SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Renoxitin 2 g Powder for solution for injection/ infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2,103 g of cefoxitin sodium equivalent to 2 g of cefoxitin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/ infusion.

A white or almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Renoxitin is indicated in adults and adolescents,

Cefoxitin should only be prescribed after consultation with physicians with appropriate expertise in the treatment of infectious diseases.

Cefoxitin may be used in the following infections when known or suspected to be caused by pathogens susceptible to cefoxitin and for which other, more commonly prescribed antibacterial agents are not appropriate.

Renoxitin is indicated for:

- complicated urinary tract infections
- pyelonephritis

Cefoxitin may have utility notably in intra- abdominal infections and some gynaecological infections. Please see section 4.4 for special warnings and precautions.

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

4.2 Posology and method of administration

Posology

There are very limited clinical safety and efficacy data supporting the dose of cefoxitin. Therapeutic guidelines should be adhered to.

Based on these very limited clinical data and some supporting pharmacokinetic/ pharmacodynamic data, the following may be appropriate:

Adults and adolescents:

2g every 4- 6 hours to a maximum of 12g/ day.

Renal impairment

There are extremely little data on the administration of cefoxitin in patients with renal impairment. Great caution is advised when cefoxitin is administered to these patients. In adults with renal impairment, an initial loading dose of 2 g can be administered. After the loading dose, the following recommendations can be used as guide for maintenance treatment:

Creatinine clearance (mL/min)	**Dose**	**Frequency**
50 - 30	2 g	Every 8 - 12 hours
29 - 10*	2 g	Every 12 - 24 hours

* In patients on haemodialysis, the loading dose of 2 g should be given after each haemodialysis, and the maintenance treatment should be given as indicated in the table above.

Paediatric population

There are insufficient data to recommend a posology in children aged up to 11 years.

Method of administration

Cefoxitin may be administered by slow intravenous injection over a period of 3 to 5 minutes.

A solution of this medicinal product may also be administered by continuous intravenous infusion.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to any other cephalosporin antibiotics or to any of the excipients listed in section 6.1.

History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefoxitin must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefoxitin, to other cephalosporins or to any other type of beta-lactam antibacterial agent. Caution should be used if cefoxitin is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Clostridium difficile-associated diarrhoea

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents and may occur with Cefoxitin (see section 4.8). These types of infection may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of the antibiotic. In such circumstances, the discontinuation of therapy with cefoxitin and the use of supportive measures together with the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Non-susceptible microorganisms

Prolonged use may result in the overgrowth of non-susceptible micro-organisms, which may require interruption of treatment or other appropriate measures.

Risk of encephalopathy

Beta-lactam antibiotics exposes to a risk of encephalopathy (confusion, disorders of consciousness, seizure, abnormal movements) and, particularly, in case of overdose or reduced renal function.

Impaired renal function

In patients with renal impairment, dosage adjustment should be based on the creatinine clearance and serum creatinine (see section 4.2).

Concurrent treatment with diuretics or aminoglycosides

Renal function should be monitored during treatment if cefoxitin is given in combination with other potentially nephrotoxic antibiotics (especially aminoglycosides), or with furosemide or etacrynic acid diuretics.

Bacterial meningitis

The use of cefoxitin in the treatment of meningitis is not substantiated by appropriate data. Therefore, cefoxitin is not indicated for the treatment of meningitis.

Important information about excipients

Renoxitin contains sodium.

This medicinal product contains 2.17 mmol (or 50 mg) of sodium, per g equivalent to 2,5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interference with laboratory tests

- Coombs test: false-positive results have been observed during treatment with cephalosporins. This may also occur in patients treated with cefoxitin.
- Glycosuria: false-positive results may be observed with reduction substances, however, no interaction has been observed with enzymatic methods.
- Jaffe (picric acid) serum creatinine test may show falsely high creatinine values. This may occur if cefoxitin serum concentrations exceed 100 mcg/ml.

Do not perform this assay on serum samples taken less than 2 hours after administration of Renoxitin.

- Urinary 17-hydroxy-corticosteroid: Porter Silber reaction may give moderate, falsely increased results in patients with high urinary concentrations of cefoxitin.

