

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clonocid 250mg/5ml granules for oral suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml reconstituted oral suspension contains 50 mg clarithromycin.
5 ml reconstituted oral suspension contains 250 mg clarithromycin.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Granules for oral suspension.
White to off-white granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Streptococcal tonsillitis, otitis media, skin and soft tissue infections of mild to moderate severity in penicillin hypersensitive patients or in cases where penicillin is inappropriate for other reasons. Available data on epidemiological resistance to macrolide antibiotics should be considered.

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

4.2 Posology and method of administration

General:

The dosage of Clarithromycin depends on the clinical condition of the patient and has to be defined in any case by the physician.

The usual dose in children aged 6 months or older is 7.5 mg/kg twice daily.

Recommendations for dosage:

Weight	Age	Dosage
12-19 kg	2-4 years	2.5 ml twice daily
20-29 kg	4-8 years	3.75 ml twice daily
30-40 kg	8-12 years	5 ml twice daily

“Children < 8 kg should be dosed on a per kg basis (approx. 7.5mg/kg twice daily) which is equal to 0.15 ml of ready to use suspension per kg body weight.”

Dosage in renal functional impairment:

Dosage adjustment is not usually required except in patients with severe renal impairment (creatinine clearance < 30 ml/min). If adjustment is necessary, the total daily standard dosage should be reduced by half. Treatments should not be continued beyond 14 days in these patients.

Duration of therapy:

The duration of therapy with Clarithromycin depends on the clinical condition of the patient. The duration of therapy has in any case to be determined by the physician.

- The usual duration of treatment is 6 to 14 days.
- Therapy should be continued at least for two days after symptoms have subsided.
- In *Streptococcus pyogenes* infections the duration of therapy should be at least 10 days in order to prevent complications such as rheumatic fever and glomerulonephritis.

Method of administration:

Clarithromycin may be given irrespective of food intake (*see section 5.2*).

Preparation for use:

Before administration the granules must be reconstituted with water, *see section 6.6*. For administration after reconstitution an oral syringe or a measuring spoon are used.

4.3 Contraindications

- Clarithromycin should not be used in patients with hypersensitivity to clarithromycin, to other macrolides or to any of the excipients.
- Clarithromycin and ergot derivatives should not be co-administered.
- Concomitant administration of clarithromycin and any of the following active substances is contraindicated: cisapride, pimozone and terfenadine. Elevated cisapride, pimozone and terfenadine levels have been reported in patients receiving either of these active substances and clarithromycin concomitantly. 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 (*see section 4.5*).
- Clarithromycin should not be administered to hypokalemic patients (prolongation of QT-time).
- Clarithromycin should not be used concomitantly with simvastatin or atorvastatin. Treatment with any of these agents should be interrupted during clarithromycin treatment (*see section 4.5*).

4.4 Special warnings and precautions for use

- Clarithromycin is mainly excreted by the liver. Therefore, caution should be taken in administering clarithromycin to patients with impaired hepatic function.
- When renal function is poor, dosage of Clarithromycin should be suitably reduced depending on the degree of the impairment (*see section 4.2*). In elderly patients, the possibility of renal impairment should be considered.
- Patients who are hypersensitive to other macrolides, clindamycin and lincomycin may also be hypersensitive to Clarithromycin. Therefore caution is required when prescribing clarithromycin for such patients.
- 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. Clarithromycin treatment should be stopped and an adequate therapy should be started. Anti-peristaltics are contraindicated.
- *Prolonged or repeated use of clarithromycin may result in superinfections with insusceptible organisms.* In case of superinfection, clarithromycin therapy should be stopped.
- Due to a risk of increased QT-interval, clarithromycin should be used with caution in patients with a coronary vessel disease, a history of ventricular arrhythmia, severe cardiac insufficiency, non-compensated hypokalemia and/or hypomagnesaemia, bradycardia (< 50 bpm), or when co-administered with other medicinal products with a QT-prolonging effect. Clarithromycin should not be used in patients with congenital or documented acquired QT prolongation (*see section 4.5*).
- Clarithromycin should be used with caution whenever indicated for use in patients receiving treatment with an inducer of CYP3A4 due to the possibility of subtherapeutic levels of clarithromycin (*see section 4.5*).
- Clarithromycin is an inhibitor of CYP3A4, and concomitant use with other 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 known for other macrolides clarithromycin may cause exacerbation or aggravation of Myasthenia gravis and should therefore be used with caution in patients with Myasthenia gravis.
- This medicinal product contains a source of phenylalanine. May be harmful for people with phenylketonuria.
- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- This medicinal product contains 2.51 g sucrose per 5 ml. This should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

