IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0711/061/004
Case No: 2070934

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

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

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

Clorom, 250/5 Micromol

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 **07/09/2009** until **12/04/2011**.

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

Clorom 250 mg/5 ml granules for oral suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of the suspension contains clarithromycin 250 mg.
1 ml of the suspension contains clarithromycin 50 mg.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

White to off-white granules forming a white to off-white suspension on reconstitution with water.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of the following infections in children when caused by clarithromycin-susceptible organisms:

- Lower respiratory tract infections such as community acquired pneumonia.

- Upper respiratory tract infections such as pharyngitis or sinusitis.

- Skin and soft tissue infections of mild to moderate severity.

- Acute otitis media.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The recommended daily dose of Clarithromycin 250mg/5ml Oral Suspension in children is given in the following table and is based on an approximate 7.5mg/ kg twice daily dosing regimen. Doses up to 500 mg twice daily have been used in the treatment of severe infections.

For some children, depending on body weight, it may be more appropriate to administer the 125mg/ 5ml oral suspension.

The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition**.**

Clarithromycin 250mg/ 5ml Oral Suspension dosage in children based on body weight (kg)

*Weight (kg)**	*Approximate age in years*	*Dose in mg of clarithromycin to be given twice daily*	*Dose in ml of 250 mg/ 5 ml oral suspension to be given twice daily by pipette****	*Number of 5ml spoonfuls to be given twice daily*
8 - 11	1 - 2	62.5	1.25 **	¼ **
12 – 19	3 - 6	125	2.5	½
20 – 29	7 - 9	187.5	3.75 **	¾ **
30 - 40	10 - 12	250	5.0	1

* children < 8 kg should be dosed based on a per kg basis (approx. 7.5 mg/ kg twice daily)

** in order to avoid the need to estimate quarter teaspoonfuls, it is recommended that the 125mg/ 5ml oral suspension is used for children in these weight bands (please consult the prescribing information for the 125mg/ 5ml oral suspension for details).

*** A graduated syringe is provided with the bottle for use as a pipette (see sections 6.5 and 6.6). This enables more accurate dosing than the 5 ml spoon (also provided with the bottle) when fractions of a spoonful are needed to achieve the right dose

Renal and hepatic insufficiency

Clarithromycin should not be administered to paediatric patients with severe hepatic or renal insufficiency. Caution is required when administering clarithromycin to children with lesser degrees of renal or hepatic insufficiency.

Method of Administration

Clarithromycin Oral Suspension may be given without regard to meals, as food does not affect the extent of bioavailability.

Clarithromycin Oral Suspension should be administered twice daily as recommended in the table above. The doses should be given at 12-hour intervals.

4.3 Contraindications

Hypersensitivity to the active substance clarithromycin, to other macrolides or to an azalide antibacterial agent or to any of the excipients.

- Patients taking ergot derivatives.
- Patients taking any of cisapride, pimozide, astemizole or terfenadine. Elevated plasma levels of cisapride, pimozide and terfenadine have been reported in patients receiving concomitant clarithromycin. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides.
- Patients with congenital or documented acquired QT prolongation or with hypokalaemia (due to the risk of prolongation of QT-time).

4.4 Special warnings and precautions for use

- Clarithromycin is principally excreted by the liver and kidney. This antibiotic should not be administered to paediatric patients with hepatic or renal failure. Caution is required when administering clarithromycin to children with lesser degrees of renal or hepatic insufficiency.
- Patients who are hypersensitive to lincosamide antibacterial agents (e.g. lincomycin or clindamycin) may also be hypersensitive to clarithromycin. Therefore, caution is required when prescribing clarithromycin for such patients.
- Prolonged or repeated use of clarithromycin may result in superinfections with insusceptible organisms. In case of superinfection, clarithromycin therapy should be stopped.

