Summary Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT:

Xtracef Injection 1gm

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each vial contains:
Cefoperazone (as Sodium)….500mg
Sulbactam (as Sodium) …….500mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:

Description:
Injection, White to off-white powder in a clear glass vial with a blue color flip-off seal.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Monotherapy: Xtracef Injection is indicated for the treatment of the following infections when caused by susceptible organisms:

i. Respiratory tract infections (upper and lower).
ii. Urinary tract infections (upper and lower).
iii. Peritonitis, cholecystitis, cholangitis, and other intra-abdominal infections.
iv. Septicaemia.
v. Meningitis.
vi. Skin and soft tissue infections.
vii. Bone and joint infections.
viii. Pelvic inflammatory disease, endometritis, gonorrhoea, and other infections of the genital tract.

Combination Therapy: Because of the broad spectrum of activity of **Xtracef** Injection, most infections can be treated adequately with this antibiotic combination alone. However, **Xtracef** Injection may also be used concomitantly with other antibiotics if such combinations are indicated. If an aminoglycoside is used, renal function should be monitored during the course of therapy.

4.2 Posology and method of administration

Posology

Adults: The usual adult dose of the combination is 2 to 4g/day (i.e, 1-2 g/day each of Cefoperazone and Sulbactam) given IV or IM in equally divided doses every 12 hours. In severe or refractory infections the daily dosage may be increased to 8g (i.e, 4g/day each of Cefoperazone and Sulbactam) given IV in equally divided doses every 12 hours. The recommended maximum daily dosage of Sulbactam is 4g (8g of the combination).

Children: The usual dosage in children is 40-80mg/kg/day (20 to 40mg/kg/day each of Cefoperazone and Sulbactam) every six to twelve hours. In serious or refractory infections, these dosages may be increased up to 240mg/kg/day (160mg/kg/day Cefoperazone activity). Doses should be administered in two to four equally divided doses.

Neonates: For neonates in the first week of life, the drug should be given every 12 hours. The maximum daily dosage of Sulbactam in pediatrics should not exceed 80mg/kg/day.

Renal Impairment: Dosage regimens of **Xtracef** Injection should be adjusted in patients with a marked decrease in renal function (creatinine clearance of less than 30ml/min) to compensate for the reduced clearance of Sulbactam. Patients with creatinine clearances between 15 and 30ml/min should receive a maximum of 1g of Sulbactam every 12 hours (maximum daily dosage of 2g Sulbactam), while patients with creatinine clearances of less than 15ml/min should receive a maximum of 500mg of Sulbactam every 12 hours (maximum daily dosage of 1g Sulbactam). The pharmacokinetic profile of Sulbactam is significantly altered by haemodialysis. The serum half-life of Cefoperazone is reduced slightly during haemodialysis. Thus, dosing should be scheduled to follow a dialysis period.

Hepatic Impairment: Cefoperazone is extensively excreted through the bile. Dose modification may be necessary in cases of severe biliary obstruction, severe hepatic disease or in cases of renal dysfunction coexistent with either of those conditions.

In such cases, dosage should not exceed 2g/day of Cefoperazone without close monitoring of serum concentrations.

Methods of Administration:

Intravenous Administration: For intravenous infusion, each vial of **Xtracef** Injection should be reconstituted with the appropriate amount of 5% Dextrose solution, 0.9% Sodium Chloride Injection or Sterile Water for Injection and then diluted to 20ml with the same solution followed by administration over 15-60 min. Lactated Ringer's solution is a suitable vehicle for IV infusion, however, not for initial reconstitution. In this case, sterile water for injection should be used for reconstitution. A two-step dilution is required using Sterile Water for Injection further diluted with Lactated Ringer.s solution to a Sulbactam concentration of 5mg/ml and Cefoperazone concentration of 5mg/ml. For intravenous injection, each vial should be reconstituted as above and administered over a minimum of 3 minutes.

