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"CEFTRIAXONE DRY POWDER INJECTABLE IP"

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ABSTRACT :

The semisynthetic, sterile, broad-spectrum cephalosporin antibiotic ceftriaxone for injection, USP, can be administered intramuscularly or intravenously. The sodium ceftriaxone is (6R, 7R). Glyoxylamido -7-[2-(2-Amino-4-thiazolyl)] ((1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-astriazin-3yl) Thio] methyl] -8-oxo-3- [[5-thia-1-zabicyclo [4.2.0] 72-(Z) -(O-methyl oxime), disodium salt, sesquaterhydrate, and oct-2-ene-2-carboxylic acid. A third-generation cephalosporin called ceftriaxone is used to treat infections that are acquired in the community, like pneumonia and UTIs.Additionally, it is used to treat bacterial infections in a variety of areas, including the skin, soft tissues, and respiratory tract. It demonstrated a significant benefit of once-daily pharmaceutical delivery and did not require renal impairment. It is stable against either the first or second generation of cephalosporins for βlactamases. Ceftriaxone is also used as an alternative first-line treatment for streptococcal endocarditis and for sexually transmitted diseases (STDs) such chancoroid and syphilis.

KEYWORDS :

- Cephalosporins
- Water for injections
- Parenteral
- Beta lactamase inhibitor
- Dry powder formulation

INTRODUCTION :

Third-generation cephalosporins include ceftriaxone sodium, also known as aminothiazole cephalosporin. In the USA, Canada, and Japan, this medication is marketed under the name Rocephin; in Mexico and Peru, it is known as Cefaxona. This substance is used to treat a variety of community-acquired illnesses, including those caused by Salmonella typhi and Neisseria gonorrhoeae. Roche created ceftriaxone in 1978. Its benefits include just needing to be administered once daily and being able to be administered intravenously or intramuscularly to outpatients in a pharmacologically suitable manner. Because it is more stable against conventional β-lactamases than first or second generations of cephalosporins, it has been used widely.

However, the activity of all third-generation cephalosporins against Enterobacteriaceae has been reduced over the past ten years due to the recent spread of derepressed mutants that hyperproduce chromosomal β-lactamases and extended-spectrum β-lactamases (ESBLs), which calls for close attention to sensitivity studies. The medical economy is driving an increase in outpatient management for infectious disease therapy. Pharmacokinetic and foundation pharmacodynamic theories serve as the for ceftriaxone's outpatient use. Since it can shorten hospital stays, it is also justified from a medical economic standpoint.

Ceftriaxone's pharmacological characterisation and mechanism of action make it suitable for both outpatient parenteral antimicrobial therapy (OPAT) and home intravenous antibiotic therapy (HIAT).

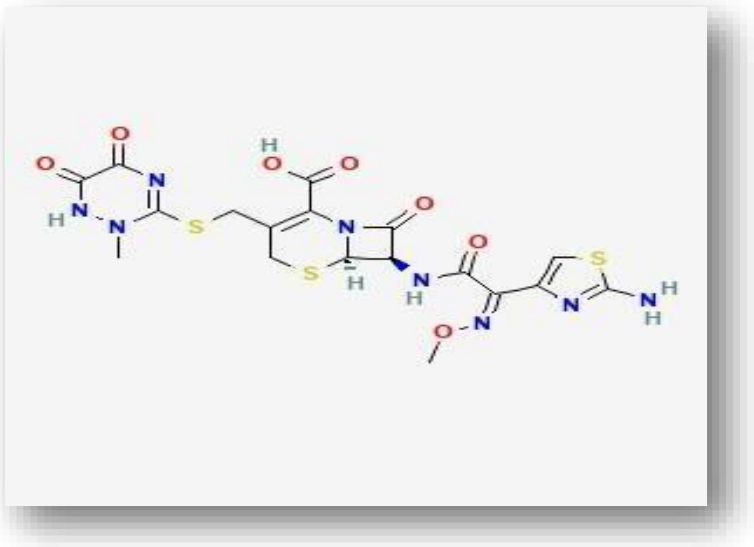
The most common side effects of ceftriaxone are rashes, haematopoietic disruption, nausea, vomiting, and diarrhoea. The medication has a fair tolerance profile. Nonetheless, these are typical side effects of beta lactam antibiotics. Although the prevalence of biliary pseudolithiasis is less than 0.1%, ceftriaxone may induce it, especially at larger dosages and/or during prolonged use (more than 2 g/day for more than 28 days).

