MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product:

Mesutyl 1.0 g

1.1 (Invented) name of the medicinal product:

Generic Name/INN Name:

Combipack of Cefoperazone & Sulbactam for Injection & Sterilised Water for Injection BP

1.2 Strength:

Cefoperazone Sodium USP eq. to
Cefoperazone 500 mg

Sulbactam Sodium USP eq to
Sulbactam 500 mg

1.3 Pharmaceutical form:

Powder for Injection

2. Qualitative and Quantitative composition:

Sr. No	Ingredients	Spec	Std. Qty. mg / Vial	Function
1.	Cefoperazone Sodium Eq. to Cefoperazone	USP	500 mg	Active Agent
2.	Sulbactam Sodium Eq. to Sulbactam	USP	500 mg	Active Agent

3. Pharmaceutical form:

Dosage Form: Powder for Injection

Visual & Physical characteristics of the product:
A white crystalline powder filled in an Intactactly sealed clear glass vials.

4. Clinical particulars
4.1. Therapeutic indications:

Combipack of Cefoperazone Sodium & Sulbactam sodium for Injection is indicated for the treatment of the following infections when caused by susceptible organisms:

Monotherapy

- Respiratory tract infections (upper and lower)

- Urinary tract infections (upper and lower)
- Peritonitis, cholecystitis, cholangitis, and other intra-abdominal infections
- Septicaemia
- Meningitis
- Skin and soft tissue infections
- Bone and joint infections
- Pelvic inflammatory disease, endometritis, gonorrhoea, and other infections of the genital tract

Combination Therapy

Because of the broad spectrum of activity of sulbactam/Cefoperazone, most infections can be treated adequately with this antibiotic combination alone. However, sulbactam/Cefoperazone 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:

Adults

Daily dosage recommendations for sulbactam/cefoperazone in adults are as follows:
Doses should be administered every 12 hours in equally divided doses.
In severe or refractory infections, the daily dosage of sulbactam/cefoperazone may be increased up to 8 g of the 1:1 ratio (i.e. 4 g of cefoperazone activity) or 12 g of the 1:2 ratio (i.e. 8 g of cefoperazone activity). Patients receiving the 1:1 ratio may require additional cefoperazone administered separately. Doses should be administered every 12 hours in equally divided doses.
The recommended maximum daily dosage of sulbactam is 4 g.
In febrile neutropenia, total daily dose can be administered twice or thrice a day in equally divided doses.

Renal Impairment

Dosage regimens of sulbactam/Cefoperazone should be adjusted in patients with a marked decrease in renal function (creatinine clearance of less than 30 mL/min) to compensate for the reduced clearance of sulbactam. Patients with creatinine clearances between 15 and 30 mL/min should receive a maximum of 1 g of sulbactam every 12 hours (maximum daily dosage of 2 g sulbactam), while patients with creatinine clearances of less than 15 mL/min should receive a maximum of 500 mg of sulbactam every 12 hours (maximum daily dosage of 1 g sulbactam). In severe infections it may be necessary to administer additional cefoperazone. 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. The serum half-life of cefoperazone is usually prolonged and urinary excretion of the drug increased in patients with hepatic disease and/or biliary obstruction. Even with severe hepatic dysfunction, therapeutic concentrations of cefoperazone are obtained in bile and only a 2 to 4 fold increase in half life is seen.

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 patients with hepatic dysfunction and concomitant renal impairment, cefoperazone serum concentrations should be monitored and dosage adjusted as necessary. In such cases, dosage should not exceed 2 g/day of cefoperazone without close monitoring of serum concentrations.

Paediatric Use
Daily dosage recommendations for sulbactam/cefoperazone in children are as follows:
Doses should be administered every 6 to 12 hours in equally divided doses.
In serious or refractory infections, these dosages may be increased up to 160 mg/kg/day or 240 mg/kg/day of the 1:2 ratio (160 mg/kg/day cefoperazone activity). Doses should be administered in two to four equally divided doses.

Use in Neonates
For neonates in the first week of life, the drug should be given every 12 hours. The maximum daily dosage of sulbactam in paediatric patients should not exceed 80 mg/kg/day. If more than 80 mg/kg/day of cefoperazone activity is necessary, additional cefoperazone should be administered separately.