4.5 Interaction with other medicinal products and other forms of interaction

Problems specific to uncontrolled INR

There are numerous reports of potentiation of oral anticoagulant activity in patients on antibiotic therapy. The infectious or inflammatory disease background, the age and general condition of the patient appear to be risk factors. In these circumstances, it can be difficult to establish whether the infectious pathology or its treatment has caused the uncontrolled INR. However, certain classes of antibiotics are more involved, including fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and certain cephalosporins.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies have not shown evidence of a teratogenic effect. As teratogenic effects have not been observed in animals, malformations are not expected in humans. To date, substances that have been found to cause malformations in humans have been shown to be teratogenic in animals during well-controlled studies on two animal species.

A large amount of clinical data on pregnant women indicate no malformative nor feto/neonatal toxicity of cefoxitin. Nevertheless, epidemiological studies would be required to verify the absence of risk.

Renoxitin should therefore only be used during pregnancy if clinically needed.

Breast-feeding

Cefoxitin is excreted in human milk.

Breast-feeding should be discontinued during administration of Renoxitin to prevent any allergic reactions in the infant.

4.7 Effects on ability to drive and use machines

Renoxitin has a major influence on the ability to drive and use machines especially because of the possible occurrence of encephalopathy (see sections 4.4, 4.8 and 4.9).

4.8 Undesirable effects

Undesirable effects are classified by frequency and system organ class. The following terminologies have been used in order to classify the occurrence of undesirable effects: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1.000 to <1/100), rare (≥1/10.000 to <1/1.000), very rare (<1/10.000), not known (cannot be estimated from the available data).

System organ class	**Frequency of undesirable effects** **Frequency not known**
Immune system disorders	Anaphylactic reaction
Blood and lymphatic system disorders	Eosinophilia Leukopenia Neutropenia (agranulocytosis) Anaemia (including haemolytic anaemia) Thrombocytopenia Bone marrow failure
Vascular disorders	Local thrombophlebitis after intravenous administration
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Pseudomembranous colitis
Nervous system disorders	Encephalopathy (confusion, disorders of consciousness, seizure, abnormal movements)*
Hepatobiliary disorders	Transaminases increased Blood lactate dehydrogenase increased Blood alkaline phosphatase increased
Skin and subcutaneous tissue disorders	Rash Urticaria Pruritus Toxic epidermal necrolysis Angioedema
Musculoskeletal and connective tissue disorders	Myasthenia gravis exacerbation

System organ class	Frequency of undesirable effects
	Frequency not known
Renal and urinary disorders	Nephritis interstitial Blood creatinine increased and/or BUN increased (especially in combination therapy with aminoglycosides and loop diuretics) Severe renal impairment
General disorders and administration site conditions	Pyrexia Local reaction

* Beta-lactam antibiotics expose to a risk of encephalopathy (confusion, disorders of consciousness, seizure, abnormal movements) and, particularly, in case of overdose or reduced renal function.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store..

4.9 Overdose

Beta-lactam antibiotics exposes to a risk of encephalopathy (confusion, disorders of consciousness, seizure, abnormal movements) and, particularly, in case of overdose or reduced renal function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives for systemic use. Antibacterials for systemic use. Second-generation cephalosporins, ATC code: J01DC01

Cefoxitin is a beta-lactam antibiotic of the group of the second-generation cephalosporins.

Spectrum of antibacterial activity

No European breakpoints for cefoxitin are recommended by EUCAST.

Acquired resistance prevalence may vary geographically and with time for some species. Therefore, information on the prevalence of local resistance is desirable, particularly for the treatment of severe infections. Data can give orientation on the susceptibility probabilities of a bacterial strain to this antibiotic.

Cefoxitin is active (*in vitro*) against the following microorganisms:

SUSCEPTIBLE SPECIES

Gram-positive aerobes
Methicillin-Susceptible Staphylococcus
Streptococcus
Streptococcus pneumoniae
Gram-negative aerobes
Moraxella catarrhalis
Citrobacter koseri
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Salmonella spp.
Shigella spp.
Anaerobes
Bacteroides fragilis
Clostridium perfringens
Fusobacterium spp.
Peptostreptococcus spp.
Prevotella
Propionibacterium acnes
Veillonella spp.

