SUMMARY OF PRODUCTS CHARACTERISTICS

1.0 NAME OF MEDICINAL PRODUCT:

MONOPIL-1000 (Ceftriaxone for Injection USP 1 g)

2.0 QUALITATIVE AND QUANTITATIVE FORMULA:

UNIT FORMULA	
Product Name	MONOPIL 1000 (Ceftriaxone for Injection USP 1 g)
Composition	Each vial contains: Ceftriaxone Sodium (Sterile) USP Eq. to Ceftriaxone 1000mg In Combipack with Sterile water for Injection USP 10ml

S. No.	**Ingredients**	**Claim/Vial**	**O.A.**	**Spec.**	**Qty./Vial (mg)**	**Qty. /Vial (%)**	**Rational**
Active:							
01	Ceftriaxone Sodium Sterile Equivalent to Ceftriaxone*	1000mg	**….**	USP	1000.00 mg	100 %w/w	Active

*****Verified on the basis of Approved License & Quantity to be taken as per Calculation Sheet.
Abbreviations: O.A.: Overages Added, **Qty.:** Quantity, **Spec.:** Specification, **API:** Active Pharmaceutical Ingredients, **USP:** United States Pharmacopoeia.

3.0 PHARMACEUTICAL FORM:

Form **:** Powder for Injection

4.0 CLINICAL PARTICULARS:

4.1 Therapeutic Indications :

Ceftriaxone sodium is a broad-spectrum bactericidal cephalosporin antibiotic. Ceftriaxone is active *in vitro* against a wide range of Gram-positive and Gram-negative organisms, which include β-lactamase producing strains.

Ceftriaxone is indicated in the treatment of the following infections either before the infecting organism has been identified or when known to be caused by bacteria of established sensitivity.

Pneumonia

Septicaemia

Meningitis

Skin and soft tissue infections

Infections in neutropenic patients

Gonorrhoea

Peri-operative prophylaxis of infections associated with surgery

Treatment may be started before the results of susceptibility tests are known.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration :

Ceftriaxone may be administered by deep intramuscular injection, slow intrave ous injection, or as a slow intravenous infusion, after reconstitution of the solution according to the d rections given below.

Dosage and mode of administration should be determined by the severity of the i fection, susceptibility of the causative organism and the patient's condition. Under most circumstances a once-daily dose - or, in the specified indications, a single dose - will give satisfactory therapeutic results.

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 solution s in the same IV administration line. There ore, Ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously.

Adults and children 12 years and over

Standard therapeutic dosage: 1g once daily.

Severe infections: 2 - 4g daily, normally as a single dose every 24 hours.

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of Ceftriaxone should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Acute, uncomplicated gonorrhoea: A single dose of 250mg intramuscularly should be administered. Simultaneous administration of probenecid is not indicated.

Peri-operative prophylaxis: Usually 1g as a single intramuscular or slow intravenous dose. In colorectal surgery, 2g should be given intra uscularly (dosages greater than 1g should be ivided and injected at more than one site), or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

Elderly

These dosages do not require modification in elderly patients provided that renal nd hepatic function is satisfactory.

Neonates, infants and children up to 12 years

The following dosage schedules are recommended for once daily administration:

Neonates

A daily dose of 20 - 50mg/kg bod y weight, not to exceed 50mg/kg. In the neonate, the intravenous dose should be given over 60 minutes to reduce the displacement of bilirubin from albumin, thereby reducing the potential risk of bilirubin encephalopathy.

Infants and children of up to 12 ɣears

Standard therapeutic dosage: 20 - 50mg/kg body weight once daily.

In severe infections up to 80mg/kg body weight daily may be given. For children with body weights of 50kg or more, the usual adult dosage should be used. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. Doses greater than 80mg/kg b dy weight should be avoided because of the increased risk of biliary precipitates.

Renal and hepatic impairment

In patients with impaired renal function, there is no need to reduce the dosage of Ceftriaxone provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance < 10ml per minute) should the daily dosage be limited to 2g or less.

In patients with liver damage there is no need for the dosage to be reduced pro ided renal function is intact.

In severe renal impairment accompanied by hepatic insufficiency, the pla ma concentration of Ceftriaxone should be determined at regular intervals and dosage adjusted.

In patients undergoing dialysis, n c additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether d sage adjustments are necessary, since the elimination rate in these patients may be reduced.

