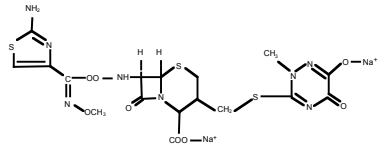
# Getofin™
(Ceftriaxone)

گیٹوفن

**250mg & 500mg IM Injection**
**250mg, 500mg & 1g IV Injection**

## DESCRIPTION
Getofin is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Chemically Ceftriaxone sodium is (6R,7R)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 72-(Z)-(O-methyloxime), disodium salt, sesquaterhydrate. The molecular formula is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$ and the following structural formula:



Ceftriaxone

## QUALITATIVE & QUANTITATIVE COMPOSITION
Getofin (Ceftriaxone) I.M/I.V Injection is available for administration as:

1. Getofin IV Injection 250mg
   Each vial contains:
   Ceftriaxone sodium USP eq. to Ceftriaxone… 250mg

2. Getofin IM Injection 250mg
   Each vial contains:
   Ceftriaxone sodium USP eq. to Ceftriaxone… 250mg

3. Getofin IV Injection 500mg
   Each vial contains:
   Ceftriaxone sodium USP eq. to Ceftriaxone… 500mg

4. Getofin IM Injection 500mg
   Each vial contains:
   Ceftriaxone sodium USP eq. to Ceftriaxone… 500mg

5. Getofin IV Injection 1g
   Each vial contains:
   Ceftriaxone sodium USP eq. to Ceftriaxone… 1000mg

## CLINICAL PHARMACOLOGY
**Mechanism of Action**
Ceftriaxone works by inhibiting the mucopeptide synthesis in the bacterial cell wall. The beta-lactam moiety of Ceftriaxone binds to carboxypeptidases, endopeptidases, and transpeptidases in the bacterial cytoplasmic membrane. These enzymes are involved in cell-wall synthesis and cell division. By binding to these enzymes, Ceftriaxone results in the formation of defective cell walls and cell death.

**Microbiology**
Ceftriaxone has been shown to be active against most strains of the following microorganisms:

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

Aerobic gram-positive microorganisms
*Staphylococcus aureus (including penicillinase-producing strains)*
*Staphylococcus epidermidis*
*Streptococcus pneumoniae*
*Streptococcus pyogenes*
Viridans group *streptococci*

Anaerobic microorganisms
*Bacteroides fragilis*
*Clostridium species*
*Peptostreptococcus species*
Aerobic gram-negative microorganisms
*Citrobacter diversus*
*Citrobacter freundii*
*Providencia species (including Providencia rettgeri)*
*Salmonella species (including Salmonella typhi)*
*Shigella species*

Aerobic gram-positive microorganisms
*Streptococcus agalactiae*

Anaerobic microorganisms
Prevotella (Bacteroides) bivius
Porphyromonas (Bacteroides) melaninogenicus

**Pharmacokinetics**
*Absorption & Distribution:*
The pharmacokinetics of Ceftriaxone are largely determined by its concentration-dependent binding to plasma 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 300mg/L. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.
Mean peak concentrations after bolus intravenous injection are about 120mg/L following a 500mg dose and about 200mg/L following a 1g dose; mean levels of 250mg/L are achieved after infusion of 2g over 30 minutes. Bioavailability after intramuscular injection is 100%.

*Excretion:*
Ceftriaxone is eliminated mainly as unchanged drug, approximately 60% of the dose being excreted in the urine (almost exclusively by glomerular filtration) and the remainder via the biliary and intestinal tracts. The total plasma clearance is 10-22 mL/min. The renal clearance is 5-12 mL/min. A notable feature of ceftriaxone is its relatively long plasma elimination half-life of approximately eight hours which makes single or once daily dosage of the drug appropriate for most patients. The half-life is not significantly affected by the dose, the route of administration or by repeated administration.
In the first week of life, 80% of the dose is excreted in the urine; over the first month, this falls to levels similar to those in the adult. In infants aged less than 8 days the average elimination half-life is usually two to three times longer than that of young adults.

