MESPORIN™

Powder and solvent for IM administration: MESPORIN™ - 250 mg; 500 mg and 1000 mg

Powder and solvent for IV administration: MESPORIN™ - 250 mg; 500 mg and 1000 mg

Powder for IV perfusion: MESPORIN™ -2 g

Injectable solutions

Qualitative and Quantitative Composition

MESPORIN™ - 250 mg IM – Powder and solvent for injectable solution

Formula per vial:	
Ceftriaxone (in the form of sodium ceftriaxone)	250 mg
Lidocaine chlorhydrate	20 mg
Water for injectable solutions enough for	2 ml

MESPORIN™ - 250 mg IV – Powder and solvent for injectable solution

Formula per vial:	
Ceftriaxone (in the form of sodium ceftriaxone)	250 mg
Formula per ampoule:	
Water for injectable solutions enough for	5 ml

MESPORIN™ - 500 mg IM – Powder and solvent for injectable solution

Formula per vial:	
Ceftriaxone (in the form of sodium ceftriaxone)	500 mg
Formula per ampoule:	
Lidocaine chlorhydrate	20 mg
Water for injectable solutions enough for.	2 ml

MESPORIN™ - 500 mg IV – Powder and solvent for injectable solution

Formula per vial:	
Ceftriaxone (in the form of sodium ceftriaxone)	500 mg
Formula per ampoule:	
Water for injectable solutions enough for	5 ml

MESPORIN™ - 1000 mg IM – Powder and solvent for injectable solution

Formula per vial:	
Ceftriaxone (in the form of sodium ceftriaxone)	1 g
Formula per ampoule:	
Lidocaine chlorhydrate	35 mg
Water for injectable solutions enough for	3,5 ml

MESPORIN™ - 1000 mg IV – Powder and solvent for injectable solution

Formula per vial:	
Ceftriaxone (in the form of sodium ceftriaxone)	1 g
Formula per ampoule:	
Water for injectable solutions enough for	10 ml

MESPORIN™ - 2 g IV – Powder and solvent for perfusion

Formula per vial:	
Ceftriaxone (in the form of sodium ceftriaxone)	2 g

Pharmaceutical Form

***MESPORIN™* 250 mg IM (vial + ampoule)**

Parenteral route administration.

Powder and solvent for injectable solution, containing in the vial 250 mg of ceftriaxone (in the form of sodium ceftriaxone) and in the ampoule 2 ml of adequate solvent.

Packages of 1 dose IM.

The product is presented in a transparent glass vial and amber ampoule with 2 ml of lidocaine chlorhydrate solution 1 %, conditioned in a cardboard box.

***MESPORIN™* 250 mg IV (vial + ampoule)**

Parenteral route administration.

Powder and solvent for injectable solution, containing in the vial 250 mg of ceftriaxone (in the form of sodium ceftriaxone) and in the ampoule 5 ml of water for injectable solutions.

Packages of 1 dose IV.

The product is presented in a transparent glass vial and ampoule with water for injectable solutions with 5 ml.

***MESPORIN™* 500 mg IM (vial + ampoule)**

Parenteral route administration.

Powder and solvent for injectable solution, containing in the vial 500 mg of ceftriaxone (in the form of sodium ceftriaxone) and in the ampoule 2 ml of adequate solvent.

Packages of 1 dose IM.

The product is presented in a transparent glass vial and amber ampoule with 2 ml of lidocaine chlorhydrate solution 1 %, conditioned in a cardboard box.

***MESPORIN™* 500 mg IV (vial + ampoule)**

Parenteral route administration.

Powder and solvent for injectable solution, containing in the vial 500 mg of ceftriaxone (in the from of sodium ceftriaxone) and in the ampoule 5 ml of water for injectable solutions.

Packages of 1 dose IV.

The product is presented in a transparent glass vial and ampoule with water for injectable solutions with 5 ml.

***MESPORIN™* 1000 mg IM (vial + ampoule)**

Parenteral route administration.

Powder and solvent for injectable solution, containing in the vial 1g of ceftriaxone (in the from of sodium ceftriaxone) and in the ampoule 3,5 ml of adequate solvent.

Packages of 1 dose IM.

The product is presented in a transparent glass vial and amber ampoule with 3,5 ml of Lidocaine chlorhydrate solution 1 %, conditioned in a cardboard box.

***MESPORIN™* 1000 mg IV (vial + ampoule)**

Parenteral route administration.

Powder and solvent for injectable solution, containing in the vial 1g of ceftriaxone (in the from of sodium ceftriaxone) and in the ampoule 10 ml of water for injectable solutions.

Packages of 1 dose IV.

The product is presented in a transparent glass vial and ampoule with water for injectable solutions with 10 ml.

MESPORIN™ 2 g IV, for Perfusion (vial)

Parenteral route administration.

Powder and solvent for injectable solution, containing in the vial 2g of ceftriaxone (in the from of sodium ceftriaxone)

Packages of 1 dose for perfusion IV.

The product is presented in a transparent glass vial.

Clinical Informations

Therapeutic Indications

Ceftriaxone is used in the treatment of lower respiratory tract infections, skin and its structures infections, bone and joint infections, intra-abdominal infections, urinary tract infections, meningitis, septicaemia and provoked gonorrhoea. Ceftriaxone is also used for peri-surgery prophylaxis.

