SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TREGS 0.5 g IV powder for injection

2. QUALITATIVE AND QUANTITAVE COMPOSITION

Active ingredient:

Each vial contains;

500 mg ceftriaxone as 596,45 mg ceftriaxone sodium.

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Powder for solution is white to yellowish powder.

Solvent is (water for injection) colourless, odorless, clear solution.

When reconstituted it is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TREGS is indicated for the treatment of following infections caused by susceptible pathogens:

- Septicaemia
- Meningitis
- Disseminated Lyme borreliosis (early and late stages)
- Abdominal infections (peritonitis, biliary and gastrointestinal tract infections),
- Bone, joint, skin and soft tissue infections including wound infections
- Infections due to immune system disorders
- Renal and urinary tract infections
- Respiratory tract infections, including pneumonia, ear-nose and throat infections, acute bacterial uncomplicated otitis media
- Genital infections including gonorrhea
- Preoperative prophylaxis of infections

4.2. Posology and method of administration

Posology/Frequency of administration and duration of therapy:

Standard therapeutic dosage

Adults and children above 12 years of age:

The usual dose is 1-2 g given once a day (once in 24 hours). In moderate to severe cases and infections caused by susceptible organisms, daily dose may be increase to 4 g as a once daily dose.

Duration of therapy:

The duration of therapy varies according to the course of the disease. Generally as in all antibiotic therapies, administration of TREGS should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Combined therapy:

Synergy between TREGS and aminoglycosides has been demonstrated against many Gram-negative bacilli under experimental conditions.

Although enhanced activity of such combinations is not always predictable, it should be considered in severe, life-threatening infections due to organisms such as *Pseudomonas aeruginos*a. Because of physical incompatibility, the two drugs must be administered separately.

Meningitis: In the treatment of meningitis in infants and children, initial therapeutic dose is 100 mg/kg (should not exceed 4 g). When culture and susceptibility information are available therapeutic dose can be reduced if necessary.

Best therapy results were obtained with the following duration of therapy:

Neisseria meningitidis: 4 days

Haemophilus influenzae: 6 days

Streptococcus pneumoniae: 7 days

Lyme borreliosis: In children and adults, 50 mg/kg to maximum 2 g is administered as once daily dose for 14 days.

Gonorrhea: A single intramuscular dose of 250 mg TREGS is recommended for the treatment of gonorrhea (including penicillinase and non-penillicinase producing strains).

Preoperative prophylaxis: A single dose of 1-2 g TREGS 30-90 minutes before surgery is recommended depending on the infection risk.

In colorectal surgery, administration of TREGS alone or in combination with a 5-nitroimidazol derivate such as ornidazol has been proven to be effective.

Mode of administration:

After reconstitution, TREGS solutions should be used immediately.

Intravenous injection: Reconstitute contents of 0.5 g and 1 g vial with 5 ml and 10 ml sterile water for injection respectively. The injection should be administered over at least 2-4 minutes.

Intravenous infusion: The infusion should be administered over at least of 30 minutes. For intravenous infusion, 2 g TREGS should be dissolved in 40 ml of one of the following calcium-free solutions.

0.9 % NaCl

5 % Dextrose

10 % Dextrose

5 % Dextrose + 0.9% NaCl

5 % Dextrose + 0.45% NaCl

6 % Hyrdroxyethyl starch

Due to possible incompatibility, TREGS solutions should not be mixed with solutions containing other antimicrobial agents or diluent solutions other than those listed above.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute TREGS vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when TREGS is mixed with calcium-containing solutions in the same IV administration line. TREGS must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, TREGS and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

Information on special patients:

Renal / Hepatic impairment:

No dosage adjustment is necessary for patients with impairment of renal or hepatic dysfunction. Only in cases of pre-terminal renal failure (creatinine clearance <10 ml per minute) daily dosage should not exceed 2 g daily.

In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of ceftriaxone should be determined at regular intervals and dosage adjusted. In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis.

However, since the elimination rate in these patients may be reduced, serum concentrations should be monitored to determine whether dosage adjustment is necessary.