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

**Special Populations**
*Elderly*
In elderly persons aged over 75 years, the average elimination half-life is usually two to three times longer than that in the young adult group. As with all cephalosporins, a decrease in renal function in the elderly may lead to an increase in half-life. Evidence gathered to date with ceftriaxone however, suggests that no modification of the dosage regimen is needed.

*Renal or hepatic dysfunction*
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. Conversely, if liver function alone is impaired, renal elimination is increased.

## THERAPEUTIC INDICATIONS
Getofin is indicated for the treatment of the following infections due to susceptible organisms. Such infections include:
- Lower respiratory tract infections
- Acute bacterial otitis media
- Skin and skin structure infections
- Urinary tract infections (complicated and uncomplicated)
- Uncomplicated gonorrhea (cervical/urethral and rectal)
- Pelvic inflammatory disease
- Bacterial septicemia
- Bone and joint infections
- Intra-abdominal infections
- Meningitis.
- Surgical prophylaxis of infections.
- Infections in neutropenic patients

## DOSAGE AND ADMINISTRATION
Getofin may be administered by deep intramuscular injection, slow intravenous injection, or as a slow intravenous infusion, after reconstitution of the solution according to the given directions for reconstitution.

**Pediatric patients**
For the treatment of skin and skin structure infections, the recommended total daily dose is 50 to 75mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 grams.

For the treatment of acute bacterial otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 gram) is recommended.

For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50 to 75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 grams.
In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 grams). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 grams daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7 to 14 days.

**Adults**
The usual adult daily dose is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 grams.
If *Chlamydia trachomatis* is a suspected pathogen, appropriate antichlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism.
For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.
For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously • to 2 hours before surgery is recommended.
Generally, Getofin therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required. When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least 10 days.
No dosage adjustment is necessary for patients with impairment of renal or hepatic function.

**Directions for reconstitution**
The reconstituted solution should be administered within 6 hours, if stored at

room temperature or 24 hours if stored in refrigerator (2-8°C). Diluents containing calcium, (e.g. Ringer's solution or 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. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously.

Preparation of solutions for injection and infusion

***Intramuscular injection***
250mg & 500mg should be dissolved in 2ml of 1% Lignocaine Hydrochloride solution. No other drug should be mixed within the same syringe.
The solution should be administered by deep intramuscular injection.

***Intravenous injection***
250mg or 500mg injection should be dissolved in 5mL, and 1gm in 10mL sterile water for injection. The intravenous administration should be given over 2 to 4 minutes.

***Intravenous infusion***
Getofin should be administered intravenously by infusion over a period of 30 minutes. Concentrations between 10mg/mL and 40mg/mL are recommended. However, lower concentrations may be used if desired. Reconstitute vials with an appropriate IV diluent.
500mg of Getofin should be dissolved in 4.8mL of diluent and for 1gm 9.6mL of diluent should be used. After reconstitution, each 1 ml of solution contains approximately 100mg equivalent of ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate IV diluent (calcium free solutions: Dextrose Injection 2.5%, 5% or 10%, Sodium Chloride 0.9%).

**CONTRAINDICATIONS**
Ceftriaxone is contraindicated in patients with:
- Hypersensitivity to ceftriaxone or to any of the cephalosporins.
- Previous immediate and/or severe hypersensitivity reaction to penicillin or to any other type of beta-lactam drug.
- Premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),
- Full-term newborns (up to 28 days of age)
- with jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired
- Patients requiring (or are expected to require) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium
- Incase of lidocaine is used as a solvent Ceftriaxone solutions should only be used for intramuscular injection.

**Pregnancy**
Ceftriaxone crosses the placental barrier. Safety in human pregnancy is not established ceftriaxone should not be used unless absolutely indicated.

**ADVERSE REACTIONS**
*Very Common*
Diarrhea, nausea and vomiting.

*Common*
Hypersensitivity reactions such as allergic skin reactions and anaphylactic reactions, secondary infections with yeast, fungi or resistant organisms as well as changes in blood cell counts.

