IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1473/040/001
Case No: 2071611

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

McDowell Pharmaceuticals

4 Altona Road, **Lisburn**, **N. Ireland**, **BT27 5QB**

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

Klacid LA 500mg Modified Release 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 **05/02/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Klacid LA 500mg Modified Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Clarithromycin 500mg

Excipients- contains Lactose Monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified Release Tablet
Product imported from the UK:
Yellow, ovaloid modified release tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Klacid LA is indicated for treatment of infections caused by susceptible organisms.
Indications include:
Lower respiratory tract infections for example bronchitis and pneumonia.
Upper respiratory tract infections for example sinusitis and pharyngitis.
Skin and soft tissue infections for example folliculitis, cellulitis and erysipelas.
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 LA.

4.2 Posology and method of administration

Adults: The usual recommended dosage of Klacid LA in adults is one 500 mg modified-release tablet daily to be taken with food.
In more severe infections, the dosage can be increased to two 500 mg modified-release tablets taken as one dose daily.
Dose must be taken at the same time every day.
Tablets must be swallowed whole.
The usual duration of treatment is 6 to 14 days.
Children older than 12 years: As for adults.
Children younger than 12 years: Use Klacid Paediatric Suspension.
Patients with renal impairment: Klacid LA should not be used in patients with renal impairment (creatinine clearance less than 30 ml/min). Klacid immediate-release tablets should be used in this patient population (see section 4.3).

4.3 Contraindications

Clarithromycin is contra-indicated in patients with known hypersensitivity to macrolide antibiotic drugs.
Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide, terfenadine, and ergotamine or dihydroergotamine.
(see section 4.5).

As the dose cannot be reduced from 500 mg daily, Klacid LA is contraindicated in patients with creatinine clearance less than 30 ml/min.
Clarithromycin should not be given to patients with hypokalaemia (QT interval prolongation).

4.4 Special warnings and precautions for use

Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment (see also section 4.3).

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome (see sections 4.5 and 4.8).

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, 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 the two months after the administration of antibacterial agents.

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

Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Each tablet contains 115 mg of lactose. 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

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

<u>Cisapride, pimozide, and terfenadine</u>
Clarithromycin has been reported to elevate plasma levels of cisapride, pimozide, astemizole, and terfenadine. Increased levels of these drugs may result in increased risk of ventricular rhythm disorders, especially Torsades de Pointes.
Concomitant administration of clarithromycin and any of these medicinal products is contraindicated (see section 4.3).

<u>Ergotamine/dihydroergotamine</u>
Post-marketing reports indicate that coadministration 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).

Effect 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:

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 (C_{min}) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14(R)-hydroxy-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir
Coadministration of clarithromycin and ritonavir increases the area under the curve (AUC), maximum concentration (C_{max}) and the minimum concentration (C_{min}) of clarithromycin. 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, such as {Klacid}, immediate release tablets, or {Klacid}, sachet, or {Klacid}, paediatric suspensions (not all presentations may be marketed).
Doses of clarithromycin greater than 1000 mg per day should not be coadministered with protease inhibitors (see section 4.2).
Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, bidirectional pharmacokinetic interactions).

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)-hydroxy-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14(R)-hydroxy-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Effect of clarithromycin on other medicinal products
CYP3A-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.

Antiarrhythmics
There have been post-marketing reports of torsade de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum concentrations of these medications should also be monitored.

Carbamazepine
During therapy with clarithromycin, the metabolism of carbamazepine may be inhibited.
Consequently the serum concentrations of carbamazepine may be increased, and dose reduction may need to be considered.

HMG-CoA Reductase Inhibitors (e.g., lovastatin, simvastatin)
Clarithromycin inhibits the metabolization of a number of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. This may result in elevated plasma levels of these drugs.
In rare cases, the occurrence of rhabdomyolysis was reported with concomitant administration of clarithromycin and HMG-CoA reductase inhibitors (statins), such as lovastatin or simvastatin.
Patients should be monitored for signs and symptoms of myopathy. Adjustment of the statin dosage or use of a statin that is less dependent on CYP3A metabolism, e.g., pravastatin, should be considered.

Oral anticoagulants (e.g., warfarin, acenocoumarol)
In isolated cases, patients receiving combination therapy with clarithromycin and oral anticoagulants may experience increased pharmacologic effects and even toxic effects of these drugs.

International normalized ratio (INR) or Prothrombin times should be carefully monitored while patients are simultaneously receiving clarithromycin and oral anticoagulants.

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. Coadministration 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 coadministered with clarithromycin.

Theophylline
During therapy with clarithromycin, the metabolism of theophylline may be inhibited.
Consequently the serum concentrations of theophylline may be increased, and dose reduction may need to be considered.

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.

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 metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not metabolised by CYP3A (temazepam, nitrazepam, lorazepam) an 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.