Due to the fact that, ceftriaxone has a prolongated half-life and can be used once daily, some clinicians suggest this drug can be useful in the treatment of infections caused by susceptible microorganisms, that require prolongated therapy in ambulatory patients (osteomyelitis). Ceftriaxone has been used successfully in the treatment of adults and children in ambulatory, in some cases the drug was self-administrated. Before initiating the therapy with ceftriaxone, the adequate samples should be collected to identify the causative microorganism and study *in vitro* sensitivity. Therapy with ceftriaxone can be initiated while waiting for the sensitivity tests results, but should be interrupted if the microorganism demonstrates resistance to this antibiotic.

Bacterial Infections caused by Gram-positive Aerobics

In general ceftriaxone has been effective in adults and children in the treatment of skin cutaneous structures infections, pneumonia, urinary tract infections, bone and joint infections or septicaemia caused by sensitive Gram-positive coccus (*Staphylococcus aureus, Streptococci* from groups A and B, *Streptococcus pneumoniae*). However, many clinicians share the opinion that ceftriaxone, like other 3rd generation cephalosporins, should not be used in the treatment of infections caused by Gram-positive bacteria when penicillin or 1st generation cephalosporins can be used.

Bacterial Infections caused by Gram-negative Aerobics

Ceftriaxone is used in the treatment of lower respiratory tract infections caused by: *Haemophilus influenza, Haemophilus parainfluenza, Enterobacter xerogenes, Escherichia coli, Klebsiella (including K. Pneumoniae), Proteus mirabilis or Serratia marcescens;* Skin and cutaneous infections caused by *E. cloacae, Klebsiella (including K. Pneumoniae, K. oxytroca), P. mirabilis, Morganella morganii, E. coli Serratia marcescens, Acinetobacter calcoaceticus or Pseudomonas aeruginosa;* bone and joint infections caused by *Enterobacter, E. coli, K. Pneumoniae, P. mirabilis* ;urinary tract infections caused by *E. coli, Klebsiella (including K. Pneumoniae), Morganella morganii, P. mirabilis or P. vulgaris;* intra-abdominal infections caused by *E. coli or K. Pneumoniae;* non-complicated gonorrhoea or pelvic inflammatory disease (PID) caused by *Neisseria gonorrhoeae;* septicaemia caused by *E. coli, H. influenza or K. Pneumoniae.*

Third generation cephalosporins have been used together with aminoglycosids in the empirical treatment of patients with severe Gram-negative sepsis.

Cancroid

A dose of 250 mg IM of ceftriaxone is effective in the treatment of genital ulcers caused by *H. ducreyi* and is recommended as an alternative to erythromycin in this infection treatment, in patients infected by the Human Immunodeficiency Virus (HIV).

Bacterial Infections caused by Enterobacteriacea

Ceftriaxone and other 3rd generation cephalosporins, are as effective as aminoglycosids in the treatment of these infections and are associated to less toxicity. In the beggining of severe infections caused by *Enterobacteriacea,* many clinicians suggest that 3rd generation cephalosporins and a large spectrum penicillin should be used together with an aminoglycosid until the sensitivity tests results are known. Some clinicians even suggest that ceftriaxone is specially useful as initial therapy in the treatment of infections known or suspected to be caused by multiresistant *Enterobacteriacea* (pneumonia or nosocomial infections of urinary tract, septicaemia suspects in neutropenic patients). However, for the treatment of urinary tract infections without complications, ceftriaxone use (like other 3rd generation cephalosporins) should not be generalized, when are available small activity spectrum antibiotics, considered the first choice.

Otitis media

A clinical trial results, randomised and double blind suggest that a single dose of 50 mg/kg of ceftriaxone IM has an equal efficacy to 40 mg/kg of amoxicillin during 10 days, in the treatment of otitis media in children between 5 months and 5 years of age. A single dose of ceftriaxone IM can therefore, be an alternative to oral antibiotics in the treatment of otitis media, especially in cases where acceptance/collaboration, from the patient can be a problem.

Gonorrhoea and Associated Infections

Ceftriaxone is used in the treatment of non-complicated gonorrhea, as well as other gonococcic infections caused by strains that produce penicillinases of *N. gonorrhoeae* (PPNG) or strains that do not produce penicillinases of this microorganism. Ceftriaxone is considered as a first choice drug in the treatment of endocervical or rectum uretral infections caused by *N. gonorrhoeae,* as well as other gonococcic infections caused by PPNG.

Non-complicated Gonorrhoea in Adults

A single dose of ceftriaxone IM is one of various therapeutic regimens effective in the treatment of uretral, endocervical, pharynge or rectal infections caused by *N. gonorrhoeae* penicillinase producer or not. A single doses of 125-250 mg of ceftriaxone IM is recommended for the treatment of non-complicated gonorrhoea, associated to an anti-infection regimen effective in Chlamydia infection. Up to now, there are no known strains of *N. gonorrhoeae* resistant to ceftriaxone.

Disseminated Gonococcic Infections in Adults

Ceftriaxone IM and IV is recommended as the elective regimen in the initial treatment of disseminated gonococcic infection (syndrome of dermatitis-gonococcic arthritis).

Gonococcic Ophtalmia in Adults

Ceftriaxone IM is recommended for the treatment of gonococcic ophtalmia treatment in the adult. It should be considered the risk of ophtalmic infection with *C. trachomatis,* especially in the patients that did not respond to ceftriaxone therapy.

Epididymitis

A single dose of 250 mg of ceftriaxone IM associated to oral doxicyclin or tetracyclin orais, in adults, in the treatment of acute epididymitis, sexually transmitted and caused by *N. gonorrhoeae* and/or *C. trachomatis.*

Gonococcic Infections in Children and Adults

Newborns from mothers with gonorrhoea bear a risk of gonococcic infections and must receive prophylaxis against this disease. In these conditions and as prophylatic is recommended a single dose of ceftriaxone IM or IV of 25-50 mg/kg not exceeding 125 mg. All newborns and children with gonococcic infections docu-

mented in any area (e.g. eye) should be evaluated as to the possibility of disseminated infections. If this is confirmed, is recommended 7 days (10-14 days for meningitis and 4 weeks for endocarditis) of therapy with ceftriaxone IM or IV.

