CEFTREX INJECTION
(Ceftriaxone sodium)

COMPOSITION :
Vials containing dry substance equivalent to 0.25 g, 0.5 g and 1 g ceftriaxone.
Solvent ampoule for IM injection contains 1% lidocaine solution and for IV injection contains sterile water for injection.

DESCRIPTION :
CEFTREX is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration.
Appearance description :
Vial with dry substance : Dry, homogeneous white to off-white powder, filled in colorless vials.
Ampoule 2 ml of 1% lidocaine : Clear, colorless solution filled in colorless ampoules.
Ampoule 5 ml, 10 ml of sterile water for injection : Clear, colorless solution filled in colorless ampoules.

ACTIONS :
Ceftriaxone is a third-generation cephalosporin. It inhibits mucopeptide synthesis in the bacterial cell wall, making it defective and osmotically unstable.

Microbiology :
Ceftriaxone exerts *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. It is highly stable to most ß-lactamases, both penicillinases and cephalosporinases of gram-positive and gram-negative bacteria. Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see indications) :
Gram-Positive Aerobes : *Staphylococcus aureus* (methicillin-sensitive), Staphylococci coagulase-negative, *Streptococcus pyogenes* (ß-hemolytic group A), *Streptococcus agalactiae* (ß-hemolytic group B), ß-hemolytic Streptococci (non-group A or B), *Streptococcus viridans* and *streptococcus pneumoniae.*
Note : Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci, eg, *Enterococcus (Streptococcus) faecalis* are resistant.
Gram-Negative Aerobes : Acinetobacter lwoffi, Acinetobacter anitratus (mostly A. baumanii)*, Aeromonas hydrophila, Alcaligenes faecalis, Alcaligenes odorans, Alcaligenes-like bacteria, Borrelia burgdorferi, Capnocytophaga sp, Citrobacter diversus (including C. amalonaticus), Citrobacter freundii*, Escherichia coli, Enterobacter aerogenes*, Enterobacter cloacae*, Enterobacter sp (other)*, Haemophilus ducreyi, Haemophilus influenzae, Haemophilus parainfluenzae, Hafnia alvei, Klebsiella oxytoca, Klebsiella pneumoniae**, Moraxella catarrhalis (formerly Branhamella catarrhalis), Moraxella osloensis, Moraxella sp (other), Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Plesiomonas shigelloides, Proteus mirabilis, Proteus penneri*, Proteus vulgaris, Pseudomonas fluorescens*, Pseudomonas sp (other)*, Providencia rettgeri*, Providencia sp (other), Salmonella typhi, Salmonella sp (nontyphoid), Serratia marcescens*, Serratia sp (other)*, Shigella and Vibrio spp, yersinia enterocolitica, Yersinia sp (other). *Some isolates of these species are resistant to ceftriaxone, mainly due to the production of the chromosomally encoded ß-lactamase. **Some isolates of these species are resistant due to production of extended-spectrum, plasmid-mediated ß-lactamase.
Note : Many strains of the above organisms that are multiply resistant to other antibiotics, eg, penicillins, cephalosporins, and aminoglycosides, are susceptible to ceftriaxone.
Anaerobic Organisms : *Bacteroides* (bile-sensitive)*** and *Clostridium* spp (excluding *C. difficile*), *Fusobacterium nucleatum, Fusobacterium* sp (other), *Gaffkia anarobica* (formerly Peptococcus), *Peptostreptococcus* sp. ***Some isolates of these species are resistant to ceftriaxone due to ß-lactamase production.
Note : Many strains of ß-lactamase-producing *Bacteroides* sp (notably *B. fragilis*) are resistant. *Clostridium difficile* is resistant.

