PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ORITAXIM 500 sterile powder for injection

ORITAXIM 1000 sterile powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ORITAXIM 500: Each vial contains cefotaxime sodium equivalent to 0,5 g cefotaxime.

ORITAXIM 1 000: Each vial contains cefotaxime sodium equivalent to 1,0 g cefotaxime.

Sugar free.

Contains sodium:

ORITAXIM 500: Each gram of cefotaxime contains approximately 24,12 mg of sodium.

ORITAXIM 1 000: Each gram of cefotaxime contains approximately 48,25 mg of sodium.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sterile powder for injection.

Dry Powder: Off-white to pale-yellow powder.

Reconstituted solution: A pale-yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ORITAXIM is primarily indicated for genito-urinary tract infections, infections of the skin and soft tissues, respiratory tract infections, infections of the gastro-intestinal tract and meningitis in children due to the following susceptible strains of organisms:

Infections due to *Streptococcus* (Group D *Streptococci* and *B-haemolytic Streptococci*):

Otitis media, sinusitis, pneumonia, pharyngitis, follicular tonsillitis, scarlet fever, urinary tract infections, (enterococci), meningitis in children, septic sore throat and cellulitis.

Infections due to *Staphylococcus* (Infections of non-penicillinase- and penicillinase producing strains included):

Bronchitis, impetigo, furunculosis and abscess.

Infections due to *Escherichia coli*:

Infections of the urinary tract, meningitis in paediatrics and lobar pneumonia.

Infections due to *Haemophilius influenzae*:

Meningitis in paediatrics, otitis media and bronchitis of the larynx and trachea.

***Gonococcal* infections:**

Gonorrhoea.

Infections due to *Neisseria meningitides*:

Paediatric meningitis.

Infections due to *Salmonella*:

Enteritis.

Infections due to *Shigella*:

Dysentery (Bacillus).

***Pseudomonoas aeruginosa* (Sensitive strains):**

Sepsis.

Infections due to *Pneumococcus*:

Cellulitis, lobar pneumonia, otitis and bronchitis.

The causative organisms and its sensitivity to cefotaxime sodium must be determined by means of bacteriological studies.

Prophylactically:

If administered peri-operatively in patients undergoing surgery, ORITAXIM may reduce the incidences of potentially contaminating post-operative infections. 1 g of ORITAXIM administered half-an-hour (30 mins) to one-and-a-half hours (90 mins) before surgery has been found to be the minimum effective dose.

4.2 Posology and method of administration

Posology

Dosage, route of administration and frequency of injections depends on the nature and severity of the infection, the condition of the patient and the sensitivity of the pathogens to ORITAXIM.

Prophylactically: The minimum effective dose has been found to be 1 g ORITAXIM 30 – 90 minutes prior to surgery.

Adults:

2 g daily administered as two injections of 1 g.

In severe infections, the dose may be increased to 3 g to 4 g daily given in two (2) to four (4) administrations.

Paediatrics:

Infants and Children:

A daily dose of 50 - 100 mg/kg body mass in two (2) to four (4) injections is usually recommended. Up to 200 mg/kg body mass daily may be administered in exceptional cases.

Neonates:

The recommended dosage regimen for neonates is as follows:

Neonates (0 to 1 week of age): 50 mg/kg body weight IV 12-hourly

Neonates (1 to 4 weeks of age): 50 mg/kg body weight IV 8-hourly

The dosages above are applicable to both premature and full-term infants.

Special populations

Renal function impairment:

Reduce the dose by 50 % in patients with a creatinine clearance of less than 20 ml/minute.

Do not alter the dosing interval.

Method of administration

For intravenous or intramuscular use.

See section 6.6 for the directions for preparation of injections.

4.3 Contraindications

- Hypersensitivity to cefotaxime, cephalosporin antibiotics or to any of the excipients of ORITAXIM (see section 6.1).
- Allergic cross reactions can exist between penicillins and cephalosporins (see section 4.4).

