzae* against which it is twice as active. The parent compound and the 14-OH-metabolite exert either an additive or synergistic effect on *Haemophilus influenzae*.

In guinea pigs with *Legionella* infection, an intraperitoneal dose of 1.6 mg/kg/day of clarithromycin was more effective than 50 mg/kg/day of erythromycin.

Susceptibility Tests: Quantitative methods that require measurement of zone diameters give the most precise estimate of susceptibility of bacteria to antimicrobial agents. One recommended procedure uses discs impregnated with 15mcg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC values for clarithromycin. The MICs are determined by the broth or agar dilution method. The recommended test medium for susceptibility testing of *Haemophilus influenzae* according to the National Committee of Clinical Laboratory Standards (NCCLS) is the Haemophilus Test Medium (H.T.M.).

The correlation of disc inhibition zone diameters with MICs is given in the following table:

Clarithromycin Interpretative Standards

	Inhibition Zone Diameter (mm)			MIC (micrograms/ml)		
Organisms	S	I	R	S	I	R
All Organisms (except *Haemophilus* and *Staphylococci*)	= 18	14-17	= 13	= 1	2-4	= 8
Staphylococci	= 20	-	= 19	= 0.5	-	= 1
Haemophilus influenzae when tested on HTM*	= 13	11-12	= 10	= 8	16	= 32

*HTM = Haemophilus Test Medium
S = Susceptible I = Intermediate R = Resistant

With these procedures, a report from the laboratory of “susceptible” indicates that the infecting organism is likely to respond to therapy. A report of “resistant” indicates that the infective organisms are not likely to respond to therapy. A report of “intermediate susceptibility” suggests that the therapeutic effect of the drug may be equivocal or that the organism would be susceptible if higher doses were used (latter also referred to as moderately susceptible).

5.2 Pharmacokinetic properties

The non-linear kinetics of orally administered clarithromycin have been studied extensively in a number of animal species and adult humans. These studies have shown that clarithromycin is rapidly and well absorbed from the gastro-intestinal tract with an absolute bioavailability of approximately 50%. No accumulation was found and the metabolic disposition did not change in any species following multiple dosing.

Results of these animal studies showed that 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) rations reached 10 to 20.

In vitro studies showed that the protein binding of clarithromycin in human plasma averaged about 70% at concentrations of 0.45 – 4.5 micrograms/ml. A decrease in binding to 41% at 45.0 micrograms/ml suggested that the binding sites might become saturated, but this only occurred at concentrations far in excess of the therapeutic drug levels.

Clarithromycin and its 14-OH-metabolite distribute readily into the body tissues and fluids. Limited data from a small number of patients suggest that clarithromycin does not achieve significant levels in cerebro-spinal fluid (CSF) after oral doses (i.e. only 1-2% of serum levels are found in CSF in patients with normal blood-CSF barriers). Concentrations in tissues are usually several fold higher than serum concentrations. Examples from tissue and serum concentrations are presented below:

CONCENTRATION (after 250mg q 12h)

Tissue Type	**Tissue (micrograms/g)**	**Serum (micrograms/ml)**
Tonsil	1.6	0.8
Lung	8.8	1.7

With BID dosing at 250mg, the peak steady state plasma concentration was attained in 2 to 3 days and averaged about 1 micrograms/ml for clarithromycin and 0.6 mcg/ml for 14-OH-clarithromycin, while the elimination half-lives of the parent drug and metabolite were 3 -4 hours and 5 – 6 hours, respectively.
With BID dosing at 500mg, the steady state C_{max} for clarithromycin and its hydroxylated metabolite averaged 2.7 – 1.9 micrograms/ml and 0.88 – 0.83 micrograms/ml, respectively. The half-life of the parent drug at the 500mg dose level was 4.5 – 4.8 hours, while that of the 14-OH-clarithromycin was 6.9 – 8.7 hours. At steady state, the 14-OH-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 higher doses. This non-linear pharmacokinetic behaviour of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation product at the higher doses, indicate that the metabolism of clarithromycin approaches saturation at high doses.

A pharmacokinetic study was conducted with clarithromycin 500mg t.i.d. and Omeprazole 40mg q.i.d. When clarithromycin was given alone at 500mg q8h, the mean steady-state C_{max} value was approximately 31% higher and C_{min} value was approximately 119% higher than when clarithromycin is compared with a previous study at 500mg q12h. The mean AUC_{0-24} for clarithromycin was 65% greater when 500mg clarithromycin was given q8h rather than q12h. Neither T_{max} nor half-life values appeared substantially different between the q8h and q12h regimens.

When clarithromycin was administered with omeprazole, increases in omeprazole half-life and AUC_{0-24} were observed. For all subjects combined, the mean AUC_{0-24} was 89% greater and the harmonic mean for omeprazole $T_{1/2}$ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max}, Cmin and AUC_{0-8} of clarithromycin was increased by 10%, 27% and 15%, respectively, over values achieved when clarithromycin was administered with placebo.

In human adults given single oral doses of 250mg or 1200mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Faecal elimination accounted for 40.2% and 29.1% of these respective doses.

At steady state, clarithromycin gastric mucus concentrations six hours after dosing where approximately 25-hold higher in the clarithromycin/ omeprazole group compared to the clarithromycin alone group. Six hours post-dosing, mean clarithromycin gastric tissue concentrations were approximately 2-fold higher when clarithromycin was given with omeprazole than when clarithromycin was given with placebo.