Pediatric population:

The following dosages are recommended for once daily administration for newborns, infants and children of up to 12 years

Neonates (Up to 14 days):

Once daily dose of 20-50 mg/kg body weight, not to exceed 50 mg/kg/day is recommended including premature and mature babies.

Administration of ceftriaxone and calcium-containing products simultaneously in newborns (aged ≤28 days) is contraindicated. TREGS should not be used in newborns receiving calcium-containing products (or expected to require these products).

Infants and children (15 days up to 12 years old):

20-80 mg/kg once daily.

For children with body weights of 50 kg more the usual adult dose should be used. For the treatment of non-complicated acute bacterial otitis media, a single dose of 50 mg/kg (not to exceed 1 g) is recommended.

Geriatric population:

Usual adult doses are used in geriatric patients.

4.3. Contraindications

TREGS is contraindicated in patients with known hypersensitivity to cephalosporin class of antibiotics.

In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind.

TREGS is contraindicated in patients with known hypersensitivity to ceftriaxone or any of the excipients.

Hyperbilirubinaemic newborns and preterm newborns should not be treated with ceftriaxone. *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.

Administration of ceftriaxone and calcium-containing products simultaneously in newborns (aged ≤28 days) is contraindicated. TREGS should not be used in newborns receiving calcium-containing products (or expected to require these products).

4.4. Special warnings and precautions for use

As with other cephalosporins, anaphylactic reactions with fatal outcome were also reported, even if a patient is not known to be allergic or previously exposed.

An immune mediated haemolytic anaemia has been observed in children and adults receiving cephalosporin class antibacterials including TREGS.

If a patient develops anaemia while on ceftriaxone, the diagnosis of cephalosporin associated anaemia should be considered and ceftriaxone discontinued until the aetiology is determined.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis have all been reported with the use of ceftriaxone. Ceftriaxone should be discontinued if severe and/or bloody diarrhoea occurs during treatment. Ceftriaxone should be prescribed with caution in individuals with gastro-intestinal disease or history of colitis.

As with other cephalosporins, prolonged use of ceftriaxone may result in the overgrowth of non-susceptible organisms, such as *enterococci* and *Candida spp.*

In the available scientific data, there are no reports of confirmed intravascular precipitations in patients other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites. (see section 4.3. Contraindications)

Superinfections with non-susceptible micro-organisms may occur as with other antibacterial agents.

Shadows which have been mistaken for gallstones have been detected by sonograms of the gallbladder, usually following doses higher than the standard recommended dose. These

shadows are, however, precipitates of calcium ceftriaxone which disappear on completion or discontinuation of ceftriaxone sodium therapy. Rarely, have these findings been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended.

Discontinuation of TREGS treatment in symptomatic cases should be at the discretion of the physician.

Cases of pancreatitis, possibly of biliary obstruction aetiology, have been rarely reported in patients treated with ceftriaxone sodium. Most patients presented with risk factors for biliary stasis and biliary sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition. A trigger or cofactor role of TREGS-related biliary precipitation can not be ruled out.

Safety and effectiveness of TREGS in newborns, infants and children have been established for the dosages described under 'Dosage and administration'. Studies have shown that ceftriaxone, like other cephalosporins, can displace bilirubin from serum albumin. For this reason, TREGS should be prescribed with caution in the treatment of newborns with hyperbilirubinemia. TREGS, should not be used in neonates at risk of developing bilirubin encephalopathy (especially prematures). During prolonged treatment, the blood cell count should be checked regularly. Hypersensitivity reactions may be observed in susceptible individuals.

Interaction with laboratory tests:

In patients treated with TREGS, the Coombs' test may rarely become false-positive. TREGS, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with TREGS should be done enzymatically.

Pediatry:

Cases of fatal outcomes with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full term newborns have been reported. Ceftriaxone and calcium-containing products can be used sequentially of one another in infants aged >28 days.

In this case, infusion lines should be thoroughly flushed between infusions with compatible fluids.

