IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1151/046/002
Case No: 2078163

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Imbat Limited

Unit L2, **North Ring Business Park**, **Santry**, **Dublin 9**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Klacid Forte 500mg Film-coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **24/02/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Klacid Forte 500mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of clarithromycin.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Product imported from UK:
Yellow, ovaloid tablets with the Abbott logo on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clarithromycin is indicated for treatment of infections due to susceptible organisms. Such infections include.

1. Lower respiratory tract infections (eg. bronchitis, pneumonia).
2. Upper respiratory tract infections (eg. pharyngitis, sinusitis).
3. Skin and soft tissue infections (eg. 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. Clarithromycin is indicated for the prevention of disseminated
Mycobacterium avium **complex infection in HIV – infected patients with CD4 lymphocyte counts less than or equal to 100/mm3.**
6. Clarithromycin in the presence of acid suppression is indicated for the eradication of *H. 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 Klacid Forte.
Further Information: *H. pylori* is strongly associated with peptic ulcer disease. Ninety to 100% of patients with duodenal ulcers are infected with this agent. Eradication of *H. pylori* has been shown to markedly reduce the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy.
In a well controlled double-blind study, *H. 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 *H. pylori*. These regimens include clarithromycin plus tinidazole and omeprazole; and clarithromycin plus tetracycline, bismuth subsalicylate, and ranitidine.

4.2 Posology and method of administration

The usual recommended dosage of clarithromycin in adults is one 250mg tablet 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. Treatment should not be continued beyond 14 days in these patients.
Treatment of mycobacterial infections: The recommended starting dose is 500mg BID. If no clinical or bacteriologic response is observed in 3 to 4 weeks, the dose may be increased to 1000mg BID. Treatment of disseminated Mycobacterium Avium Complex (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 nontuberculous 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 *H. 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 amoxycillin 1000mg twice daily for 7 days
Triple Therapy (7 days):
Clarithromycin 500mg twice daily and a proton pump inhibitor (at the approved daily dose)* should be given with metronidazole 400mg twice daily for 7 days.
Triple Therapy (7-10 days):
Clarithromycin 500mg twice daily should be given with amoxycillin 1000mg twice daily and omeprazole 20 mg daily for 7 to 10 days.
* see individual data sheets/ SPCs for the dose recommended for H. pylori eradication

4.3 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs.
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 Torsade de Pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

4.4 Special warnings and precautions for use

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, 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 also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

Prolonged administration of an anti-infective may result in superinfection due to organisms resistant to that anti-infective. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. *Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile.*

CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy.

4.5 Interaction with other medicinal products and other forms of interaction

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Elevated cisapride levels have been reported in patients receiving clarithromycin 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 clarithromycin and pimozide concomitantly (see section 4.3, Contraindications).
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 section 4.3, Contraindications). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin 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 other macrolides.

Ergotamine/dihydroergotamine
Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3, Contraindications).

Effects of Other Medicinal Products on Clarithromycin
The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine
Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-(R)-clarithromycin (14-OH-clarithromycin), a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Fluconazole
Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir
A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin 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-OH-clarithromycin was noted. 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 1 gm/day should not be coadministered with ritonavir.

Effect of Clarithromycin on Other Medicinal Products

Antiarrhythmics

There have been postmarketed reports of torsade de points occurring with the concurrent use of clarithromycin and quinidine or disopyramide.Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy.

CY3A4-based interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively metabolized by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolized 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 isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

HMG-CoA Reductase Inhibitors

As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Omeprazole

Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

Oral anticoagulants

Spontaneous reports in the post-marketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

Sildenafil, tadalafil and vardenafil

Each of these phosphodiesterase inhibitors is metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

Theophylline, carbamazepine

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 administered concomitantly with clarithromycin.

Tolterodine
The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.
There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other drug interactions
Colchicine
Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity (see section 4.4 Warnings and Precautions).

Digoxin
Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine
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 largely avoided by staggering the doses of clarithromycin and zidovudine. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine.