The effect of Clarithromycin granules for oral 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. A dose reduction may be necessary for medicinal products that are substrates for CYP3A4 if co-administered with clarithromycin. Alternatively, treatment with these products may be interrupted during clarithromycin treatment.

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 has 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 closely monitored to allow dose adjustment.

Caution is warranted when clarithromycin is administered to patients treated taking other medicinal products with the potential to prolong QT (*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 have in rare cases been reported in patients treated with clarithromycin and simvastatin. Clarithromycin may produce a similar interaction with atorvastatin and a lesser interaction with cerivastatin.

Clarithromycin should not be used concomitantly with simvastatin and atorvastatin. Treatment with any of these agents should be interrupted during clarithromycin treatment (*see section 4.3*). When treatment with clarithromycin is indicated in patients receiving treatment with cerivastatin patients should be monitored for signs and symptoms of myopathy.

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*).

Benzodiazepines

When midazolam was co-administered with clarithromycin tablets (250 mg twice daily), midazolam AUC (area under the plasma curve) 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 but also alprazolam. For benzodiazepines which 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} (minimal plasma concentration)-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, ciclosporin, tacrolimus or sirolimus plasma levels must be closely monitored and their doses 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

The concentration of digoxin may be increased when co-administered with clarithromycin. Monitoring of plasma levels of digoxin should be considered when co-treatment with clarithromycin is initiated or terminated since a dose adjustment may be warranted.

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 (Human Immunodeficiency Virus) 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.

The effect of other medicinal products on Clarithromycin granules for oral suspension

Clarithromycin is metabolised by the enzyme CYP3A4. Hence, strong inhibitors of this enzyme may inhibit the metabolism of clarithromycin, resulting in increased plasma concentrations of clarithromycin.

Although the plasma concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no adjustment to the dosage is necessary. Increased plasma concentrations of clarithromycin may also occur when it is co-administered with antacids or ranitidine. No adjustment to the dosage is necessary.

Ritonavir (200 mg three times daily) have been shown to inhibit the metabolism of clarithromycin (500 mg twice daily), with an increase in C_{max} (maximal plasma concentration), C_{min} and AUC of 31, 182 and 77%, respectively, when co-administered with ritonavir. Formation of the active 14- 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 with 50%, and at a creatinine clearance of < 30 ml/min the dose should be reduced with 75%.

Products that are inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St. Johns wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to a reduced efficacy. When clarithromycin is clearly indicated 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 levels, followed by an increased risk of uveitis.

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

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 only be given to pregnant women after a careful benefit/risk assessment.

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

There are no data available on the effect of clarithromycin on the ability to drive or use machines. When performing these activities the possible occurrence of the adverse reactions dizziness, vertigo, confusion and disorientation should be taken into account.

4.8 Undesirable effects

The most frequently reported events in adults taking clarithromycin granules for oral suspension 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 (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated reports.

Infections and infestations

Common: Oral monilia

Prolonged use may result in the overgrowth of non-susceptible organisms.

Blood and the lymphatic system disorders

Uncommon: Decreased leucocyte 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 Torsades 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 BUN (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*Symptoms of intoxication:*

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Symptoms of overdose may largely correspond to the profile of adverse reactions. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

Therapy of intoxication:

There is no specific antidote on overdose. Serum levels of clarithromycin cannot be reduced by haemodialysis or peritoneal dialysis.

Adverse reactions accompanying overdose should be treated by gastric lavage and supportive measures. Severe acute allergic reactions may be seen very rarely, e.g. anaphylactic shock. At first signs of hypersensitivity reactions therapy with clarithromycin must be discontinued and the required measures should be initiated immediately.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Macrolides

ATC code J01FA09.