In patients of any age ceftriaxone should not be administered simultaneously with calcium-containing solutions. Ceftriaxone should not be diluted or mixed with calcium-containing solutions like Ringer's and Hartmann's solution or calcium-containing total parenteral

nutrition solutions. There have been no reports of interaction between intravenous ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).
Each vial contains 41.47 mg sodium. This should be taken into consideration for patients on a controlled sodium diet.

4.5. Interactions with other medicinal products and other forms of interaction

No impairment of renal function has so far been observed after concurrent administration of large doses of ceftriaxone and potent diuretics (e.g. furosemide). There is no evidence that ceftriaxone increases renal toxicity of aminoglycosides.
No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone sodium.
Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins.
The elimination of ceftriaxone is not altered by probenecid.
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.
Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute TREGS vials or to further dilute a reconstituted vial for IV administration because a precipitate can form.
Precipitation of ceftriaxone-calcium can also occur when TREGS is mixed with calcium-containing solutions in the same IV administration line.
TREGS must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site.
However, in patients other than neonates, TREGS and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.
In patients treated with TREGS, the Coombs' test may rarely become false-positive. TREGS, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with TREGS should be done enzymatically.

Ceftriaxone may adversely affect the efficacy of oral hormonal contraceptives. Consequently, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.

4.6. Pregnancy and lactation

Pregnancy category B

Women of childbearing potential / Birth control (Contraception)

Clinical data are not available regarding the use of ceftriaxone sodium in women of childbearing potential.

However, ceftriaxone may adversely affect on the efficacy of hormonal contraceptives. Therefore, it is advisable to use supplementary (non-hormonal) contraceptive measures during treatment and in the month following treatment.

Pregnancy

Ceftriaxone crosses the placental barrier. Safety in human pregnancy has not been established. Reproductive studies in animals have shown no evidence of embryotoxicity, fetotoxicity, teratogenicity or adverse effects on male or female fertility, birth or perinatal and postnatal development. In primates, no embryotoxicity or teratogenicity have been observed.

Ceftriaxone should be prescribed with caution to pregnant women.

Lactation

Low concentrations of ceftriaxone are excreted in human milk. This should be considered when administered to a nursing woman.

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.

4.7. Effects on ability to drive and use machines

There are no data about a negative impact on ability to use machines or motor vehicles. Since ceftriaxone sodium sometimes induces dizziness, the ability to drive and use machines can be impaired.

4.8. Undesirable effects

Very common (≥1/10); common (≥1/100-<1/10); uncommon (≥1/1.000-<1/100); rare (≥1/10.000-<1/1.000); very rare (<1/10.000), unknown (can not be estimated from the avaliable data)

Undesirable effects commonly disappear during treatment or after discontinuation of treatment.

Infections and infestations

Rare: Mycosis in the genital area

Superinfections of various sites with yeasts, fungi or other resistant microorganisms are possible.

Blood and lymphatic system disorders

Rare: Neutrapenia, eosinophilia, leucopenia, granolocytopenia, anaemia including haemolytic anaemia, thrombocytopenia, slight prolongation of prothrombin time

Very rare: Coagulation disorders

Unknown frequency of agranulocytosis (<500/mm^3) has been reported, mostly after 10 days of treatment and following total doses of 20g or more.

Immune system disorders

Rare: Anaphylactic (e.g. bronchospasm) or anaphylactoid reactions

Nervous system disorders

Rare: Headache and dizziness

Gastrointestinal system disorders

Common: Loose stools or diarrhoea, nausea, vomiting.

Rare: Stomatitis and glossitis.

These side effects are usually mild and often disappear during or after discontinuation of treatment.

Very rare (isolated cases): Pseudomembranous colitis (mostly caused by *Clostridium difficile*), pancreatitis (most likely occurs due to contraction of the bile duct). Therefore, the possibility of biliary disease should be considered in patients with antibacterial associated diarrhoea .

Hepatobiliary system disorders

Rare: Elevations in serum liver enzymes (AST, ALT, alkaline phosphatase).

