PRESENTATION

Proprietary name and description
Clarithromycin 500 mg Powder for Concentrate for Solution for Infusion is a lyophilised powder appearing as a white, or almost white, uniform, porous cake. Each vial contains Clarithromycin Ph Eur 500 mg blended with lactobionic acid as a solubilizing agent. The powder is reconstituted with water for injection prior to use.

Clarithromycin 500 mg Powder for Concentrate for Solution for Infusion is packaged in a 30 ml vial composed of clear type II glass, closed with a bromobutyl stopper especially designed for lyophilised products and sealed with a tamper-proof aluminium flip-off cap.

USES

Pharmacotherapeutic group
ATC7: J01FA09 - Macrolides

Actions
Clarithromycin is a semi-synthetic macrolide antibiotic obtained by methoxy substitution of the hydroxyl group in the erythromycin lactonic ring at position 6. Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible bacteria and suppresses protein synthesis.

The principal metabolite of clarithromycin in man and other primates is a microbiologically-active metabolite, 14-hydroxyclarithromycin. This metabolite is as active or 1 to 2 fold less active than the parent compound for most organisms, except for H. influenzae against which it is twice as active. The parent compound and the 14-hydroxy metabolite exert either an additive or synergistic effect on H. influenzae in vitro and in vivo, depending on bacterial strains.

Clarithromycin was found to be 2 to 10 times more active than erythromycin in several experimental animal infection models. It was shown, for example, to be more effective than erythromycin in mouse systemic infection, mouse subcutaneous abscess, and mouse respiratory tract infections caused by S. pneumoniae, S. aureus, S. pyogenes, and H. influenzae. In guinea pigs with Legionella infection this effect was more pronounced; an intraperitoneal dose of 1.6 mg/kg/day of clarithromycin was more effective than 50 mg/kg/day of erythromycin.

Microbiology
Clarithromycin has demonstrated excellent in vitro activity against both standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms. In vitro and in vivo data show that this antibiotic has activity against clinically significant mycobacterial species.

In vitro data also indicate clarithromycin has excellent activity against Legionella pneumophila, Mycoplasma pneumoniae, and Helicobacter (Campylobacter) pylori. Clarithromycin is bactericidal to Helicobacter pylori, with activity greater at neutral pH than at acid pH.
The minimum inhibitory concentrations (MICs) of clarithromycin are generally one log (base 2) dilution more potent than the MICs of erythromycin.

Beta-lactamase production should have no effect on clarithromycin activity.

The in vitro data indicate Enterobacteriaceae, pseudomonas species and other non-lactose fermenting Gram-negative bacilli are not sensitive to clarithromycin.

Clinical and in vitro susceptibility demonstrated

Clarithromycin has been shown to be active against most strains of the following pathogens both in vitro and when present in clinical infections listed in the Indications section:

Gram-positive aerobes - Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Listeria monocytogenes; Gram-negative aerobes - Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Legionella pneumophila; Mycobacteria - Mycobacterium leprae, Mycobacterium kansasi, Mycobacterium chelonae, Mycobacterium fortuitum, Mycobacterium avium complex (MAC) consisting of Mycobacterium avium and Mycobacterium intracellulare; Other microorganisms - Mycoplasma pneumoniae, Chlamydia pneumoniae (TWAR), Helicobacter pylori. In cultures performed prior to therapy, H. pylori was isolated and clarithromycin MIC’s were determined pre-treatment in 104 patients. Of these, four patients had resistant strains, two patients had strains with intermediate susceptibility, and 98 patients had susceptible strains.

NOTE: Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

In vitro susceptibility demonstrated

The following in vitro data are available, but their clinical significance is unknown. Clarithromycin exhibits in vitro activity against most strains of the following microorganisms:

Gram-positive aerobes - Streptococcus agalactiae, Streptococci (Groups C, F, G), Viridans group streptococci; Gram-negative aerobes - Bordetella pertussis, Pasteurella multocida; Gram-positive anaerobes - Clostridium perfringens, Peptococcus niger, Propionibacterium acnes; Gram-negative anaerobes - Bacteroides melaninogenicus; Spirochetes - Borrelia burgdorferi, Treponema pallidum; Campylobacter - Campylobacter jejuni.

However, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Susceptibility test

Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of bacteria to antimicrobial agents. One recommended procedure uses discs impregnated with 15 mcg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC values for clarithromycin. The MIC's are determined by the broth or agar dilution method. The recommended test medium for susceptibility testing of Haemophilus influenzae according to the National Committee of Clinical Laboratory Standards (NCCLS) is the Haemophilus Test Medium (H.T.M.). The correlation of disc inhibition zone diameters with MIC’s is given in Table 1.


Table 1: Clarithromycin interpretive standards

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Inhibition zone diameter (mm)</th>
<th>MIC (mcg /ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All organisms (except Haemophilus and Staphylococci)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>All organisms</td>
<td>O18</td>
<td>14-17</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>O20</td>
<td>-</td>
</tr>
<tr>
<td>Haemophilus influenzae when tested on HTM*</td>
<td>O13</td>
<td>11-12</td>
</tr>
</tbody>
</table>

Where: HTM = Haemophilus Test Medium; S=susceptible; I=intermediate; R=resistant.

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

Pharmacokinetics

The pharmacokinetics of orally administered clarithromycin has been studied extensively. These studies have shown that clarithromycin is readily and rapidly absorbed, with an absolute bioavailability of approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change following multiple dosing.

Absorption

In a single-dose clinical study in volunteers, clarithromycin was administered intravenously at 75, 125, 250 or 500 mg doses in 100 ml volume infused over 30 minutes, and 500, 750 or 1,000 mg doses in 250 ml volume infused over a 60-minute period. The mean peak concentration (Cmax) of parent drug ranged from 1.23 mcg/ml after 75 mg (30 minute infusion) to 9.40 mcg/ml after 1000 mg (60 minute infusion).

The mean peak concentration (Cmax) of the 14-hydroxy metabolite ranged from 0.21 mcg/ml after 125 mg (30 minute infusion) to 1.06 mcg/ml after 1000 mg (60 minute infusion); levels of this metabolite were generally undetectable after the 75 mg dose.

The mean terminal phase plasma half-life of parent drug was dose-dependent and ranged from 2.1 hours after 75 mg (30 minute infusion) to 4.5 hours after 1000 mg (60 minute infusion). The mean estimated plasma half-life for the 14-hydroxy metabolite showed some dose-dependent increases at higher doses and ranged from 5.3 hours after 250 mg (30 minute infusion) to 9.3 hours after the 1000 mg (60 minute infusion). The mean estimated plasma half-life for the 14-hydroxy metabolite after a 30-minute infusion of 125 mg was 7.2 hours.

The mean area under the concentration-time curve (AUC) showed a nonlinear dose-dependent increase for parent drug of 2.29 h.mcg/ml after the 75 mg dose to 53.26 h.mcg/ml after the 1000 mg dose. The mean area under the concentration vs. time curve (AUC) for the 14-hydroxy metabolite ranged from 2.10 h.mcg/ml after the 125 mg dose (30 minute infusion) to 14.76 h.mcg/ml after the 1000 mg dose (60 minute infusion).

In a seven-day multiple dose clinical study subjects were infused with either 125 and 250 mg clarithromycin intravenously in 100 ml final volume over a 30 minute period or 500 and 750
mg of the formulation in final volumes of 250 ml over a 60-minute period; dosing was given at 12-hour intervals.

In this study, the observed mean steady-state peak clarithromycin (Cmax) concentration increased from 2.1 mcg/ml with the 125 mg dose to 3.2, 5.5 and 8.6 mcg/ml with the 250, 500 and 750 mg doses, respectively. The mean apparent terminal half-lives increased gradually from 2.8 hours after infusion of the 125 mg dose over a 30-minute period to 6.3 hours after infusion of the 500 mg dose over a 60 minute period. The mean apparent terminal half-life after a 60 minute infusion of 750 mg was 4.8 hours.

