AUSTRALIAN PRODUCT INFORMATION

KEFLOR® CD

(cefaclor (as monohydrate)) modified release tablets

1 NAME OF THE MEDICINE

Cefaclor monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each KEFLOR CD modified release tablet contains 375 mg of cefaclor (as monohydrate) as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

KEFLOR CD 375 mg is a film-coated compressed tablet. Blue paracapsule shaped, dual radii, 7.62mm, approx length 16mm.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

KEFLOR CD is indicated for the treatment of the following types of infections caused by susceptible organisms, in adults and children aged 12 years or older:

- Acute bronchitis and acute exacerbations of chronic bronchitis.
- Upper respiratory infections, including pharyngitis, tonsillitis and acute bacterial sinusitis.
- Community-acquired pneumonia of mild to moderate severity (excluding atypical pneumonia).
- Symptomatic lower urinary tract infections, including cystitis.
- Skin and skin structure infections.

Note:

1. Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. KEFLOR CD is generally effective in the eradication of streptococci from the oropharynx; however, substantial data establishing the efficacy of KEFLOR CD in the subsequent prevention of rheumatic fever are not available.

2. Bacteriologic studies to determine the causative organism and its susceptibility to cefaclor should be performed. Therapy may be started while awaiting the results of these studies. Once these results become available, antimicrobial therapy should be adjusted accordingly.

4.2 DOSE AND METHOD OF ADMINISTRATION

KEFLOR CD can be taken with or without food. However, absorption is enhanced when KEFLOR CD is administered with food (see Section 5.2 PHARMACOKINETIC PROPERTIES). The tablets should not be cut, crushed or chewed.

The usual adult dosage is 375 mg twice daily.

For lower urinary tract infections, 500 mg once daily may be given. For pneumonia and acute bacterial sinusitis, the recommended dosage is 750 mg twice daily. For acute bacterial sinusitis, KEFLOR CD should be taken for 10 days.

In the treatment of infections caused by *S. pyogenes* (group A streptococci), a therapeutic dosage of KEFLOR CD should be administered for at least 10 days.

For patients with markedly impaired renal function - see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

4.3 CONTRAINDICATIONS

KEFLOR CD is contraindicated in patients with known allergy to the cephalosporin group of antibiotics or who have previously experienced a major allergy to penicillin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with antibiotic therapy in general, administration of KEFLOR CD should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained. A minimum of ten days of treatment is recommended in infections caused by group A beta-haemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis.

Prolonged use of KEFLOR CD may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, KEFLOR CD should be discontinued immediately and an alternative treatment should be considered.

Except under special circumstances, this medication should not be used when the following medical problem exists:

Allergic Reaction (Anaphylaxis)

In penicillin-sensitive patients, cephalosporin antibiotics should be administered cautiously. There is clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins and there are instances in which patients have had reactions, including anaphylaxis, to both drug classes. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions have been reported in patients on penicillin/cephalosporin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins/cephalosporins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin/cephalosporin hypersensitivity who have experienced severe reactions when treated with a penicillin/cephalosporin.

Past history of a severe allergic reaction to penicillin/cephalosporin is a contraindication to the use of KEFLOR CD. Before initiating therapy with any cephalosporin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, KEFLOR CD should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline (epinephrine). Oxygen, intravenous steroids and airway management, including intubation, should also be administered as indicated.

Risk-benefit should be considered when the following medical problems exist:

History of Colitis or Gastrointestinal disease

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, especially ulcerative colitis, regional enteritis, or antibiotic-associated colitis.

Pseudomembranous colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including cefaclor. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

History of bleeding disorders

All cephalosporins may cause hypoprothrombinemia and, potentially, bleeding.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy, seizures and/or myoclonus (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity.

Use in Renal Impairment

Many cephalosporins are excreted renally. KEFLOR CD should be administered with caution in the presence of markedly impaired renal function. Since the half-life of cefaclor in anuria is 2.3 to 2.8 hours, dosage adjustments for patients with moderate or severe renal impairment are usually not required. Clinical experience with cefaclor under such conditions is limited; therefore, careful clinical observation and laboratory studies should be made.