Precipitation of ceftriaxone calcium salt has been observed, mostly in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application. The incidence seems

to be lower with slow infusion (20-30 minutes). This effect is usually asymptomatic, but in rare cases, the precipitation has been accompanied by clinical symptoms such as pain, nausea, and vomiting. Precipitation is usually reversible upon discontinuation of treatment with ceftriaxone.

Skin and subcutaneous tissue disorders

Uncommon: Allergic skin reactions such as maculopapular rash or exanthema, urticaria, dermatitis, pruritus, oedema.

Very Rare: In isolated cases Erythema multiforme, Stevens Johnson Syndrome, Lyell's Syndrome/toxic epidermal necrolysis.

Renal and urinary disorders

Rare: Increase in serum creatinine, oliguria, glycosuria, haematuria.

Very Rare: Including isolated reports; renal precipitation, mostly in children older than 3 years who have been treated with either high daily doses (≥80 mg/kg/day) or total doses exceeding 10 g and have other risk factors (such as dehydration or immobilization). Renal precipitation is reversible upon discontinuation of ceftriaxone. Anuria and renal impairment have been reported in association.

General disorders and administration site conditions:

Rare: Fever, rigor, phlebitis, and IV injection site pain depending on the application. This can be minimized by slow injection over at least 2-4 minutes.

An intramuscular injection without lidocaine solution is painful.

Research:

Interaction with calcium.

4.9 Overdose

In the case of overdosage, nausea, vomiting, diarrhoea can occur. Ceftriaxone concentrations would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other beta-lactam antibacterial drugs-Cephalosporins (3rd Generation)

ATC code: J01DD04

Ceftiaxone has bactericidal activity resulting from the inhibition of cell wall synthesis.

Ceftriaxone exerts *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. Ceftriaxone is highly stable to most beta-lactamases, both penicillinases and cephalosporinases of Gram-positive and Gram-negative bacteria. Ceftriaxone is effective against the following microorganisms *in vitro* and in clinical infections (see section 4.1. Indications).

Gram-positive aerobes:

- Methicillin-susceptible *staphylococcus aureus*[1]
- Methicillin-susceptible coagulase-negative *staphylococcus*[1] (e.g. *S. epidermidis*)
- *Streptococcus pyogenes* (Group A, β-hemolytic)
- *Streptococcus agalactiae* (Group B, β-hemolytic)
- *β-hemolytic streptococcus* (not included in Group A and B)
- *Streptococcus viridans*[1]
- *Streptococcus bovis*
- *Streptococcus pneumoniae*[1]

[1]: Species for which the efficacy of ceftriaxone has been demonstrated both *in vitro* and *in vivo*

Note: Methicillin-resistant coagulase-negative *Staphylococcus spp*. are resistant to cephalosporins, including ceftriaxone. In general *Enterococcus faecalis, Enterococcus faecium, Listeria monocytogenes* are resistant to ceftriaxone.

Methicillin-resistant coagulase-negative *Staphylococcus* species (e.g. *S. epidermidis*) are resistant to ceftriaxone.

Gram-negative aerobes:

- [+]*Acinetobacter* species (*Acinetobacter lwoffi, Acinetobacter anitratus* [especially *A. baumanii]*, Acinetobacter calcoaceticus*)[1]
- *Aeromonas hydrophila*
- *Alcaligenes faecalis*
- *Alcaligenes odorans*
- *Alcaligenes* species
- *Borrelia burgdorferi*
- *Capnocytophaga* species
- *Citrobacter* specie (*Citrobacter diversus* [including *C. amalonaticus*], *Citrobacter freundii***)
- *Escherichia coli*[1]
- [+]*Enterobacter aerogenes*[1]*