Ceftriaxone sodium has the chemical formula C18H16N8Na2O7S3•3.5H2O. Its estimated molecular weight is 661.60 gm.

Properties :

1. Solid in nature
2. Melting Point - >155 °C
3. CaCo2 Permeability - (-6.88)
4. Molecular Weight -544.6

Chemical structure :



Fig(1) : Chemical Structure of Ceftriaxone

PHARMACODYNAMICS :

A cephalosporin/cephamycin beta-lactam antibiotic, ceftriaxone is used to treat bacterial infections brought on by gram-positive bacteria. Gram-positive, gram-negative, and anaerobic bacteria are all susceptible to its in vitro action. Ceftriaxone's interaction to penicillin binding proteins (PBPs) mediates the bactericidal action. A beta-lactam cephalosporin/cephamycin antibiotic, ceftriaxone is used to treat bacterial infections brought on by susceptible, typically gram-positive organisms. Gram-positive, gram-negative, and anaerobic bacteria are all susceptible to ceftriaxone's in vitro action. By attaching to penicillin-binding proteins (PBPs), ceftriaxone inhibits the formation of cell walls, which results in its bactericidal action. Penicillinases, cephalosporinases, and extended-spectrum beta-lactamases are among the betalactamases that cannot hydrolyse ceftriaxone. However, beta-lactamase is typically the cause of ceftriaxone resistance.

PHARMACOKINETICS :

- **Absorption:**

The only way to administer ceftriaxone is by injection, either intramuscularly or intravenously. When taken orally, ceftriaxone has a bioavailability of less than 1%. using the intramuscular method, more bioavailable.

- **Route of Elimination:**

The majority of ceftriaxone's excretion occurs in the urine (33-67%). The remainder is expelled from the body through the faeces and eliminated through secretion in the bile.

- **Volume of Distribution:**

In healthy individuals, an intravenous or intramuscular dosage has an apparent volume of distribution ranging from 5.78 to 13.5 L. In septic patients, an intravenous or intramuscular dose has a volume of distribution of 6.48 to 35.2 L. Ceftriaxone

Both glomerular filtration (60%) and biliary (40%) remove ceftriaxone in urine in its unaltered form (A633). Method of Elimination: Between 33 and 67 percent of a ceftriaxone dosage was eliminated in the urine as an unaltered medication, with the remaining portion being secreted in the bile and eventually discovered in the faeces as compounds that were microbiologically inactive. can be utilised as a good and efficient treatment for bacterial meningitis because of its strong CSF penetration.

- **Clearance:**

When healthy persons take 0.15–3g of ceftriaxone, their plasma clearance ranges from 0.58 to 1.45 L/hour. Ceftriaxone has a renal clearance of 0.32 to 0.73 L/hour. Ceftriaxone's unbound drug clearance was 1.91 L/h (1.46-6.20 L/h) and its total drug clearance was 0.96 L/h (0.55-1.28 L/h) in patients in the intensive care unit.