4.4 Special warnings and precautions for use

Anaphylactoid reactions

Preliminary enquiry about hypersensitivity to penicillin and other β -Lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5 – 10 % of cases. The use of cefotaxime as in ORITAXIM is strictly contraindicated in subjects with a previous history of immediate-type hypersensitivity to cephalosporins. Since cross allergy exists between penicillins and cephalosporins, use of the latter should be undertaken with extreme cautionin penicillin sensitive subjects. Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime as in ORITAXIM (see sections 4.3 and 4.8). If a hypersensitivity reaction occurs, treatment must be stopped.
Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8).

Superinfection

Prolonged use of ORITAXIM may result in the overgrowth of non-susceptible organisms i.e. superinfection with *Candida*, *Enterococci* or *Clostridium difficile*.

Clostridium difficile associated disease (e.g. pseudomembranous colitis)

Pseudomembranous colitis has been reported with the use of ORITAXIM. This side effect, which may occur more frequently in patients receiving higher doses for prolonged periods, should be considered as potentially serious.
Diarrhoea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment, may be symptomatic of *Clostridium difficile* associated disease (CDAD). CDAD may range in severity from mild to life-threatening, the most severe form of which is pseudo-membranous colitis.
The diagnosis of this rare but possibly fatal condition can be confirmed by endoscopy and/or histology.

It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of ORITAXIM.

If a diagnosis of pseudomembranous colitis is suspected, ORITAXIM should be stopped immediately, and appropriate specific antibody therapy should be started without delay.

Clostridium difficile associated disease can be favoured by faecal stasis.

Medicines that inhibit peristalsis should not be given.

Severe skin reactions

Severe cutaneous adverse reactions (SCARs) including acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with cefotaxime treatment.

At the time of prescription patients should be advised of the signs and symptoms for skin reactions.

If signs and symptoms suggestive of these reactions appear, ORITAXIM should be withdrawn immediately. If the patient has developed AGEP, SJS, TEN or DRESS with the use of ORITAXIM, treatment with ORITAXIM must not be restarted and should be permanently discontinued.

In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and medical practitioners should consider the possibility of a reaction to ORITAXIM in children that develop symptoms of rash and fever during therapy with ORITAXIM.

Patients with renal insufficiency

The dosage should be modified according to the creatinine clearance calculated. Patients with severe renal dysfunction should be placed on the dosage schedule recommended under section 4.2.

Caution should be exercised if ORITAXIM is administered together with aminoglycosides, probenecid or other nephrotoxic medicines (see section 4.5). Renal function must be monitored in these patients, the elderly, and those with pre-existing renal impairment.

Haematological reactions:

Leukopenia, neutropenia, and less frequently, agranulocytosis may develop during treatment with ORITAXIM, particularly if given over long periods. For treatment courses lasting longer than 7 - 10 days, the blood white cell count should be monitored and treatment stopped in the event of neutropenia.

Some cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of haemolytic anaemia have also been reported (see section 4.8).

Neurotoxicity

High doses of beta-lactam antibiotics, including ORITAXIM, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8).

Patients should be advised to contact their doctor immediately prior to continuing treatment if such reactions occur.

Precautions for administration

During post-marketing surveillance, potentially life-threatening dysrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter. The recommended time for injection or infusion should be followed (see section 4.2).

Sodium

ORITAXIM 500 contains 24,12 mg sodium per 500 mg vial, equivalent to 1,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

ORITAXIM 1 000 contains 48,25 mg sodium per 500 mg vial, equivalent to 2,4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Aminoglycoside antibiotics and diuretics

ORITAXIM may potentiate the nephrotoxic effects of nephrotoxic medicines such as aminoglycosides or potent diuretics (e.g. furosemide). Renal function must be monitored (see section 4.4).

Uricosurics

Probenecid interferes with renal tubular transfer of cefotaxime, thereby increasing cefotaxime exposure about 2-fold and reducing renal clearance to about half at therapeutic doses. Due to the large therapeutic index of ORITAXIM, no dosage adjustment is needed in patients with normal renal function. Dosage adjustment may be needed in patients with renal impairment (see sections 4.4 and 4.2).

Interactions with Laboratory Tests

A false positive Coombs test may be seen during treatment with ORITAXIM. Haemolysis is not usually associated with the phenomenon, but it may interfere with cross-matching of blood.