Omeprazole
The AUC of omeprazole is increased by 89% when administered concomitantly with clarithromycin for *H. pylori* eradication; however the change in the mean 24-hour gastric pH value from 5.2 (omeprazole alone) to 5.7 (omeprazole + clarithromycin) is not considered clinically significant.
There are no in-vivo human data available describing an interaction between clarithromycin and the following drugs: aprepitant, eletriptan, halofantrine, and ziprasidone. However, because *in vitro* data suggest these drugs are CYP3A substrates, caution should be used when they are co-administered with clarithromycin.

Eletriptan should not be coadministered with CYP3A inhibitors such as clarithromycin.
There have been spontaneous or published reports of drug interactions of CYP3A inhibitors, including clarithromycin, with cyclosporine, tacrolimus, methylprednisolone, vinblastine, and cilostazol.

Other 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).

Digoxin
Digoxin is 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
Due to reduced gastrointestinal absorption of zidovudine in the presence of clarithromycin, reduced serum levels of zidovudine were observed in adults during concomitant therapy with clarithromycin and zidovudine.
Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, patients should observe a 4-hour interval between taking these two drugs.

This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate
There have been spontaneous or published reports of interactions with CYP3A inhibitors, including clarithromycin, and drugs not thought to be metabolized by CYP3A, including phenytoin and valproate.
Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin.
Increased concentrations have been reported.

Bidirectional pharmacokinetic 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(R)-hydroxy-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, such as {Klacid}, immediate release tablets, or {Klacid}, sachet, or {Klacid}, paediatric suspensions (not all presentations may be marketed).

Doses of clarithromycin greater than 1000 mg per day should not be coadministered 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 bidirectional 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 area under the curve (AUC) and maximum concentration (Cmax) 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 done with unboosted saquinavir may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is coadministered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section above, effect of other medicinal products on clarithromycin).

4.6 Pregnancy and lactation

The safety of clarithromycin for use during pregnancy and breast feeding of infants has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk. Clarithromycin is excreted into human breast milk.

4.7 Effects on ability to drive and use machines

There are no data on the effect of this product on the driving ability. When driving or using machines, one should take into account that dizziness may occur.

4.8 Undesirable effects

Clinical experience
The most commonly reported ADR were gastro-intestinal disorders (nausea, diarrhoea, dyspepsia, abdominal pain).

*	Common: Frequency from ≥1/100 (1%) to <1/10 (10%) Uncommon: Frequency from ≥1/1000 (0.1%) to ≤1/100 (1%).

System Organ Class	**Frequency***	**Adverse Drug Reactions**
Infections and infestations	Uncommon	Gastroenteritis Oral candidiasis Rash pustular Rhinitis Vaginal candidiasis Vaginal infection

Blood and the lymphatic system disorders	Uncommon	Anaemia Eosinophilia Hypochromic anaemia Leukopenia Thrombocythaemia White blood cell disorders
Metabolism and nutrition disorders	Uncommon	Anorexia Hyperchloraemia Hyperuricaemia Hypocalcaemia Increased appetite
Psychiatric disorders	Uncommon	Depression Insomnia Nervousness Somnolence
Nervous system disorders	Common Uncommon	Dysgeusia Dizziness Headache Tremor
Eye disorders	Uncommon	Conjunctivitis Visual disturbance
Ear and labyrinth disorders	Uncommon	Ear disorder Tinnitus Vertigo
Vascular disorders	Uncommon	Vasodilatation
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma Dyspnoea Lung disorder
Gastrointestinal disorders	Common	Abdominal pain Diarrhoea Dyspepsia Nausea
Gastrointestinal disorders	Uncommon	Abdominal distension Constipation Dry mouth Eructation Flatulence Gastrointestinal disorder Gastrointestinal haemorrhage Stomatitis Tongue discolouration Vomiting
Hepato-biliary disorders	Uncommon	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Uncommon	Dry skin Eczema Hyperhidrosis Pruritus Rash Rash maculo-papular Urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Back Pain

Renal and urinary disorders	Uncommon	Albuminuria Haematuria Pyuria
Reproductive system and breast disorders	Uncommon	Genital discharge
General disorders and administration site conditions	Uncommon	Asthenia Chest pain Drug interaction Face oedema Malaise Pain Thirst
Investigations	Uncommon	Alanine aminotransferase increased Alkaline phosphate increased Aspartate aminotransferase increased Blood creatinine increased Blood lactate dehydrogenase increased Blood urea increased Laboratory test abnormal Liver function test abnormal Prothrombin decreased

Post-Marketing Experience

The ADR reported are consistent with those observed in clinical studies.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.