Intramuscular Administration: Lidocaine HCl 2% is a suitable vehicle for IM administration, however, not for initial reconstitution. Sterile Water for Injection should be used for reconstitution. For a concentration of Cefoperazone greater than or equal to 250mg/ml, a two-step dilution is required using Sterile Water for Injection further diluted with 2% Lidocaine to yield solutions containing up to 125mg Cefoperazone and 125mg Sulbactam/ml in approximately 0.5% Lidocaine HCl solution.

4.3 Contraindications:

Cautions for Usage:

Xtracef Injection should not be mixed in the syringe with aminoglycoside antibiotics.

Patients with known hypersensitivity to cephalosporins and penicillins, Sulbactam or Cefoperazone.

4.4 Special warnings and precautions for use:

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving b-lactam or cephalosporin therapy. These reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted. As with other antibiotics, overgrowth of non-susceptible organisms may occur during the prolonged use of Sulbactum+Cefoperazone Injection.

It has not been extensively studied in premature infants or neonates. Therefore, in treating premature infants and neonates, the potential benefits and possible risks involved should be considered before instituting therapy.

Hepatic Impairment: In severe hepatic dysfunction, therapeutic concentrations of Cefoperazone are obtained in the bile and only a two-to four-fold increase in the half-life is seen. Dose modification may be necessary in case of severe biliary obstruction, severe hepatic disease or in case of renal dysfunction coexistent with either of those conditions.

Use in pregnancy and lactation: There is no experimental evidence of embryopathic or teratogenic effects attributable to Cefoperazone or Sulbactam but, as with all drugs, it should be administered with caution during the early months of pregnancy. Although both drugs pass poorly into breast milk of nursing mothers, caution should be exercised when **Xtracef** Injection is administered to a nursing mother.

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

A reaction characterized by flushing, sweating, headache and tachycardia has been reported when alcohol was ingested during and as late as the fifth day after Cefoperazone administration. A similar reaction has been reported with certain other cephalosporins and patients should be cautioned concerning ingestion of alcoholic beverages in conjunction with administration of Sulbactum+Cefoperazone Injection. For patients requiring artificial feeding orally or parenterally, solutions containing ethanol should be avoided.

4.6. Fertility, Pregnancy and Lactation

No studies available.

4.7. Effects on ability to drive and use machines:

No report is available.

4.8. Undesirable effects:

Xtracef Injection is generally well-tolerated. The majorities of adverse events are of mild or moderate severity and are tolerated with continued treatment. The most frequent side effects observed with **Xtracef** Injection have been gastrointestinal.

Others include dermatologic reactions, headache, injection pain, chills, and anaphylactoid reactions

4.9. Overdose:

Symptoms: Limited information is available on the acute toxicity of Cefoperazone and Sulbactam in humans. Overdosage of XTRACEF Injection would be expected to produce manifestations that are principally extensions of the adverse reactions reported with the drug. The fact that high CSF concentrations of b-lactam antibiotics may cause neurologic effects, including seizures, should be considered. Treatment: Because Cefoperazone and Sulbactam are both removed from the circulation by haemodialysis, these procedures may enhance elimination of the drug from the body if overdosage occurs in patients with impaired renal function.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic Properties:

The antibacterial component of **Xtracef** Injection is Cefoperazone, a third generation cephalosporin, which acts against sensitive organisms during the stage of active multiplication by inhibiting the biosynthesis of cell wall mucopeptide. Cefoperazone is highly stable to hydrolysis by most b-lactamases produced by most gram-negative pathogens.

Sulbactam does not possess any useful antibacterial activity, except against Neisseriaceae and Acinetobacter. As Sulbactam also binds with some penicillin-binding proteins, sensitive strains are also often rendered more susceptible to Sulbactam+Cefoperazone than to Cefoperazone alone. The combination of Sulbactam and Cefoperazone is active against all organisms sensitive to Cefoperazone. In addition, it demonstrates synergistic activity (up to 4-fold reduction in the minimum inhibitory concentrations for the combination versus those for each component) in a variety of organisms.