A false positive reaction to urinary glucose may occur with copper reduction methods (Benedict's, Fehling's or Clinitest), but not with the use of specific glucose oxidase methods.

There is a potential for mezlocillin and azlocillin to reduce the clearance of cefotaxime.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of ORITAXIM has not been established in human pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There are, however, no adequate and well controlled studies in pregnant women. Cefotaxime crosses the placental barrier. Therefore, ORITAXIM should not be used during pregnancy.

Breastfeeding

The safety of ORITAXIM has not been established in lactation. Cefotaxime passes into human breast milk in small amounts. Effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, colonisation by yeast-like fungi, and sensitisation of the infant cannot be excluded.

4.7 Effects on ability to drive and use machines

ORITAXIM has been associated with dizziness, which may affect the ability to drive or operate machinery.

There is no evidence that ORITAXIM directly impairs the ability to drive or to operate machines. High doses of ORITAXIM, particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised not to drive or operate machinery if any such symptoms occur.

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequency unknown	Superinfection (see section 4.4)
Blood and lymphatic system disorders	Less frequent	Leukopenia, eosinophilia, thrombocytopenia
	Frequency unknown	Neutropenia, granulocytopenia, agranulocytosis (see section 4.4), haemolytic anaemia
Immune system disorders	Less frequent	Jarisch-Herxheimer reaction
	Frequency unknown	Anaphylactic reactions, angioedema, bronchospasm, anaphylactic shock
Nervous system disorders	Less frequent	Convulsions (see section 4.4)
	Frequency unknown	Headache, dizziness, encephalopathy (e.g. impairment of consciousness, abnormal movements) (see section 4.4)
Cardiac disorders	Frequency unknown	Dysrhythmia following rapid bolus infusion through central venous catheter. Kounis syndrome (see section 4.4)
Gastrointestinal disorders	Less frequent	Diarrhoea
	Frequency unknown	Nausea, vomiting, abdominal pain, Pseudomembranous colitis (see section 4.4)
Hepato-biliary disorders	Less frequent	Increase in liver enzymes (ALT, AST, LDH, gamma-GT and/or alkaline

MedDRA system organ class	Frequency	Adverse reactions
		phosphatise) and/or bilirubin
	Frequency unknown	Hepatitis (sometimes with jaundice)
Skin and subcutaneous tissue disorders	Less frequent	Rash, pruritus, urticaria, drug fever
	Frequency unknown	Erythema multiforme, Stevens-Johnson syndrome SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4), linear IgA disease
Renal and urinary disorders	Less frequent	Decrease in renal function/ increase of creatinine (particularly when co-prescribed with aminoglycosides)
	Frequency unknown	Interstitial nephritis, candidiasis
General disorders and administration site conditions	Frequent	Tenderness and pain at the injection site
	Less frequent	Fever, inflammatory reactions at the injection site, including phlebitis/thrombophlebitis

Description of selected adverse reactions

Jarisch-Herxheimer reaction

For the treatment of borreliosis, a Jarisch-Herxheimer reaction may develop during the first days of treatment.

The occurrence of one or more of the following symptoms has been reported after several week's treatment of borreliosis: skin rash, itching, fever, leukopenia, increase in liver enzymes, difficulty of breathing, joint discomfort.

Hepatobiliary disorders

Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been observed. These laboratory abnormalities may rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms of overdose:

Encephalopathy (impairment of consciousness, abnormal movements and seizures) has been reported.

Treatment of overdose:

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins.

ATC code: J01D A10

Mechanism of action

Cefotaxime is a bactericidal semi-synthetic third-generation cephalosporin. The antibacterial action results from inhibition of bacterial cell wall synthesis by binding to essential target proteins in bacterial cytoplasmic membranes. Cefotaxime has activity against a wide range of bacterial organisms (Gram-positive and Gram-negative) including beta-lactamase producing strains.

Mechanisms of resistance

Resistance to cefotaxime may be due to production of extended-spectrum beta-lactamases that can efficiently hydrolyse the medicine, to the induction and/or constitutive expression of AmpC enzymes, to impermeability or to efflux pump mechanisms. More than one of these possible mechanisms may co-exist in a single bacterium.