Paediatric Gonococcic Infections

For the treatment of gonococcic vulvovaginitis, urethritis, proctitis or pharyngitis in children weighing less than 45 kg a single dose of mg de ceftriaxone IM. In the treatment of arthritis and gonococcic bacteraemia in children weighing less than 45 kg is recommended the therapy of 7 days with ceftriaxone IM or IV in the dose of 50 mg/kg/day (up to 1 g).

For the treatment of gonococcic meningitis or endocarditis in these children, the same dose is recommended (up to 2 g daily, in 1 or 2 doses) during at least, 7-14 days or 3 to 4 weeks, respectively.

Acute Pelvic Inflammatory Disease

Ceftriaxone is used in the treatment of Pelvic Inflammatory Disease (PID), in general with a multi-microorganism basis caused by *N. gonorrhoeae, C. trachomatis,* anaerobic bacteria, facultative Gram-negative bacillus, streptococcus and mycoplasma.

Infections by Pseudomonas

For the treatment of skin, soft tissues, urinary and respiratory infections caused by *Pseudomonas aeruginosa* ceftriaxone is recommended in association with another antibiotic due to risk of resistant strains, being present.

Infections by Neisseria meningitidis

Ceftriaxone is used as an alternative in the treatment of invasive infections caused by *Neisseria meningitidis,* to eliminate the rhynopharyngeal presence of this pathogenic agent and as prophylaxis to avoid menigococcic disease.

Infections by Salmonella and Shigella

Ceftriaxone IV administrated in a single daily dose (3-4 g daily in adults or 75 mg/kg, in children) during 7 days is as effective as 14 days of chloramphenicol oral or IV, in the treatment of thyphoid fever caused by *Salmonella typhi.* It is considered that ceftriaxone is an effective alternative in the treatment of infections caused by resistant *Shigella* strains.

Aerobic and Anaerobic Bacteria Mixed Infections

Ceftriaxone is used in treatment of skin and cutaneous structures infections or intra-abdominal infections caused by *Bacteroides fragilis, Peptostreptococcus* and some *Clostridium* strains. However *C. difficile* is generally resistant to ceftriaxone.

Central Nervous System Bacteria Infections

Ceftriaxone is effective when used isolated in newborns, children or adults in the treatment of meningitis caused by sensitive *H. Influenzae, N. meningitidis or S. pneumoniae.* It has also been successfully used, though in a limited number of patients, in the treatment of menigitis and derived infections caused by sensitive strains of E. *coli* and *S. epidermidis,* however more studies are still necessary to prove ceftriaxone efficacy in these specific cases.

Syphilis

Ceftriaxone has some efficacy against *Treptonema pallidum* and can have a positive action in the initial incubation of syphilis. Ceftriaxone IM has been successfully used, in a limited number of male patients, for the treatment of primary syphilis, and at lower doses, for the treatment of primary and secondary syphilis.

Lyme Disease

Ceftriaxone has been used in the treatment of severe late complications of Lyme disease, a spirochetes disease caused by *Borrelia burgdorferi,* when there is no satisfactory response with other antibiotics. Ceftriaxone (1 to 2g IM or IV BID during 14 days) promotes clinical status improvements including arthritis and chronic fatigue elimination.

In cases of severe manifestations of Lyme disease, is preferable to use ceftriaxone instead of penicillin G, because it has an higher activity *in vitro* and *in vivo* against *B. burgdorferi* and a larger plasma concentration timing with a single daily dose.

Prophylaxis

Pre-Surgery Prophylaxis

Ceftriaxone revealed efficacy when used in pre-surgery to reduce infection incidence in patients undergoing contaminated or potentially contaminated surgical interventions including cholecystotomy, intra-abdominal surgery or vaginal, abdominal hysterectomy and in patients undergoing non-contaminated surgical interventions, in which the infections development at surgery site presents a serious risk, like coronary arterial bypass, open-air surgery or orthopaedic surgery. This drug has also been used pre-surgery in patients undergoing prostate transurethral resection. When used as pré-surgery prophylaxis, ceftriaxone should be administrated 0,5 – 2 hours before surgery initiation to guarantee an adequate anti-infectious tissue concentration.

Rape Victims Prophylaxis

In the anti-infectious empirical prophylaxis of teenagers and adults victims of rape, ceftriaxone IM is recommended associated to oral metronidazole and doxicyclin. The anti-infectious prophylaxis benefits rape victims because usually covers the risk of infection by *Thrycomonas, Chlamydia,* gonorrhoea and bacterial vaginitis, the sexually transmissible diseases more frequent after sexual abuse.

Posology and Method of Administration

Ceftriaxone is usually administrated by IV infusion or IM profound injection. It can also be administrated by rapid injection.

Intermittent IV Infusion

For intermittent IV infusion, the vials containing 250 mg, 500 mg, 1 or 2 g of ceftriaxone should be reconstituted with 2.4, 4.8, 9.6 or 19.2 ml, respectively, of an IV compatible solution with the aim of obtaining a solution containing approximately 100 mg/ml.

The substance reconstituted solutions should be first diluted in an IV adequate solution, usually in the concentration of 10-40 mg/ml, though if you wish to, lower concentrations can be used.

