Ocexone®

Ceftriaxone

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Description:
Ocexone® is a sterile, semi-synthetic, broad-spectrum cephalosporin antibiotic. It is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The colour of **Ocexone**® solution ranges from light yellow to amber depending on the length of storage, concentration and diluents used. **Ocexone**® contains approximately 83 mg (3,6 mEq) of sodium per gram of Ceftriaxone. It is administered by intramuscular injection, intravenous injection and intravenous infusion.

Pharmacokinetics:
Distribution:
The volume of distribution of Ceftriaxone is 7-12 L. Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1-2 g; concentration well above the minimal inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in over 60 tissues or body fluids. On intravenous administration, Ceftriaxone diffuses rapidly into the interstitial fluid, where bactericidal concentrations against susceptible organisms are maintained for 24 hours.
Protein binding:
Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in concentration, e.g. from 95% binding at plasma concentrations of <100 mg/L to 85% binding at 300 mg/L.
Penetration into particular tissues:
Ceftriaxone penetrates the inflamed meninges of neonates, infants and children: Ceftriaxone concentrations exceed 1,4 mg/L in the Cerebro-spinal Fluid (CSF) 24 hours after i.v. injection of **Ocexone**® in doses of 50-100 mg/Kg (neonates and infants respectively). Peak concentration in CSF is reached about 4 hours after i.v. injection. In adult meningitis patients, administration of 50 mg/Kg leads within 2-24 hours to CSF concentrations several times higher than the minimum inhibitory concentrations required for the most common meningitis pathogens. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.
Metabolism:
Ceftriaxone is not metabolized systemically; but is converted to inactive metabolites by the gut flora.
Elimination:
50-60 % of Ceftriaxone is excreted unchanged in the urine, while 40-50 % is excreted unchanged in the bile. The elimination half-life in adults is about 8 hours. If the kidney function alone is impaired, biliary elimination of Ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

Microbiology:
The bactericidal activity of Ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria. Ceftriaxone has been shown to be active against most strains of the following micro-organisms:

Aerobic gram-negative microorganisms:
Acinetobacter calcoaceticus
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant and beta-lactamase producing strains)
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Serratia marcescens

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa.*

Aerobic gram-positive microorganisms:
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogens
Viridans group *Streptococci.*

Note: Methicillin-resistant staphylococci are resistant to cephalosporins, including Ceftriaxone. Most strains of Group D streptococci and enterococci, e.g., *Enterococcus (Streptococcus) faecalis,* are resistant.

Anaerobic microorganisms:
Bacteroides fragilis
Clostridium species
Peptostreptococcus species

Note: Most strains of *Clostridium difficile* are resistant.

Indications and Usage:
To reduce the development of drug-resistant bacteria and maintain the effectiveness of **Ocexone**® and other antibacterial drugs, **Ocexone**® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.
Ocexone® is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogens, Proteus mirabilis, or Serratia marcescens.*

ACUTE BACTERIAL OTITIS MEDIA caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including beta-lactamase producing strains) or *Moraxella catarrhalis* (including beta-lactamase producing strains).

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staphylococcus aureus, Staphylococcus epidermis, Streptococcus pyogenes,* Viridans group *streptococci, Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis or Peptostreptococcus species.*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii,* or *Klebsiella pneumoniae.*

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae,* including both penicillinase-producing and non-penicillinase-producing strains, and pharyngeal gonorrhea caused by non-penicillinase-producing strains of *Neisseria gonorrhoeae.*

PELVIC INFLAMMATORY DISEASE caused by *Neisseria gonorrhoeae.* **Ocexone**® , like other cephalosporins, has no activity against *Chlamydia trachomatis.* Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *Chlamydia trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

BACTERIAL SEPTICEMIA caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae,* or *Klebsiella pneumoniae.*

BONE AND JOINT INFECTIONS caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae* or *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS caused by *Escherichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium species* (Note: most strains of *Clostridium difficile* are resistant) or *Peptostreptococcus species.*

MENINGITIS caused by *Haemophilus influenzae, Neisseria meningitidis* or *Streptococcus pneumoniae.* **Ocexone**® has also been used successfully in a limited number of cases of meningitis and shunt infection caused by *Staphylococcus epidermidis* and *Escherichia coli.*

SURGICAL PROPHYLAXIS: The pre-operative administration of a single 1 g dose of **Ocexone**® may reduce the incidence of post-operative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated.