The observed mean steady-state Cmax for the 14-hydroxy metabolite increased from 0.33 mcg/ml with the 125 mg dose to 0.55, 1.02 and 1.37 mcg/ml for the 250, 500 and 750 mg doses, respectively. The mean terminal phase half-lives for this metabolite were 4.8, 5.4, 7.9, and 5.4 hours for the 125, 250, 500, and 750 mg dose groups, respectively. No dose-related trend was evident.

Distribution

*In vitro*, at a concentration of 0.45 to 4.5 mg/ml in human plasma, protein-binding of clarithromycin averaged about 70%. In humans, clarithromycin and its 14-hydroxy metabolite distribute readily into body tissues and fluids. Concentrations in tissues are usually several fold higher than serum concentrations. Examples from tissue and serum concentrations are presented below in Table 2.

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>tissue levels (mcg/g)</th>
<th>serum levels (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tonsil</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>lung</td>
<td>8.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Biotransformation

The major metabolite in human plasma was the 14-hydroxy (R) epimer of clarithromycin, with peak levels of 0.5 mcg/ml and 1.2 mcg/ml after doses of 250 mg and 1200 mg, respectively. In humans given single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Faecal excretion accounted for 40.2% and 29.1% (this included a subject with only one stool sample containing 14.1%) of these respective doses.

Elimination

Refer to the clinical study summaries in *Absorption*.

Pharmacokinetics in special populations

Hepatic impairment

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

Renal impairment
A study was conducted to evaluate and compare the pharmacokinetic profile of multiple 500 mg oral doses of clarithromycin in subjects with normal and decreased renal function. The plasma levels, half-life, Cmax and Cmin for both clarithromycin and its 14-hydroxy metabolite were higher and AUC was larger in subjects with renal impairment. Kelim and urinary excretion were lower. The extent to which these parameters differed was correlated with the degree of renal impairment; the more severe the renal impairment, the more significant the difference (refer to Dosage and administration).

Elderly subjects
A study was also conducted to evaluate and compare the safety and pharmacokinetic profiles of multiple 500 mg oral doses of clarithromycin in healthy elderly male and female subjects to those in healthy young adult male subjects. In the elderly group, circulating plasma levels were higher and elimination slower than in the younger group for both parent drug and 14-hydroxy metabolite. However, there was no difference between the two groups when renal clearance was correlated with creatinine clearance. It is concluded from those results that any effect on the handling of clarithromycin is related to renal function and not to age itself.

Indications
Clarithromycin intravenous infusion is indicated whenever parenteral therapy is required for treatment of sensitive microorganisms in the following conditions:

- upper respiratory tract infections;
- lower respiratory tract infections;
- skin and soft tissue infections.

DOSAGE AND ADMINISTRATION

Adults
The recommended dosage of clarithromycin intravenous infusion in adults 18 years of age or older is 1.0 gram daily, divided into 2 equal doses, each infused, after further dilution with an appropriate intravenous diluent, over a 60-minute time period. At the present time, there are no data supporting intravenous use of clarithromycin in children. Clarithromycin should not be given as a bolus or an intramuscular injection

Intravenous therapy may be limited for up to 2 to 5 days in the very ill patient and should be changed to oral therapy whenever possible as determined by the physician.

In patients with renal impairment who have creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be reduced to one half of the normal recommended dose.

The final solution for infusion is prepared as follows:

1. Prepare the initial solution of clarithromycin intravenous infusion by adding 10 ml of Sterile Water for Injection to the 500 mg vial. Use only Sterile Water for Injection, as
other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts.

Note: When the product is reconstituted as directed above, each ml contains 50 mg of clarithromycin. The reconstituted product should be used within 24 hours if stored at room temperature (25°C), or within 48 hours if stored at 5°C.

2. The reconstituted product (500 mg in 10 ml Water for Injection) should be added to a minimum of 250 ml of one of the following diluents before administration: 5% Dextrose in Lactated Ringer’s Solution; 5% Dextrose; Lactated Ringer’s; 5% Dextrose in 0.3% sodium chloride; 5% Dextrose in 0.45% sodium chloride; 0.9% sodium chloride. Other brands of clarithromycin intravenous infusion have shown to be stable when Normosol-M in 5% Dextrose and Normosol-R in 5% Dextrose are used as diluents.