Mechanism of action:

Clarithromycin exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. 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 two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin 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.

Breakpoints:

According to the NCCLS (US National Committee on Clinical Laboratory Standards) in January 2004 the following breakpoints have been defined for Clarithromycin:

NCCLS: *Staphylococcus* spp.: $S \leq 2 \mu\text{g/ml}$, $R \geq 8 \mu\text{g/ml}$
 Haemophilus spp.: $S \leq 8 \mu\text{g/ml}$, $R \geq 32 \mu\text{g/ml}$
 Streptococcus pneumoniae: $S \leq 0.25 \mu\text{g/ml}$, $R \geq 1 \mu\text{g/ml}$
 Streptococcus spp. other than *S. pneumoniae*: $S \leq 0.25 \mu\text{g/ml}$, $R \geq 1 \mu\text{g/ml}$
 Helicobacter pylori: $S \leq 0.25 \mu\text{g/ml}$, $R \geq 1 \mu\text{g/ml}$

SRGA (Swedish Reference Group of Antibiotics): other relevant micro-organisms (i.e. *Moraxella*, *Enterococci*, *Bordetella*, *Chlamydia*, *Mycoplasma*, *Legionella* and *Mycobacterium*): $S \leq 0.5 \mu\text{g/ml}$, $R \geq 8.0 \mu\text{g/ml}$

Susceptibility:

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an appropriate guidance on the probabilities whether micro-organisms will be susceptible to clarithromycin or not. As far as applicable the information on the European range of acquired resistance for the individual micro-organism is indicated in brackets.

Species	Frequency of resistance ranges in EU (if >10 %) (extreme values)
<u>Commonly susceptible species</u> Gram-positive aerobes Group C, F, G Streptococci Corynebacterium diphtheriae Gram-negative aerobes <i>Legionella</i> spp. <i>Moraxella catarrhalis</i> * <i>Pasteurella multocida</i> Anaerobes <i>Bacteroides</i> spp. <i>Clostridium</i> spp. other than <i>C. difficile</i> <i>Fusobacterium</i> spp. <i>Peptococcus/Peptostreptococcus</i> spp. Others <i>Chlamydia trachomatis</i> <i>Chlamydia pneumoniae</i> * <i>Mycoplasma pneumoniae</i> *	
<u>Species for which acquired resistance may be a problem</u> Gram-positive aerobes <i>Staphylococcus aureus</i> * methicillin-susceptible Group A,B Streptococci (beta-hemolytic) <i>Streptococcus pneumoniae</i> + Gram-negative aerobes <i>Haemophilus influenzae</i> *	(18.1%) (21,4 %) (37.8%)
<u>Inherently resistant organisms</u> Gram-positive aerobes <i>Enterococcus</i> spp. <i>Staphylococcus aureus</i> (Erythromycin resistant or MRSA)	

+ comments regarding resistance see below

Other information:
Susceptibility and resistance of *Streptococcus pneumoniae* and *Streptococcus* spp. to clarithromycin can be predicted by testing erythromycin.
The mechanisms of acquired resistance in macrolides are: efflux of active substance by an active pump mechanism, inducible or constitutive production of a methylase enzyme that modifies the ribosomal target, hydrolysis of macrolides by esterases, chromosomal mutations that alter a 50s ribosomal protein. Cross-resistance between clarithromycin and other macrolides and clindamycin and lincomycin may therefore occur. Methicillin-resistant staphylococcus aureus (MRSA) and penicillin-resistant pneumococci are resistant to all currently available beta-lactam antibiotics and macrolides such as clarithromycin.

5.2 Pharmacokinetic properties

Absorption:

Clarithromycin has a significant first-pass metabolism. Its absolute bioavailability is about 55%, and concurrent food intake does not affect it. Plasma peak concentrations occur in about 2 hours after administration. The elimination kinetics are dose-dependent (non-linear). At a dosage of 7.5 mg/kg/bodyweight in the morning and the evening, plasma peak concentrations in steady state after 5 days of treatment are about 4.6 mg/l. Protein binding is 70%.