Method of administration:

Intramuscular administration

1g Ceftriaxone should be dissolved in 3.6 ml water for Injection. The injection should be administered by deep intramuscular injection. Intramuscular injections should be injected well within the bulk of a

relatively large muscle and not more than 1 g should be injected at one site. D sages greater than 1g should be divided and injected at more than one site.

Intravenous administration

For IV injection 1 g Ceftriaxone is dissolved in 9.6 ml of water for injections. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intraven us infusion.

Ceftriaxone can be administered by intravenous infusion over at least 30 minutes (preferred route) or by slow intravenous injection over 5 minutes. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses sh uld be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy. Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient. For doses greater than 2 g intravenous administration should be used.

Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium containing intravenous solutions, including continuo s calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of Ceftri xone-calcium.

4.3 Contraindications:

Ceftriaxone is contraindicated in patients with known hypersensitivity to beta lactam antibiotics. In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind.

Hyperbilirubinaemic newborns and preterm newborns should not be treated wit Ceftriaxone. In vitro studies have shown that Ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in these patients.

Ceftriaxone is contraindicated in:

• 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)

4.4 Special warnings and precautions for use:

As with other cephalosporin, anaphylactic shock cannot be ruled out even if a thorough patient history is taken. Before therapy with Ceftriaxone is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to Ceftriaxone, cephalosporin,

penicillins, or other beta-lactam drugs. Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. Care is required when administering Ceftriaxone to patients who have previously shown hypersensitivity to penicillins or other non-cephalosporin beta-lactam antibiotics, as occasional instances of cross allergencity between cephalosporin and these antibiotics have been recorded. Anaphylactic shock requires immediate counter measures.

In vivo and *in vitro* studies have shown that Ceftriaxone, like some other cephalosporin, can displace bilirubin from serum albumin. Clinical data obtained in neonates have confirmed this finding. Ceftriaxone should therefore not be used in neonates (especially premature) at risk of developing bilirubin encephalopathy.

Cases of fatal reactions with calcium-Ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns aged less than 1 month have been described. At least one of them had received Ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than newborns, treated with Ceftriaxone and calcium-containing solutions or any other calcium-containing products. In vitro studies demonstrated that newborns have an increased risk of precipitation of Ceftriaxone-calcium compared to other age groups.

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.

In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of Ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and Ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of Ceftriaxone infusion, considering the advice to flush infusion lines between solutions.

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

precipitates of calcium Ceftriaxone which disappear on completion or discontinuation of Ceftriaxone therapy. Rarely have these findings been associated with symptoms. In symptomatic cases, conservative nonsurgical management is recommended. Discontinuation of Ceftriaxone treatment in symptomatic cases should be at the discretion of the physician. These shadows can appear in patients of any age, but are 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. There is no clear evidence of gallstones or of acute cholecystitis developing in children or infants treated with Ceftriaxone.

Cephalosporin as a class tend to be absorbed onto the surface of the red cell membranes and react with antibodies directed against the drug to produce a positive Coombs' test and occasionally a rather mild haemolytic anaemia. In this respect, there may be some cross-reactivity with penicillins.

Regular blood counts (haemoglobin, erythrocyte, leucocyte and platelet counts and screening for prolongation of prothrombin time) should be carried out during treatment.

Cephalosporin may cause bleeding due to hypoprothrombinaemia and should be used with caution in patients with renal or hepatic impairment, malnourished patients or those with low vitamin K levels and also in patients receiving prolonged cephalosporin therapy who are at increased risk of developing hypoprothrombinemia.

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

Super infections with non-susceptible micro-organisms (such as yeasts, fungi) may occur as with other anti-bacterial agents. A rare side-effect is pseudomembranous colitis which has resulted from infection with *Clostridium difficile* during treatment with Ceftriaxone.

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*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C.difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients

who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C.difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C.difficile*, and surgical evaluation should be instituted as clinically indicated.

An immune mediated haemolytic anaemia has been observed in patients receivi g cephalosporin class antibacterials including Ceftriaxone. Severe cases of haemolytic anaemia, includi g fatalities, have been reported during treatment in both adults and children. If a patient develo s anaemia while on Ceftriaxone, the diagnosis of a cephalosporin associated anaemia should be considered and Ceftriaxone discontinued until the aetiology isc etermined.