The final diluted product should be used within 6 hours if stored at room temperature (25°C), or within 48 hours if stored at 5°C.

No medicine or chemical agent should be added to a clarithromycin intravenous infusion fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.

Paediatric
There are insufficient data to recommend a dosage regimen for use of the clarithromycin intravenous infusion formulation in patients less than 18 years of age.

CONTRAINDICATIONS

- Hypersensitivity to macrolide antibiotics or any of its excipients. Allergic or hypersensitivity reactions should be managed by prompt supportive measures.
- Concomitant administration of clarithromycin and any of the following medicines is contraindicated: astemizole, cisapride, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (refer to Warnings and precautions).
- Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity.
- Concomitant administration of clarithromycin and oral midazolam is contraindicated (refer to Interactions).
- Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (refer to Warnings and precautions).
- Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time).
- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolised by CYP3A4 (lovastatin or simvastatin) due to the increased risk of myopathy, including rhabdomyolysis (refer to Warnings and precautions).
• Clarithromycin (and other strong CYP3A4 inhibitors) should not be used concomitantly with colchicine in patients with renal or hepatic impairment (refer to Warnings and precautions and Interactions).

WARNINGS AND PRECAUTIONS

All patients
Hypersensitivity
In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens Johnson Syndrome, toxic epidermal necrolysis, DRESS, and Henoch-Schonlein purpura clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Pseudomembranous colitis
Pseudomembranous colitis has been reported with nearly all anti-bacterial agents, including macrolides, and may range in severity from mild to life-threatening. *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori* infection may select for drug-resistant organisms.

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

Specific patient groups
Prolongation of the QT Interval
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides including clarithromycin (see Adverse Effects section). Therefore as the following situations may lead to an increased risk of ventricular arrhythmias (including torsades de pointes, clarithromycin should be sued with caution in the following patients;

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
- Patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia (see Contraindications)
- Patients concomitantly taking other medicinal products associated with QT prolongation (see Interactions).
NEW ZEALAND DATA SHEET

Clarithromycin 500 mg Powder for Concentrate for Solution for Infusion

Powder for concentrate for solution for infusion, Clarithromycin Ph Eur 500 mg

- Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine is contraindicated (see Contraindications)
- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see Contraindications).

Hepatic and renal impairment

Clarithromycin is principally excreted by the liver and kidney. Therefore, caution should be exercised in administering clarithromycin to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal failure.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Myasthenia gravis

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

Pneumonia

In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity

These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where beta-lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections and in situations where penicillin treatment cannot be used.

Concurrent treatments

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (refer to Interactions).

Colchicine

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (refer to Interactions). If concomitant administration of colchicine and clarithromycin is necessary, patients should be monitored for clinical symptoms of colchicine toxicity. The dose of colchicine should be reduced in all patients receiving colchicine and clarithromycin.
Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment (refer to Contraindications).

Triazolobenzodiazepines
Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and intravenous midazolam (refer to Interactions).

Oral hypoglycemic agents/insulin
The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended.

Oral anticoagulants
There is a risk of serious haemorrhage and significant elevations in INR and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

HMG-CoA reductase inhibitors (statins)
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (refer to Contraindications) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment. As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Patients should be monitored for signs and symptoms of myopathy.

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin concomitantly with clarithromycin. When used with clarithromycin, atorvastatin or rosuvastatin should be administered in the lowest possible doses. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin or pravastatin) should be considered.

Pregnancy and lactation
Use in pregnancy
Assigned Category B3 in the Australian Categorisation of risk system. Category B3 refers to medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have
shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

There are no adequate and well-controlled studies in pregnant women. The safety of clarithromycin for use during pregnancy has not been established. Therefore, use during pregnancy, especially during the first trimester, is not advised without carefully weighing the benefits against risk.

Use in lactation
The safety of clarithromycin for use during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

Effects on ability to drive and use machinery
There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines. Advise patient to report any difficulties.

Preclinical data and toxicology
Acute, subchronic, and chronic toxicity
Studies were conducted in mice, rats, dogs and/or monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for 6 consecutive months.