- +*Enterobacter cloacae*[1]*
- +*Enterobacter* species (other)[1]*
- *Haemophilus ducreyi*
- *Haemophilus influenzae* (including *beta-laktamase* pozitive isolates[1])
- *Haemophilus parainfluenzae*[1]
- *Hafnia alvei*
- *Klebsiella* species[1] (*Klebsiella oxytoca, Klebsiella pneumoniae***)
- *Moraxella catarrhalis*[1] (*Branhamella catarrhalis*)
- *Moraxella osloensis*
- *Moraxella* species (other)
- *Morganella morganii*[1]
- *Neisseria gonorrhoea*[1] (penicillin-resistant isolates*)*
- *Neisseria meningitidis*[1]
- *Pasteurella multocida*
- *Plesiomonas shigelloides*
- *Proteus* species[1] (*Proteus mirabilis*[1]*, Proteus penneri**, *Proteus vulgaris*[1]**)
- *Pseudomonas fluorescens**
- *Pseudomonas* species (other)*
- *Providentia rettgeri**
- *Providentia* species (other)
- *Salmonella typhi*
- *Salmonella* species(non-typhoid)
- *Serratia* species[1] (*Serratia marsescens**)
- *Serratia* species (other)*
- *Shigella* species
- *Vibrio* species
- *Yersinia enterocolitica*
- *Yersinia* types (other)

[1]: Species for which the efficacy of ceftriaxone has been demonstrated both *in-vitro and in-vivo*

* Some strains shows resistance to ceftriaxone by producing especially chromosomal β-lactamase

** Some strains shows resistance to ceftriaxone by producing especially broad spectrum and plasmid- mediated β-lactamase.

[+]: Species for which high rates of resistance have been observed in more regions within the EU.

Note: Many strains of the above organisms that are multiply resistant to other antibiotics, e.g. amino- and ureido- penicillins, older cephalosporins and aminoglycosides are susceptible to ceftriaxone. *Treponema pallidum* is found sensitive *in vitro* and in animal studies. Clinical investigations indicate that primary and secondary syphilis respond well to ceftriaxone therapy. With a few exceptions, clinical *P. aeruginosa* isolates are resistant to ceftriaxone.

Listeria monocytogenes, Mycoplasma species*, Stenotrophomanas maltophilia, Ureplasma urealyticum, Chlamydia* types of organisms are also resistant to ceftriaxone.

Anaerobic organisms:

- *Bacteroides* species (bile-sensitive)*,
- *Clostridium* species[1] (except *C. difficile* group),
- *Fusobacterium nucleatum*,
- *Fusobacterium* species (other),
- *Gaffkia anaerobica* (*peptococcus*),
- *Peptostreptococcus* species[1]

[1]: Species for which the efficacy of ceftriaxone has been demonstrated both in-vitro and in-vivo

* Some strains shows resistance to ceftriaxone by producing especially chromosomal β-lactamase

Note: Many of β-lactamase-producing *Bacteroides* species (especially *B. fragilis*) are resistant. *Clostridium difficile* is also resistant.

Limit values :

Susceptibility to ceftriaxone can be determined by the disc diffusion test or by the agar or broth dilution test using standardized techniques recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The NCCLS issued the following interpretative breakpoints for ceftriaxone:

Using 30 mg/l drug concentration, values are reported as mg/l (MIC test) or mm (disc diffusion test).

National Committee for Clinical Laboratory Standards (NCCLS)-(M100-S12)

	Susceptible	Moderately Susceptible	Resistant
Enterobacteriaceae, P. aeruginosa ad other *non-Enterobacteriaceae, Staphylococcus* species	≤ 8 Disc: < 13	16-32 Disc: 14-20	≥ 64 Disc: ≥ 21
Haemophilus species	≤ 2 Disc: ≥ 26	-	-
Neisseria species	≤ 0.25 Disc: ≥ 35	-	-
*Streptococcus pneumoniae**	≤ 0.5	1	≥ 2
Other *Streptococcus* species**	*Beta strep* (Streptococcal pharyngitis) ≤ 0.5 Disc: ≥ 24 *Viridans* group: ≤ 0.5 Disc: ≥ 27	- *Viridans* group: 1 Disc: 25 - 26	- *Viridans* group: ≥ 2 Disc: ≤ 24

* 2002 *S. pneumoniae* limit values (NCCLS M100-S12) ; for non-meningitis samples ≤1 (Susceptible), 2 (Moderate) and ≥4 (Resistant) and for meningitis samples ≥0.5 (Susceptible), 1 (Moderate) and > 2 (Resistant)

** 2002 *Streptococcus viridans* group limit values (NCCLS M100-S12) ; ≤1 (Susceptible), 2 (Moderate) and ≥4 (Resistant)

Organisms should be tested with ceftriaxone disc since it has been shown by *in vitro* tests to be active against certain strains resistant to cephalosporin class discs.

