SUMMARIES OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Invented name of the medicinal product:

ALFAXONE (Ceftriaxone for Injection USP 1g)

1.2 Strength:

1g

1.3 Pharmaceutical Form:

Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each vial contains:

Ceftriaxone Sodium USP (Sterile) equivalent to Ceftriaxone.....1000 mg

Sr. No.	Ingredient	Specification	Label Claim/ Vial	Qty. /Vial
1	Ceftriaxone Sodium (Sterile) Equivalent to Ceftriaxone	USP	1000 mg	1 gm

3. PHARMACEUTICAL FORM

Powder for injection

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

Lower Respiratory Tract Infection:

Etiology - *S. Pneumoniae*, other *streptococci* exclusive of *Enterococci, S. aureus, H. influenzae, H. parainfluenzae, Klebsiella spp.* (including *K. pneumoniae*), *E. coli, E. aerogenes, P. mirabilis* and *S. marcescens.*

Skin and Skin Structure Infections

Etiology - *Staph. aureus, Staph. epidermidis, streptococci* (excluding *Enterococci), E. cloacae, Klebsiella spp.* (including *K. pneumoniae*), *P.mirabilis* and *P. aeruginosa.*

Urinary Tract Infections (complicated and uncomplicated)

Etiology - *E. coli, P. mirabilis, P. vulgaris, M. morganil* and *Klebsiella spp*. (including *K. pneumoniae*)

Uncomplicated Gonorrhoea - Cervical / Urethral / Rectal

Etiology - *N. gonorrhoea* including penicillinase producing strains.

Pelvic Inflammatory Disease

Etiology - *N. gonorrhoea*

Bacterial Septicemia

Etiology - *S. aureus, Strep. pneumoniae, E. coli, H. influenzae* and *K. pneumoniae*.

Bone and Joint infections

Etiology - *S. aureus, Strep. pneumoniae, streptococci* other than *Enterococci, E. coli, P. mirabilis, K. pneumoniae* and *Enterobacter spp.*

Intra-Abdominal Infections

Etiology - E. *coli, K. pneumoniae*

Meningitis

Etiology - *H. influenzae, N. meningitides* and *Strep. pneumoniae*, *Staph. epidermidis* and *E. Coli.*

Prophylaxis

A single dose of Ceftriaxone preoperatively may reduce chances of postoperative infections.

4.2 Posology and method of administration

The usual adult doses is 1-2 g.o.d./b.d. Total daily dose should not exceed 4g.

In infants and young children : 20 – 80 mg/kg/day

Premature babies / Neonates : Less than 50 mg/kg/day.

In Gonorrhoea:

A single intramuscular dose of 250 mg is recommended. (Ceftriaxone regimen should be continued for 72 hours after fever abates or after evidence of bacterial eradication).

(Ceftriaxone for intramuscular injection should be given in 1% lidocaine and administered by a deep intragluteal injection to minimize pain).

For the treatment of serious infections in children other than meningitis the recommended total daily dose is 50-75 mg/kg/body weight (not to exceed 2 g) given in 2 divided doses.

For pre-operative use (surgical prophylaxis) a single dose given ½ to 2 hours, before surgery is recommended.

For *Strep. pyogenes* infections 10 days regimen is required.

No dose adjustment is required in renal or hepatic dysfunction but serum levels should be monitored in patients with other severe renal impairment (e.g. dialysis patients) or in patients suffering from both renal and hepatic malfunction.

Pediatrics:

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 (see Special warning and precautions for use).

Children under 12 years

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

Up to 80mg/kg body-weight daily may be given in severe infections, except in premature neonates where a daily dosage of 50mg/kg should not be exceeded. For children with body weights of 50kg or more, the usual 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 body weight should be avoided because of the increased risk of biliary precipitates.

Directions for use:

- Intramuscular Injection : 1g ceftriaxone should be dissolved in 3.5ml of 1% Lidocaine hydrochloride Solution. The solution should be administered by deep intramuscular injection.
- Intravenous Injection : 1g ceftriaxone should be dissolved in 9.6ml of water for injection. The injection should be administered over at least 2-4min directly into the vein or via the tubing of an intravenous infusion.

Adult and children 12 years and over:

Standard therapeutic dosage: 1g once daily

Severe infections : 2-4 g daily, normally as a once daily dose.

Peri-operative prophylaxis : Usually one dose of 1g given by intramuscular or slow intravenous injection. In colorectal surgery, 2g should be given intramuscularly (in divided doses at different injection sites), by slow intravenous injection or by slow intravenous infusion, in conjunction with a suitable agent against anaerobic bacteria.

Children under 12 years

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

Up to 80mg/kg body - weight daily may be given in severe infections, except in premature neonates where a daily dosage of 50mg/kg should not be exceeded. For children with body weights of 50kg or more, the usual dosage should be used. Dosage of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. Doses greater than 80mg/kg body weight should be avoided because of the increased risk of biliary precipitates.

4.3 Contraindications

Ceftriaxone for Injection is contraindicated in patients with known allergy to Cephalosporin group of antibiotics.