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

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

The major clinical signs at toxic doses in these studies described above included emesis, weakness, reduced food consumption and reduced weight gain, salivation, dehydration, and hyperactivity. Two of 10 monkeys receiving 400 mg/kg/day died on treatment day 8; yellow discoloured faeces were passed on a few isolated occasions by some surviving monkeys given a dose of 400 mg/kg/day for 28 days.

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

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

The LD50 of clarithromycin administered intravenously in mice was found to be 184 mg/kg and 227 mg/kg in two separate studies. This was several times higher than the LD50 in rats (64 mg base/kg). These values were lower than those obtained following administration to mice by other routes. Signs of toxicity in both species were decreased activity, ataxia, jerks, tremors, dyspnoea and convulsions.

**Impairment of fertility**

Fertility and reproduction studies have shown daily dosages of 150 to 160 mg/kg/day (10 times the maximal human dose) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring.

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

**Embryotoxicity**

Rats were administered 15, 50 and 160 mg base/kg/day of clarithromycin intravenously via tail vein. Significant signs of maternal toxicity were elicited at 160 mg/kg/day (reduced weight gain and reduced food consumption) and 50 mg/kg/day (reduced food consumption). Local effects of the test agent included swollen, bruised, necrotic and ultimate loss of a portion of the tail among high-dose animals. No effects on mean incidences of implantation sites or resorptions were noted. No visceral or skeletal abnormalities due to medicine administration were noted, except for the dose-related trend in the proportion of male foetuses with an undescended testis. Thus, despite significant maternal toxicity, manifested as vein irritation and reduced food consumption and weight gain, there was no evidence of embryotoxicity, embryolethality or teratogenicity at any doses.

Groups of mated rabbits were given clarithromycin intravenously at doses of 3, 10 and 30 mg base/kg/day. One dam treated at 3 mg/kg/day died on gestational day 29. Vein irritation was seen in control and all treatment groups. The incidence and severity of irritation were directly related to the concentration of the medicine in the formulation. Signs of maternal toxicity were elicited at 30 mg/kg/day (reduced weight gain and reduced food consumption). This incidence of abortion in the 30 mg/kg/day treatment group was significantly higher than that of the control group, but all aborted foetuses were found to be grossly normal. The no-effect levels for maternal and foetal toxicity were 10 and 30 mg/kg/day, respectively.

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

Two teratogenicity studies in both Wistar (oral dosing) and Sprague-Dawley (oral and intravenous dosing) rats, one study in New Zealand White rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony. Two studies in mice also revealed a variable incidence of cleft palate (3 to 30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg twice daily), but not at 35 times the maximal daily human clinical dose, suggesting maternal and foetal toxicity but not teratogenicity.

Mutagenicity

Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagenic potential at drug concentrations of 25 mcg/petri plate or less. At a concentration of 50 mcg/petri plate, the drug was toxic for all strains tested. A dominant lethal test in mice given at approximately 70 times the maximal human daily clinical dose was clearly negative for any mutagenic activity.

Vein irritation

Solutions of intravenous clarithromycin were evaluated for potential to cause vein irritation in the marginal ear vein of rabbits. This study demonstrated that administration of single doses at very high concentrations (7.5 to 30 mg/base/ml) were mildly irritating.

ADVERSE EFFECTS

All patients

Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin. The most frequent and common adverse reactions related to clarithromycin therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics. There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without pre-existing mycobacterial infections.

Adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin intravenous infusion are categorised by frequency, then system organ class.

Adverse reactions reported during post-marketing experience cannot be estimated from the available data. 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.

Very common (1 in 10 or more)

General disorders and administration site conditions

Injection site phlebitis.
Common (from 1 in 100 to <1 in 10)
Gastrointestinal disorders
Diarrhoea; vomiting; dyspepsia; nausea; abdominal pain.
General disorders and administration site conditions
Injection site pain, injection site inflammation.
Hepatobiliary disorders
Liver function test abnormal.
Nervous system disorders
Dysgeusia; headache; taste perversion.
Psychiatric disorders
Insomnia.
Skin and subcutaneous tissue disorders
Rash; hyperhidrosis.
Vascular disorders
Vasodilation.