Antibiotic-associated diarrhoea, cc litis and pseudomembranous colitis have all been reported with the use of Ceftriaxone. These diagnose s should be considered in any patient who develops diarrhoea during or shortly after treatment. Ceftriaxone should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted. Ceftriaxone should be used with caution in individuals with a previous history of gastro-intestinal disease, particularly colitis.

4.5 Interaction with other medicinal products and other forms of interaction:

Do not use diluents containing cal cium, such as Ringer's solution or Hartmann's solution, to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for IV administration be ause a precipitate can form.

The elimination of Ceftriaxone is not altered by probenecid.

Aminoglycoside antibiotics and diuretics: No impairment of renal function has so far been observed after concurrent administration of large doses of Ceftriaxone and potent diuretics (e.g.furosemide). There is no evidence that Ceftriaxone incre ases renal toxicity of aminoglycosides.

Alcohol: No effect similar to tha t of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of Ceftriaxone. Ceftriaxone does not contain an N-methylthiotetrazole moiety associated with possibl e ethanol intolerance and bleeding problems of certain other cephalosporins.

Antibiotics: In an *in vitro* study, antagonistic effects have been observed wit the combination of chloramphenicol and Ceftriaxone.

Anticoagulants: As Ceftriaxone has an N-methylthiotriazine side-chain, it might have the potential to cause hypoprothrombinaemia resulting in an increased risk of bleeding in patients treated with anticoagulants.

Oral Contraceptives: 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.

Based on literature reports Ceftriaxone is incompatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Interference with Laboratory Tests:

In patients treated with Ceftriaxone, the Coombs' test may in rare cases be false-positive.

Ceftriaxone, like other antibiotics, may result in false-positive tests for galactosaemia. Likewise, non-enzymatic methods such as copper reduction methods (Benedict's, Fehling's or Clinitest) for glucose determination in urine may give false-positive results. For this reason, urine-glucose determination during therapy with Ceftriaxone should be carried out enzymatically.

4.6 Pregnancy and Lactation

Pregnancy:

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

Lactation:

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

4.7 Effects on ability to drive and use machines

During the treatment with Ceftriaxone, undesirable effects may occur (e.g. dizziness), which my influence the ability to drive and use machine. Patients should be cautions when driving or operating machinery.

4.8 Undesirable effects

The undesirable effects usually are mild and short-term. Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full term newborns (aged <28 days) who had been treated with intravenous Ceftriaxone and calcium. Precipitations of Ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in newborns is due to their low blood volume and the longer half life of Ceftriaxone compared with adults.

Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines.

Gastrointestinal

Common (≥ 1% - <10%): Loose stools or diarrhoea (diarrhoea may sometimes be a symptom of pseudomembranous colitis, nausea, vomiting, stomatitis and glossitis.

Rare (≥ 0.01% - < 0.1%): Abdominal pain.

Infections

Super infection caused by microorganisms non-susceptible to Ceftriaxone such as yeasts, fungi (mycosis of the genital tract) or other resistant microorganisms may develop. Pseudomembraneous colitis is a rare undesirable effect caused by infection with *Clostridium difficile* during treatment with Ceftriaxone. Therefore, the possibility of the disease should be considered in patients who present with diarrhoea following antibacterial agent use.

Hypersensitivity

Uncommon (≥ 0.1% - < 1%): Maculopapular rash or exanthema, pruritus, urticaria, oedema, shivering and anaphylactic or anaphylactoid reactions (e.g. bronchospasm) and allergic dermatitis have occurred.

Rare (≥ 0.01% - < 0.1%): Drug fever, shivering. Anaphylactic-type reactions such as bronchospasm are rare. Very rare (< 0.01%): Isolated cases of severe cutaneous adverse reactions (erythema multiforme, Stevens Johnson Syndrome and Lyell's Syndrome/toxic epidermal necrolysis) have been reported.

Blood and lymphatic system disorders

Common (≥1% - ≤10%):

Haematological reactions have included anaemia (all grades), haemolytic anaemia, granulocytopenia, leucopenia, neutropenia, thrombocytopenia and eosinophilia. Coagulation disorders have been reported as very rare side effects.

Unknown frequency: Immune mediated haemolytic anaemia

Unknown frequency of agranulocytosis (<500/mm3) has been reported, mostly after 10 days of treatment and following total doses of 20g or more.