Distribution:

Clarithromycin is highly lipophilic, and its distribution volume is 200-400 l. Clarithromycin easily penetrates tonsillar tissue and middle ear secretions, where twofold concentrations compared to plasma have been found.

Biotransformation and elimination:

Clarithromycin is metabolised in the liver by hydroxylation and demethylation. The half-life of the active 14-hydroxy metabolite (about 75% of clarithromycin activity) is about 5 h, and plasma peak concentration 0.6 mg/l. About 20% of the dose is excreted renally as unchanged clarithromycin; the proportion increases with increasing dose. The hydroxy metabolite is metabolised and excreted in the feces. The calculated plasma clearance is about 700 ml/min and renal clearance about 170 ml/min. In renal failure, clarithromycin levels are elevated in plasma.

Severe hepatic failure lowers hydroxy metabolite concentrations because of an impaired capacity for metabolism.

Special populations:

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

In 4-week-studies in animals, toxicity of clarithromycin was found to be related to the dose and to the duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The systemic levels of exposure, related to this toxicity, are not known in detail, but toxic doses (300 mg/kg/day) were clearly higher than the therapeutic doses recommended for humans. Cardiovascular malformations were observed in rats treated with doses of 150 mg/kg/d.

No mutagenic effects were found in in-vitro and in-vivo studies with clarithromycin. Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (iv) and x10 the clinical dose in monkey (po) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. In mouse at doses x70 the clinical dose cleft palate occurred at varying incidence (3-30%).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Coated granules:

Hypromellose
Microcrystalline cellulose
Hydroxypropyl cellulose
Croscarmellose sodium
Alginic acid
Metacrylic acid-ethylene-acrylate copolymer (1:1) dispersion 30 per cent
Macrogol 1500
Talc
Carbomer

Other ingredients:

Sucrose
Aspartame (E951)
Xanthan gum
Silica colloidal anhydrous
Monosodium citrate
Sodium benzoate (E211)
Titanium dioxide (E171)
Sodium chloride
Flavouring tutti frutti
Flavouring pepper mint

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years
Ready-to-use suspension: 14 days.

6.4 Special precautions for storage

Do not refrigerate or freeze.
Keep the bottle tightly closed.

6.5 Nature and contents of container

Package: HDPE bottle with child resistant PP cap having induction seal liner.
Package sizes: 50, 60, 70, 100, 140 ml.

The package includes an oral syringe with a 5 ml scale graduated in steps of 0.25 ml on one side of the scale and marked at 2.5/3.75/5 ml with the corresponding body weight-range in kg on the other side of the scale and/or a measuring spoon for 2.5 ml and 5 ml doses.

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:*

The bottle has to be knocked gently, until all granules move freely. For preparation of the ready-to-use suspension the water has to be added until the mark of the bottle (if applicable) or by addition of the mentioned volume of water in two lots. After each addition the suspension should be shaken vigorously. After reconstitution with water the medicinal product results in an off-white suspension.

Preparation of the ready-to-use suspension if there is no mark:

50 ml bottle: 28 ml of purified water should be added to the granules in the bottle in two lots to yield 50 ml of reconstituted suspension. After each addition the suspension should be shaken vigorously.

60 ml bottle: 34 ml of purified water should be added to the granules in the bottle in two lots to yield 60 ml of reconstituted suspension. After each addition the suspension should be shaken vigorously.

70 ml bottle: 40 ml of purified water should be added to the granules in the bottle in two lots to yield 70 ml of reconstituted suspension. After each addition the suspension should be shaken vigorously.

100 ml bottle: 55 ml of purified water should be added to the granules in the bottle in two lots to yield 100 ml of reconstituted suspension. After each addition the suspension should be shaken vigorously.

140 ml bottle: 77 ml of purified water should be added to the granules in the bottle in two lots to yield 140 ml of reconstituted suspension. After each addition the suspension should be shaken vigorously.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0126/136/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 April 2005

10 DATE OF REVISION OF THE TEXT

July 2005