Uncommon (from 1 in 1,000 to <1 in 100)
Blood and lymphatic system
Leukopenia.
Cardiac disorders
Cardiac arrest; atrial fibrillation; electrocardiogram QT prolonged; extrasystoles; palpitations.
Ear and labyrinth disorders
Vertigo, hearing impaired, tinnitus.
Gastrointestinal disorders
Esophagitis gastrooesophageal; gastritis; stomatitis; glossitis; constipation; dry mouth; eructation; flatulence.
General disorders and administration site conditions
Asthenia.
Hepatobiliary disorders
Alanine aminotransferase increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased.
Immune system disorders
Anaphylactoid reaction; hypersensitivity.
Infections and infestations
Cellulitis; candidiasis; vaginal infection.
Investigations
Albumin globulin ratio abnormal.
Metabolism and nutrition disorders
Anorexia; decreased appetite.

Musculoskeletal and connective tissue disorders
Musculoskeletal stiffness; myalgia.

Nervous system disorders
Loss of consciousness; dyskinesia; dizziness; somnolence; tremor.

Psychiatric disorders
Anxiety.

Renal and urinary disorders
Blood creatinine increased; blood urea increased.

Respiratory, thoracic and mediastinal disorders
Asthma; pulmonary embolism.

Skin and subcutaneous tissue disorders
Dermatitis bullous; pruritus; urticaria.

Indeterminate frequency (cannot be estimated from the available data)
Blood and lymphatic system
Agranulocytosis; thrombocytopenia.

Cardiac disorders
Torsade de pointes; ventricular tachycardia.

Ear and labyrinth disorders
Deafness.

Gastrointestinal disorders
Pancreatit is acute; tongue discolouration; tooth discolouration.

Hepatobiliary disorders
Hepatic failure; jaundice hepatocellular.

Immune system disorders
Anaphylactic reaction.

Infections and infestations
Pseudomembranous colitis; erysipelas; erythrasma.

Investigations
International normalised ratio increased; prothrombin time prolonged; urine color abnormal.

Metabolism and nutrition disorders
Hypoglycaemia.
Musculoskeletal and connective tissue disorders
Rhabdomyolysis, however in some of the reports, clarithromycin was administered concomitantly with other drugs known to be associated with rhabdomyolysis (such as statins, fibrates, colchicine or allopurinol); myopathy.

Nervous system disorders
Convulsions; ageusia; parosmia; anosmia; paraesthesia.

Psychiatric disorders
Psychotic disorder; confusional state; depersonalisation; depression; disorientation; hallucination; abnormal dreams; mania.

Renal and urinary disorders
Renal failure; nephritis interstitial.

Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome; toxic epidermal necrolysis; drug rash with eosinophilia and systemic symptoms (DRESS); acne; Henoch-Schonlein Purpura.

Vascular disorders
Haemorrhage.

Specific patient groups
Colchicine treatment
There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (refer to Interactions, Warnings and precautions).

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

In adult patients, the most frequently reported adverse events by patients treated with total daily doses of 1,000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, SGOT and SGPT elevations. Additional low-frequency events included dyspnoea, insomnia, and dry mouth.

In these immunocompromised patients evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (i.e., the extreme high or low limit) for the specified test. On the basis of this criterion, about 2% to 3% of these patients who received 1,000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated BUN levels.
NEW ZEALAND DATA SHEET

Clarithromycin 500 mg Powder for Concentrate for Solution for Infusion
Powder for concentrate for solution for infusion, Clarithromycin Ph Eur 500 mg

INTERACTIONS

Contraindicated medicines
The use of the following medicines is strictly contraindicated due to the potential for severe medicine interaction effects.

Cisapride and pimozide
Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly (refer to Contraindications).

Terfenadine
Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsade de pointes (refer to Contraindications). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin (tablets) and terfenadine resulted in a 2 to 3 fold increase in the serum level of the acid metabolite of terfenadine and in the prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergot alkaloids
Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated (refer to Contraindications).