Use in Hepatic Impairment

KEFLOR CD should be used with caution in patients with liver disease, as documented clinical experience in this group of patients is lacking.

Dental

Long-term therapy with cephalosporins may allow for the overgrowth of *Candida albicans*, resulting in oral candidiasis.

Use in the Elderly

Cephalosporins have been used in the geriatric population, and no geriatrics-specific problems have been documented to date. However, elderly patients are more likely to have an age-related decrease in renal function, which may require and adjustment in dosage and/or dosing interval in patients receiving cephalosporins.

Paediatric Use

The safety and efficacy of KEFLOR CD has not been studied in children. Serum sickness-like reactions including arthritis and arthralgia have been reported more frequently in children than in adults with the use of cefaclor.

Effects on Laboratory Tests

Glucose, urine:

Administration of KEFLOR CD may result in a false-positive reaction for glucose in the urine. This phenomenon has been seen in patients taking cephalosporin antibiotics when the test is performed using Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP).

Coombs' (antiglobulin) tests:

Positive direct Coombs' tests have been reported during treatment with cefaclor. In haematologic studies or in transfusion cross-matching procedures when anti-globulin tests are performed on the minor side, or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the drug.

Prothrombin time (PT):

May be prolonged.

Creatinine, serum:

Concentrations may be increased.

Carnitine or Haematocrit:

Values may decrease during therapy.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Anticoagulants, coumarin- or indandione-derivative, or Heparin or Thrombolytic agents

Because all cephalosporins can inhibit vitamin K synthesis by suppressing gut flora, prophylactic vitamin K therapy is recommended when any of these medications is used for prolonged periods in malnourished or seriously ill patients.

Platelet aggregation inhibitors

Hypoprothrombinemia induced by large doses of salicylates and/or cephalosporins, and the gastrointestinal ulcerative or haemorrhagic potential of nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, or sulfinpyrazone may increase the risk of haemorrhage.

Antacids

The extent of absorption of sustained release cefaclor is diminished if magnesium- or aluminium hydroxide-containing antacids are taken within 1 hour of administration

Probenecid

Probenecid decreases renal tubular secretion of those cephalosporins excreted by this mechanism, resulting in increased and prolonged cephalosporin serum concentrations, prolonged elimination half-life, and increased risk of toxicity.

Cimetidine

Cimetidine did not alter either the rate or the extent of absorption of sustained release cefaclor.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Adequate and well-controlled studies in humans have not been done. However, studies in animals have not shown that cefaclor causes impaired fertility.

Use in Pregnancy (Category B1)

The oral administration of high dose cefaclor (500 mg/kg) in pregnant rats and mice has resulted in a slight increase of minor skeletal malformations. Safety of this product for use during pregnancy has not been established. Cefaclor should not be used in women of child bearing potential unless, in the judgement of the treating clinician, its use is considered essential to the welfare of the patient and the expected benefits outweigh potential risks.

Labour and Delivery

KEFLOR CD has not been studied for use during labour and delivery. Treatment should be given only if clearly needed.

Use in Lactation

No studies have been done with KEFLOR CD. Small amounts of cefaclor have been detected in mother's milk following administration of single 500 mg doses of cefaclor. Average levels were 0.18, 0.20, 0.21 and 0.16 µg/mL at 2, 3, 4 and 5 hours respectively. Trace amounts were detected at 1 hour. The effect on nursing infants is not known. Caution should be exercised when KEFLOR CD is administered to a nursing woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The majority of adverse reactions observed in clinical trials of sustained release cefaclor were mild and transient. Drug related adverse reactions requiring discontinuation of therapy occurred in 1.7% of patients. The following adverse reactions have been reported following the use of sustained release cefaclor in clinical trials. Incidence rates were less than 1%, except as otherwise noted.

Gastrointestinal Disorders

Diarrhoea (3.4%), nausea (2.5%), vomiting and dyspepsia.

Immune System Disorders

Rash, urticaria or pruritus occurred in approximately 1.7% of patients. One serum-sickness-like reaction (0.03%) was reported among the 3,272 patients treated with sustained release cefaclor during the controlled clinical trials.

Blood and Lymphatic System Disorders

Eosinophilia.

