Otid®
(Cephradine)

1. NAME OF THE PRODUCT

Otid® (Cephradine) 250mg Injection

Otid® (Cephradine) 500mg Injection

Otid® (Cephradine) 1g Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Otid® 250mg Injection

Each vial contains:
Sterile powder of Cephradine BP....250mg
Also contains Arginine

Otid® 500mg Injection

Each vial contains:
Sterile powder of Cephradine BP....500mg
Also contains Arginine

Otid® 1g Injection

Each vial contains:
Sterile powder of Cephradine BP……1g
Also contains Arginine

3. PHARMACEUTICAL FORM

Powder for injection

Appearance:

Otid® 250mg Injection: White to off white crystalline hygroscopic powder.

Otid® 500mg Injection: White to off white crystalline hygroscopic powder.

Otid® 1g Injection: White to off white crystalline hygroscopic powder.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

The treatment of infections of the urinary, respiratory tracts and of the skin and soft tissues, bones and joints; also, septicemia and endocarditis. These include:

- Upper respiratory infections pharyngitis, sinusitis, otitis media, tonsillitis, laryngo-tracheo bronchitis.
- Lower respiratory infections acute and chronic bronchitis, lobar and bronchopneumonia.

- Urinary tract infections cystitis, urethritis, pyelonephritis.
- Skin and soft tissue infections abscess, cellulitis, furunculosis, impetigo.

Otid® has been shown to be effective in reducing the incidence of postoperative infections in patients undergoing surgical procedures associated with a high risk of infection. It is also of value where post-operative infection would be disastrous and where patients have a reduced host resistance to bacterial infection. Protection is best ensured by achieving adequate local tissue concentrations at the time contamination is likely to occur. Thus, Cephradine should be administered immediately prior to surgery and continued during the postoperative period. Bacteriological studies to determine the causative organisms and their sensitivity to Cephradine should be performed. Therapy may be instituted prior to receiving the results of the sensitivity test. **Otid®** injection is indicated primarily for those patients unable to tolerate oral medication. It is also indicated for intravenous use either by direct injection or by intravenous infusion for the treatment of serious and life-threatening infections.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Intramuscular or intravenous injection and intravenous infusion.

Adults and children over 10 years:

Treatment: The usual dose range of **Otid®** for injection is 2-4g daily in four equally divided doses. This may be increased up to 8g a day for severe infections, e.g. septicemia and endocarditis. For the majority of infections, the usual dose is 500mg q.i.d. (four times a day) in equally spaced doses, severe or chronic infections may require larger doses. Prolonged intensive therapy is needed for complications such as prostatitis and epididymitis. Patients who are severely ill and who require high serum levels of Cephradine for treating their infections should be started on intravenous therapy. Limited experience indicates that intraperitoneal administration of Cephradine may be effective after surgery in cases of peritonitis where a surgical drainage system has been established.

Surgical Prophylaxis: The recommended dose for surgical prophylaxis is a single, pre-operative 1-2g IM or IV dose. Subsequent parenteral or oral doses can be administered as appropriate.

Children under 10 years: The usual dose is 50-100mg/kg/day total given in four equally divided doses. More serious illnesses (e.g. typhoid fever) may require 200-300mg/kg/day.

Elderly: There are no specific dosage recommendations or precautions for use in the elderly except, as with other drugs, to monitor those patients with impaired renal or hepatic function.

All patients, regardless of age and weight: Therapy should be continued for a minimum of 48-72 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. In infections caused by haemolytic

strains of streptococci, a minimum of 10 days of treatment is recommended to guard against the risk of rheumatic fever or glomerulonephritis. In the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisal is necessary during therapy and may be necessary for several months afterwards. Persistent infections may require treatment for several weeks. Smaller doses than those indicated above should not be used. Doses for children should not exceed doses recommended for adults. As **Otid®** is available in both injectable and oral form, patients may be changed from the **Otid®** injectable to **Otid®** oral at the same dosage level.

Renal Impairment Dosage:

Patients not on dialysis: The following dosage schedule is suggested as a guideline based on a dosage of 500mg Q6H and on creatinine clearance. Further modification in the dosage schedule may be required because of the dosage selected and individual variation.

Creatinine Clearance	Dose	Time interval
More than 20ml/min	500mg	6 hours
5-20ml/min	250mg	6 hours
Less than 5ml/min	250mg	12 hours

Patients on chronic, intermittent haemodialysis:

250mg	At start of haemodialysis
250mg	6-12 hours after start
250mg	36-48 hours after start
250mg	At start of next haemodialysis if >30 hours after previous dose.

