AUSTRALIAN PRODUCT INFORMATION

CEPHAZOLIN VIATRIS

(cefazolin sodium) powder for injection

1 NAME OF THE MEDICINE

Cefazolin sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of CEPHAZOLIN VIATRIS 2 g powder for injection contains 2 grams of cefazolin (as sodium) as the active ingredient.

3 PHARMACEUTICAL FORM

CEPHAZOLIN VIATRIS 2 g powder for injection is supplied as a white to off white crystalline powder. It is presented in a clear glass vial and must be reconstituted prior to use.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of the following serious infections due to susceptible organisms.

Respiratory tract infections due to Strep. pneumoniae, Klebsiella sp., H. influenzae, Staph. aureus (penicillin sensitive and penicillin resistant) and group A beta-haemolytic Streptococci. Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefazolin is effective in the eradication of Streptococci from the nasopharynx; however, data establishing the efficacy of cefazolin in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to E. coli, P. mirabilis, Klebsiella sp. and some strains of Enterobacter and enterococci.

Skin and skin structure infections due to Staph. aureus (penicillin sensitive and penicillin resistant) and group A beta-haemolytic Streptococci and other strains of Streptococci.

Bone and joint infections due to Staph. aureus.

Septicaemia due to Strep. pneumoniae, Staph. aureus (penicillin sensitive and penicillin resistant), P. mirabilis, E. coli and Klebsiella sp.

Endocarditis due to Staph. aureus (penicillin sensitive and penicillin resistant) and group A beta-haemolytic Streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to cefazolin.

4.2 DOSE AND METHOD OF ADMINISTRATION

Cefazolin may be administered intramuscularly or intravenously after reconstitution. The intrathecal administration of cefazolin is not an approved route of administration for this antibiotic; in fact, there have been reports of severe CNS toxicity including seizures when cefazolin was administered in this manner.

Intramuscular administration

Reconstitute with water for injections, sodium chloride 0.9% injection or lidocaine 0.5% injection according to the dilution table (see Table 1). Shake well until dissolved. To facilitate putting the product into solution, the vial should be warmed in the hands while shaking. Do not use the reconstituted injection solution if there is any sign of turbidity. Cefazolin should be injected into a large muscle mass.

Table 1 Dilution table

Vial size	Solvent to be added	Approx. avail. volume	Approx. average concentration
1 g	2.5 mL	3.0 mL	333 mg/mL
2 g	5 mL	6.0 mL	333 mg/mL

Intravenous administration

Cefazolin may be administered by direct intravenous injection or by intermittent or continuous infusion. Total daily dosages are the same as with intramuscular injection.

Direct intravenous injection

Dilute the reconstituted cefazolin 1 g or 2 g in a minimum of 10 mL of water for injections. Inject solution slowly over three to five minutes. It may be administered directly into a vein or through the tubing for a patient receiving one of the following intravenous solutions: sodium chloride 0.9% injection, glucose 5 or 10% injection, glucose 5% in lactated Ringer's injection, glucose 5% and sodium chloride 0.9% injection (also may be used with glucose 5% and sodium chloride 0.4 or 0.2% injection), lactated Ringer's injection, invert syrup 5 or 10% in water for injections, Ringer's injection, Normosol-M in glucose 5%, Ionosol B with glucose 5%, Plasma-Lyte with glucose 5%.

Intermittent intravenous infusion

Cefazolin can be administered along with primary intravenous fluid management programs in a volume control set or in a separate, secondary intravenous bottle. Reconstituted cefazolin 1 g or 2 g may be diluted in 50 to 100 mL of water for injections or one of the previously listed parenteral fluids and infused over a period of three to five minutes. If a Y-type administration set is used, it is desirable to discontinue the other solution during the infusion of the solution containing cefazolin.

Continuous intravenous infusion

The total daily dose of cefazolin, diluted and well mixed with at least 50 mL of water for injections, may be added to an intravenous bottle containing one of the previously listed parenteral fluids. Alternatively, fill up the CEPHAZOLIN VIATRIS 2 g infusion bottle with 50 to 100 mL of the listed intravenous solution. The choice of saline or glucose solution and the volume to be employed are dictated by fluid and electrolyte management.

Dosage

Adults

Usual dosage for mild Gram-positive infections is cefazolin 250 to 500 mg every eight hours.

In mild to moderate infections of the respiratory tract caused by Strep. pneumoniae, or mild to moderate infections of the genitourinary tract caused by susceptible organisms, a dosage of 1 g every 12 hours may be used.

In moderate or severe infections, the usual adult dosage is cefazolin 1 g every six to eight hours. Cefazolin has been administered in dosages of 6 g/day in serious infections such as endocarditis.

In patients with renal impairment, cefazolin is not readily excreted. After a loading dose of 500 mg, the recommendations in Table 2 for maintenance dosage may be used as a guide.