- **Metabolism / Metabolites:**

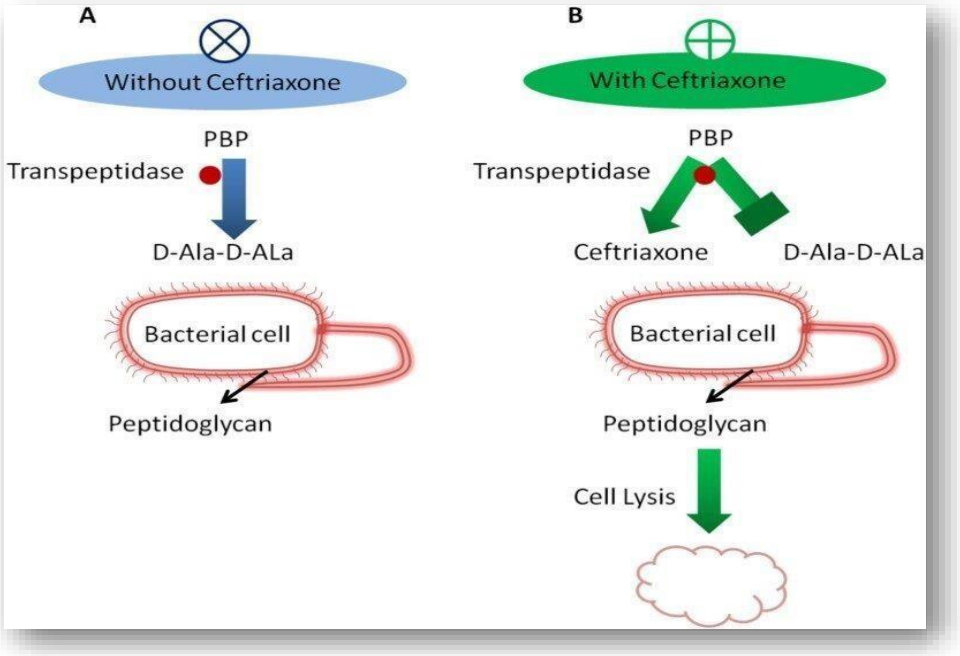
Metabolism of ceftriaxone is negligible.

The elimination half-life of ceftriaxone is 5.8-8.7 hours. The half-life of ceftriaxone in the middle ear fluid has been estimated to be 25 hours.

MECHANISM OF ACTION:

The mechanism of ceftriaxone is comparable to that of the other beta-lactam antibiotics. Transpeptidases function as a catalysing agent by inhibiting the peptidoglycan layer of the bacterial cell wall. Although ceftriaxone and D-alanyl D alanine share structural similarities, transpeptidases attach to ceftriaxone irreversibly. As a result, the peptidoglycan's final cross-linking is prevented, causing the bacterial cell wall to crumble and ultimately causing bacterial cell lysis or death. An antibacterial substance called ceftriaxone works by preventing the formation of cell walls.

Ceftriaxone has activity in the presence of some beta-lactamases.



Fig(2) : Mechanism of Action of Ceftriaxone

PREPARATION OF CEFTRIAXONE DRY POWDER:

1. **Gather Supplies:**

- Ceftriaxone is dry powder vial. o Appropriate diluent (usually sterile water for injection or 0.9% sodium chloride, depending on the manufacturer's instructions should be used). o Syringe and needle. o Alcohol swabs. o Sterile vial or syringe for drawing up the medication. o Gloves

2. **Hand Hygiene:**

- Wash your hands thoroughly with soap and water or use hand sanitizer.

3. **Inspect the Vial:**

- Check the ceftriaxone vial for any signs of damage or contamination. o Check whether the powder is not discoloured or clumped. It should be a white to light yellow powder.

4. **Prepare the Vial:**

- Properly Wipe the vial's rubber stopper with an alcohol swab to disinfect it.