Infection and infestations:	Oral candidiasis.
Blood and lymphatic system disorders:	Leukopenia, thrombocytopenia.
Immune system disorders:	Anaphylactic reaction, hypersensitivity.
Metabolism and nutrition disorders:	Hypoglycaemia.
Psychiatric disorders:	Abnormal dreams, anxiety, confusional state, depersonalization, disorientation, hallucination, insomnia, psychotic disorder.
Nervous system disorders:	Convulsions, dizziness, dysgeusia, parosmia.
Ear and labyrinth disorders:	Deafness, tinnitus, vertigo.
Cardiac disorders:	Electrocardiogram QT prolonged, torsades 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 increase, hepatic enzyme increased.

Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.
There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome. (see sections 4.5 and 4.4).

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia. Adverse reactions accompanying overdosage should be treated by gastric lavage 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

General Properties
ATC classification
Pharmacotherapeutic group: Anti-infectious, ATC code: J01FA09.
Mode of Action
Clarithromycin is an antibiotic belonging to the macrolide antibiotics group. It exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria. It selectively binds to the 50S subunit of bacterial ribosomes and thus prevents the translocation of activated amino acids.
Clarithromycin has relevant bactericidal activity against several bacterial strains.
The organisms include *H. influenzae, S. pneumoniae, S. pyogenes, S. aureus, M. catarrhalis, H. pylori, C. pneumoniae, M. pneumoniae, L. pneumophila, M. avium,* and *M. intracellulare*.
The 14(R)-hydroxy metabolite of clarithromycin, a product of parent drug metabolism in humans, also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including Mycobacterium spp. An exception is *Haemophilus influenzae* against which the metabolite is 1 to 2 times more active than the parent compound. Clarithromycin combined with the metabolite showed a strain-dependent additive or synergistic effect both *in vitro* and *in vivo*.

PK/PD Relationship
Clarithromycin is extensively distributed in body tissues and fluids. Because of high tissue penetration, intracellular concentrations are higher than serum concentrations.

Clarithromycin concentrations in tonsil and whole lung tissue are 2- to 6-fold higher than those observed in the serum. Tissue and serum concentrations observed in Abbott studies with immediate-release (IR) tablets are presented below.

Mean Clarithromycin Concentration [250mg BID]		
Tissue Type	Tissue	Serum
Tonsil	1.6 µg/g	0.8 µg/ml
Lung	8.8 µg/g	1.7 µg/ml

The pharmacokinetics of orally administered modified-release (MR) clarithromycin tablets have been studied in adult humans (refer to section 5.2) and compared with clarithromycin 250 mg and 500 mg IR tablets. The extent of absorption – area under curve (AUC) – was found to be equivalent when equal total daily doses were administered. The equivalent AUCs would be expected to drive tissue levels equivalent to those observed for clarithromycin IR tablets.

In a study in healthy volunteers, it was shown that the concentrations of clarithromycin in epithelial lining fluid (ELF) following administration of the MR formulation remained above 1 µg/ml for 24 hours and above 10 µg/ml for up to 18 hours. In most subjects, the concentrations of clarithromycin in ELF were approximately 30 times greater than those in plasma, and the ratio appeared to be independent of formulation and time of assessment.
A peak tissue concentration above 40 µg/ml was observed for the MR formulation, demonstrating extensive uptake of clarithromycin into lung tissue. This level is well above the minimum inhibitory concentration (MIC) values of all common community-acquired respiratory pathogens.

Clarithromycin accumulated extensively in the alveolar macrophages (AM), with AM levels approximately 100- to 600-fold higher than those in plasma and 4- to 18-fold higher than those in ELF for most subjects. While concentrations of 14(R)-hydroxy-clarithromycin in AM were not quantifiable in some subjects and were rather variable, the AM levels were generally similar for the MR and IR tablets. The concentrations in AM were greater than those in plasma, but accumulation was less for the metabolite than for parent clarithromycin.

Mechanism of Resistance
Acquired macrolide resistance in *S. pneumoniae*, *S. pyogenes*, and *S. aureus* is mediated primarily by the presence of one of two mechanisms (i.e. *erm* and *mef* or *msr*).
Ribosomal binding of the antimicrobial is prevented through methylation of the ribosome by an enzyme (*erm*). Alternatively an efflux mechanism (*mef* or *msr*) can prevent the antimicrobial from reaching its ribosomal target by pumping the antimicrobial out of the cell. No acquired resistance mechanisms have been identified in Moraxella or Haemophilus spp. Macrolide resistance mechanisms are equally effective against 14- and 15-membered macrolides including erythromycin, clarithromycin, roxithromycin, and azithromycin. The mechanisms for penicillin resistance and macrolide resistance are unrelated.

Attention should be paid to the erm-mediated cross-resistance between macrolides such as clarithromycin and lincosamides such as lincomycin and clindamycin.

Clarithromycin antagonises the bacterial effects of beta-lactam antibiotics. Also the effects of lincomycin and clindamycin are antagonised, at least *in vitro*.

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).