Pharmacokinetics :
The pharmacokinetics of ceftriaxone are nonlinear and all basic pharmacokinetic parameters, except the elimination half-life, are dose-dependent if based on total drug concentrations.
Absorption : The maximum plasma concentration after a single IM dose of 1 g is about 81 mg/L and is reached in 2-3 hours after administration. The area under the plasma concentration-time curve after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of IM administered ceftriaxone.
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 ; concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection are detectable for >24 hours in >60 tissues or body fluids including lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone as well as cerebrospinal, pleural, prostatic and synovial fluids. On IV 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, eg from 95% binding at plasma concentrations of <100 mg/L to 85% binding, at 300 mg/L. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.
Penetration into Particular Tissues : Ceftriaxone penetrates the inflamed meninges of neonates, infants, and children. Ceftriaxone concentrations exceeds 1.4 mg/L in the cerebrospinal fluid (CSF) 24 hours after IV injection of CEFTREX in doses of 50-100 mg/kg (neonates and infants, respectively). Peak concentration in CSF is reached about 4 hours after IV injection and gives an average value of 18 mg/L.
Mean CSF levels are 17% of plasma concentrations in patients with bacterial meningitis and 4% in patients with aseptic meningitis. 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 : Total plasma clearance is 10-22 mL/min. Renal clearance is 5-12 mL/min, 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.
Special clinical situations : In neonates, urinary recovery accounts for about 70% of the dose. In infants <8 days and in elderly persons >75 years the average elimination half-life is usually 2-3 times that in young adults. In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are 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.

INDICATIONS :
CEFTREX is used for the treatment of infections caused by pathogens sensitive to ceftriaxone eg :-
- lower respiratory tract infections
- skin and skin structure infections
- bone and joint infections
- intra-abdominal infections
- urinary tract infections
- meningitis, septicemia and gonorrhea caused by susceptible organisms

DOSAGE AND ADMINISTRATION : Direction for use :
Intramuscular injection : CEFTREX 0.25 g is dissolved in 2 ml of 1% lidocaine solution and administered by deep intragluteal injection. It is recommended that not more than 1 g be injected on either side. *The lidocaine solution must never be administered intravenously.
Intravenous injection : CEFTREX 0.5 g is dissolved in 5 ml, and 1 g in 10 ml of sterile water for injection and then administered by IV injection lasting two to four minutes
Intravenous infusion : The infusion should last at least 30 minutes. 2 g of CEFTREX 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 5% dextrose, sterile water for injection.
Standard dosage :
Adults and children over 12 years : Administered 1-2 g once daily (every 24 hours)
In severe cases the dosage may be raised to a maximum dose of 4 g administered once daily.
Infants and children (three weeks to 12 years) : 20-80 mg/kg body weight administered once daily.
Neonates (up to two weeks) : 20-50 mg/kg body weight, administered once daily. (not exceed 50 mg/kg/day)
Elderly : The dosages recommended for adults require no modification in geriatric patients.
Special dosage :
In bacterial meningitis in infants and children, treatment begins with doses of 100 mg/kg body weight (not to exceed 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly.
The duration of therapy is as the following :
Neisseria meningitidis 4 days
Streptococcus pneumoniae 7 days
Haemophilus influenzae 6 days
For the treatment of Gonorrhea : a single IM dose of 250 mg is advised.
Impaired Renal and Hepatic Function : In patients with impaired renal function, there is no need to reduce the dosage provided hepatic function is intact. Only in cases of preterminal renal failure (creatinine clearance <10 mL/min.) should the CEFTREX dosage not exceed 2 g daily. In patients with liver damage, there is no need to reduce the dosage provided renal function is intact. 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 dialysis. Plasma concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be altered.

STABILITY OF RECONSTITUTED SOLUTION :
Reconstituted solution retain their physical and chemical stability for six hours at room temperature (or 24 hours at 5°C). As a general rule, however, the solutions should be used immediately after preparation. They range in colour from pale yellow to amber, depending on the concentration and the length of storage. This characteristic of the active ingredient is of no significance for the efficacy or tolerance of the drug.

INCOMPATIBILITIES :
CEFTREX should not be added to solutions containing calcium, eg Hartmann's solution and Ringer's solution. Based on literature reports, ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

OVERDOSAGE :
In appropriately large doses may cause seizures, particularly in renal impairment.
If seizures occur, promptly discontinue the drug ; administer anticonvulsant therapy if clinically indicated. 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.