5. **Draw Up Diluent:**

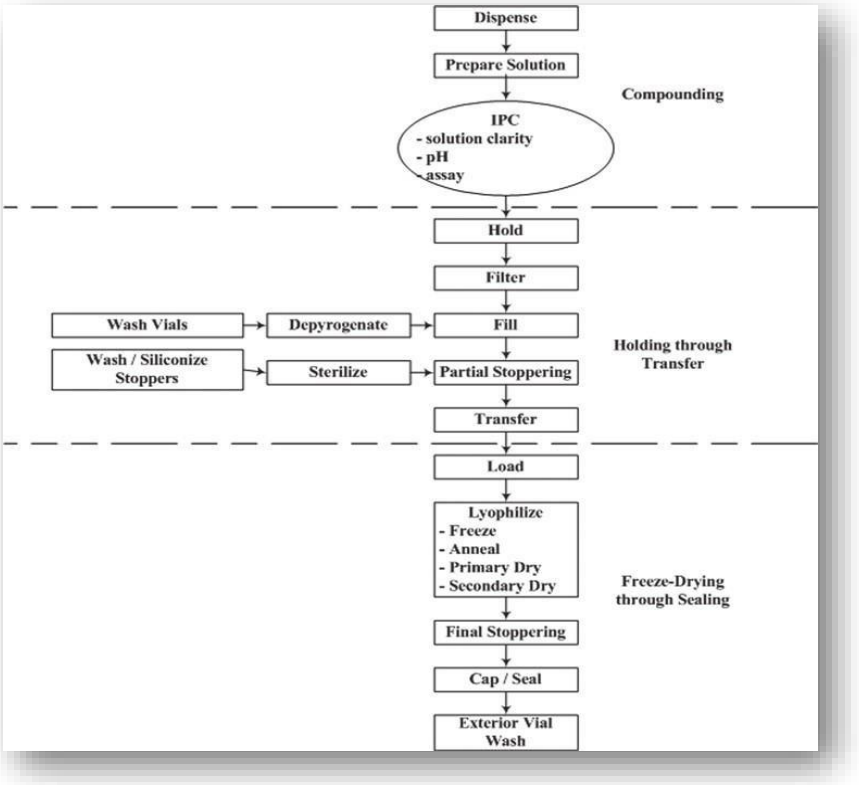
- Using a sterile syringe and needle, draw the appropriate amount of diluent as specified in the product's instructions or based on the dose required.

6. **Reconstitute the Powder :**

- Fill the vial with the powdered ceftriaxone and inject the diluent. To accomplish this, slowly inject the needle into the diluent after passing it through the rubber stopper.
- To combine the solution, gently swirl the vial. Avoid shaking too hard as this could harm the solution or create froth.

7. **Check for Complete Dissolution:**
- Make sure the powder dissolves completely. Clear to faintly yellow is the ideal colour for the solution. Do not use the solution if it is hazy or contains particle debris; instead, speak with your supervisor or chemist.

8. **Draw the Solution:**
- Once the powder is completely dissolved, withdraw the required amount of solution into a new sterile syringe.



Fig(3) : Preparation of Ceftriaxone Dry Powder

ADMINISTRATION OF CEFTRIAXONE:

1. **Prepare the Injection Site:**
- Select a suitable injection location. Depending on the clinical circumstances and the doctor's orders, ceftriaxone can be given intramuscularly (IM) or intravenously (IV).

2. **Clean the Injection Site:**
- Use an alcohol swab to clean the area where the injection will be administered.

3. **Administer the Medication:**

Intramuscular Injection:
- Insert the needle at a 90-degree angle to the skin.
- Inject the medication slowly into the muscle.
- Withdraw the needle and apply gentle pressure to the site.

Intravenous Injection:
- If administering IV, you may need to dilute the solution further or administer it as an infusion, depending on the dose and protocol.
- Insert the needle or catheter into the vein.
- Inject the medication slowly, or connect to an infusion pump if administering as an infusion.
- Withdraw the needle or secure the catheter as needed.

4. **Dispose of Supplies:**
- Dispose of the needle, syringe, and any other used supplies in a proper sharp container.

5. **Document the Administration:**
- Record the dose, time, and site of administration in the patient’s medical record.

Important Considerations:
- **Compatibility:** Check for drug compatibility if ceftriaxone is being used with other medications or fluids.
- **Dosage and Dilution:** Always follow the specific dosage and dilution instructions provided by the manufacturer or your healthcare provider.

CEFTRIAXONE DRUG INTERACTIONS :

A broad-spectrum cephalosporin antibiotic called ceftriaxone is used to treat a number of bacterial illnesses. It may interact with other prescriptions, as is the case with many medications, which could reduce its effectiveness or raise the possibility of adverse effects. Ceftriaxone interacts with the following significant medications:

1. **Goods Containing Calcium:**
- Ceftriaxone has the ability to bind with calcium and produce precipitates, especially when taken with goods that include calcium. This can be especially harmful for young children and infants. Ceftriaxone and calcium products should be administered at least 48 hours apart to prevent this.

2. **Warfarin and Other Anticoagulants:**
- Ceftriaxone may compound the effects of warfarin and other anticoagulants, making bleeding more likely. If these medications are taken concurrently, it is advised to monitor the International Normalised Ratio (INR).