In a study comparing one group of healthy human subjects with a group of subjects with liver impairment who were given 250mg of clarithromycin BID for 2 days and a single 250mg dose on the third day, steady state plasma levels and systemic clearance of clarithromycin were not significantly different between the two groups. In contrast, steady state concentrations of the 14-OH metabolite were markedly lower in the group of hepatic-impaired subjects. This decreased metabolic clearance of the parent compound by 14-hydroxylation was partially offset by an increase in the renal clearance of parent drug, resulting in comparable steady state levels of parent drug in the hepatic impaired and healthy subjects. These results indicate that no adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function.

A study was conducted to evaluate and compare the pharmacokinetic profile of multiple 500mg oral doses of clarithromycin in subjects with normal and decreased renal function. Plasma levels, half-life, C_{max} and C_{min} were higher for both clarithromycin and its 14-OH metabolite and AUC was larger in subjects with renal impairment. K_{elim} and urinary excretion were lower. The extent to which these parameters differed was correlated with the degree of renal impairment: the more severe the renal impairment, the more significant the difference.

Pharmacokinetics in elderly subjects: A study was also conducted to evaluate and compare the safety and pharmacokinetic profiles of multiple 500mg oral doses of clarithromycin in healthy elderly male and female subjects to those in healthy young adult male subjects. In the elderly group, circulating plasma levels were higher and elimination slower than in the younger group for both the parent drug and the 14-OH metabolite.

However, there was no difference between the two groups when renal clearance was correlated with creatinine clearance. It is concluded from these results that any effect on the handling of clarithromycin is related to renal function and not to age *per se*.

Pharmacokinetics in patients with mycobacterial infections: Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following 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 2000mg/day in two divided doses, steady-state clarithromycin C_{max} values ranged from 5 – 10 micrograms/ml. C_{max} values as high as 27 micrograms/ml have been observed in HIV-infected adult patients taking 4000 mg/day in two divided doses. 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 of clarithromycin pharmacokinetics.

5.3 Preclinical safety data

Acute, Subchronic and Chronic Toxicity:
Studies were conducted in mice, rats, dogs and/ or monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for 6 consecutive months.

In acute mouse and rat studies, 1 rat, but no mice, died following a single gavage of 5g/kg bodyweight. The median lethal dose, therefore, was greater than 5g/kg, the highest feasible dose for administration.

No adverse effects were attributed to clarithromycin in primates exposed to 100 mg/kg/day for 14 consecutive days or 35 mg/kg/day for 1 month. Similarly, no adverse effects were seen in rats exposed to 75 mg/kg/day for 1 month, to 35 mg/kg/day for 3 months, or 8 mg/kg/day for 6 months. Dogs were more sensitive to clarithromycin, tolerating 50 mg/kg/day for 14 days, 10 mg/kg/day for 1 and 3 months, and 4 mg/kg/day for 6 months without adverse effects.

The major clinical signs at toxic doses in these studies included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. Two of ten monkeys receiving 400 mg/kg/day died on treatment day 8; yellow discoloured faeces were passed on a few isolated occasions by some surviving monkeys given a dose of 400 mg/kg/day for 28 days.

The primary target organ at toxic dosages in all species was the liver. The development of hepatotoxicity in all species was detectable by early elevation of serum concentrations of alkaline phosphatase, alanine and aspartat aminotransferase, gamma-glutamyl transferase, and/ or lactic dehydrogenase. Discontinuation of the drug generally resulted in a return to or toward normal concentrations of these specific parameters.

Additional tissues less commonly affected included the various studies included the stomach, thymus and other lymphoid tissues and the kidneys. Conjunctival injection and lacrimation, following near therapeutic dosages, occurred in dogs only. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/ or oedema.

Fertility, Reproduction and Teratogenicity:
Fertility and reproduction studies have shown daily dosages of 150 – 160 mg/kg/day to male and female rats caused no adverse effects on the oestrous cycle, fertility, parturition and the number or viability of offspring. Two teratogenicity studies in both Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.) rats, 1 study in New Zealand White rabbits and one study in cynomologous monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony.

Two mouse studies in mice also revealed a variable incidence (3-30%) of cleft palate following doses of 70 times the upper range of the usual daily human clinical dose (500mg BID), but not at the 35 times the maximal daily human clinical dosage, suggesting maternal and foetal toxicity but not teratogenicity.

Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately 10 times the upper range of the usual daily human dose (500mg BID), starting at gestation day 20. This effect has been attributed to maternal toxicity of the drug at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage produced no unique hazard to the conceptus.

A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose) was clearly negative for any mutagenic activity, and, in a Segment I study of rats treated with up to 500 mg/kg/day (approximately 35 times the maximal daily human clinical dose) for 80 days, no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.

Mutagenicity:
Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver microsome-activated test systems (Ames test). Results of these studies showed no evidence of mutagenic potential at drug concentrations of 25 micrograms/petri plate or less. At a concentration of 50 micrograms, the drug was toxic for all strains tested.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate
Opadry II 31F8914 white coating containing hypromellose, lactose monohydrate, titanium dioxide (E171), macrogol 4000, sodium citrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

PVC/Aluminium blister. Carton containing 14, 20, 28, 42, 84, or 168 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pliva Pharma Limited
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GU32 3QB
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8 MARKETING AUTHORISATION NUMBER

PA0585/011/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 31 March 2006

10 DATE OF REVISION OF THE TEXT

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