Bi-directional drug interactions
Atazanavir
Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Itraconazole
Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma

levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir
Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state AUC and C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with the combination therapy of saquinavir and ritonavir, therefore when this combination therapy is co-administered with clarithromycin consideration should be given to the potential effects of ritonavir on clarithromycin (see Section 4.5-Ritonavir).

Verapamil
Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

4.6 Pregnancy and lactation

The safety of clarithromycin during pregnancy and breast feeding 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

Table 1 displays adverse events reported in patients taking clarithromycin in clinical studies. Adverse events are displayed by body system and frequency (common 1/100, < 1/10).

Table 1.

Adverse Events Reported in Clinical Studies

System Organ Class	Frequency	Adverse Events
Nervous system disorders	Common	headache taste perversion
Gastrointestinal disorders	Common	diarrhoea nausea abdominal pain dyspepsia vomiting
Investigations	Common	hepatic enzyme increased

Post Marketing Experience

Clarithromycin is marketed in several different formulations. Table 2 is a compilation of adverse reactions for all formulations including clarithromycin immediate release tablets. 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 estimated to be greater than 1 billion patient treatment days for clarithromycin**.**

Table 2

Adverse Reactions from Post-Marketing Surveillance

System Organ Class	**Adverse Reaction**
Infections and infestations	oral candidiasis
Blood and lymphatic system disorders	leukopaenia thrombocytopaenia
Immune System disorders	anaphylactic reaction hypersensitivity
Metabolism and nutrition disorders[1]	hypoglycaemia
Psychiatric disorders	psychotic disorder hallucination disorientation confusional state depersonalization depression anxiety insomnia abnormal dreams
Nervous system disorders	convulsion dizziness ageusia anosmia dysgeusia parosmia
Ear and labyrinth disorders	deafness vertigo tinnitus
Cardiac disorders[2]	torsade de pointes

	electrocardiogram QT prolonged ventricular tachycardia
Gastrointestinal disorders	pancreatitis acute glossitis stomatitis tongue discolouration tooth discolouration
Hepatobiliary disorders[3]	hepatic failure hepatitis hepatitis cholestatic jaundice cholestatic jaundice hepatocellular hepatic function abnormal
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome toxic epidermal necrolysis urticaria rash
Musculoskeletal and connective tissue disorders	myalgia
Renal and urinary disorders	nephritis interstitial
Investigations	blood creatinine increase hepatic enzyme increased

[1] There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.

[2] As with other macrolides, QT prolongation, ventricular tachycardia, and torsades de pointes have rarely been reported with clarithromycin.

[3] In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see sections 4.4 Warnings and Precautions and 4.5 Interaction with other medicinal products and other forms of interactions).

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 2000mg of clarithromycin 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 1000mg and 2000mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000mg of clarithromycin.

In these immuncompromised 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 1000mg or 2000mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen (BUN) levels. Slightly higher incidences of abnormal values were noted for patients who received 4000mg daily for all parameters except WBC.

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. 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. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxemia.

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 CH3O 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 log2 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:

Please see below for table of MIC breakpoints.

USUALLY SENSITIVE	NON-SENSITIVE
BACTERIA	BACTERIA
Streptococcus agalactiae	*Enterobacteriacae*
Streptococcus pyogenes	*Pseudomonas species*
Streptococcus viridans	

Streptococcus pneumoniae

Haemophilus influenzae

Haemophilus parainfluenzae

Neisseria gonorrhoea

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

Bacterioides melaninogenicus

Mycobacterium avium

Mycobacterium leprae

Mycobacterium kansaii

Mycobacterium chelonae

Mycobacterium fortuitum

Mycobacterium intracellulare

The principal metabolite of clarithromycin in man and other primates is a microbiologically-active metabolite, 14-OH-clarithromycin. 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-OH-metabolite exert either an additive or synergistic effect on *H. 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 disc impregnated with 15 mcg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC value 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 (mcg/ml)		
Organisms	S	I	R	S	I	R
All Organisms (except Haemophilus and Staphylocci)	≥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 organism is 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).