The injection should not be used in series with other plastic vials, because that can cause residual air gas embolism from the primary vial, before fluid administration from the secondary vial is complete.

Ceftriaxone intermittent IV infusions should usually be run in 15-30 minutes in newborns and children.

Although intermittent IV infusion is the recommended, it has also been administrated by direct IV intermittent injection, injecting an adequate dose of ceftriaxone directly in the vein during a period of 2-4 minutes.

IM Injection

Ceftriaxone IM injections are prepared adding 0.9, 1.8, 3.6 or 7.2 ml of:

- Sterile water for injection of sodium chloryde 0.9%
- Injection with dextrose 5%
- Bacteriostatic water for injections containing benzilic alcohol a 0.9%
- Lidocaine chlorhydrate 1% (without epinephrine)

In vials containing 250 mg, 500 mg, 1 or 2 g of ceftriaxone, respectively, to obtain solutions containing approximately 250 mg/ml.

Dose

The dose of sodium ceftriaxone is expressed in terms of ceftriaxone and is identical to administer IM or IV.

Adult Dose

Ceftriaxone usual adult dose for treatment of the most part of infections caused by sensitive microorganisms is 1-2 g administrated once daily (QD) or divided and administrated twice daily (BID), depending on the type and severity of the infection. However, some clinicians suggest that CNS infections in adults may need 4 g daily. The maximum recommended dose of ceftriaxone for adults is 4g daily.

For the treatment of non-complicated gonorrhoea caused by strains of *Neisseria gonorrhoeae* producers of penicillinase with the dose of 125 mg IM can also be effective in this type of infections, however it can speed up the development of resistant *N. gonorrhoeae* strains, to the substance. For the treatment of gonococcic disseminated infection, adults can receive 1 g of ceftriaxone IM or IV once daily, during 7 days. In non- septicaemic gonococcic ophtalmia treatment, the usual adult dose is 1 g of ceftriaxone IM.

For the treatment of acute sexually transmitted epididymitis, adults can receive a dose of 250 mg of ceftriaxone IM followed by erythromycin or tetracyclin by oral route.

In the treatment of pelvic inflammatory disease when the patient is not hospitalized, teenagers and adults can receive a dose of 250 mg of ceftriaxone IM, followed by 100 mg of doxicyclin by oral route twice a day during 10-14 days.

For the treatment of severe joint manifestations, cardiac or neurologic of early or late Lyme disease is recommended as an alternative to therapy with penicillin G IV, the dose of 2 g ceftriaxone IV daily, during 10-21 days for adults and of 15-100 mg/kg/day during 10-21 days in children.

If ceftriaxone is used for pre-surgery prophylaxis in adults, is recommended 1 g IV 0.5-2 hours before surgery, in order to ensure anti-infectious tissue concentrations.

Paediatric Dose

Children over 12 years can receive the usual adult dose.

In newborns and children up to 12 years, the usual ceftriaxone dose in the treatment of severe infections, others than those of CNS (e.g. meningitis) caused by sensitive microorganisms is 50-75 mg/kg (not exceeding 2 g) daily, administrated in doses equally divided in 12/12 h or in a single dose.

In the treatment of CNS infections (ex. meningitis) caused by sensitive microorganisms, the usual ceftriaxone dose for newborns and children up to 12 years is 100 mg/kg daily, divided in equal doses and administrated each 12/12 hours.

If using the once daily dose regimen in children over 1 month of age, for meningitis treatment should be administrated in the dose of 80-100 mg/kg of ceftriaxone until diagnosis is concluded, followed by two doses of 80 mg/kg administrated in intervals of 12 hours during the 1st day of therapy, and after this one, 80-100 mg of ceftriaxone each 24/24 hours.

For the treatment of non-complicated pharyngitis, proctitis, urethritis, gonococcic vulvovaginitis in children weighing less than 45 kg can receive a dose of 125 mg of ceftriaxone IM.

In gonococcic infections prophylaxis in newborns of mothers with pre-natal gonococcic infection, a dose of 25-50 mg/kg of ceftriaxone IM or IV at birth, is recommended.

In the treatment of children with gonococcic ophtalmia or with non-complicated gonococcic disseminated infection the normal dose is 25-50 mg/kg/day of ceftriaxone IM or IV during 7 days.

In the treatment of acute pelvic inflammatory disease of children in pre-puberty, ceftriaxone IV regimens are 100 mg/kg daily associated with erythromycin (oral or IV) or sulfisoxazole oral. In children over 7 years daily regimens of 100 mg/kg of ceftriaxone IV in association with tetracyclin IV have also been used.

Therapy Duration

Ceftriaxone therapy duration depends on the type and severity of the infection and can be determined by clinical and bacteriological patient's response. For many infections, except gonorrhoea, therapy should be continued, until at least 48 hours, after the patient is asymptomatic or shows evidence of infection suppression. In invasive infections, therapy should continue during 5 to 7 days after bacteriological cultures become negative.

Ceftriaxone therapy usual duration is 4-14 days but more complicated infections can requiere more prolongated therapy. Although the infection severity, has for clinicla and bacteriological response the determination of therapy duration, a 7 days therapy with ceftriaxone demonstrated to be as effective as 10 days in a trial with children with *H. influenzae, S. pneumoniae, Streptococcus* from group B or *N. meningitidis*. However is recommended that meningitis by Streptococcus from group B, should be treated during a minimum period of 10 days, meningitis by bacillus Gram – should be treated during a minimum of 21 days and a treatment period longer than 7 days in patients with continued irritability or meninges inflammation signs, patients with extreme CNS anomalies (leukocytes count higher than 200-300 mm^3 and a predominance of polymorphonuclears, glucose concentrations lower than 30 mg/dl, proteins concentrations higher than 200 mg/dl) and in patients with superinfections.