Method of Administration
Intravenous/Intramuscular Administration
Reconstitution
Sulbactam/cefoperazone is available in vials of 1.0 g along with a 10 ml vial of Sterile Water for injection for reconstitution.

4.3. Contraindications:
It is contraindicated in patients with a known allergy to penicillins, sulbactam, cefoperazone or any of the cephalosporins.

4.4. Special warnings and precautions for use:

Hypersensitivity
Serious and occasionally, fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-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. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management, including intubation, should be administered as indicated.

Hepatic Dysfunction
Cefoperazone is extensively excreted in bile. The serum half-life of cefoperazone is usually prolonged and urinary excretion of the drug increased in patients with hepatic diseases and/or biliary obstruction. Even with severe hepatic dysfunction, therapeutic concentrations of cefoperazone are obtained in bile and only a 2- to 4-fold increase in half-life is seen.

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 patients with hepatic dysfunction and concomitant renal impairment, cefoperazone serum concentrations should be monitored and dosage adjusted as necessary. In these cases dosage should not exceed 2 g/day of cefoperazone without close monitoring of serum concentrations.

General

As with other antibiotics, vitamin K deficiency has occurred in a few patients treated with cefoperazone. The mechanism is most probably related to the suppression of gut flora, which normally synthesize this vitamin. Those at risk include patients with poor diet, malabsorption states (e.g. cystic fibrosis) and patients on prolonged intravenous alimentation regimens. Prothrombin time should be monitored in these patients and in patients receiving anticoagulant therapy, and exogenous vitamin K administered as indicated.

As with other antibiotics, overgrowth of non-susceptible organisms may occur during the prolonged use of sulbactam/cefoperazone. Patients should be observed carefully during the treatment. As with any potent systemic agent, it is advisable to check periodically for organ system dysfunction during extended therapy; this includes the renal, hepatic and hematopoietic systems. This is particularly important in neonates, especially when premature, and other infants.

Clostridium difficile associated diarrhoea has been reported with nearly all antibacterial agents, including cefoperazone and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C.difficile.

Infancy

Sulbactam/cefoperazone has been effectively used in infants. 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.
Cefoperazone does not displace bilirubin from plasma protein binding sites.

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 the ingestion of alcoholic beverages in conjunction with the administration of sulbactam/cefoperazone. For patients requiring artificial feeding orally or parentally, solutions containing ethanol should be avoided.

4.6. Pregnancy and lactation:

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Only small quantities of sulbactam and cefoperazone are excreted in human milk. Although both drugs pass poorly into breast milk of nursing mothers, caution should be exercised when sulbactam/cefoperazone is administered to a nursing mother.

4.7. Effects on ability to drive and use machines:

Clinical experience with sulbactam/cefoperazone indicates that it is unlikely to impair a patient's ability to drive or use machinery.

4.8. Undesirable effects:

Sulbactam/cefoperazone is generally well tolerated. The majority of adverse events are of mild or moderate severity and are tolerated with continued treatment. The most frequent side effects observed with sulbactam/cefoperazone have been gastrointestinal. Others include dermatologic reactions, headache, injection pain, chills, and anaphylactoid reactions.

Gastrointestinal: As with other antibiotics, the most frequent side effects observed with sulbactam/cefoperazone have been gastrointestinal. Diarrhoea/loose stools have been reported most frequently, followed by nausea and vomiting.

Dermatological Reactions: As with all penicillins and cephalosporins, hypersensitivity manifested by maculopapular rash and urticaria has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin.

Haematological Reactions: Slight decrease in neutrophils (0.4%) has been reported. As with other beta-lactam antibiotics, reversible neutropenia (0.5%) may occur with prolonged administration. Some individuals developed a positive direct Coomb's test (5.5%) during treatment. Decreased haemoglobin (0.9%) or haematocrit (0.9%) have been reported. Transient eosinophilia (3.5%) and thrombocytopenia (0.8%) have occurred, and hypo-prothrombinaemia (3.8%) has been reported.

Miscellaneous: Headache fever, injection pain and chills.