- Pseudomembranous colitis has been reported with the use of broad-spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop severe diarrhoea during or after therapy with clarithromycin.
- Due to a risk of increased QT-interval, clarithromycin is contraindicated in persons with hypokalaemia, those with congenital or documented acquired QT prolongation and those taking any of the medications listed in section 4.3. Caution is needed when administering clarithromycin to patients with coronary vessel disease, a history of ventricular arrhythmia, severe cardiac insufficiency, hypomagnesaemia, bradycardia (< 50 bpm), or when co-administered with other medicinal products (other than listed in section 4.3) with a QT-prolonging effect. (see section 4.5).
- Clarithromycin should be used with caution in patients receiving treatment with an inducer of CYP3A4 (see section 4.5).
- Clarithromycin is an inhibitor of CYP3A4. Concomitant use with medicinal products that are metabolised to a large extent by this enzyme should be restricted to situations where it is clearly indicated (see section 4.5).
- Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products (see section 4.5).
- As with other macrolides, clarithromycin may cause exacerbation or aggravation of myasthenia gravis.
- Each 5 ml of Clarithromycin Oral Suspension contains approximately 3g of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- Each 5ml of Clarithromycin Oral Suspension also contains approximately 20 mg of aspartame, which is source of phenylalanine. The suspension should not be administered to children with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

<u>The effect of other medicinal products on Clarithromycin suspension</u>
Clarithromycin is metabolised by the enzyme CYP3A4. Hence, strong inhibitors of this enzyme may inhibit the metabolism of clarithromycin, resulting in increased plasma concentrations.

Ritonavir (200 mg three times daily) has been shown to inhibit the metabolism of clarithromycin (500 mg twice daily), with an increase in C_{max}, C_{min} and AUC of 31, 182 and 77%, respectively. Formation of the active 14-OH-hydroxy metabolite was almost completely inhibited. A general dose reduction is probably not required in patients with normal renal function, but the daily dose of clarithromycin should not exceed 1 g. Dose reduction should be considered in patients with renal impairment. For patients with a creatinine clearance of 30 to 60 ml/min, the clarithromycin dose should be reduced by 50%, and at a creatinine clearance of < 30 ml/min the dose should be reduced by 75%.

Products that are inducers of CYP3A4 (e.g. rifampicin, rifabutin phenytoin, carabamazepine, phenobarbital, St. John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to a reduced efficacy. It might be necessary to increase the dose of clarithromycin and monitor the efficacy and safety of clarithromycin carefully. Furthermore monitoring the plasma levels of the CYP3A4 inducer might be necessary because the latter could be increased owing to the inhibition of CYP3A4 by clarithromycin (see also the relevant product information for the CYP3A4 inducer administered).

Concomitant administration of rifabutin and clarithromycin resulted in an increase and decrease, respectively, in serum level, followed by an increased risk of uveitis.

A 39% reduction in AUC for clarithromycin and a 34% increase in AUC for the active 14-OH-hydroxy metabolite have been seen when clarithromycin was used concomitantly with the CYP3A4 inducer efavirenz.

<u>Omeprazole and ranitidine</u>
Although the plasma concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no adjustment to the dosage is necessary. At the dosages recommended, there is no clinically significant interaction between clarithromycin and lansoprazole. Increased plasma concentrations of clarithromycin may also occur when it is co-administered with antacids or ranitidine. No adjustment to the dosage is necessary.

The effect of Clarithromycin suspension on other medicinal products
Clarithromycin is an inhibitor of the metabolising enzyme CYP3A4 and the transport protein P-glycoprotein. The degree of inhibition with different CYP3A4 substrates is difficult to predict. Hence, clarithromycin should not be used during treatment with other medicinal products that are substrates for CYP3A4, unless plasma levels, therapeutic effect or adverse events of the CYP3A4 substrate can be closely monitored. During therapy with clarithromycin, dose reduction or interruption of therapy with medicinal products that are substrates for CYP3A4 may be necessary.