There have been rare reports of fatal haemolysis in association with Ceftriaxone. Ceftriaxone has rarely been associated with prolongation of prothrombin time, however, bleeding and bruising due to hypoprothrombinemia may be more prevalent in patients with renal or hepatic impairment, malnourished patients or those with low vitamin K levels and patients receiving prolonged Ceftriaxone therapy.

Central Nervous system

Rare (≥ 0.01% - < 0.1%): Headache, vertigo and dizziness.

Administration of high doses of cephalosporins, particularly in patients with renal insufficiency, may result in convulsions.

Renal and Urinary

Rare (≥ 0.01% - < 0.1%): Glycosuria, oliguria, haematuria, increase in serum creatinine.

Very rare (< 0.01%): Cases of renal precipitation have been reported, mostly in children older than 3 years and who have been treated with either high daily doses (e.g.≥ 80mg/kg/day) or total doses exceeding 10 grams and presenting other risk factors (e.g. fluid restrictions, confinement to bed, etc.). The risk of precipitate formation is increased in immobilized or dehydrated patients. This event may be symptomatic or asymptomatic, may lead to renal insufficiency and anuria, and is reversible upon discontinuation of Ceftriaxone.

Acute renal tubular necrosis may occur rarely with Ceftriaxone.

Hepatobiliary system

Rare (≥ 0.01% - < 0.1%): Hepatitis and/or cholestatic jaundice increase in liver enzymes. Transient elevations in liver function tests have been reported in a few cases.

Shadows which have been mistaken for gallstones, but which are precipitates of calcium Ceftriaxone, have been detected by sonograms. These abnormalities are commonly observed after an adult daily dose of two grams per day or more, or its equivalent in children; these abnormalities were particularly observed in children with an incidence of above 30% in isolated reports. At doses of two grams a day or above these biliary precipitates may occasionally cause symptoms. Should patients develop symptoms, non-surgical management is recommended and discontinuation of Ceftriaxone should be considered.

The evidence suggests biliary precipitates usually disappear once Ceftriaxone has been stopped. The risk of biliary precipitates may be increased by treatment duration greater than 14 days, renal failure, dehydration or total parenteral nutrition.

Pancreas

Very rare (< 0.01%): There have been isolated reports of pancreatitis although a causal relationship to Ceftriaxone has not been established.

Local effects

Rare (≥ 0.01% - < 0.1%): Pain or discomfort may be experienced at the site of intramuscular injection immediately after administration but is usually well tolerated and transient. Intramuscular injection without Lidocaine solution is painful. Local phlebitis has occurred rarely following intravenous administration but can be minimized by slow injection over at least 2-4 minutes.

4.9 Overdose

Overdose can cause massive diuresis resulting in dehydration, volume depletion and electrolyte disturbances with consequent hypɔtension and cardiac toxicity. High doses have the potential to cause transient deafness and may precipitate gout (disturbed uric acid secretion).

Treatment

In patients presenting within 1 ho ι r of ingestion, consider activated charcoal (50g for adults: 1g/kg for children)

Observe for a minimum of 4 hours - monitor pulse and blood pressure.

Treat hypotension and dehydration with appropriate IV fluids.

5. PHARMACOLOGICAL PROPERTIES :

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group:

ATC Code: J01DD04

Mechanism of action

Ceftriaxone has bactericidal activity resulting from the inhibition of bacteri l cell wall synthesis ultimately leading to cell death. Ceftriaxone is stable to a broad range of bacterial -lactamases.

5.2 Pharmacokinetic Properties :

Absorption

Intramuscular administration

Following intramuscular injection, mean peak plasma Ceftriaxone levels are ap roximately half those observed after intravenous administration of an equivalent dose. The maximum plasma concentration after a single intramuscular dos ϵ 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 intramuscular administration is equivalent to that after intravenous administration of an equivalent dose.

Intravenous administration

After intravenous bolus administration of Ceftriaxone 500 mg and 1 g, mean pe k plasma Ceftriaxone levels are approximately 120 and 200 mg/l respectively. After intravenous infusion of Ceftriaxone 500 mg, 1 g and 2 g, the plasma Ceftriaxone levels are approximately 80, 150 and 250 mg/l respectively.

Distribution

The volume of distribution of Ceftriaxone is 7 – 12 l. Concentrations well above he minimal inhibitory concentrations of most relevant pathogens are detectable in tissue includin lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids. An 8 - 15 % increase in mean peak plasma concentration (Cmax) is seen on repeated administration; steady state is reached in most cases within 48 - 72 hours depending on the route of administration.