Countries where NCCLS recommendations are not in daily use, alternative, well standardized, susceptibility interpretative guidelines such as those issued by DIN, ICS and others may be substituted.

5.2. Pharmacokinetic properties

Absorption: Maximum plasma concentration of ceftriaxone following an intramuscular administration of a single 1 g dose is 81 mg/l achieved between 2-3 hours post dose.

Mean peak concentrations after bolus intravenous injection are about 120 mg/l following a 500 mg dose and about 200 mg/l following a 1g dose. Mean levels of 250 mg/l are achieved after infusion of 2 g over 30 minutes.

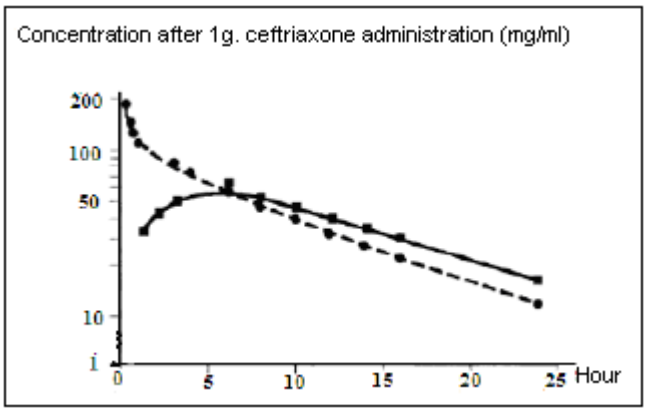
Intramuscular injection of 500 mg TREGS IM in 1% lidocaine hydrochloride solution produces mean peak plasma concentrations of 40-70 mg/l within 1 hour. Bioavailability after intramuscular injection is 100%.

Distribution: Volume of distribution of ceftriaxone is 7-12 litre. After a dose of l-2 g; ceftriaxone provides excellent penetration over the minimum inhibitory concentration of most causative pathogens in lung, heart, bile duct / liver, tonsils, middle ear and the nasal mucosa, bone, cerebrospinal, pleural, synovial fluids, including prostate and over 60 tissues and body fluids for a periods of longer than 24 hours.

Ceftriaxone diffuses fastly through interstitial fluid after intravenous administration and bactericidal concentrations against susceptible organisms are maintained for 24 hours (see figure).

The pharmacokinetics of TREGS is largely determined by its concentration-dependent binding to serum albumin. The plasma free (unbound) fraction of the drug in man is approximately 5% over most of the therapeutic concentration range, increasing to 15% at concentrations of 300 mg/l.

Ceftriaxone is reversibly bound to albumin and the binding decreases as the drug concentration in blood increases, e.g; the binding decreased from a value of 95% bound at plasma concentrations of lower than 100 mg/l to a value of 85% bound at 300 mg/l of plasma concentrations. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.



Ceftriaxone penetrates the inflamed meninges of newborns, infants and children. Following a 50-100 mg/kg IV TREGS administration in infants and children, cerebrospinal fluid concentration of ceftriaxone is above 1.4 mg/l within 24 hours. Mean peak concentration of 18 mg/l in cerebrospinal fluid is achieved in approximately 4 hours following IV administration. Average concentrations in cerebrospinal fluid are, 17% of the plasma concentration in bacterial meningitis and 4% of the plasma concentration in aseptic meningitis. In adults with meningitis, after administration of 50 mg/kg, for a period of 2-24 hours, cerebrospinal fluid concentrations are significantly higher than the MIC values of the most common causative pathogens of meningitis. Ceftriaxone crosses the placental barrier and low concentrations are excreted in human milk.

Biotransformation: Ceftriaxone is not metabolized, but it is converted to inactive metabolites by the intestinal flora.