Table 2 Maintenance dosage in adults with reduced renal function

Renal function	Serum urea* (mg)	Creatinine clearance (mL/min)	Serum creatinine (micromol/L)	Dosage		Serum half-life (hours)
				Mild to moderate infection	Moderate to severe infection	
Mild impairment	20 - 34	70 - 40	115 - 180	250-500 mg 12 hourly	0.5 – 1.25 g 12 hourly	3 - 5
Moderate impairment	34 - 49	40 -20	181 - 310	125-250 mg 12 hourly	250-600 mg 12 hourly	6 - 12
Severe impairment	50 -75	20 - 5	311 - 620	75-150 mg 24 hourly	150-400 mg 24 hourly	15 – 30
Essentially no function	>75	<5	>620	37.5-75 mg 24 hourly	75-200 mg 24 hourly	30 – 40

*if used to estimate degree of renal impairment, serum urea concentrations should reflect a steady state of renal azotaemia.

Children

A total daily dosage of 25 to 50 mg/kg bodyweight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg/kg bodyweight for severe infections.

In children with mild to moderate impairment of renal function (creatinine clearance of 70 to 40 mL/minute), 60% of the normal daily dose given in divided doses every 12 hours should be sufficient. In patients with moderate impairment (creatinine clearance of 40 to 20 mL/minute), 25% of the normal daily dose given in divided doses every 12 hours should be sufficient. In children with marked impairment (creatinine clearance of 20 to 5 mL/minute), 10% of the normal daily dose given every 24 hours should be adequate. All dosage recommendations apply after an initial loading dose.

Since safety for use in premature infants and in infants aged under one month has not been established, the use of cefazolin in these patients is not recommended (see Table 3).

Table 3 Part A: Paediatric dosage guide for 25 mg/kg/day dose

Weight	25 mg/kg/day divided into 3 doses		25 mg/kg/day divided into 4 doses	
kg	Approximate single dose (mg/8 hours)	Volume needed with dilution of 125 mg/mL	Approximate single dose (mg/6 hours)	Volume needed with dilution of 125 mg/mL
4.5	40 mg	0.35 mL	30 mg	0.25 mL
9.0	75 mg	0.6 mL	55 mg	0.45 mL
13.6	115 mg	0.9 mL	85 mg	0.7 mL
18.1	150 mg	1.2 mL	115 mg	0.9 mL
22.7	190 mg	1.5 mL	140 mg	1.1 mL

Part B: Paediatric dosage guide for 50 mg/kg/day dose

Weight	50 mg/kg/day divided into 3 doses		50 mg/kg/day divided into 4 doses	
kg	Approximate single dose (mg/8 hours)	Volume needed with dilution of 225 mg/mL	Approximate single dose (mg/6 hours)	Volume needed with dilution of 225 mg/mL
4.5	75 mg	0.35 mL	55 mg	0.25 mL
9.0	150 mg	0.7 mL	110 mg	0.5 mL
13.6	225 mg	1.0 mL	170 mg	0.75 mL
18.1	300 mg	1.35 mL	225 mg	1.0 mL
22.7	375 mg	1.7 mL	285 mg	1.25 mL

CEPHAZOLIN VIATRIS contains no antimicrobial preservative. It is for single use in one patient only. Discard any residue. To reduce microbiological hazard, use as soon as practicable after initial reconstitution. If storage is necessary, store at 2 degrees to 8 degrees Celsius for not more than 24 hours.

4.3 CONTRAINDICATIONS

Known allergy to the cephalosporin group of antibiotics or previous experience of a major allergy to penicillin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Lidocaine should not be used as a diluent for intramuscular injection in patients who are hypersensitive to lidocaine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before cefazolin therapy is instituted, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins and penicillin. Cephalosporin C derivatives should be given cautiously in penicillin sensitive patients. Serious acute hypersensitivity reactions may require adrenaline (epinephrine) and other emergency measures. There is some clinical and laboratory evidence of partial cross allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs. Antibiotics, including cefazolin, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to cefazolin occurs, the drug should be discontinued, and the patient treated with the usual agents (e.g. adrenaline (epinephrine) or other pressor amines, antihistamines or corticosteroids).

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including cefazolin. A toxin produced by 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 Cl. difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine (e.g. Lomotil), may prolong and/or worsen the condition and should not be used.

Prolonged use of cefazolin may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

The intrathecal administration of cefazolin is not an approved route of administration for this antibiotic; in fact, there have been reports of severe CNS toxicity including seizures when cefazolin was administered in this manner.

Tremulousness, headache, agitation, light headedness, sensation of seeing flashing lights have been reported after patients receiving cefazolin intraventricularly for the treatment of infected ventricular shunts. Cefazolin is not to be used via this route for the treatment of shunt infections.