The prevalence of acquired resistance rates may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of an agent in at least some types of infections is questionable.

Clarithromycin has a pronounced effect against a wide variety of aerobic, anaerobic, Gram-positive, Gram-negative, and acid-resistant bacteria.
The activity of 14(R)-hydroxy-clarithromycin is greater than that of clarithromycin against *Haemophilus influenzae*. Studies done *in vitro* have suggested an additive activity of the 14(R)-hydroxy-clarithromycin and the parent molecule against *H. influenzae*.

Category 1: susceptible organisms		
Gram-positive	Gram-negative	Others
Listeria monocytogenes Clostridium perfringens Peptococcus niger Proprionibacterium acnes Streptococcus group F	Bordetella pertussis Haemophilus influenzae§ Legionella pneumophila Moraxella catarrhalis Pasteurella multocida	Borrelia burgdorferi Chlamydia pneumoniae (TWAR) Chlamydia trachomatis Mycobacterium avium Mycobacterium chelonae Mycobacterium fortuitum Mycobacterium intracellulare Mycobacterium kansasii Mycobacterium leprae Mycoplasma pneumoniae
Category 2: organisms for which acquired resistance may be problematic#		
Staphylococcus aureus (resistant or susceptible* to methicillin) + Staphylococcus coagulase negative + Streptococcus pneumoniae *+ Streptococcus pyogenes * Streptoccoccus group B, C, G Streptococcus spp.		
Category 3: intrinsic resistant organisms		
Enterobacteriaceae Non-lactose fermenting Gram negative rods		
* species against which efficacy has been demonstrated in clinical investigations (if susceptible)		
§ Breakpoints for macrolides and related antibotics were set to categorise wild type H. influenzae as intermediate.		
+ Indicates species for which a high rate of resistance (i.e. greater than 50%) has been observed in one or more area/country/region(s) of the EU		
# ≥ 10% resistance in at least one country of the European Union		

5.2 Pharmacokinetic properties

The kinetics of orally administered modified-release clarithromycin have been studied in adult humans and compared with clarithromycin 250 mg and 500 mg immediate release tablets. The extent of absorption was found to be equivalent when equal total daily doses were administered. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Based upon the finding of equivalent absorption the following *in vitro* and *in vivo* data are applicable to the modified-release formulation.

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

In vivo: Clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were found in the liver and lung tissue, where the tissue to plasma ratios reached 10 to 20.

The pharmacokinetic behaviour of clarithromycin is non-linear. In fed patients given 500 mg clarithromycin modified-release daily, the peak steady state plasma concentration of clarithromycin and its active metabolite, 14-hydroxy clarithromycin were 1.3 and 0.48 µg/ml, respectively. When the dosage was increased to 1000 mg daily, these steady-state values were 2.4 µg/ml and 0.67 µg/ml respectively. Metabolism is in the liver involving the P450 cytochrome system. Three metabolites are described: N-demethyl clarithromycin, decladinosyl clarithromycin and 14-hydroxy clarithromycin.

Elimination half-lives of the parent drug and metabolite were approximately 5.3 and 7.7 hours respectively. The apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at higher doses.

Urinary excretion accounted for approximately 40% of the clarithromycin dose.

Faecal elimination accounts for approximately 30%.

5.3 Preclinical safety data

In repeated dose studies, clarithromycin toxicity was related to dose and duration of treatment. The primary target organ was the liver in all species, with hepatic lesions seen after 14 days in dogs and monkeys. Systemic exposure levels associated with this toxicity are not known but toxic mg/kg doses were higher than the dose recommended for patient treatment.

No evidence of mutagenic potential of clarithromycin was seen during a range of *in vitro* and *in vivo* tests.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and in monkeys embryonic loss was seen but only at dose levels which were clearly toxic to the mothers.

No other toxicological findings considered to be of relevance to the dose level recommended for patient treatment have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric Acid anhydrous (E330)
Sodium Alginate (E401)
Sodium calcium alginate
Lactose Monohydrate
Povidone K30
Talc (E553b)
Stearic acid
Magnesium Stearate
Hypromellose 6cps
Macrogol 400
Macrogol 8000
Titanium Dioxide (E171)
Sorbic Acid (E200)
Quinoline yellow (dye) Aluminium Lake (E104)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the overlabelled blister and outer carton of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C
Keep in the outer carton in order to protect from light

6.5 Nature and contents of container

7 or 14 tablets in an overlabelled outer carton.

The overlabelled blisters, of PVC/PVdC, are heat sealed with 20 micron hard tempered aluminium foil and packaged in a cardboard carton with a pack insert.

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

McDowell Pharmaceuticals
4 Altona Road
Lisburn
N. Ireland
BT27 5QB

8 Parallel Product Authorisation Number

PPA1473/40/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th February 2010

10 DATE OF REVISION OF THE TEXT