Elimination: TREGS is eliminated mainly as unchanged ceftriaxone, approximately 50-60% of the dose being excreted in the urine (almost exclusively by glomerular filtration) and the remainder via the biliary and intestinal tract. The total plasma clearance is 10-22ml/min. The renal clearance is 5-12ml/min. The elimination half-life in adults is about 8 hours. The half-life is not significantly affected by the dose, the route of administration or by repeated administration.

Linearity/Non-Linearity case: The pharmacokinetics of ceftriaxone is not linear. Except the elimination half-life based on the total drug concentration, all the main pharmacokinetic parameters are dose-dependent.

Pharmacokinetics in special patients:

Elderly patients: In elderly patients aged over 75 years, the average elimination half-life is usually 2 to 3 times longer than in the young adult group. As with all cephalosporins, a decrease in renal function in the elderly may lead to an increase in elimination half life. All scientific data show that dose adjustment is not necessary for elderly patients.

Newborns: In the first week of life, 80% of the dose is excreted in the urine. In newborns aged less than 8 days the average elimination half-life is usually two to three times longer than that of young adults.

Patients with renal and hepatic impairment: In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone is only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

Cerebrospinal fluid: TREGS crosses non-inflamed and inflamed meninges, attaining concentrations 4-17 % of the simultaneous plasma concentration.

5.3. Preclinical safety data

Reproduction studies have no evidence of embryotoxicity, foetotoxicity, teratogenicity or any harmful effect on impairment of male or female fertility, birth, perinatal and postnatal development. Embryotoxicity or teratogenicity was not observed in primates.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Ampoule (solvent):

Water for injection

6.2. Incompatibilities

Solutions containing ceftriaxone, should not be mixed with solutions containing other drugs or solutions other than those listed in 6.6.

In particular, diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form.

Based on literature reports ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole or aminoglycosides.

6.3. Shelf life

Unopened vial: 24 months

Chemical and physical stability has been demonstrated for 24 hours at room temperature (25°C) and for 72 hours at refrigerator (2-8°C), after reconstitution or reconstitution and solvent.

From a microbiological point of view; reconstituted solutions should be used immediately. If not, in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage

Unopened vial: Store below 25°C. Keep the vial in the outer carton in order to protect from light.

6.5. Nature and contents of container

Supplied in packs of 1 vial containing powder for injection and 1 ampoule containing solvent.

Vial:

10 ml colorless glass vial (type III) closed with bromobutyl rubber stopper and sealed with aluminum flip-off cap.

Ampoule:

Colorless glass ampoule (type I) containing 5 ml water for injection.

6.6. Special precautions for disposal and other handling

Any unused product or residual material should be disposed in accordance with "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

Preparation of parenteral solution:

After reconstitution, parenteral drugs should be shaken thoroughly before administration and should be inspected for particulate matter. Do not use if particles are present.

The color of reconstituted solutions range from honey to light yellow, depending on the concentration and length of storage time. Variations in the color of solutions do not indicate a change in potency or safety.

Intravenous administration:

-Intravenous injection: TREGS 0.5 g vial should be dissolved in 5 ml of water for injection. The injection should be administered over at least 2-4 minutes directly into the vein (or through the tubing system by which the patient is also receiving total parenteral nutrition solutions).

-Intravenous infusion: Infusion should be administered over a period of at least 30 minutes. For intravenous infusion, TREGS 0.5 g vial is dissolved in 5 ml of water for injection and may further be diluted to concentrations of 10-40 mg/ml in the following solutions:

0.9 % NaCl

5 % dextrose

10 % dextrose

5 % dextrose + 0.9 % NaCl

5 % dextrose + 0.45 % NaCl

6 % hyrdroxyethyl starch

TREGS solutions for intravenous infusion (diluted as directed in the above listed solutions), maintain their chemical and physical stability for 24 hours at room temperature (25°C) and for 72 hours at refrigerator (2-8°C).

From a microbiological point of view, reconstituted solutions should be used immediately. If not, in-use storage times and conditions are the responsibility of the user.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

247/45

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 28.12.2012

Date of renewal:

10. DATE OF REVISION OF THE TEXT

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