Infections and Infestations

Vaginal moniliasis (2.5%) and vaginitis (1.7%).

Acute Bacterial Sinusitis:

Adverse experiences reported among patients with acute bacterial sinusitis treated with sustained release cefaclor (750 mg b.i.d.) or cefaclor capsules (500 mg t.i.d.) during a controlled clinical trial are shown in

Table 1 below. Included are all adverse experiences occurring with an incidence of 2% or greater in either treatment group.

Table 1. Adverse experiences reported by patients with acute bacterial sinusitis and treated with cefaclor during a controlled clinical trial

Event Classification Term	Sustained Release Cefaclor N=147	Cefaclor N=150
Headache	8 (5.4%)	4 (2.7%)
Diarrhoea	6 (4.1%)	4 (2.7%)
Abdominal pain	5 (3.4%)	7 (4.7%)
Asthenia	3 (2.0%)	5 (3.3%)
Epistaxis	3 (2.0%)	0 (0.0%)
Pain	3 (2.0%)	1 (0.7%)
Vaginitis	2 (1.4%)	3 (2.0%)

The following adverse effects have been reported in patients treated with sustained release cefaclor; causal relationship is uncertain. Incidence rates were less than 1%, except as otherwise noted.

Nervous System Disorders

Headache (3.2%), dizziness and somnolence.

Hepatobiliary Disorders

Transient elevations in AST, ALT and alkaline phosphatase.

Renal and Urinary Disorders

Transient increase in serum urea or creatinine; and abnormal urinalysis.

Blood and Lymphatic System Disorders

Transient thrombocytopenia, leucopenia, lymphocytosis and neutropenia.

In addition, the following adverse reactions and altered laboratory tests have been reported in patients treated with cefaclor:

Immune System Disorders

Fever and angioedema have been reported rarely.

Cases of serum-sickness-like reactions have been reported with the use of cefaclor. These have been reported more frequently in children than in adults with an overall occurrence ranging from 0.5% (1 in 200) in one trial, to 0.024% (2 in 8,346) in overall clinical trials (with an incidence in children in clinical trials of 0.055%). The worldwide reporting rate for serum-sickness-like reactions in adults is very rare (<0.01). Serum-sickness-like reactions are characterised by findings of erythema multiforme, rashes and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes and no evidence to date of sequelae of the reaction. While further investigation is ongoing, serum sickness-like reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with cefaclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a

few days after cessation of therapy; occasionally these reactions have resulted in hospitalisation usually of short duration (median hospitalisation = 2 to 3 days, based on postmarketing surveillance studies). In those requiring hospitalisation, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported. More severe hypersensitivity reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy. The worldwide reporting rate for anaphylaxis in the total population is very rare (<0.01%). Positive direct Coombs' test and genital pruritus have been reported. Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.

The following reactions have been reported rarely in patients treated with cefaclor:

Renal and Urinary Disorders

Reversible interstitial nephritis.

Hepatobiliary Disorders

Hepatic dysfunction including hepatitis and cholestatic jaundice.

Blood and Lymphatic System Disorders

Increased prothrombin time in patients receiving cefaclor and warfarin concomitantly, haemolytic anaemia, agranulocytosis and aplastic anaemia.

Nervous System Disorders

Reversible hyperactivity, nervousness, insomnia, confusion, hallucinations and hypertonia.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, KEFLOR CD should be discontinued immediately and an alternative treatment should be considered.

Post-marketing Experience

Nervous System Disorders

Frequency not known: seizures, encephalopathy and/or myoclonus.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

The toxic symptoms following an overdose of KEFLOR CD may include nausea, vomiting, epigastric distress and diarrhoea. The severity of the epigastric distress and the diarrhoea are dose related. If other symptoms are present, it is probable that they are secondary to an underlying disease state, an allergic reaction, or the effects of other intoxication.

Treatment

In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics in your patient.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing charcoal.

Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of cefaclor.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

KEFLOR CD (cefaclor sustained release) is a pharmaceutically-modified form of the orally active cephalosporin, cefaclor monohydrate. It is a semisynthetic cephalosporin antibiotic for oral administration. KEFLOR CD differs from other available products containing cefaclor in its rate of dissolution, producing a lower peak serum concentration, but retaining sustained measurable serum concentrations, which provides the advantage of twice daily dosing.