3. **Probenecid:**
- By preventing its renal elimination, probenecid can raise the blood levels of ceftriaxone. Increased side effects could result from this, albeit the clinical importance varies.

4. **Aminoglycosides:**
- Although there isn't a direct interaction, ceftriaxone and aminoglycosides should be used with caution because of the possibility of additive nephrotoxicity. When using these medications simultaneously, it is advised to monitor renal function.

CEFTRIAXONE SPECTRAL INFORMATION:

A broad-spectrum cephalosporin antibiotic, ceftriaxone is well-known for its ability to effectively combat a variety of bacteria. The range of bacterial organisms it is effective against is indicated by its spectral information. This is a thorough summary of its antibacterial range:

1. **Gram-Positive Bacteria:**
- Streptococcus species: The majority of Streptococcus pneumoniae and Streptococcus pyogenes (Group A Streptococcus) strains are susceptible to Ceftriaxone.
- Staphylococcus species: Methicillin-resistant Staphylococcus aureus (MRSA) is typically not affected, but Staphylococcus aureus, including certain methicillin-susceptible strains, is well treated.
- Enterococcus species: Enterococcus faecalis and Enterococcus faecium are typically not susceptible to ceftriaxone.

2. **Gram-Negative Bacteria:**
- **Escherichia coli**: Ceftriaxone is effective against most strains of E. coli.
- **Klebsiella species**: Effective against Klebsiella pneumoniae and Klebsiella oxytoca.
- **Proteus species**: Effective against Proteus mirabilis, though it may be less effective against Proteus vulgaris.

3. **Anaerobes:**
- Bacteroides species: Anaerobes such as Bacteroides fragilis are not very susceptible to ceftriaxone's effects. Anaerobic infections typically do not benefit from its use.

CLINICAL USES:

- Ceftriaxone is often used for treating a wide range of infections, including:
- Respiratory tract infections (e.g., pneumonia, bronchitis)
- Urinary tract infections
- Skin and soft tissue infections
- Bone and joint infections
- Gonorrhoea
- Meningitis

In conclusion, ceftriaxone is a broad-spectrum antibiotic that is adaptable, although the effectiveness of this medication can differ based on the particular strain of bacteria and patterns of resistance in the area. For the most precise and efficient use, always consult local antibiograms and clinical guidelines.

SIDE-EFFECTS OF CEFTRIAXONE :

Like all antibiotics, ceftriaxone has the potential to induce adverse effects. Some adverse effects can be more serious, but most are minor and transient. The following is a thorough summary of the possible adverse effects of ceftriaxone:

COMMON SIDE-EFFECTS .

Gastrointestinal Issues:

- **Diarrhoea**: A common side effect, often mild, but it can be more severe or persistent in some cases.
- **Nausea and Vomiting**: Can occur, though they are less common.
- **Abdominal Pain**: May be experienced by some individuals.

Skin Reactions:

- **Rash**: Mild rash or itching can occur.
- **Erythema**: Redness or swelling of the skin.

Local Reactions:

- **Injection Site Reactions**: Pain, redness, or swelling at the site of injection, especially with intramuscular administration.

CEFTRIAXONE CHEMICAL STRUCTURE AND CO - OCCURRENCE

Chemical Structure:

- Ceftriaxone is a β-lactam antibiotic with a structure that includes a β-lactam ring and a dihydrothiazine ring. Its side chains influence its antibacterial activity and solubility.

Laboratory Interactions:

- Ceftriaxone may cause false-positive findings when used in conjunction with specific glucose tests, such as the urine glucose test. For precise monitoring, it's critical to employ particular techniques.

Stability and Storage:

- pH Sensitivity: Ceftriaxone should be reconstituted and diluted with suitable solutions due to its sensitivity to pH variations. Its stability and effectiveness may be impacted by improper diluent use or storage condition

CEFTRIAXONE DRY POWDER INJECTABLES COMPOSITION

Ceftriaxone is frequently offered as a dry powder that must be reconstituted prior to delivery. Ceftriaxone dry powder injectable's ingredients can differ slightly from manufacturer to manufacturer, but generally speaking, they consist of the following:

Active Ingredient:

- **Ceftriaxone Sodium:** The active component of the medication.
- Ceftriaxone is a broad-spectrum cephalosporin antibiotic used to treat a variety of bacterial infections.