Effect of other medicines on clarithromycin

Microsomal enzyme inducers
Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John’s Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

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

**Specific drug interactions**

**Etravirine**

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

**Fluconazole**

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

**Ritonavir**

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every 8 hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with a creatinine clearance 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with a creatinine clearance < 30 ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

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 (refer to Bi-directional drug interactions).

**Effects of clarithromycin on other medicines**

**Antiarrhythmics**

There have been post-marketed reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these medicines. Serum levels of these medications should be monitored during clarithromycin therapy.

**CYP3A substrates**

Co-administration of clarithromycin, known to inhibit CYP3A, and a medicine primarily metabolised by CYP3A may be associated with elevations in medicine concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant medicine.
Clarithromycin should be used with caution in patients receiving treatment with other medicines 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 metabolised by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of medicines primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following medicines or medicine classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Medicines interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Omeprazole
Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (Cmax, AUC0-24 and t1/2 increased by 30%, 89% and 34% respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

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

Theophylline, carbamazepine
Results of clinical studies indicate there was a modest but statistically significant (p ≤0.05) increase of circulating theophylline or carbamazepine levels when either of these medicines are administered concomitantly with clarithromycin. Serum theophylline or carbamazepine levels should be monitored in patients receiving concomitant clarithromycin.

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

Triazolobenzodiazepines (e.g. triazolam and alprazolam) and related benzodiazepines (e.g. midazolam)
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 dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of medicine interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

**Other medicine 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. The dose of colchicine should be reduced when co-administered with clarithromycin in patients with normal renal and hepatic function. Concomitant use of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment (refer to **Warnings and Precautions**).

**Digoxin**

When clarithromycin and digoxin are administered together, inhibition of P-glycoprotein (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 concentration should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

**Zidovudine**

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. This interaction does not appear to occur in paediatric HIV-infected patients taking a clarithromycin suspension formulation concurrently with zidovudine or dideoxyinosine. Because clarithromycin appears to interfere with the absorption in adults of simultaneously administered oral zidovudine, this interaction would most likely not be a problem when clarithromycin is administered intravenously. This interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine.

**Phenytoin and valproate**

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolized by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.
Bi-directional medicine interactions

**Atazanavir**
Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional medicine 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-hydroxyclarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 ml/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance < 30 ml/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

**Itraconazole**
Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bi-directional medicine interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

**Saquinavir**
Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional medicine interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and 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 medicines are co-administered for a limited time at the doses/formulations studied. Observations from medicine interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from medicine interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (refer to Effects of other medicines on clarithromycin).

**Oral contraceptives**
There is no loss of efficacy of oral contraceptives when used in combination with clarithromycin.

**Calcium channel blockers**
Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.
OVERDOSAGE

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

Treatment
In the case of overdosage, clarithromycin intravenous infusion should be discontinued and all other appropriate supportive measures should be instituted.

Contact the National Poisons Centre by telephoning 0800 POISON or 0800 764 766 for further advice on management.

PHARMACEUTICAL PRECAUTIONS

Incompatibilities
There are no clinically relevant studies addressing physical compatibility of clarithromycin with intravenous admixtures other than those listed in Dosage and administration.

Storage conditions
Unopened container
Store below 30°C. Protect from light by removing the vial from the carton only when required.

Reconstituted contents
Protect from light. Store at 2° to 8°C (Refrigerate, do not freeze).

For reconstituted and diluted solutions, the chemical and physical in-use stability has been demonstrated for 6 hours at 25°C. However, from a microbiological point of view, the reconstituted and diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not exceed 24 hours at 2 to 8°C, unless the product is reconstituted and diluted under controlled and validated aseptic conditions.

Preparation for use
Clarithromycin 500 mg Powder for Concentrate for Solution for Infusion must be reconstituted and diluted exactly as directed in Dosage and administration.

The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

MEDICINE CLASSIFICATION

Prescription Medicine
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Clarithromycin 500 mg Powder for Concentrate for Solution for Infusion
Powder for concentrate for solution for infusion, Clarithromycin Ph Eur 500 mg

PACKAGE QUANTITIES
Single vial packs.

FURTHER INFORMATION
List of inactive ingredients
Lactobionic acid Ph Eur.

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