4.4 Special warning and Precautions for use.

Warning:

This product should be given cautiously to Penicillin sensitive patients. Antibiotics should be given cautiously to patients with any kind of allergy particularly to drugs. Serious hypersensitivity reactions may require use of subcutaneous epinephrine and other emergency measures. Pseudomembraneous colitis has been reported with use of Cephalosporins and other broad spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of colon and promote growth of Clostridia.

Precautions

In renal failure no adjustment may be necessary but serum level should be monitored periodically and the dosage reduced if required.

Dosage adjustment is similarly not essential in hepatic failure but in patients with both hepatic and significant renal malfunction. Ceftriaxone for Injection doses should not exceed 2 g/day without close serum monitoring.

Rarely, alterations in Prothrombin time have occurred and may require coadministration of vitamin K (10 mg weekly). Prolonged use may cause overgrowth of non-susceptible organism and cause hyperinfection. Administer with caution to patients with history of G.I. diseases, especially, colitis. CARCINOGENESIS, MUTAGENESIS AND IMPAIREMENT OF FERTILITY. No evidences seen in doses upto 20 times the clinical dose.

4.5 Interactions with other medicinal products and other forms of interaction

Potentially hazardous interactions

No impairment of renal function or increased nephrotoxicity has been observed in humans after simultaneous administration of Ceftriaxone with diuretics or with aminoglycosides.

A possible disulfiram like reaction may occur with alcohol.

Other significant interactions

Ceftriaxone does not interfere with the protein binding of bilirubin.

Simultaneous administration of probenecid does not alter the elimination of ceftriaxone

Experimentally, in vitro, ceftriaxone has been shown to enhance bacterial killing by human neutrophils.

Potentially useful interactions

Experimentally in vitro ceftriaxone has been shown to enhance bacterial killing by human neutrophils.

4.6 Pregnancy and Lactation

Pregnancy

No evidence of embryotoxicity, fetotoxicity or teratogenicity seen upto 20 times the usual human dose given to mice. As there are no adequate trials in pregnant women, administer only if clearly necessary

Lactation

As low concentrations are excreted in milk administer with caution.

4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while taking Ceftriaxone for Injection refrain from driving or using machines.

4.8 Undesirable effects

Ceftriaxone for Injection is generally well tolerated. In clinical trials following reactions were encountered which may or may not be related to Ceftriaxone for Injection therapy.

1. Local reactions - Pain, induration, tenderness at the site of injection (1%) Less frequently phlebitis was seen after intravenous doses.
2. Hypersensitivity - Rash (1.7%) pruritus, fever, chills (1%),
3. Hematological - Eosinophilia (6%), thrombocytosis (5.1%), - leukopenia (2.7%), Anaemeia, neutropenia, lymphopenia, thrombocytopenia (<1%)
4. G.I.T. - Diarrhoea (2.7%), - nausea, vomiting, diageusia(<1%)
5.Hepatic - SGOT elevation (3.1%), - SGPT elevation (3.3%), Alkaline phosphatase/bilirubin elevation (<1%)
6. Renal - BUN elevation (1.2%), Creatinine elevation (<1%), Casts in urine (<1%)
7. C.N.S. - Headache/dizziness (<1%)
8. Genitourinary - Moniliasis/Vaginitis (<1%)

4.9 Overdose

Severe effects would not be anticipated after oral overdosage with Ceftriaxone and it is unlikely that any treatment would be needed.

Drug concentrations are only minimally reduced by hemodialysis in the presence of normal renal and hepatic function. There is not specific antidote.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

ALFAXONE has a broad-spectrum activity in vitro which includes Gram – positive and Gram – negative aerobic and some anaerobic bacteria.

ALFAXONE has a high degree of stability in presence of Beta – lactamase, both penicillinases and cephalosporinases of Gram –negative and Gram – positive bacteria.

ALFAXONE usually shows good in vitro activity against the following organisms.

Gram – Negative Aerobes:

Enterobacter aerogenes

Enterobacter clocae

E coli

H. influenzae (including Ampicillin resistant strains)

H. Parainfluenzae

Klebsiella spp (including *K. pneumoniae*)

N. gonorrhoeae (including penicillinase and non – penicillinase producing strains)

N. meningitides

Serratia marcescens

Citrobacter freundil

Citrobacter diversus

Providential spp

Salmonella spp

Shigella spp

Acinetobacter calcocetius

Note : Many strains of above organisms that are multiply – resistant to other antibiotics. E.g. *Penicillins , cephalosporins* and *aminoglycosides* are susceptible to ceftriaxone. Ceftriaxone is also active against many strains of Ps. aeruginosa

Gram-Positive Aerobes:

Strep. Aureus including penicillinase producing strains

Staph. Epidemidis

(Note: Methicillin resistant staphylococcal are resistant to all cephalosporins including Ceftriaxone)

Strep. Pyogenes (Group A Beta-hemolytic)

Strep. Agalactoae (Group B Streptococci)

Stre.pneumoniae

Anaerobes: *Bacteroids spp*

5.2 Pharmacokinetic properties

Absorption

Ceftriaxone is completely absorbed following intramuscular administration with mean maximum plasma concentrations occurring 2-3 hours post dosing.