CONTRAINDICATION :
Hypersensitivity of Cephalosporin antibiotics. In patients hypersensitive to penicillin, the allergic cross-reactions may occur.
Ceftriaxone is contraindicated in neonates (≤28 days of age) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

WARNINGS :
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with CEFTREX, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, CEFTREX must be discontinued immediately and appropriate alternative therapy instituted.
In patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.
Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.

PRECAUTIONS :
As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken. Anaphylactic shock requires immediate countermeasures such as intravenous epinephrine followed by a glucocorticoid. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftriaxone.
Therefore, it is important to consider this diagnosis in patients with diarrhea subsequent to the administration of antibacterial agents. Superinfections with nonsusceptible microorganisms may occur with other antibacterial agents. Shadows which have been mistaken for gallstones have been detected on 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 CEFTREX therapy. Rarely have these findings been associated with symptoms. In symptomatic cases, conservative non-surgical management is recommended. Discontinuation of treatment in symptomatic cases should be at the discretion of the physician.
Use in pediatric :
Safety and effectiveness of CEFTREX in neonates, infants and children have been established for the dosages described in the Dosage and Administration section.
In vitro studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. CEFTREX should not be administered to hyperbilirubinemic neonates, especially prematures.
Use in pregnancy :
Although there is no experimental evidence of mutagenic or teratogenic effects, CEFTREX should not be used in pregnancy (particularly in the first trimester) unless absolutely indicated.
Use in lactation :
Ceftriaxone is excreted in human milk, usually in low concentration. Caution should be exercised if CEFTREX is given to nursing mother.
ADVERSE EFFECTS :
Gastrointestinal disturbances : Loose stools or diarrhea, nausea, vomiting, stomatitis and glossitis. Pseudomembranous enterocolitis has been reported as very rare side effects.
Hematological changes : Eosinophilia, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia.
Skin reaction : Exanthema, allergic dermatitis, pruritus, urticaria, edema. Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome/toxic epidermal necrolysis) have been reported.
Other rare adverse effects : Headache and dizziness, increase in liver enzymes, gallbladder sludge, oliguria, increase in serum creatinine, mycosis of the genital tract, shivering and anaphylactoid reactions.
Local adverse effects : In rare cases, phlebitic reaction occurred after IV administration. These may be prevented by slow injection (2-4 minutes).
Nervous system disorders : Frequency 'not known': Encephalopathy*
* Reversible encephalopathy has been reported with the use of ceftriaxone, particularly when high doses are administered in patients with renal impairment and additional predisposing factors such as older age, pre-existing central nervous system disorders.

DRUG INTERACTIONS :
No impairment of renal function has been observed after concurrent administration of large doses of ceftriaxone and loop diuretic (eg. furosemide). There is no evidence that ceftriaxone increases renal toxicity of aminoglycosides. No effects similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of ceftriaxone.
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.
Influence on Diagnostic Tests : In patients treated with CEFTREX, the Coombs' test may rarely become false-positive. CEFTREX, like other antibiotics, may result in false-positive tests for galactosemia. Likewise, non-enzymatic methods for the glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with CEFTREX should be done enzymatically.

STORAGE :
Store below 30°C, protect from light.

SUPPLY :
Packs for IM injection : 1 vial with dry substance equivalent to 0.25 g ceftriaxone and 1 ampoule 2 ml of 1% lidocaine solution.
Packs for IV injection : 1 vial with dry substance equivalent to 0.5 g or 1 g ceftriaxone and 1 ampoule 5 ml or 10 ml of sterile water for injection.

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Manufactured by
BIOLAB CO., LTD.
625 Bangpoo Industrial Estate,
Samutprakarn, Thailand

EEI 030/C

Note :
- Draft Rev 0-เพิ่มข้อความข้อ ADVERSE (Nervous system disorders) (17/06/21)

Color Guide
Black

Final Artwork Revision : C
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Code : EEI030/C
Name : AW_LEAFLET CEFTREX INJ NEW ADVERSE MAL.ai
Remark :

Approved by
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Specification
Size 235 x 273 mm. (+/- 3 mm.)
Color พิมพ์ 1 สี คือ ดำ
Material ใช้กระดาษปอนด์ น้ำหนัก 55 แกรม
Other