5.2 Pharmacokinetics:

Serum concentrations have been shown to be proportional to the dose administered. Mean peak Sulbactam and Cefoperazone concentrations after the IV administration of 2g of **Xtracef** Injection (1g Sulbactam, 1g of Cefoperazone) over 5 min were 130.2 and 236.8mcg/ml, respectively. This reflects the larger volume of distribution for Sulbactam (Vd=18-27.6 l) compared to Cefoperazone (Vd=10.2-11.3 l). After IM administration of 1.5g of **Xtracef** Injection (0.5g Sulbactam, 1g Cefoperazone), peak serum concentrations of Sulbactam and Cefoperazone are seen from 15 min to 2 hours after administration. Mean peak serum concentrations were 19 and 64.2 mcg/ml for Sulbactam and Cefoperazone, respectively. Both Sulbactam and Cefoperazone distribute well into a variety of tissues and fluids including bile, gallbladder, skin, appendix, fallopian tubes, ovary, uterus and others.

There is no evidence of any pharmacokinetic drug interaction between Sulbactam and Cefoperazone when administered together in the form of Sulbactam+Cefoperazone injection. Approximately 84% of the Sulbactam dose and 25% of the Cefoperazone dose administered as Sulbactam+Cefoperazone injection is excreted by the kidney.

Most of the remaining dose of Cefoperazone is excreted in the bile. After **Xtracef** Injection administration, the mean half-life for Sulbactam is about 1 hour while that
for Cefoperazone is 1.7 hours.

Pharmacokinetics in Special Groups: Renal Insufficiency Patients: No significant
changes observed compared to normal patients.

Hepatic Insufficiency Patients: In patients with hepatic dysfunction, the serum half life is prolonged and urinary excretion is increased. In patients combined with renal and hepatic insufficiency, Cefoperazone may accumulate in the serum.

5.3 Preclinical safety data:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No studies available.

Pregnancy, Teratogenic Effects, Pregnancy Category B:

When given to mice, rats and rabbits at doses up to 10 times the human dose, did not find this product to damage fertility and toxicity to the fetus. But the full and rigorous study of pregnant women, information on animals and people is not yet clear.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients

Sterile water for injection.....5ml

6.2 Incompatibilities:

Aminoglycosides: Solutions of **Xtracef** Injection and aminoglycosides should not be directly mixed, since there is a physical incompatibility between them. If combination therapy with **Xtracef** Injection and an aminoglycoside is contemplated, this can be accomplished by sequential intermittent intravenous infusion provided that separate secondary intravenous tubing is used, and that the primary intravenous tubing is adequately irrigated with an approved diluent between doses. It is also suggested that doses of **Xtracef** Injection be administered throughout the day at times as far removed from the administration of the aminoglycoside as possible.

Lactated Ringer's Solution: Initial reconstitution with Lactated Ringer's Solution should be avoided since this mixture has been shown to be incompatible. However, a two-step dilution process involving initial reconstitution in Sterile Water for Injection will result in a compatible mixture when further diluted with Lactated Ringer's Solution.

Lidocaine: Initial reconstitution with 2% Lidocaine HCl solution should be avoided since this mixture has been shown to be incompatible. However, a two-step dilution process involving initial reconstitution in Sterile Water for Injection will result in a compatible mixture when further diluted with 2% Lidocaine HCl solution.

6.3 Shelf life:

24 months.

6.4 Special precautions for storage:
Store below 30°C.
Protect from sunlight & moisture.
Keep out of the reach of children.

6.5 Nature and contents of container:
Each pack contains a glass vial containing 1gm or 2gm of sterile Cefoperazone+Sulbactam dry powder with 5ml or 10ml of sterile water for injection as diluent.

6.6 Special precautions for disposal and other handling
Reconstituted solution remains stable for 7 days at 2-8°C and for 24 hours at 8-25°C. All unused portions after the above stated time periods should be discarded.

7. MARKETING AUTHORISATION HOLDER:
Surge Laboratories (Pvt.) Ltd.
10th, KM Faisalabad Road, Bikhi,
District Sheikhupura – Pakistan.

8. MARKETING AUTHORISATION NUMBER:

H2022/CTD8332/15090

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