Renal and Hepatic Impairment Dose

Ceftriaxone usual dose alteration is in general, not necessary in renal or hepatic impaired patients. However, the drug's serum concentrations can be monitored when ceftriaxone is used in patients with renal or hepatic impairment. If there is evidence of ceftriaxone accumulation, the dose should be decreased according to this parameter. The adult dose with renal or hepatic impairment should not exceed 2 g/day, unless the ceftriaxone serum concentration is rigorously controlled.

Suplemental doses of ceftriaxone during or after dialysis are unnecessary because ceftriaxone is not removed by haemodialysis.

Contra-indications

Ceftriaxone is contra-indicated in patients with hypersensitivity to cephalosporins.

There are no adequate or controlled studies using ceftriaxone in pregnant women, and for that, it should only be used when necessary.

Ceftriaxone therapy should be discontinued if the patient develops symptoms or signs susceptible of biliary vesicle disease.

Ceftriaxone should not be administrated to newborns with hyperbilirubinemia, especially to prematures.

Reconstituted ceftriaxone with bacteriostatic water, containing benzilic alcohol for IM administration should not be used in newborns. Toxicity appears to result from administration of large quantities of benzilic alcohol to newborns (around 100-400 mg/kg daily).

Warnings and Special Precautions for Use

Ceftriaxone shares the toxic potential with cephalosporins, and the usual precautions in therapy with cephalosporins must be observed. Before initiating therapy with ceftriaxone, the patient's clinical history should be evaluated, as to previous

hypersensitivity reactions to cephalosporins, penicillins or other antibiotics. There is clinical and laboratorial evidence of cross-allergenicity between cephalosporins and other beta-lactamic antibiotics, including penicillins, cephamicin and 1-oxa-beta-lactamics.

Ceftriaxone should be used with caution in patients with hypersensitivity history to penicillins.

Some clinicians suggest that the use of ceftriaxone should be avoided in patients with any registrated immediate hypersensitivity reaction to (anaphylactic) penicillins. Although is has not been proven that allergic reactions to antibiotics are more frequent in atopic individuals, caution is recommended when using ceftriaxone in patients with an allergic history to medicines.

Ceftriaxone use can result in the overgrowth of non-sensitive microorganisms, especially *Candida, Enterococcus, Bacteroides fragilis* or *Pseudomonas aeruginosa*. Resistant strains of *Pseudomonas aeruginosa* and *Enterobacter* developed during therapy with ceftriaxone, and the patients submitted to this therapy should be carefully monitored.

Ceftriaxone should be administrated with caution in patients with gastrintestinal disease history, especially colitis. Pseudomembranous colitis associated to antibiotics has been notified with cephalosporins use, and should be considered in the differential diagnosis of patients that developed diarrhea during ceftriaxone therapy. Because ceftriaxone can precipitate in the biliary vesicle, is recommended that this drug is used with caution in patients with pre-existent disease in the vesicle, biliary tract, liver or pancreas. If ceftriaxone is used in these patients, an abdominal ecography should be performed.

Although prothrombin time (PT) is seldom prolongated in patients on therapy with ceftriaxone, it should be monitored when the medicine is used in patients with vitamine K synthesis and storage alterations (e.g. patients with chronic hepatic disease, malnutrition). Vitamine K administration (10mg/week) can be necessary if TP is prolongated before or during therapy with ceftriaxone.

Usually ceftriaxone dose adjustments are not necessary in patients with renal or hepatic impairment. However, ceftriaxone serum concentrations can be monitored in patients with severe renal impairment (hemodialyzed patients) and in patients with simultaneous renal and hepatic impairment. In this group of patients, a dose higher than 2g, should not be used.

Paediatric Precautions:

Ceftriaxone can be administrated to children.

Ceftriaxone, in therapeutical concentrations, demonstrated to displace bilirubin from binding sites to albumin *in vitro*. Ceftriaxone addition to blood samples obtained from newborns with hyperbilirubinemia result in increased concentrations of free and conjugated bilirubin to erythrocytes and decreases bilirubin binding to albumin concentrations. Because ceftriaxone can displace bilirubin from serum albumin, ceftriaxone administration should not be performed on newborns with hyperbilirubinemia, especially prematures.

Ceftriaxone IM reconstitutes with bacteriostatic water for injections containing benzilic alcohol, should not be administrated to newborns.

Medicine Interactions and Others

Probenecid

Probenecid concomitant administration (500 mg/day) does not appear to affect ceftriaxone pharmacokinetics, probably because ceftriaxone is excreted mainly by glomerular filtration and non-renal mechanisms. However, probenecid high doses concomitant administration (1 or 2 g/day) can partly block the biliary secretion of ceftriaxone and also displace the substance from plasma proteins. As a consequence ceftriaxone serum clearance can be increased in around 30% and the elimination half-life decreased in around 20%.

Aminoglycosids

In vitro studies indicate that the anti-bacterial activity of ceftriaxone and aminoglycosids can have additive or synergic effect against some strains of Enterobacteria and some strains of *Pseudomonas aeruginosa*. Although the clinical importance was not established, to this date, there was also antagonism *in vitro*, when ceftriaxone was used in association with an aminoglycosid.

Alcohol

Only one patient with a reaction dissulfiram-like was reported, when during treatment with ceftriaxone ingested alcohol. However, this effect, has only been mentioned with β-lactamic antibiotics.

Use in Pregnancy and Lactation

Ceftriaxone safe use during pregnancy was not yet adequately established.