Micro-organisms resistant to cefotaxime

Most strains of *enterococci* are resistant.

Most strains of *Clostridium difficile* are resistant.

Pseudomonas aeroginosa, *Listeria monocyogenes*

5.2 Pharmacokinetic properties

Cefotaxime is metabolised in the liver to both active and inactive metabolites, and is approximately 90 % excreted in the urine. Approximately 30 % of the dose of cefotaxime is excreted as the desacetyl derivative, the major active metabolite. The mean terminal half-life is about 80 minutes.

IM injection:

Peak plasma levels are reached 30 minutes after IM injection of 0,25 g; 0,5 g and 1 g doses.

The peak plasma level attained is dose-dependent - approximately 24 µg/ml after the 1 g injection. Urinary excretion is 50 % to 60 % of the administered dose within 24 hours after injection (44 % to 55 % within the first six hours). Cefotaxime crosses the blood- brain barrier.

IV injection:

Initial phase half-lives for whole blood and plasma are 4,5 and 8 minutes respectively. Terminal phase half-lives for whole blood and plasma are 1,3 and 2,2 hours respectively. Most of the dose is excreted within 4 hours of dosing. The elimination half-life is prolonged with renal impairment. Between 85 % and 90 % of the administered dose is ·excreted in the urine and 7 % to 9,5 % is excreted in the faeces. Cefotaxime is metabolised in the liver to active and inactive metabolites. Approximately 20 % to 36 % of an IV dose is excreted as the desacetyl derivative, the major active metabolite. Two other inactive urinary metabolites account for 20 % to 25 % of the excreted dose.

IV infusion:

A loading dose of 0,5 g, 1 g or 2 g administered over 15 minutes followed by sustaining infusions of 0,5, 1 or 2 g per hour produces mean peak serum levels of 41 µg/ml, 93 µg/ml or 160 µg/ml respectively. The mean terminal half-life is 75 ± 7 minutes. Most of the administered dose (63 ± 9 %) is renally excreted within 24 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

Cefotaxime sodium has been reported to be incompatible with alkaline solutions such as sodium bicarbonate.

ORITAXIM should be given separately from aminoglycosides. If they are used concurrently, they should be administered in separate sites.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not remove the product form the outer carton until required for use.

Dry powder: Store below 25°C, protected from light.

If the reconstituted solution cannot be used immediately, it may be kept for 24 hours in the refrigerator at 2-8 °C and for 24 hours at below 25 °C, when reconstitution/dilution is carried out under validated aseptic conditions. Discard any unused portion.

Note that the reconstituted solution should not be used if there are any signs of turbidity.

6.5 Nature and contents of container

ORITAXIM 500: 10 ml clear colourless glass vial, 20 mm grey butyl stoppers with a 20 mm aluminium flip off opaque green coloured seal.

ORITAXIM 1 000: 10 ml clear colourless glass vial, 20 mm grey butyl stoppers with a 20 mm aluminium flip off blue coloured seal.

6.6 Special precautions for disposal and other handling

Directions for preparation of injections:

IV and IM injections:

Dissolve ORITAXIM in Water For Injection (WFI) BP (0,5 g vial in 2 ml WFI; 1 g vial in 4 ml WFI). Shake vial until dissolved. Withdraw the entire contents of the vial into the syringe and use immediately.

Intravenous infusions:

Dissolve ORITAXIM 1 g or 2 g vials in 40 to 100 ml of: Water For Injection, 0,9 % sodium chloride, 5 % dextrose for Ringer's solution.

The prepared infusion solutions should be administered over 20 to 60 minutes.

Note: Use freshly prepared solution. ORITAXIM IV infusion solution in a concentration of 1 g per 250 ml is stable for 24 hours in a refrigerator or for 12 hours at a temperature not exceeding 23 °C.

Do not mix ORITAXIM with another antibiotic in the same syringe or infusion solution.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

ORITAXIM 500: 36/20.1.1/0482

ORITAXIM 1 000: 36/20.1.1/0483

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 November 2004

10 DATE OF REVISION OF THE TEXT

8 August 2025