History of gastrointestinal disease

Cefazolin, as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease.

Use in Renal Impairment

As with other beta-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function. When cefazolin is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see Section 4.2 DOSE and METHOD OF ADMINISTRATION).

Encephalopathy has been reported with the use of cefazolin in patients with renal failure. The symptoms have included tonic clonic seizures, lethargy, disorientation, memory loss, asterixis and multifocal myoclonus. Toxicity has been attributed to increased cefazolin serum levels and increased permeability of the blood brain barrier caused by uraemia. The dose of cefazolin should be reduced or the dosing interval increased in patients with renal failure.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include seizures and/or myoclonus. 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 the Elderly

No data available.

Paediatric Use

Safety for use in premature infants and infants under 1 month of age has not been established.

Effects on Laboratory Tests

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest tablets, but not with Tes-Tape.

Several cases of positive direct and indirect antiglobulin (Coombs') tests have been reported following cefazolin therapy. These may also occur in neonates whose mothers received cefazolin prior to delivery.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Probenecid

Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

Aminoglycoside antibiotics

Coadministration of aminoglycoside antibiotics with cephalosporins could produce additive nephrotoxic effects. Use of these agents should be avoided in patients with prior renal insufficiency. If coadministration of these two antibiotic classes is necessary, patients should be monitored for evidence of nephrotoxicity.

Live typhoid vaccine

Antibiotics which possess bacterial activity against Salmonella typhi organisms may interfere with the immunological response to the live typhoid vaccine. Allow 24 hours or more to elapse between the administration of the last dose of the antibiotic and the live typhoid vaccine.

Warfarin

Patients receiving oral anticoagulant therapy with warfarin should be closely monitored using the prothrombin time ratio or international normalised ratio (INR) during concurrent therapy with cefazolin. Adjustment of the warfarin dosage to maintain the desired anticoagulant effect may be necessary. An alternative would be to use a cephalosporin which does not possess hypoprothrombinaemic properties.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: B1

Safety of this product for use during pregnancy has not been established in human clinical trials. Studies in animals are inadequate or lacking, but available data show no evidence of an increased occurrence of fetal damage. Studies of cord blood show prompt transfer of cefazolin across the placenta. Drug levels in cord blood were approximately one-quarter to one-third maternal drug levels.

Use in Lactation

Cefazolin is present in very low concentrations in the milk of breastfeeding mothers. Caution should be exercised when cefazolin is administered to a breastfeeding mother.

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 following reactions have been reported.

Hypersensitivity

Drug fever, skin rash, vulvar pruritus, eosinophilia, itching and Stevens-Johnson syndrome have occurred.

Haematological

The most common blood disorder associated with cefazolin has been eosinophilia. Neutropenia, leucopenia, thrombocythaemia, thrombocytopenia and positive direct and indirect Coombs' tests have occurred.

Hepatic and renal

Isolated transient rise in AST, ALT, serum urea, and alkaline phosphatase levels has been observed without evidence of renal or hepatic impairment.

Gastrointestinal

Nausea, anorexia, vomiting, diarrhoea and oral candidiasis (oral thrush) have been reported. As with other broad spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with cefazolin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Other

Pain at the site of injection after intramuscular administration has occurred, some with induration. Phlebitis at the site of injection has been noted. Other reactions have included genital and anal pruritus, genital candidiasis and vaginitis.

Post-marketing experience

Nervous system disorders. Seizures, encephalopathy, myoclonus – frequency not known.

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

Symptoms

Toxic signs and symptoms following an overdose of cefazolin may include pain, inflammation and phlebitis at the injection site.

The administration of inappropriately large doses of parenteral cephalosporins may cause dizziness, paraesthesias and headaches. Seizures may occur following overdosage with some cephalosporins, particularly in patients with renal impairment, in whom accumulation is likely to occur.

Laboratory abnormalities may include elevations in creatinine, serum urea, liver enzymes and bilirubin, a positive Coombs' test, thrombocytosis, thrombocytopenia, eosinophilia, leucopenia and prolongation of the prothrombin time.

Treatment

In managing overdosage, the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics should be considered.

If seizures occur, the drug should be discontinued promptly; anticonvulsant therapy may be administered if clinically indicated. 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.

In cases of severe overdosage, especially in a patient with renal failure, combined haemodialysis and haemo-perfusion may be considered if response to more conservative therapy fails. However, no data supporting such therapy are available.

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

Semisynthetic cephalosporin for parenteral administration.

Microbiology

In vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. Cefazolin is active against the following organisms in vitro: Staphylococcus aureus (penicillin sensitive and penicillin resistant); group A beta-haemolytic Streptococci and other strains of Streptococci

(many strains of enterococci are resistant); Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella sp., Enterobacter aerogenes, Haemophilus influenzae. Most strains of E. cloacae and indole positive proteus (P. vulgaris, P. morganii, P. rettgeri) are resistant. Methicillin resistant Staphylococci, Serratia, Pseudomonas, Acinetobacter calcoaceticus (formerly mima and herellea sp.) are almost uniformly resistant to cefazolin.