Others
Actinomyces

MODERATELY SUSCEPTIBEL SPECIES
(moderate *in-vitro* susceptibility)
Gram-negative aerobes
Morganella morganii
Anaerobes
Eubacterium

RESISTANT SPECIES
Gram-positive aerobes
Enterococcus
Listeria monocytogenes
*Methicillin-Resistant Staphylococcus**
Gram-negative aerobes
Acinetobacter
Campylobacter
Citrobacter freundii
Enterobacter aerogenes

Enterobacter cloacae
Legionella
Pseudomonas aeruginosa
Serratia marcescens
Vibrio
Yersinia enterocolitica
Anaerobes
Clostridium difficile
Others
Chlamydia
Mycobacteria
Mycoplasma

5.2 Pharmacokinetic properties

Distribution

In adults:

- After an intravenous injection of 1 g, plasma concentrations of cefoxitin reached 125 µg/mL in 3 minutes, 72 µg/ml in 30 minutes and 15 µg/mL in 120 minutes.
- After an intravenous injection of 2 g, plasma concentrations of cefoxitin reached 220 µg/mL in 3 minutes.
- Elimination half-life is 45 minutes.

In patients with renal impairment whose creatinine clearance is between 10 and 30 mL/min, half-life exceeds 6 hours.

In patients with renal impairment whose creatinine clearance is < 10 mL/min, half-life exceeds 13 hours.

Diffusion

- Extracellular fluid;
- Synovial fluid;
- Pericardial fluid;
- Pleural fluid;
- Mucus;
- Aqueous humour;
- Bile;
- Human milk;
- Umbilical cord and amniotic fluid;
- Bone,
- Gallbladder,
- Heart,
- Liver,
- Lungs,

- Myometrium,
- Cerebrospinal fluid,

Plasma protein binding: 65-80%.

Biotransformation

Cefoxitin does not undergo significant biotransformation.

Elimination

Cefoxitin is eliminated unchanged by the kidney.

In a number of studies investigating cefoxitin at intravenous doses of 1 g, the average amount of cefoxitin recovered in the urine ranged from 77-99% of the injected cefoxitin dose.

5.3 Preclinical safety data

Repeated dose toxicity studies and studies on reproduction and development did not reveal special hazard for humans. No safety pharmacology studies, genotoxicity assays nor carcinogenic study were performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

After reconstitution:

Chemical and physical in-use stability has been demonstrated for 8 hours at 25°C and 2-8°C with Water for Injections. From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user.

After dilution of the reconstituted solution with the solvents listed in section 6.6:

Do not refrigerate.

Chemical and physical in-use stability has been demonstrated for 4 hours at 25 °C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Renoxitin is supplied in vials containing 1 g or 2 g cefoxitin as the sodium salt, closed with chlorobutyl rubber stopper and sealed with an aluminium capsule with polypropylene flip-off.

Renoxitin 2 g Powder for solution for injection is available in packs of 1, 5, 10, 20, 25, 50 and 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Cefoxitin may be reconstituted with 10 ml water for injections. Immediately after reconstitution, this Cefoxitin solution can be also added to 40 ml of the following solutions, frequently used in infusion(1g or 2g into 50 ml solution, corresponding to 20 to 40mg/ml):

- sodium chloride 0.9%,
- glucose 5% or 10%,
- mixed solution of glucose 5% and sodium chloride 0.9%,
- glucose 5% buffered with sodium bicarbonate 0.02%,
- glucose 5% supplemented with saline solution 0.2% or 0.45%,
- Ringer's Lactate solution,
- mixed solution of glucose 5% and Ringer Lactate,
- mixed solution of fructose 5% or 10% in water for injections,
- fructose 10% solution in saline solution,
- Sodium lactate solution at M/6.

This medicine may be given together with other antibiotics (intravenously with separate syringes or infusions).

When this medicine is administered at the same time as another antibiotic, it is important that the antibiotics are not mixed in the same syringe or infusion.

Reconstitution

Renoxitin should be reconstituted with water for injections: 1 g is soluble in 2 ml. Although, Renoxitin is very soluble, for intravenous use it is preferable to add 10 ml of water for injections to the 1 g vial or to the 2 g vial. It should be shaken to dissolve and then withdraw the entire contents of the vial into a syringe.

Dilution

The reconstituted solution should be diluted with the solvents mentioned above in section 6.6: add around 40 ml of the solvent to the reconstituted solution in order to reach a total volume of 50 ml.

The product should be used immediately after reconstitution/dilution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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