Breakpoints

The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

Breakpoints (MIC, µg/ml)		
Microorganism	Susceptible (≤)	Resistant (>)
Streptococcus spp.	0.25 µg/ml	0.5 µg/ml
Staphylococcus spp.	1 µg/ml	2 µg/ml

Haemophilus spp.	1 µg/ml	32 µg/ml
Moraxella catarrhalis	0.25 µg/ml	0.5 µg/ml
Clarithromycin is used for the eradication of *H. pylori* ; minimum inhibitory concentration (MIC) ≤0.25 µg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI)		

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 readily and rapidly absorbed 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) ratios 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 mcg/ml. A decrease in binding to 41% at 45.0 mcg/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 to 2 percent of serum levels 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 250 mg q 12h)

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

With BID dosing at 250 mg, the peak steady state plasma concentration was attained in 2 to 3 days and averaged about 1 mcg/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 500 mg, the steady state Cmax for clarithromycin and its hydroxylated metabolite averaged 2.7 - 2.9 mcg/ml and 0.88 - 0.83 mcg/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-clarithromcyin 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 the 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 metabolism of clarithromycin approaches saturation at high doses.
A pharmacokinetic study was conducted with clarithromycin 500 mg t.i.d. and omeprazole 40 mg q.i.d. When clarithromycin was given alone at 500 mg q8h, the mean steady-state Cmax value was approximately 31% higher and Cmin 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 500 mg clarithromycin was given q8h rather than q12h. Neither Tmax 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 AUC0-24 were observed. For all subjects combined, the mean omeprazole AUC0-24 was 89% greater and the harmonic mean for omeprazole T1/2 was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state Cmax Cmin and AUC0-8 of clarithromycin were increased by 10%, 27%, and 15%, respectively over values achieved when clarithromycin was administered with placebo.
In human adults given 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. Faecal elimination accounted for 40.2% and 29.1% of these respective doses.
At steady state, clarithromycin gastric mucus concentrations six hours after dosing were approximately 25-fold higher in the clarithromycin/omeprazole group compared with 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 250 mg of clarithromycin BID for two days and a single 250 mg dose the third day, steady state plasma levels and systemic clearing 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 500 mg oral doses of clarithromycin in subjects with normal and decreased renal function. This plasma levels, half-life, Cmax and Cmin for both clarithromycin and its 14-OH metabolite were higher and AUC was larger in subjects with renal impairment. Kelim 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 500 mg 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 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 those 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 2000 mg/day in two divided doses, steady-state clarithromycin Cmax values ranged from 5-10 mcg/ml. Cmax values as high as 27 mcg/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 nonlinearity in 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 body weight. 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 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 described above 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 faces 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 hepatotoxocity in all species was detectable by early elevation of serum concentrations of alkaline phosphatase, alanine and aspartate 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 in 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 dosage of 400 mg/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 a number of 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 studies in mice also revealed a variable incidence of cleft palate (3-30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg BID), but not at the 35 times the maximal daily human clinical dose, 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 (500 mg 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 provided no evidence of mutagagenic potential at drug concentrations of 25 mcg/petri plate or less. At a concentration of 50 mcg, the drug was toxic for all strains tested.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Microcrystalline cellulose
Silicon dioxide
Povidone
Stearic acid
Magnesium stearate
Talc
Hypromellose
Hyprolose
Propylene glycol
Sorbitan oleate
Titanium dioxide (E171)
Sorbic acid
Vanillin
Quinoline Yellow Aluminium Lake (E104)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25˚C. Store in the original package.

6.5 Nature and contents of container

Calendar blister strip in a cardboard carton containing 14 tablets.

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 Parallel Product Authorisation Holder

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 Parallel Product Authorisation Number

PPA 1151/46/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 19th October 2007

10 DATE OF REVISION OF THE TEXT

February 2010