Ergot vasoconstrictors (e.g. dihydroergotamine, ergotamine)
Cases of ergotism due to increased plasma levels of ergot alkaloids have been reported when these products have been co-administered with macrolides. The combination is contraindicated (see section 4.3).

Medicinal products with a potential to prolong QT-interval
Clarithromycin has been reported to inhibit the metabolism of cisapride and terfenadine, with a 2 to 3-fold increase in plasma levels reported for terfenadine. This has been associated with QT-prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar symptoms have been described for patients treated with pimozide when combined with clarithromycin. Concomitant administration of clarithromycin and terfenadine, cisapride or pimozide is contraindicated (see section 4.3)

Cases with torsades de pointes have been reported in patients where clarithromycin has been co-administered with quinidine or disopyramide. These combinations should therefore be avoided or plasma levels of quinidine or disopyramide should be closely monitored to allow dose adjustment.

Caution is warranted when clarithromyin is administered to patients who are taking other medicinal products with the potential to prolong QT interval (see section 4.4).

HMG-CoA reductase inhibitors
Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products. Rhabdomyolysis in association with increased plasma concentrations of HMG-CoA reductase inhibitors has been reported rarely in patients treated with clarithromycin and simvastatin or lovastatin. Clarithromycin may produce a similar interaction with atorvastatin. Patients should be monitored for signs and symptoms of myopathy during co-administration of clarithromycin with these HMG Co-A reductase inhibitors.

Benzodiazepines
When midazolam was co-administered with clarithromycin tablets (250 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 CYP3A4, especially triazolam and alprazolam. For benzodiazepines that are not metabolised by CYP3A4 (temazepam, nitrazepam, lorazepam) an interaction with clarithromycin is unlikely.

Ciclosporin, tacrolimus and sirolimus
Concomitant use of oral clarithromycin and ciclosporin or tacrolimus have resulted in more than a 2-fold increase of the C_{min}-levels of both ciclosporin and tacrolimus. Similar effects are also expected for sirolimus. When initiating treatment with clarithromycin in patients already receiving any of these immunosuppressive agents, plasma levels of ciclosporin, tacrolimus or sirolimus must be closely monitored and the dose decreased as necessary. When clarithromycin is discontinued in these patients, close monitoring of plasma levels of ciclosporin, tacrolimus or sirolimus, is again necessary to guide dose adjustment.

Digoxin and other active substances transported by P-glycoprotein
Clarithromycin is a potent inhibitor of the transport protein P-glycoprotein (Pgp). This could give rise to increased plasma concentrations of active substances that are transported by this mechanism and may also increase their distribution to organs having Pgp as a distribution barrier e.g. CNS. The plasma concentration of digoxin may be increased when co-administered with clarithromycin and monitoring of plasma levels should be considered when co-treatment with clarithromycin is initiated or terminated since a dose adjustment may be warranted.

Warfarin
The use of clarithromycin in patients receiving warfarin may result in potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients.

Theophylline
The administration of clarithromycin to patients who are receiving theophylline has been associated with an increase in serum theophylline levels and potential theophylline toxicity.

Zidovudine
Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV infected adult patients may result in decreased steady-state zidovudine levels. This can be largely avoided by staggering the doses of clarithromycin and zidovudine by 1-2 hours. No such reaction has been reported in children.

4.6 Pregnancy and lactation

Pregnancy
Data on the use of clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects, or of adverse effects on the health of the neonate. Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of abortions. To date no other relevant epidemiological data are available.

Data from animal studies have shown reproductive toxicity (see section 5.3). The risk for humans is unknown. Clarithromycin should not be given to pregnant women unless it is clearly needed.

Lactation
Clarithromycin and its active metabolite are excreted in breast milk. Therefore, diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be born in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When performing these activities the possible occurrence of dizziness, vertigo, confusion and disorientation (see section 4.8) should be taken into account.

4.8 Undesirable effects

The most frequently reported events in adults taking clarithromycin tablets were diarrhoea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%).