Further modification of the dosage schedule may be necessary in children.

4.3. CONTRAINDICATIONS:

Patients with known hypersensitivity to the cephalosporin antibiotics or any excipient of the formulation.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Renal Impairment Dosage: Use of this antibiotic in patients with renal dysfunction should be monitored intensively. A modified dosage schedule in patients with decreased renal function is necessary. After treatment with Cephradine, a false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with reagent tablets such as Clinitest, but not with enzyme-based tests such as Clinistix or Diastix. As with all antibiotics, prolonged use may result in overgrowth of non-susceptible organisms.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

There is evidence of partial cross-allergenicity between the penicillin and the cephalosporins. Therefore, Cephradine should be used with caution in those patients with known hypersensitivity to penicillin. There have been instances of patients who have had reactions to both drug classes (including anaphylaxis). Concurrent uses of probenecid delays excretion of cephradine. Active drug substances of high molecular weight are incompatible with cephalosporins in parenteral mixtures.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Pregnancy and Lactation: Although animal studies have not demonstrated any teratogenicity, safety in pregnancy has not been established. Therefore, this antibiotic should not be used during pregnancy or lactation unless considered essential by the physician. Cephradine is excreted in breast milk and should be used with caution in lactating mothers.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

None known

4.8. UNDESIRABLE EFFECTS:

Limited essentially to gastro-intestinal disturbances and on occasion to hypersensitivity phenomena. The latter are more likely to occur in individuals who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever or urticaria. The majority of reported side-effects have been mild and are rare, and include glossitis, heartburn, dizziness, tightness in the chest, nausea, vomiting, diarrhoea, abdominal pain, vaginitis, candidal overgrowth. Skin and hypersensitivity reactions include urticaria, skin rashes, joint pains, oedema. As with other cephalosporins, there have been rare reports of erythema multiforme, Stevens Johnson Syndrome, anaphylaxis and toxic epidermal necrolysis. Also, mild transient eosinophilia, leucopenia and neutropenia, positive direct Coombs tests and pseudomembranous colitis have been reported. Elevations of blood urea nitrogen (BUN) and serum creatinine have been reported. Transient hepatitis and cholestatic jaundice have been reported very rarely. Elevations of alanine amino-transferase (ALT), aspartate amino-transferase (AST), total bilirubin and alkaline phosphatase have been observed.

Injection: As with other parenterally administered antibiotics, transient pain may be experienced at the injection site, but is seldom the cause for discontinuing treatment. Thrombophlebitis has been reported following intravenous injection. Since sterile abscesses have been reported following accidental subcutaneous injection, the preparation should be administered by deep intramuscular injection.

4.9. OVERDOSE:

None known.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: First generation cephalosporin.

ATC Code: J01DB09.

Mechanism of action: Cephradine is a broad-spectrum, bactericidal antibiotic active against both Gram-positive and Gram-negative bacteria. It is also highly active against most strains of penicillinase-producing *Staphylococci.*The following organisms have shown in vitro sensitivity to Cephradine.

Gram-positive: *Staphylococci* (both penicillin sensitive and resistant strains), *Streptococci, Streptococcus pyogenes* (beta haemolytic) and *Streptococcus pneumoniae.*

Gram-negative: *Escherichia coli, Klebsiella spp, Proteus mirabilis, Haemophilus influenzae, Shigella spp., Salmonella spp.* (including *Salmonella typhi*) and *Neisseria spp.*

Because Cephradine is unaffected by penicillinase, many strains of *Escherichia coli* and *Staphylococcus aureus* which produce this enzyme are susceptible to Cephradine but resistant to ampicillin.

5.2. PHARMACOKINETICS PROPERTIES:

Absorption: Following intramuscular administration of a single 0.5g dose of Cephradine to normal volunteers, the average peak serum concentration was 8.41µg/ml with the time to peak concentration being 0.93 hours.

Distribution: Cephradine has a high degree of stability to many beta-lactamases. It has a low degree of protein-binding and a large volume of distribution. Therefore, tissue levels are generally found to be high.