There are no controlled and adequate studies about ceftriaxone use in pregnant women, and so the drug should only be used during pregnancy when absolutely necessary.

Ceftriaxone is distributed in human milk. This way, ceftriaxone administration to women breast-feeding should be done with caution.

Effects on the Ability to Drive and Use Machines

It is not likely any effect on the ability to drive and use machines.

Undesirable Effects

Ceftnaxone is in general well tolerated, though, adverse reactions have been notified in about 10% of patients taking this antibiotic, and the therapy had to be interrupted in less than 2% of these patients.

Ceftriaxone adverse reactions are similar to those that usually occur by administration of other cephalosporins.

Haematologic

Are the most frequent.Eosinophilia was verified in 6%, thrombocytosis in 5% and leukopenia in about 2% of patients taking ceftriaxone. Anemia, neutropenia, lymphocytopenia and thrombocytopenia have been reported in at least 1%, and leukocytosis, lymphocytosis, monocytosis and basophylia were notified in less than 0,1% of patients taking ceftriaxone. Hypoprothrombinemia or prolongation of prothrombin with or without haemorrhage have been rarely reported in less than 0,1% of patients taking ceftriaxone.

Gastrointestinal

Diarrhea has been notified in 2-4% of patients taking ceftriaxone. However, in 2 clinical trials transient cases of diarrhea were notified in 42-44% of children and in 28% of adults taking ceftriaxone. Nausea and vomiting have been notified in less than 1% of patients taking ceftriaxone and abdominal pain, flatulence, dyspepsia and colitis, in less than 0,1% of patients.

Mild cases of colitis, respond to therapy with ceftriaxone discontinuation. Pseudomembranous colitis associated to antibiotics can occur during or after discontinuation of therapy with cephalosporins. If the colitis is moderate to severe, or does not improve with ceftriaxone discontinuation, we should consider anti-infectious therapy (oral vancomycin). Although many are assymptomatic, biliary symp-

toms can occur (colics, nausea, vomiting, anorexia) that if become severe can require ceftriaxone interruption. Therapy with ceftriaxone should be discontinued, if suspicious manifestations develop of biliary vesicle disease and /or in patients with characteristic sonographic anomalies. The precipitation risk can depend on the dose and IV flux of administration of ceftriaxone, and is more frequent with doses and fluxs of administration relatively high.

In surgical interventions, were taken from some patients with renal impairment or in those that received high doses of ceftriaxone, precipitation crystals, that presented ceftriaxone residues and possible combination with calcium.

Cutaneous Hypersensitivity

In about 2% of patients in therapy with ceftriaxone, have been mentioned cutaneous reactions like eruptions (eritematous rash and urticaria) and other symptoms like chills, pruritus and fever were described in 1% of patients.

Less than 0,1% of patients registrated bronchospasms, anaphylaxia and serum disease.

Hepatic

Hepatic transaminases elevation was verified in 3% of patients (GOT and GPT) and in less than 1% of patients, increase of alkaline phosphatase and bilirubin. Jaundice has been notified in less than 0,1% of patients receiving ceftriaxone.

Renal

In about 1% of patients receiving ceftriaxone, has been notified increase in urea, nitrogen and creatinine serum concentrations and presence of urinary cylinders. Glycosuria and hematuria occurred in less than 0,1%of patients. At least in one patient, was verified during therapy with ceftriaxone, urolithiasis (with renal colic) and transitory renal impairment (increase in creatinemia concentration, decrease in glomerular filtration) in combination with colelithiasis, and these effects are reversible after therapy discontinuation.

Local

Local reactions, including pain, thickning, echimosis and sensitivity reaction at the injection site, were notified in around 1-2% of patients with ceftriaxone IM administration. Local reactions occur with less intensity and frequency when ceftriaxone IM is reconstituted with lidocaine chlorhydrate 1% (without epinephrine). Only in less than 1% of patients receiving ceftriaxone IV occurred phlebitis.

Other Adverse Effects

Other adverse effects notified in less than 1% of patients treated with ceftriaxone include: disphoresis and rubor, headache, dizziness, oral candidiasis and vaginitis by Candida. Also occurred, epistaxis and palpitations in less than 0,1% of patients treated with ceftriaxone.

Overdose

The occurrence of overdose in unlikely due to the route of administration. In its presence, we recommend the institution of symptomatic therapy.

Pharmacologic Properties

Pharmacodynamic Properties

Ceftriaxone is a semi-synthetic antibiotic from the 3rd generation cephalosporins group, for intramuscular or intravenous parenteral administration, just as for other cephalosporins, the bactericidal activity results from the inhibition of the bacteria cell wall mucopeptide.

Spectrum of Action

Similarly to what happens with other 3rd generation cephalosporins, ceftriaxone is in general, less active *in vitro* against *staphylococcus* than the 1st generation cephalosporins, but has a broader activity spectrum against Gram-negative bacteria when compared with 1st and 2nd generation cephalosporins. ceftriaxone is very stable in relation to the majority of β-lactamases, penicillinases or cephalosporinases of Gram-positive and Gram-negative bacteria. Ceftriaxone, in general, is active against the following microorganisms *in vitro*:

MIC_{50} = Minimum inhibitory concentration for 50% of microorganisms

MIC_{90} = Minimum inhibitory concentration for 90% of microorganisms.