In this section undesirable effects are defined as follows:
Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Infections and infestations
Common: Oral monilia
As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.

Blood and the lymphatic system disorders
Uncommon: Decreased leukocyte levels
Very rare: Thrombocytopenia

Immune system disorders
Uncommon: Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis.

Psychiatric disorders
Very rare: Anxiety, insomnia, hallucinations, psychosis, disorientation, depersonalisation, bad dreams and confusion.

Nervous system disorders
Common: Headache, smell alteration.
Very rare: Dizziness, vertigo, paraesthesia, convulsions.

Ear and labyrinth disorders
Rare: Tinnitus
Very rare: Reversible hearing loss

Cardiac disorders
Very rare: QT prolongation, ventricular tachycardia and Torsade de Pointes.

Gastrointestinal disorders
Common: Nausea, diarrhoea, vomiting, abdominal pain, dyspepsia, stomatitis, glossitis, reversible tooth and tongue discoloration, and taste perversion, i.e. metallic or bitter taste.

Very rare: Pancreatitis. Pseudomembranous colitis has been reported very rarely with clarithromycin, and may range in severity from mild to life threatening.

Hepato-biliary disorders
Uncommon: Hepatic dysfunction, which is usually transient and reversible, hepatitis and cholestasis with or without jaundice.
Very rare: Fatal hepatic failure has been reported particularly in patients with pre-existing liver disease or taking other hepatotoxic medicinal products.

Skin and subcutaneous tissue disorders
Very rare: Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders
Uncommon: Arthralgia, myalgia.

Renal and urinary disorders
Very rare: Interstitial nephritis, renal failure.

Investigations
Common: Elevated blood urea nitrogen
Uncommon: Prolongation of prothrombin time, elevated serum creatinine, altered liver function tests (increased transaminase levels).
Very rare: Hypoglycaemia has been observed especially after concomitant administration with antidiabetic medicinal products and insulin

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, hypokalemia and hypoxemia. Adverse reactions accompanying overdosage should be treated by gastric lavage and general 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

Pharamacotherapeutic group: macrolides
ATC Code: J01FA09

General properties

Mode of action
Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppressing protein synthesis. The 14-hydroxy metabolite of clarithromycin, formed in man by first pass metabolism, also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Mechanisms of resistance

Resistance of gram-positive organisms to the macrolides usually involves an alteration of the antimicrobial binding site. The MLS_B type of resistance, which may be constitutive or induced by exposure to certain macrolides in staphylococci and which is inducible in streptococci, is mediated by a variety of acquired genes (*erm* family) encoding methylases targeted at the peptidyl transferase centre of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides and type B streptogramins but not to type A streptogramins. Less frequent mechanisms of resistance include antimicrobial degradation by inactivating enzymes such as esterase and active efflux of the antimicrobial from the bacteria.

Gram negative organisms may be intrinsically resistant to the macrolides because of the inability of the macrolide to effectively penetrate the outer cell membrane; macrolides having a better penetration may have activity against some gram-negative organisms.

Gram-negative organisms may also produce ribosomal methylase or macrolide inactivating enzymes.

Breakpoints
The following MIC breakpoints, separating susceptible (S) from resistant (R) organisms are suggested:

BSAC recommendations:
For staphylococci, streptococci and M. catarrhalis: S: ≤0.5 mg/L, R: ≥1.0 mg/L
For H. influenzae: S: ≤0.5 mg/L, R: ≥32.0 mg/L

NCCLS recommendations:
For staphylococci: S: ≤2.0 mg/L, R: ≥8.0 mg/L
For streptococci: S: ≤0.25 mg/L, R: ≥1.0 mg/L
For H. influenzae: S: ≤8.0 mg/L, R: ≥32.0 mg/L

Susceptibility
The prevalence of acquired resistance 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 the agent in at least some types of infections is questionable.