Biotransformation: The serum half-life averaged 1.25 hours. A single 1g intravenous dose resulted in serum concentrations of 86µg/ml at 5 minutes and 12µg/ml at 1 hour; these concentrations declined to 1µg/ml at 4 hours. Continuous infusion of 500mg per hour into a 70kg man maintained a concentration of about 21.4µg/ml Cephradine activity; this study showed that a serum concentration of approximately 3µg/ml can be obtained for each milligram of Cephradine administered per kg of body weight per hour of infusion.

Elimination: Cephradine is excreted unchanged in the urine. The kidneys excrete 57% to 80% of an intramuscular dose in the first six hours; this results in a high urine concentration, e.g. 880µg/ml of urine after a 500mg intramuscular dose. Probenecid slows tubular secretion and almost doubles peak serum concentration. Assays of bone obtained at surgery have shown that Cephradine penetrates bone tissue.

5.3. PRECLINICAL SAFETY DATA:

No further relevant data available.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Otid® 50mg Injection: L-Arginine

Otid® 500mg Injection: L-Arginine

Otid® 1g Injection: L-Arginine

6.2. INCOMPATIBILITIES:

The injection is compatible with following and should not be mixed with other diluents:

For direct intravenous administration:

Suitable reconstitution solutions for intravenous injection are:

- Sterile Water for Injection
- 5% Dextrose Injection
- 0.9% Sodium Chloride Injection.

For continuous or intermittent intravenous infusion:

Suitable reconstitution solutions for intravenous infusion are:

- Sterile Water for Injection (50mg/ml Cephradine solutions are approximately isotonic)
- 5% or 10% Dextrose Injection
- 0.9% Sodium Chloride Injection
- Sodium Lactate Injection (M/6 sodium lactate)
- Dextrose and Sodium Chloride Injection
- Lactated Ringer's Injection; Ringer's Injection
- 5% Dextrose in lactated Ringer's Injection
- 5% Dextrose in Ringer's Injection.

6.3. SHELF LIFE:

Unopened vial: See expiry on the pack.

Reconstituted solution:

For solution for IM and direct IV injection: Chemical and physical in-use stability has been demonstrated for 2 hours at room temperature (25°C) and 12 hours when stored in a refrigerator at 2-8°C.

For solution for IV infusion: Using Water for Injection, Glucose 5% or Sodium Chloride 0.9% for concentration of 10mg/ml (1%), chemical and physical in-use stability has been demonstrated for 2 hours at room temperature (25°C) and 12 hours when stored in a refrigerator at 2-8°C. For prolonged infusions, replace the infusion every 10 hours with a freshly-prepared solution.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C, and protect from heat, light and moisture.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Otid® 250mg Injection:

Powder for Injection: Clear glass vial (USP Type-III) with bromobutyl rubber stopper, sealed with flip off seal.
Water for Injection: Clear 5ml glass ampoule (USP Type-I).
Pack size is 1 vial and 1 ampoule.

Otid® 500mg Injection:

Powder for Injection: Clear glass vial (USP Type-III) with bromobutyl rubber stopper, sealed with flip off seal.
Water for Injection: Clear 5ml glass ampoule (USP Type-I).
Pack size is 1 vial and 1 ampoule.

Otid® 1g Injection:

Powder for Injection: Clear glass vial (USP Type-III) with bromobutyl rubber stopper, sealed with flip off seal.
Water for Injection: Clear 10ml glass ampoule (USP Type-I).
Pack size is 1 vial and 1 ampoule.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:

For single use only. Discard any remaining contents. Shake the vial to effect solution and withdraw the entire contents.

6.7. DRUG PRODUCT SPECIFICATION:

Otid® 250mg Injection: BP Specs.

Otid® 500mg Injection: BP Specs.

Otid® 1g Injection: BP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
Sealthtek (Pvt.) Limited
Plot No. 14, Sector 19, Korangi
Industrial Area Karachi - Pakistan

Associate of:
SAMI Pharmaceuticals (Pvt.) Ltd.
Karachi-Pakistan
www.samipharma.com

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

Otid® 250mg Injection: 075880

Otid® 500mg Injection: 075879

Otid® 1g Injection: 075878

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Otid® 250mg Injection: 8th May, 2013

Otid® 500mg Injection: 8th May, 2013
Otid® 1g Injection: 8th May, 2013

10. DATE OF REVISION OF THE TEXT

اوٹیڈ® انجکشن

(سیفراڈِن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

صرف ایک مرتبہ استعمال کے لئے ہے غیر استعمال شدہ دوا کو ضائع کر دیں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