Aerobic Gram-negative	**MIC_{50} (mg/l)**	**MIC_{90} (mg/l)**
Aeromonas spp.	Max. 0.13	2
Alkaligenes spp.	0.5	32
Branhamella catarrhalis (β-lactamase negative and positive)	0.25	4
Citrobacter spp.	0.1	32
Enterobacter spp. (some strains are resistant)	0.2	64
Escherichia coli	0,025	0.05
Haemophilus ducreyi	0.0015	0.003
Haemophilus influenzae (including strains producers of penicillinase)	<0.008	0.008
Haemophilus parainfluenzae	0.003	0.003
Klebsiella spp. (including *Klebsiella pneumoniae*)	0.04	0.6
Moraxella spp.	<0.125	2
Morganella morganii	0.03	0.5
Neisseria gonorrhoeae (including strains producers of penicillinase)	<0.008	<0.008
Neisseria meningitidis	<0.008	<0.008
Plesiomonas shigelloides	<0.06	<0.06
Proteus mirabilis	<0.008	<0.01
Proteus vulgaris	0.03	64
Providencia spp.	0.02	0.1
Pseudomonas aeruginosa (some strains are resistant)	16	>64
Salmonella spp. (including *Salmonella typhi*)	0.04	0.08
Serratia spp. (including *Serratia marcescens*)	2	32
Shigella spp.	0.025	0.2
Vibrio spp. (including *Vibrio cholerae*)	<0.06	0.25
Yersinia spp. (including *Yersinia enterocolitica*)	<0.12	0.12

Many strains of the microorganisms above described resistant to multiple antibiotics (penicillins, cephalosporins and aminoglycosids), are sensitive to ceftriaxone.

Aerobic Gram-positive	MIC_{50} (mg/l)	MIC_{90} (mg/l)
Staphylococcus aureus (including strains producers of penicillinase)	2	4
Staphylococcus epidermidis	4	25
Streptococcus pneumoniae	0.01	0.025
Streptococcus from Group A *Streptococcus pyogenes*	0.025	0.05
Streptococcus from Group B		

Aerobic Gram-positive	MIC_{50} (mg/l)	MIC_{90} (mg/l)
Streptococcus agalactiae	0.05	0.1
Streptococcus viridans	0.25	1.0
Streptococcus bovis	1.6	3.1

Streptococcus meticillin-resistant are resistant to cephalosporins, including ceftriaxone. The majority of Streptococcus strains from group D and Enterococcus are also resistant.

Anaerobics	MIC_{50} (mg/l)	MIC_{90} (mg/l)
Bacteroides spp. (including some strains of *Bacteroides fragilis*)	8	> 128
Clostridium spp. (except *Clostridium difficile*)	0.5	25
Fusobacterium spp. (except *F. mortiferum e F.varium*)	máx. 0.5	> 128
Peptococcus spp.	máx. 0.5	2
Peptostreptococcus spp.	máx. 0.5	4

The majority of strains of *C. difficile* are resistant.

Ceftriaxone demonstrated activity *in vitro* against most of the strains of the microorganisms described above, however, its clinical significance is not yet known.

Spirochetes: studies in rabbits with syphilis experimentally induced indicate that ceftriaxone has some activity against *Treponema pallidum*. Ceftriaxone also has activity *in vitro* against *Borrelia burgdorferi*, the organism responsible for Lyme's disease.

Resistance

Ceftriaxone is usually stable against hydrolysis by β-lactamases classified as Richmond-Sykes types II, III (types TEM), and V; some types PSE; and to the majority of β-lactamases produced by *Neisseria gonorrhoeae, Haemophilus influenzae*, and *Staphylococcus*. Ceftriaxone can be inhibited by β-lactamases Richmond type IV, and some β-lactamases produced by *Bacteroides, Citrobacter, Enterobacter, Morganella, Proteus*, and *Pseudomonas* according to some *in vitro* studies.

Sensitivity Tests

Ceftriaxone effect can be determined by the diffusion disk test or agar test or dilution using standardized procedures for sensitivity tests. The results from sensitivity tests can be interpreted in the following manner:

	Sensitive	Moderately Sensitive	Resistant
Dilution Test Inhibitory concentration (mg/l)	≤ 8	16-32	≥ 64
Diffusion Test (disks with 30 mg of ceftriaxone) inhibition halo (diameter in mm)	≥ 21	20-14	≤ 13

The microorganisms should be tested with the ceftriaxone disk, because there could be strains resistant to cephalosporins disks, but sensible to ceftriaxone.

Pharmacokinetics Properties

Ceftriaxone has a non-linear pharmacokinetics dose-dependent. The plasma concentrations, area under the curve (plasma concentration *versus* time – AUC), and the majority of pharmacokinetic parameters (except elimination half-life and the drug's unaltered fraction excreted in urine) of total ceftriaxone are dose-dependent and increase in a non-linear form with dose increase. However, the pharmacokinetic parameters of free ceftriaxone (not binding to plasma proteins) are independent from dose and increase linearly with it.

Absorption

Ceftriaxone is not significantly absorbed from gastrintestinal tract and should be administrated by parenteral route. After IM administration of a single dose of 0,5-1g to healthy individuals, the drug is completely absorbed and the plasma concentration peak occurrence is verified 1,5-4 hours after administration. The administration of a 2g/day dose, 1 g every 12 hours or 2g every 24 hours, by IV perfusion during 30 minutes, originated plasma concentrations peaks of 132-213 μg/ml on individuals that received g every 12 hours and of 216-281 μg/ml in those who received 2 g every 24 hours. In multiple doses studies, in healthy individuals who received a ceftriaxone dose of 0,5-2g every 12 or 24 hours by IM injection or IV perfusion during 30 minutes, was verified that the drug's plasma concentrations in steady-state at the 4th day of therapy were 15-36%higher than the plasma concentrations achieved with a single dose of ceftriaxone.