Microbiology

The *in vitro* bactericidal activity of KEFLOR CD is due to cefaclor. *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell-wall synthesis. Cefaclor is stable in the presence of bacterial β-lactamases; consequently, β-lactamase-producing organisms resistant to penicillins and some cephalosporins may be susceptible to cefaclor. Cefaclor has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections:

Gram-positive organisms:

- *Staphylococcus aureus*
- *Staphylococcus saprophyticus*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes* (group A streptococci)

Note: Cefaclor is inactive against methicillin-resistant staphylococci.

Gram-negative organisms:

- *Haemophilus influenzae*
- *Moraxella (Branhamella) catarrhalis*
- *Escherichia coli*
- *Klebsiella pneumoniae*

- *Proteus mirabilis*

Note: *Pseudomonas sp, Acinetobacter calcoaceticus*, enterococci, Enterobacter sp, indole-positive *Proteus* and *Serratia sp* are resistant to cefaclor.

Susceptibility Testing

Dilution or Diffusion Techniques - either quantative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of Intermediate indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

KEFLOR CD is well absorbed from the gastrointestinal tract after oral administration. Although KEFLOR CD can be taken with or without food, total absorption is enhanced with food. When it was given within one hour after a meal, the bioavailability of sustained release cefaclor was greater than 90%, using cefaclor taken fasting as a reference. When taken in the fasting state, the bioavailability of sustained release cefaclor was 77% that of cefaclor. Compared to cefaclor (fasted state), mean peak plasma concentrations of sustained release cefaclor (both fed and fasted states) were delayed 40 to 90 minutes and were lower. Concomitant administration of cimetidine does not affect the rate or extent of absorption. Administration of magnesium- or aluminium hydroxide-containing antacids 1 hour after sustained release cefaclor had no effect on the rate of absorption but resulted in a 17% decrease in the extent of absorption. The effect of antacids taken at other times is uncertain.

Following administration of 375 mg, 500 mg and 750 mg tablets to fed subjects, average peak serum concentrations of 4, 8, and 11 µg/mL, respectively, were obtained within 2.5 to 3 hours. No drug accumulation was noted when it was given twice daily for 2½ days.

Metabolism

There is no evidence of metabolism of cefaclor in humans.

Excretion

The plasma half-life in healthy subjects is independent of dosage form and averages 40-60 minutes. In elderly subjects (over age 65) with normal serum creatinine values, a higher peak plasma concentration and AUC are effects resulting from mildly diminished renal function and are not expected to have clinical significance. Therefore, dosage changes are not necessary in elderly subjects with normal renal function.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Long-term studies in animals have not been performed to evaluate the mutagenic potential of cefaclor.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of cefaclor.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the inactive ingredients mannitol, hypromellose, hyprolose, methacrylic acid copolymer, stearic acid, magnesium stearate, propylene glycol, purified talc and Colour Mixture Dark Blue YS-1-4273 (ARTG PI No: 1444).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Container Type: KEFLOR CD is available in blister packs (PVC/PCTFE (Aclar)/Al)

Pack sizes: 2 (sample), 10 tablets

Some pack sizes may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 58655 - KEFLOR CD cefaclor 375mg (as monohydrate) sustained release tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

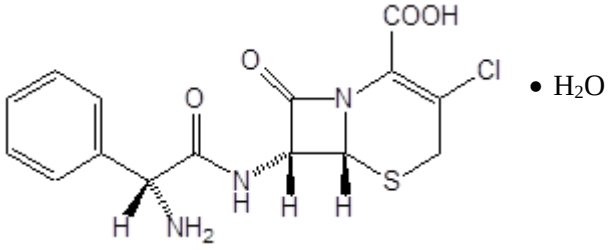
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate

Structural formula :



• H_2O

Molecular formula : $C_{15}H_{14}ClN_3O_4S \cdot H_2O$

Molecular weight : 385.83

CAS Number

53994-73-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

16/12/1997

10 DATE OF REVISION

07/03/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.4	Added warning of neurotoxicity.
4.8	Added adverse effects of nervous system disorders in section of post-marketing experience.

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