The susceptibility pattern of various micro-organisms to clarithromycin is presented below:

Commonly susceptible species
Aerobic Gram-negative microorganisms
Moraxella catarrhalis
Anaerobic microorganisms
Peptococcus species
Peptostreptococcus species
Propionibacterium acnes
Clostridium perfringens
Other microorganisms
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus
Staphylococcus aureus (methicillin-resistant)*
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Aerobic Gram-negative microorganisms
Haemophilus influenzae

* Resistance to macrolides among MRSA is commonly more than 50% in the EU and affects nearly all strains in some areas.

5.2 Pharmacokinetic properties

Absorption:
Clarithromycin is rapidly and well absorbed from the gastrointestinal tract – primarily in the jejunum - but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250-mg clarithromycin tablet is approximately 50%. The bioavailability of the suspension is identical to or slightly higher than the bioavailability of the tablets. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin may be given without regard to food. Due to its chemical structure (6-O-Methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid.

Peak plasma levels of 1 – 2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 µg/ml. The pharmacokinetic profile of the suspension in children corresponds to the pharmacokinetic profile of the suspension in adults. In children the following steady-state parameters were observed after the ninth dose in a dose regimen of 7,5 mg/kg twice daily on average for clarithromycin: C_{max} 4,60 µg/ml, AUC 15,7 µg.hour/ml and T_{max} 2,8 hours. The corresponding average values for the 14-OH metabolite were respectively:1.64 µg/ml, 6,69 µg.hour/ml and 2,7 hours.

After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of 0.6 µg/ml. Steady state is attained within 2 days of dosing.

Distribution:
Clarithromycin penetrates well into different compartments, with an estimated volume of distribution of 200-400 L Clarithromycin provides concentrations in some tissues that are several times higher than the circulating level of the active substance. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus.

Clarithromycin is approximately 80% bound to plasma proteins at therapeutic levels.

Biotransformation and elimination:
Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism involves mainly N-dealkylation, oxidation and stereospecific hydroxylation at position C 14.

The pharmacokinetics of clarithromycin is non-linear due to saturation of hepatic metabolism at high doses. Elimination half-life increased from 2-4 hours following administration of 250 mg clarithromycin twice daily to 5 hours following administration of 500 mg clarithromycin twice daily. With a 250 mg every 12 hours dosing, the half-life of the active 14-hydroxy metabolite ranges between 5 to 6 hours.

After oral administration of radioactive clarithromycin 70 - 80% of the radioactivity was found in the faeces. Approximately 20 -30% of clarithromycin appears as the unchanged active substance in the urine. This proportion is increased when the dose is increased. Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased.

Total plasma clearance has been estimated to approximately 700 ml/min, with a renal clearance of approximately 170 ml/min.

Renal impairment: Reduced renal insufficiency function results in increased plasma levels of clarithromycin and the active metabolite levels in plasma.

5.3 Preclinical safety data

The acute oral LD50 values for a clarithromycin suspension administered to 3-day old mice were 1290 mg/kg for males and 1230 mg/kg for females. The LD50 values in 3-day old rats were 1330 mg/kg for males and 1270 mg/kg for females. For comparison, the LD50 of orally-administered clarithromycin is about 2700 mg/kg for adult mice and about 3000 mg/kg for adult rats. These results are consistent with other antibiotics of the penicillin group, cephalosporin group and macrolide group in that the LD50 is generally lower in juvenile animals than in adults.

In both mice and rats, body weight was reduced or its increase suppressed and suckling behaviour and spontaneous movements were depressed for the first few days following drug administration. Necropsy of animals that died disclosed dark-reddish lungs in mice and about 25% of the rats; rats treated with 2197 mg/kg or more of a clarithromycin suspension were also noted to have a reddish - black substance in the intestines, probably because of bleeding. Deaths of these animals were considered due to debilitation resulting from depressed suckling behaviour or bleeding from the intestines.