Distribution

After IV or IM administration, ceftriaxone is extensively distributed in the tissues and body fluids including the biliary vesicle, bones, bile, prostate, myometrium, endometrium, appendix, saliva, tears, pleural, peritoneal, synovial, ascitic and cephalorachidian liquids.

Ceftriaxone volume distribution is dose-dependent and varies between 5,8 to 13,5 L in healthy individuals. The average drug's distribution volume varies between 8,5-9,4 L in healthy individuals after administration of a single dose of 500 mg and

between 10-11,4 L after administration of a single dose of 2 g.
Ceftriaxone volume distribution after administration of a single dose of 50-100 mg/kg, is of 0,497-0,608 L/kg in newborns with 1-45 days of age and 0,26-0,54 L/kg in children of 1,5 months to16 years of age.
Ceftriaxone binds reversibly to plasma proteins, albumin, the protein binding decreases with concentration increases, i.e., for concentrations <100 mg/l, ceftriaxone binds to albumin on an extension of 95% and for concentrations of 300 mg/l on an extension of 85%.

Elimination

In adults with normal renal and hepatic functions, distribution half-life ($t1/2\alpha$) of ceftriaxone is 0,12-0,7 hours and elimination half-life ($t1/2\alpha$) is 5,4-10,9 hours.
The drug is excreted essentially in the urine by glomerular filtration and is also excreted in stools. After IM or IV administration of a single dose of ceftriaxone to adults with normal renal and hepatic functions, 33-67% of the dose is excreted in the urine in the unaltered form, the rest of the dose is excreted in stools in the unaltered form and in the form of microbiologically inactive metabolites. Ceftriaxone in metabolized in a weak extension in the bowel after biliary excretion.
Ceftriaxone elimination half-life is slightly higher in patients with moderate renal impairment, varying between 10 to16 hours in adults with a creatinine clearance between 5-73 ml/minute. In patients with creatinine clearance lower than 5 ml/minute the ceftriaxone elimination half-life usually varies between 12,2 to18,2 hours.
Studies performed in patients with hepatic impairment indicate that ceftriaxone pharmacokinetics is not usually altered in these patients. Although ceftriaxone elimination half-life is not prolongated in patients with ascites, the distribution volume and the drug's plasma clearance are slightly increased.
Ceftriaxone is not removed by haemodialysis or peritoneal dialysis.

Pre-clinical Safety Data

In vitro studies using mammals cells or with Ames test demonstrated that ceftriaxone was not mutagenic.
Specific studies for ceftriaxone carcinogenic potential determination were not yet performed and the animal toxicity studies were performed only up to 6 months, at the most. There are no adequate or controlled studies using ceftriaxone in pregnant women, and it should only be used when absolutely necessary, always evaluating the risk/benefit relation.

Pharmaceutical Informations

Excipients List

The powder and solvent for injectable solution *MESPORIN™ - 250 IM, MESPORIN™ - 500 IM* and *MESPORIN™ - 1000 IM*, contains a solvent formulation, lidocaine chlorhydrate and water for inectable preparations.

The powder and solvent for injectable solution *MESPORIN™ - 250 IV, MESPORIN™ - 500 IV* and *MESPORIN™ - 1000 IV* has only, as solvent, water for injectable preparations.

The powder for injectable for *IV* perfuson *MESPORIN™- 2 g* does not have any excipient.

Incompatibilities

There are no known compatibilities.

Do not administrate ceftriaxone together with other anti-infectious agents, do not mix the reconstituted solution of ceftriaxone with other solutions containing anti-infectious agents due to the risk of incompatibilities occurrence.

Special Precautions for Storage

Keep under 25ºC in a dry place and protected from light.
The reconstituted solution remains stable during, at least, 6 hours at room temperature (25ºC) and 24 hours in the refrigerator, always protected from light.
Do not use this medication after the expiry date stated "EXP" on the packaging.

Nature and Contents of the Container

MESPORIN™ 250 mg IM (vial + ampoule)
The product is presented in a transparent glass vial and amber ampoule with 2 ml of lidocaine chlorhydrate solution 1 %, conditioned in a cardboard box.

***MESPORIN™* 250 mg IV (vial + ampoule)**
The product is presented in a transparent glass vial and ampoule with water for injectable solutions with 5 ml.

***MESPORIN™* 500 mg IM (vial + ampoule)**
The product is presented in a transparent glass vial and amber ampoule with 2 ml of lidocaine chlorhydrate solution 1 %, conditioned in a cardboard box.

***MESPORIN™* 500 mg IV (vial + ampoule)**
The product is presented in a transparent glass vial and ampoule with water for injectable solutions with 5 ml.

***MESPORIN™* 1000 mg IM (vial + ampoule)**
The product is presented in a transparent glass vial and amber ampoule with 3,5 ml of Lidocaine chlorhydrate solution 1 %, conditioned in a cardboard box.

***MESPORIN™* 1000 mg IV (vial + ampoule)**
The product is presented in a transparent glass vial and ampoule with water for injectable solutions with 10 ml.

***MESPORIN™* 2 g IV, for perfusion (vial)**
The product is presented in a transparent glass vial.

Instructions for Use and Handling

Not applicable – see point 4.2 Posology and Method of Administration.

Presentation

Mesporin-250 I.M., -500 I.M., -1000 I.M.: packings of 1 vial (incl. 1 ampoule of 1% lidocaine HCl solution). Mesporin-250 I.V., -500 I.V., -1000 I.V.: packings of 1 vial (incl. 1 ampoule of sterile water for injection). Mesporin-2000 I.V.: packings of 1 vial.

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