Contraindications:
Ocexone® is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.
Neonates (≤ 28 DAYS) : Hyperbilirubinemic neonates, epecially prematures, should not be treated with **Ocexone**®. In vitro studies have shown that Ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.
Ocexone® must not be co-administered with calcium-containing i.v. solutions, including continuous calcium-containing infusions such as parenteral nutrition, in neonates because of the risk of precipitation of Ceftriaxone-calcium salt. Cases of fatal reactions with Ceftriaxone-calcium precipitates in lung and kidneys in neonates have been described even in cases where the infusion lines and the times of administration of Ceftriaxone and calcium-containing solutions differed. Therefore **Ocexone**® and calcium-containing i.v. solutions should not be administered within 48 hours of each other in any patient.

Warning:
Do not use diluents containing calcium such as Ringer's or Hartman's solution to reconstitute **Ocexone**®. Particulate formation can result. Co-administration via different infusion lines or different sites should also be avoided with calcium containing infusions.

Hypersensitivity: Before therapy with **Ocexone**® is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Precautions:
General: Prescribing **Ocexone**® in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication increases the risk of the development of drug-resistant bacteria.
Dosage adjustments should not be necessary in patients with hepatic or renal dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, **Ocexone**® dosage should not exceed 2 g daily without close monitoring of serum concentrations.
Alterations in prothrombin times have occured rarely in patients treated with **Ocexone**®. Patients with impaired vitamin K synthesis or low vitamin K stores (e.g. Chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during **Ocexone**® treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.
Clostridium difficile: *Clostridium difficile* associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents including **Ocexone**®, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile.*

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis; Considering the maximum duration of treatment and the class of the compound, carcinogenesis studies with Ceftriaxone in animals have not been performed.
Mutagenesis; Ceftriaxone showed no potential for mutagenic activity in studies.
Impairment of fertility; Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day.
Pregnancy: Pregnancy Category B. Reproductive studies have been performed in rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose.
There are however, no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: Low concentrations of Ceftriaxone are excreted in human milk. Caution should be exercised when **Ocexone**® is administered to a nursing woman.
Paediatric Use: Safety and effectiveness of **Ocexone**® in neonates, infants and paediatric patients have been established. In vitro studies have shown that Ceftriaxone like some other cephalosporins can displace bilirubin from serum albumin. **Ocexone**® should not be administered to hyperbilirubinemic neonates especially prematures.

Adverse reactions:
Ocexone® is generally well tolerated. In clinical trials the following adverse reactions which were considered to be related to **Ocexone**® therapy or of uncertain etiology, were observed:
Local Reactions: Pain, induration and tenderness was 1% overall. Phlebitis was reported in less than 1% after i.v. administration.
Hypersensitivity: Rash (1,7%). Less frequently reported (less than 1%) were pruritus, fever or chills.
Hematology: Eosinophilia (6%), thrombocytosis (5,1%) and leukopenia (2,1%). Less frequently reported (less than 1%) were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.
Gastrointestinal: Diarrhea (2,7%). Less frequently reported (less than 1%) were nausea or vomiting and dysgeusia. The onset of pseudomembranous colitis symptoms may also occur during or after antibacterial treatment.
Hepatic: Elevations of SGOT (3,1%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.
Renal: Elevations of the BUN (1,2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.
Central Nervous System: Headache or dizziness were reported occassionally (less than 1%).
Genitourinary: Moniliasis or vaginitis were reported occasionally (less than 1%)
Miscellaneous: Diaphoresis and flushing were reported occasionally (less than 1%).

Interactions:
In an *in vitro* study antagonistic effects have been observed with the combination of chloramphenicol and Ceftriaxone. Based on literature reports Ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Overdosage:
In the case of overdosage, drug concentration would not be reduced by hemodialysis or peritoneal dialysis. There is no specific antidote. Treatment of overdosage should be symptomatic.

Dosage and Administration:
Standard dosage
Adults and children over 12 years
The usual dosage is 1- 2 g of **Ocexone**® once daily (every 24 hours). In severe cases or in infections caused by moderately sensitive organisms, the dosage may be raised to 4 g, once daily.