Penetration into particular tissues

Ceftriaxone penetrates the menin ges. Penetration is greatest when the meninges are inflamed. Mean peak Ceftriaxone concentrations in CSF in patients with bacterial meningitis are reported to be up to 25 % of plasma levels compared to 2 % of plasma levels in patients with uninflamed meninges. Peak Ceftriaxone concentrations in CSF are reached approximately 4-6 hours after intravenous injection. Ceftriaxone crosses the placental barrier and is excreted in the breast milk at low concentrations.

Protein binding

Ceftriaxone is reversibly bound to albumin. Plasma protein binding is ab ut 95 % at plasma concentrations below 100 mg/l. Binding is saturable and the bound portion decreases with rising

concentration (up to 85 % at a plasma concentration of 300 mg/l).

Biotransformation

Ceftriaxone is not metabolized systemically; but is converted to inactive metabolites by the gut flora.

Elimination Plasma clearance of total Ceftriaxone (bound and unbound) is 1 - 22 ml/min. Renal clearance is 5 - 12 ml/min. 50 – 60 % of Ceftriaxone is excreted unchanged in the urine, primarily by glomerular filtration, while 40 - 50 % is excreted unchanged in the bile. The elimination half-life of total Ceftriaxone in adults is about 8 hours.

Patients with renal or hepatic impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of Ceftriaxone are only minimally altered with the halflife slightly increased (less than two fold), even in patients ith severely impaired renal function. The relatively modest increase in half-life in renal impairment is explained by a compensatory increase in non-renal clearance, resulting from a decrease in protein binding and corresponding increase in non-renal clearance of total Ceftriaxone.

In patients with hepatic impairment, the elimination half-life of Ceftriaxone is not increased, due to a compensatory increase in renal clearance. This is also due to an increase in plasma free fraction of Ceftriaxone contributing to the observed paradoxical increase in total drug clearance, with an increase in volume of distribution paralleling that of total clearance.

Older people

In older people aged over 75 years the average elimination half-life is usually tw to three times that of young adults.

Paediatric population

The half-life of Ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels of free Ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. During childhood, the half-life is lower than in neonates or adults.

The plasma clearance and volume of distribution of total Ceftriaxone are greater i neonates, infants and children than in adults.

Linearity/non-linearity

The pharmacokinetics of Ceftriaxone are non-linear and all basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations, increasing less than

proportionally with dose. Nonlinearity is due to saturation of plasma protein binding and is therefore observed for total plasma Ceftriaxone but not for free (unbound) Ceftriaxone.

Pharmacokinetic/pharmacodynamic relationship

As with other beta-lactams, the pharmacokinetic-pharmacodynamic index d monstrating the best correlation with in vivo efficacy is the percentage of the dosing interval that the nbound concentration remains above the minimum inhibitory concentration (MIC) of Ceftriaxone for individual target species (i.e. %T > MIC).

5.3 Preclinical safety data:

Not Applicable

6.0 Pharmaceutical Particulars:

6.1 List of Excipients

Not Applicable

6.2 Incompatibilites:

Solutions containing Ceftriaxone should not be mixed with or added to solutions containing other agents except 1% Lidocaine Injection (for intramuscular injection only) & Sterile ater for Injection. In particular, diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions.

6.3 Shelf life:

24 months

6.4 Special precaution for storage :

Store at a temperature not exceeding 30°C.Protected from light and moisture.

6.5 Nature and contents of container :

20ml clear USP Type-III glass vial with rubber bung aluminium seal having flip on top seal. Such One vial packed in printed carton with 10ml ampoule of Sterile Water for Injection and leaflet.

6.6 Special precautions for disposal and other handling:

Not Applicable

7.0 Marketing authorisation holder:

Psychotropics India Limited

Plot No.12 & No.12 & 12A, Industrial Park-II, Phase-I, Sallempur Mehdood-2, Haridwar-249403,249403, (Uttarakhand)

8.0 Marketing authorization numbers :

08263/08717/NMR/2020

9.0 Date of the first authorisation or renewal :

Dec 26, 2022

10.0 Date of revision of the text :

Not Applicable

11.0 Dosimetry (If Applicable) :

Not Applicable

12.0 Instructions for Preparation of Radiopharmaceuticals (If Applicable) : Not Applicable