Ceftriaxone Plasma Concentrations after a single I.V. dose administration infused over 30 minutes.

AVERAGE PLASMA CONCENTRATIONS (µG/ML)

Dose	0.5 h	1 h	2 h	4 h	6 h	8 h	12 h	16 h	24 h
0.5 G	82	59	48	37	29	23	15	10	5
1 G	151	111	88	67	53	43	28	18	9
2 G	257	192	154	117	89	74	46	31	15

Multiple dosing resulted in 15-36% accumulation.

Ceftriaxone plasma concentrations after a single I.M. dose administration.

AVERAGE PLASMA CONCENTRATIONS (µG/ML)

(MEAN ± STANDARD DEVIATION)

Dose	0.5 h	1 h	2 h	4 h	6 h	8 h	12 h	16 h	24 h
0.5 G	30.2	42.5	45.7	40.7	35.2	30.2	25.5	21.4	8.4
	(±14.5)	(±13.1)	(±9.8)	(±8.0)	(±6.9)	(±6.4)	(±5.5)	(±5.2)	(±3.6)
5 G	49	64.3	80.5	65.5	63.2	54.6	46	39.6	14.9
	(±27)	(±26)	(±6.4)	(±7.1)	(±9.8)	(±8.5)	(±6.5)	(±7)	(±3.5)

Ceftriaxone Urinary Concentrations after a single dose administration are high.

AVERAGE URINARY CONCENTRATIONS (µG/ML)

Dose / Route	0.2h	2 – 4 h	4 – 8 h	8 – 12 h	12 – 24 h	24 – 48 h
0.5 G/ I.V.	526	366	142	87	70	15
0.5 G/ I.M.	115	425	308	127	96	18
1 G / I.V.	995	855	293	147	132	32
1 G / I.M.	504	628	418	237	ND*	ND*
2 G / I.M.	2692	1976	418	757	274	198

*ND = Not determined

Distribution

Apparent volume of distribution of ceftriaxone is 5.78 – 13.5 L. ceftriaxone is reversibly bound to plasma proteins.

Concentrations of ceftriaxone inhibitory for most Gram – negative bacteria are attained in the meninges, in purulent sputum and in synovial, prostatic and pleural fluid. Ceftriaxone also reaches high concentrations in the blister and peritoneal fluid, bone, myometrium, endometrium and salpinges tissue.

Ceftriaxone is excreted in breast milk (AUC in milk is 3 – 4% of AUC in serum). High concentrations are also seen in bile. Elimination half life of ceftriaxone is 6 – 9 hours.

Excretion

Major excretory pathway is urine (40 –60%) by glomerular filtration. Some amount is eliminated via bile (11 – 65%).

In infants and children

Elimination half-life in neonates is prolonged (almost equal to adults) but decreases with increasing postnatal age.

In patients with renal failure, non – renal elimination may compensate

5.3 Preclinical safety data

Studies in the mouse, rat, rabbit, dog, and monkey have demonstrated very good tolerance of both single and repeated intravenously doses for up to 26 weeks. Short-lived respiratory depression and vomiting were noted, but only after rapid administration of large volume doses.
In monkeys, doses of 400 - 700 mg daily over 26 weeks caused moderate renal tubular degeneration and one death. Sandy deposits of insoluble calcium salts were found in some dogs after dosing over 4 weeks, and in some monkeys after 26 weeks.
No mutagenicity from Ceftriaxone has been observed.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients

No excipients are used in manufacture of **ALFAXONE** (Ceftriaxone for Injection 1 g).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C, protected from light & moisture.

6.5 Nature and contents of container

10 ml flint USP type I, clear colourless glass vial, plugged with grey bromo butyl rubber plug & sealed with dark pink coloured flip off aluminium seal & labeled. One such vial along with 5ml Lidocaine ampoule & 10ml SWFI are to be placed in a plastic tray. Tray to be inserted in a mono carton along with its package insert. Top & bottom flaps of mono cartons are sealed with Kilitch Printed tamper proof sticker labels. Such 10 mono cartons are packed in Outer carton. Such cartons are packed in a shipper.

6.6 Special precautions for disposal

No special requirements.

7. REGISTRANT

Marketing Authorisation holder

Name: Alpha Pharmacy and Stores Ltd.

Address: 2B Alabi Street off Toyin Street, Ikeja, Lagos, NIGERIA.

Manufacturer:

Name: Kilitch Drugs India Ltd.

Address: Plot no. C-301/2, M.I.D.C. T.T.C., Industrial area, Pawane, Navi Mumbai- 400 705. Maharashtra, INDIA

Telephone: +91 22 27680913

Fax no.: 022-61214101

E-mail: bhavinmehta@kilitch.com

8. DATE OF REVISION OF THE TEXT:

Not Applicable.

The Summary of Product Characteristics (SPC) is satisfactory.

9. DOSIMETRY (IF APPLICABLE):

Not Applicable.

10. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

Not Applicable.