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Duration of therapy:
The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of **Ocexone®** should be continued for a minimum of 48 - 72 hours after patient has become afebrile or evidence of bacterial eradication has been obtained.

Combination therapy:
Synergy between **Ocexone®** and aminoglycosides has been demonstrated with many gram-negative Bacteria under experimental conditions. Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life threatening infections due to microorganisms such as Pseudomonas aeruginosa. Because of physical incompatibility the two drugs must be administered separately at the recommended dosages.

Method of administration:
As a general rule the solutions should be used immediately after preparation. Reconstituted solutions retain their physical and chemical stability for 6 hours at room temperature (or 24 hours in the refrigerator at 2 - 8°C). The solutions range in colour from pale yellow to amber, depending on the concentration and length of storage. The coloration of the solutions is of no significance for the efficacy or tolerance of the drug.

Intramuscular injection: For i.m. injection **Ocexone®** 1 g is dissolved in 3.5 ml, of 1% lidocaine hydrochloride solution and injected well within the body of a relatively large muscle. It is recommended that not more than 1 g be injected at one site. The lidocaine solution should never be administered intravenously.

Intravenous injection: For i.v. Injection, **Ocexone®** 1 g is dissolved in 10 ml sterile water for injections. The intravenous administration should be given over 2 - 4 minutes.

Intravenous Infusion: The infusion should be given over at least 30 minutes. For i.v. Infusion, 2 g **Ocexone®** is dissolved in 40 ml of one of the following calcium-free infusion solutions: sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5 %, dextrose 5%, dextrose 10%, dextran 6% in dextrose 5%, hydroxy ethyl starch 6 - 10%, water for injections. **Ocexone®** solutions should not be mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, owing to possible incompatibility.

Special Dosage instructions:
Patients with hepatic impairment
In patients with liver damage, there is no need for the dosage to be reduced provided renal function is intact.

Patients with renal impairment
In patients with impaired renal function, there is no need to reduce the dosage of **Ocexone®** provided hepatic function is intact. Only in cases of preterminal renal failure (creatinine clearance <10 ml/min) should the **Ocexone®** dosage not exceed 2 g daily. In patients with both severe renal and hepatic dysfunction, the plasma concentrations of Ceftriaxone should be determined at regular intervals and if necessary the dose should be adjusted.
In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Plasma concentrations should however, be monitored to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be altered.

Elderly
The dosage recommended for adults require no modification in geriatric patients.

Children
Neonates, infants and children up to 12 years
The following dosage schedules are recommended for once daily administration:
Neonates (up to 14 days): 20 - 50 mg/kg bodyweight once daily. This daily dose should not exceed 50 mg/kg. It is not necessary to differentiate between premature and term infants. Infants and children (15 days to 12 years): 20-80 mg/kg once daily.
For children with bodyweights of 50 kg or more, the usual adult dosage should be used.
Intravenous doses of ≥50 mg/kg bodyweight should be given by slow infusion over at least 30 minutes.

Meningitis
In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg (up to a maximum of 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly. The following duration of therapy has shown to be effective:

Neisseria meningitidis	4 days
Haemophilus influenzae	6 days
Streptococcus pneumoniae	7 days

Lyme borreliosis
50 mg/kg to a maximum of 2 kg in children and adults, once daily for 14 days.

Gonorrhoea
(Penicillinase-producing and nonpenicillinase-producing strains) A single i.m. dose of 250 mg.

Perioperative prophylaxis
A single dose of 1 - 2 g (depending on the risk of infection) 30 - 90 minutes prior to surgery. In colorectal surgery, administration of **Ocexone®** with or without a 5-nitroimidazole e.g. Ornidazole (separate administration, see Method of administration) has proven effective.

Storage:
Do not store above 30°C.

Presentation:
Ocexone® is supplied in vials containing 1 g and 2 g equivalent of Ceftriaxone. The 1 g i.m. **Ocexone®** is co-packaged with 3.5ml lidocaine and the i.v. **Ocexone®** is co-packaged with 10ml water for injection.

MEDICINE: KEEP OUT OF REACH OF CHILDREN

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