*Rare*
Mycosis of the genital tract, neutropenia, leucopenia, eosinophilia, thrombocytopenia, anaemia (including haemolytic anaemia), slight prolongation of prothrombin time, anaphylactic (e.g. bronchospasm) and anaphylactoid reactions, headache, dizziness, Increase in serum liver enzymes (AST, ALT, alkaline phosphatase), rigors and pyrexia. Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, mostly in patients treated with doses higher than the recommended standard dose. This effect is usually asymptomatic, but in rare cases, the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone. Increase in serum creatinine, oliguria, glycosuria, haematuria, phlebitis and injection site pain following intravenous administration. This can be minimised by slow injection over at least 2-4 minutes.

**WARNING & PRECAUTIONS**
*General*
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. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used, or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation.

*Hypersensitivity*
Before therapy with ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, Penicillins or other drugs.

*Clostridium difficile*
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. 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.

Hemolytic Anemia
An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including Ceftriaxone. Severe cases of hemolytic anemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anemia while on ceftriaxone, the diagnosis of a cephalosporin associated anemia should be considered and ceftriaxone stopped until the etiology is determined.

*Drug-resistance*
Ceftriaxone in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

*Prothrombin time alteration*
Patients with impaired vitamin K synthesis or low vitamin K stores (eg, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Ceftriaxone treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

*Superinfections*
Prolonged use of Ceftriaxon may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

*Gastrointestinal disease*
Ceftriaxone should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

*Gallbladder abnormalities*
Ceftriaxone may precipitate in the gallbladder and then be detectable as shadows on ultrasound. This can happen in patients of any age, but is more likely in infants and small children who are usually given a larger dose of Ceftriaxone on a body weight basis. In children, doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates. The condition apperars to be transient and reversible upon discontinuation of ceftriaxone and institution of conservative management.

*Nephrotoxicity*
The nephrotoxic potential of ceftriaxone is similar to that of other cephalosporins.

*Hepatic and renal dysfunction*
In patients with both hepatic dysfunction and significant renal disease, caution should be exercised and the Ceftriaxone dosage should not exceed 2 gm daily.

**Nursing Mothers**
Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Ceftriaxone is administered to a nursing woman.

**Drug Interactions**
- In vitro, chloramphenicol has been shown to be antagonistic with respect to ceftriaxone and other cephalosporins Caution is advised if concurrent administration of ceftriaxone with chloramphenicol is proposed.
- 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.

**Laboratory findings**
In patients treated with Ceftriaxone, the Coombs' test may rarely become false-positive. Ceftriaxone, 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 Ceftriaxone should be done enzymatically.

**OVERDOSAGE**
In the case of overdosage, drug concentrations would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment should be symptomatic.

**STORAGE**
Store at 25°C (Excursions permitted between 15°C to 30°C). The reconstituted solution should be administered within 6 hours, if stored at room temperature or 24 hours if stored in refrigerator (2°C-8°C). Protect from light & moisture.
The expiration date refers to the product correctly stored at the required conditions.

**HOW SUPPLIED**
Getofin (Ceftriaxone) IV Injection 250mg is available in unit pack size of 1 vial along with a 5mL ampoule of sterile water for Injection.

Getofin (Ceftriaxone) IM Injection 250mg is available in unit pack size of 1 vial along with a 2mL ampoule of 1% Lignocaine solution.

Getofin (Ceftriaxone) IV Injection 500mg is available in unit pack size of 1 vial along with a 5mL ampoule of sterile water for Injection.

Getofin (Ceftriaxone) IM Injection 500mg is available in unit pack size of 1 vial along with a 2mL ampoule of 1% Lignocaine solution.

Getofin (Ceftriaxone) IV Injection 1g is available in unit pack size of 1 vial along with a 10mL ampoule of sterile water for Injection.

***Keep out of reach of children.***

***To be sold on a prescription of a registered medical practitioner only .***

**Please read the contents carefully before use.**
**This package insert is continually updated from time to time.**

Manufactured for:

Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

Manufactured by: NovaMed Pharmaceuticals
28 km, Ferozepur Road, Lahore Pakistan