Pre-weaning rats (5 days old) were administered a clarithromycin suspension formulation for two weeks at doses of 0, 15, 55 and 200 mg/kg/day. Animals from the 200 mg/kg/day group had decreased body-weight gains, decreased mean haemoglobin and haematocrit values, and increased mean relative kidney weights compared to animals from the control group. Treatment-related minimal to mild multifocal vacuolar degeneration of the intrahepatic bile duct epithelium and an increased incidence of nephritic lesions were also observed in animals from this treatment group. The "no-toxic effect" dosage for this study was 55 mg/kg/day.

An oral toxicity study was conducted in which immature rats were administered a clarithromycin suspension (granules for suspension) for 6 weeks at daily dosages of 0, 15, 50 and 150 mg base/kg/day. No deaths occurred and the only clinical sign observed was excessive salivation for some of the animals at the highest dosage from 1 to 2 hours after administration during the last 3 weeks of treatment. Rats from the 150 mg/kg dose group had lower mean body weights during the first three weeks, and were observed to have decreased mean serum albumin values and increased mean relative liver weight compared to the controls. No treatment-related gross or microscopic histopathological changes were found. A dosage of 150 mg/kg/day produced slight toxicity in the treated rats and the "no effect dosage" was considered to be 50 mg/kg/day.

Juvenile beagle dogs, 3 weeks of age, were treated orally daily for four weeks with 0, 30, 100, or 300 mg/kg of clarithromycin, followed by a 4-week recovery period. No deaths occurred and no changes in the general condition of the animals were observed. Necropsy revealed no abnormalities. Upon histological examination, fatty deposition of centrilobular hepatocytes and cell infiltration of portal areas were observed by light microscopy and an increase in hepatocellular fat droplets was noted by electron microscopy in the 300 mg/kg dose group.

The toxic dose in juvenile beagle dogs was considered to be greater than 300 mg/kg and the "no effect dose" 100 mg/kg.

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 oestrus cycle, fertility, parturition and number and viability of offspring. Two teratogenicity studies in both Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.) rats, one study in New Zealand white rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Hypromellose
Hyprolose
Croscarmellose sodium
Alginic acid
Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%
Macrogol 1500
Talc
Carbomer (Carbopol 974 P)
Colloidal anhydrous silica
Sucrose
Aspartame (E951)
Xanthan gum
Monosodium citrate
Sodium benzoate (E211)
Titanium dioxide (E171)
Peppermint flavour
Tutti frutti flavour
Sodium chloride

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 years (granules),
14 days (reconstituted suspension)

6.4 Special precautions for storage

Granules: No special requirements for storage.

Reconstituted suspension: Do not store above 25°C. Do not refrigerate or freeze. Keep the bottle tightly closed.

6.5 Nature and contents of container

Natural translucent HDPE bottle white, opaque, child resistant cap having induction seal liner

Or

Natural translucent HDPE bottle with continuous ring mark for filling volume and white, opaque, child resistant cap having induction seal liner.

Natural translucent PP/HDPE dosing pipette having filling marks for weight and volume and LDPE cap adapter.

Transparent polystyrene measuring spoon with fill marks at 2.5ml and 5.0ml

Pack Size – 50, 60, 70, 100 or 140 ml.
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

Preparation for use:
Required quantity of water should be added to the granules in the bottle and shaken well. The concentration of clarithromycin in the reconstituted suspension is 125 mg per 5 ml.

The quantity of water required for each pack is tabulated below:

Pack	**Volume of water to be added**
50 ml Bottle	28ml
60 ml Bottle	34 ml
70 ml Bottle	40 ml
100 ml Bottle	55 ml
140 ml Bottle	80 ml

After reconstitution with water, the product results in a white to off-white suspension.

7 MARKETING AUTHORISATION HOLDER

ROWEX LTD
Bantry
Co Cork

8 MARKETING AUTHORISATION NUMBER

PA 711/61/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13th April 2006

10 DATE OF REVISION OF THE TEXT