Excipients:

- **Sodium:** Usually in the form of sodium salt (e.g., ceftriaxone sodium). This helps maintain the stability as well as solubility of the drug.

Additional excipients:

- These may consist of stabilisers, buffering agents to preserve pH equilibrium, and other materials that guarantee the medication's effectiveness and security. Excipients differ depending on the manufacturer and formulation.

Common Dosage Forms

- Ceftriaxone dry powder for injection is typically available in various strengths, such as:
- 500 mg
- 1 g
- 2 g

Reconstitution

The dry powder is reconstituted with an appropriate diluent, such as sterile injection water or an intravenous fluid that is compatible, to create the injectable solution. The labelling or package insert for the medication contains the precise reconstitution instructions, including the amount of diluent and the final concentration of the solution.

PHYSICAL ANALYSIS :

Physical testing looks at the drug form's colour, particle size, solubility, and disintegration, among other physical characteristics. Raw materials, intermediates, and finished products are all subjected to physical testing.

CHEMICAL ANALYSIS :

1. **Average weight: Cefoperazone & Sulbactam**
2. **Materials:**
   - Sample
   - Ethanol • Hot air oven
3. **Procedure:**
   - Remove seal and weigh powder present in vial (pre-weight).
   - Wash the vial with ethanol
   - Dry the vial iv. Weigh it again (post-weight).
4. **Result:**

- Pre-weight - post-weight (29111.53 mg – 27526.47mg)
- Average weight -1591.06 mg

ASSAY OF CEFTRIAXONE AND SULBACTUM :

Ceftriaxone's inhibitory action on the Bacillus subtilis strain employed as the test organism is the basis for the experiment.
The assays of ampicillin and sulbactam, a beta lactamase inhibitor, in serum were contrasted. Agar Diffusion Bioassay is the method.

MICROBIOLOGICAL ANALYSIS

1. **Sterility Test:**

To make sure there are no visible viable contaminating microorganisms in a product, sterility testing is necessary.
Direct inoculation or membrane filtering techniques are used for this testing, which can be carried out in a clean room or an isolator.

What is a membrane filtration method?

Sterile, enclosed units allow for the filtration of equal volumes of test samples through two membrane filters. Samples are incubated, for the detection of both aerobic and anaerobic microorganisms.

Requirements:

- Sample
- Peptone water
- Filtration assembly
- SCDM media & FTM media

Procedure:

- 1.Take product vial and spray it with Isopropyl Alcohol
- 2.Mix sample with peptone water.
- 3.Pour through membrane filtration assembly.
- 4.Connect with vacuum pump.
- 5.Remove the filter membrane and cut it.
- 6.Put one part into in SCDM and other in FTM media.
- 7.Incubate it for 7-10 days.

2. **Bacterial Endotoxin Test (BET):**

Principle:

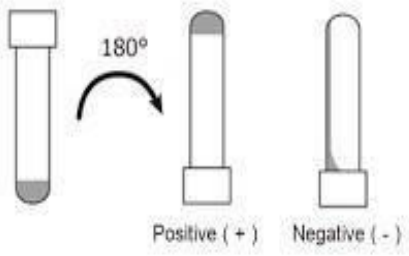
Endotoxin + LAL (Limulus Amebocyte Lysate) = Clotting Endotoxin testing (LAL test) verifies the safety of sterile pharmaceutical products for human consumption. Bacterial endotoxins are structural elements. If given to people or animals, these substances are poisonous (raise body temperature).

Requirements:

- CSE (Controlled Standard Endotoxin)
- LAL (Limulus Amybiocyte Lysate)
- LRW (LAL Reagent Water)
- Test sample
- Standard endotoxin Heating block

Procedure:

1. Get two test tubes.
2. Fill the tubes with 100 µL of the sample.
3. Fill test tubes with 100µL of LAL reagent, then incubate them for 60 minutes.
4. Now flip the tubes over and see what happens.
5. If solid medium remains intact the product is considered to contain endotoxin.



3.Environment monitoring:

It provides information of presence or absence of contaminants in the environment o Swab method to Settle plate method

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