Local Reactions: Sulbactam/cefoperazone is generally well tolerated following intramuscular administration. Occasionally, transient pain may follow administration by this route. As with other cephalosporins and penicillins, when sulbactam/cefoperazone is administered via an intravenous catheter, some patients may develop phlebitis at the injection site.

4.9. Overdose:

Limited information is available on the acute toxicity of cefoperazone sodium and sulbactam sodium in humans. Overdosage of the drug would be expected to produce manifestations that are principally extensions of the adverse reactions reported with the drug. The fact that high cerebrospinal fluid concentrations of beta-lactam antibiotics may cause neurological effects, including seizures, should be considered. Because cefoperazone and sulbactam are both removed from the circulation by haemodialysis, these procedures may enhance the elimination of the drug from the body if overdosage occurs in patients with impaired renal function.

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5. Pharmacological properties:

Pharmacotherapeutic group: Antibiotics.,

ATC Code: J01DD62.

5.1. Pharmacodynamic properties:

Mechanism of action

The anti-bacterial component of sulbactam/cefoperazone is cefoperazone, a third-generation cephalosporin, which acts against sensitive organisms during the stage of active multiplication by inhibiting biosynthesis of cell wall mucopeptide. Sulbactam does not possess any useful antibacterial activity, except against Neisseriaceae and Acinetobacter. However, biochemical studies with cell-free bacterial systems have shown it to be an irreversible inhibitor of most important beta-lactamases produced by beta-lactam antibiotic-resistant organisms.

The potential for sulbactam's preventing the destruction of penicillins and cephalosporins by resistant organisms was confirmed in whole-organism studies using resistant strains in which sulbactam exhibited marked synergy with penicillins and cephalosporins. 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 fourfold reduction in minimum inhibitory concentrations for the combination versus those for each component) in a variety of organisms.

5.2. Pharmacokinetic properties:

Approximately 84% of the sulbactam dose and 25% of the cefoperazone dose administered as sulbactam/cefoperazone is excreted by the kidneys. Most of the remaining dose of cefoperazone is excreted in the bile. After sulbactam/cefoperazone administration, the mean half-life for sulbactam is about 1 hour while that for cefoperazone is 1.7 hours. Serum concentrations have been shown to be proportional to the dose administered. These values are consistent with previously published values for these agents when given alone.

Mean peak sulbactam and cefoperazone concentrations after the administration of 2 g of sulbactam/cefoperazone (1 g sulbactam, 1 g of cefoperazone) intravenously over 5 minutes were 130.2 and 236.8 mcg/mL, respectively. This reflects the larger volume of distribution for sulbactam (Vd = 18.0 to 27.6 L) compared to cefoperazone (Vd = 10.2 to 11.3 L).

After intramuscular administration of 1.5 g cefoperazone sulbactam (0.5 g sulbactam, 1 g cefoperazone), peak serum concentrations of sulbactam and cefoperazone are seen from 15 minutes to 2 hours after administration. Mean peak serum concentrations were 19.0 and 64.2 mcg /mL for sulbactam and cefoperazone, respectively.

Both sulbactam and cefoperazone distribute well into a variety of tissues and fluids, including the bile, gall bladder, 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.

After multiple dosing, no significant changes in the pharmacokinetics of either component of sulbactam/cefoperazone have been reported and no accumulation has been observed when administered every 8 to 12 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, Genotoxicity, carcinogenic potential and toxicity to reproduction.

6. Pharmaceutical particulars:

6.1. List of Excipients:
Not applicable

6.2. Incompatibilities:
Not applicable.

6.3. Shelf life:
24 months

6.4. Special precautions for storage:
Store below 30 °C. protect from light

6.5. Nature and contents of container:

Primary Pack: 10 ml Clear glass vial USP Type III

Secondary Pack: Combipack of One 10 ml Clear glass vial USP Type III & 10 ml FFS of Sterilized Water for Injection BP kept in a tray pack in Mono carton along with package Insert.

6.6. Special precautions for disposal:
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Applicant:
Chez Resources Pharmaceutical Limited
No. 7, Calabar Street, Fegge, Onitsha, Anambra State, NIGERIA

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Name and Address of manufacturer:

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