Susceptibility tests

Dilution or diffusion techniques, either quantitative (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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Table 4 demonstrates the blood levels and duration of cefazolin following intramuscular administration.

Table 4 Serum concentrations (microgram/mL) of cefazolin after intramuscular administration

Dose	Time after dose (hours)					
	0.5	**1**	**2**	**4**	**6**	**8**
250 mg	15.5	17.0	13.0	5.1	2.5	-
500 mg	36.2	36.8	37.9	15.5	6.3	3.0
1 g*	60.1	63.8	54.3	29.3	13.2	7.1

* Average of two studies

Clinical pharmacology studies in patients hospitalised with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers. In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5 mg/kg for one hour (approximately 250 mg) and 1.5 mg/kg for the next two hours (approximately 100 mg) cefazolin produced a steady serum level at the third hour of approximately 28 microgram/mL. Table 5 shows the average serum concentration after intravenous injection of a single 1 g dose; average half-life was 1.4 hours.

Table 5 Serum concentrations (microgram/mL) of cefazolin after intravenous administration

Dose	Time after dose (min)					
	5	**15**	**30**	**60**	**120**	**240**
1 g	188.4	135.8	106.8	73.7	45.6	16.5

Controlled studies on adult normal volunteers receiving 1 g four times daily for ten days, monitoring complete blood count, AST, ALT, bilirubin, alkaline phosphatase, serum urea, creatinine and urinalysis, indicated no clinically significant changes attributed to cefazolin. Cefazolin is excreted unchanged in the urine. Following intramuscular injection of 500 mg, 56 to 89% of the administered dose was recovered within six hours and 80 to nearly 100% was recovered in 24 hours. Cefazolin achieves peak urine concentrations greater than 1,000 microgram/mL and 4,000 microgram/mL respectively following 500 mg and 1 g intramuscular doses. When cefazolin is administered to patients with unobstructed biliary tracts, high concentrations, well over serum levels, occur in the gall bladder tissue and bile. In the presence of obstruction, however, concentration of the antibiotic in bile is considerably lower than the serum level. Cefazolin readily crosses an inflamed synovial membrane and the concentration of the antibiotic achieved in the joint space is comparable to levels measured in serum. Cefazolin readily crosses the placental barrier into the cord blood and amniotic fluid. Cefazolin is present in very low concentrations in the milk of breastfeeding mothers.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Mutagenicity studies have not been performed.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The product contains no excipients or preservatives.

6.2 INCOMPATIBILITIES

CEPHAZOLIN VIATRIS must not be reconstituted with other products except those mentioned in Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

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

Powder for injection: Store below 25°C. Protect from light and moisture.

Reconstituted solution: Store at 2°C to 8°C. Refrigerate. Do not freeze. Use within 24 hours after initial reconstitution.

6.5 NATURE AND CONTENTS OF CONTAINER

CEPHAZOLIN VIATRIS 2 g powder for injection is presented in a type III clear glass vial sealed with a polytetrafluoroethylene (PTFE) membrane-coated chlorobutyl rubber stopper and aluminium flip-off cap. Each carton contains 1 or 10 vials.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 154640 – CEPHAZOLIN VIATRIS cefazolin 2g powder for solution for injection vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

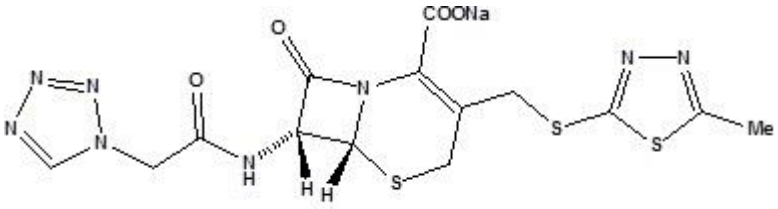
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name: Sodium (6R,7R)-3-[(5-methyl-1,3,4-thiadiazol-2-yl)thiomethyl]-8-oxo-7-[2-(1H-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Structural formula:



Molecular formula: $C_{14}H_{13}N_8NaO_4S_3$ Molecular weight: 476.5

CAS Number

27164-46-1

Cefazolin sodium is a white to off white crystalline powder with a solubility in water of greater than or equal to 100 mg/mL.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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9 DATE OF FIRST APPROVAL

09/04/2010

10 DATE OF REVISION

19/01/2024

Summary Table of Changes

Section Changed	Summary of New Information
4.2, 4.3, 6.5	Minor editorial change
4.4	Include neurotoxicity in warnings and precautions; minor editorial change
4.8	Include post-marketing experience in adverse effects

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