Physician's Package Insert

ORBENIL®

INJECTION

Composition
Each vial contains:

Active Ingredient
Cloxacillin (as sodium salt)  500 mg or 2 g

Sodium content:
Orbenil 500 mg:  27.5 mg per vial
Orbenil 2 g:          110  mg per vial.

Mechanism of Action
Cloxacillin is an isoxazolyl semisynthetic penicillin which is markedly resistant to cleavage by penicillinase. It is a potent inhibitor of the growth of most penicillinase-producing staphylococci.

Cloxacillin is effective both by the oral and parenteral routes. However, in serious life-threatening staphylococcal infections, initiation of therapy with Orbenil injection is recommended.

Indications
Orbenil is indicated primarily for the treatment of infections caused by penicillinase-producing staphylococci. Because of the high incidence of staphylococcal isolates resistant to penicillin G, both within and outside the hospital environment, Orbenil is recommended as initial therapy in patients with suspected staphylococcal infections.

Orbenil is also effective in the treatment of other commonly encountered Gram-positive coccal infections.

Typical indications include:
• respiratory tract infections, such as pneumonia and sinusitis
• infected wounds and burns
• osteomyelitis and septic arthritis
• other infections due to staphylococci (including penicillin-resistant strains) such as septicemia, endocarditis, enterocolitis and urinary tract infections.

Contraindications
Known hypersensitivity to a penicillin-type drug.

This drug should not be administered to babies born to mothers with a history of hypersensitivity to a penicillin-type drug.

Warnings
Serious and occasionally even fatal hypersensitivity (anaphylactoid) reactions due to penicillin therapy have been reported. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients receiving oral penicillins. Such reactions are more likely to occur in individuals with a history of hypersensitivity to penicillins and/or a history of sensitivity to multiple allergens. There have also been reports of individuals with a history of penicillin hypersensitivity experiencing severe reactions when treated with cephalosporins.
Therefore before initiating therapy with this drug, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens, because of the risk of anaphylactoid reactions. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted.

Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation, should also be administered as indicated.

Use in Pregnancy
Safety for use in pregnancy has not been established.

Use in Breastfeeding
Since penicillins are excreted in breast milk, administration of this drug to nursing mothers may lead to sensitization, diarrhea, candidiasis and skin rash in infants. Therefore, having taken into account the importance of the drug to the mother, either discontinue nursing or discontinue the drug.

Use in Pediatrics
Penicillins are excreted largely unchanged by the kidney. Because renal function is incompletely developed in infants, the rate of elimination of the drug tends to be slow. Penicillin-type drugs should therefore be administered with caution, particularly in neonates, and organ system function should be evaluated frequently.

Adverse Reactions
As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. These reactions are more likely to occur in individuals who have previously demonstrated hypersensitivity to pencillins and in those with a history of allergy, asthma, hay fever, or urticaria. In common with other β-lactam antibiotics, angioedema and anaphylaxis may occur. The following adverse reactions have been reported as being associated with the use of penicillins.

Hypersensitivity
Anaphylaxis is the most serious potential adverse reaction to a penicillin drug. It is usually associated with the administration of parenteral rather than oral dosage forms. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation, should also be administered as indicated (see Warnings).

Erythematous maculopapular rashes, urticaria, and occasional cases of exfoliative dermatitis, erythema multiforme and Stevens-Johnson syndrome have been reported. Laryngeal edema and serum sickness-like reactions including chills, fever, serum sickness, edema and arthralgia have also been reported. Such reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy.

Gastrointestinal
Glossitis, stomatitis, glossitis, black "hairy" tongue, nausea, vomiting, enterocolitis, pseudomembranous colitis and diarrhea have been observed.
**Hepatic**

A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) and/or serum glutamic pyruvic transaminase (SGPT) has been noted, particularly in infants, but the significance of this finding is unknown. Rare cases of transient hepatitis and cholestatic jaundice have been reported.

**Renal**

Interstitial nephritis (rare).

**Hematological**

Hematological reactions including hemolytic anemia, transient neutropenia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been observed. These are believed to be hypersensitivity phenomena and are usually reversible upon discontinuation of therapy.

**Central Nervous System**

Rare cases of reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported.

**Precautions**

In the treatment of group A \( \beta \)-hemolytic streptococcal infections, therapy with this drug should be continued for at least 10 days to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

Following completion of treatment, cultures should be taken to determine whether streptococci have been eradicated.

As with any potent drug, periodic assessment of renal, hepatic and hematopoietic functions should be made during prolonged therapy. This is particularly important in infants including prematures and neonates.

The possibility of superinfection with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfection occurs, appropriate therapy should be instituted.

**Drug Interactions**

**Cloxacillin/Fusidic Acid:** May diminish the therapeutic effect of cloxacillin. Therefore, administer cloxacillin at least 2 hours before fusidic acid.

**Cloxacillin/Methotrexate:** Serum methotrexate concentrations may be elevated, increasing the risk of toxicity. Thus, monitor for methotrexate toxicity. Measure methotrexate concentrations twice a week for at least the first 2 weeks in patients receiving low-dose oral methotrexate. May need a dosage adjustment for methotrexate during therapy with cloxacillin. Avoid cloxacillin immediately before and during IV methotrexate treatment.

**Cloxacillin/Warfarin:** Effects of warfarin may be increased, resulting in an increased risk of bleeding; therefore UNR should be closely monitored upon addition and withdrawal of cloxacillin. UNR should also be reassessed periodically during therapy since an adjustment in the warfarin dose may be necessary to maintain an effective level of anticoagulation.

**Penicillins/Aminoglycosides:** Concurrent therapy with penicillins has resulted in inactivation of aminoglycosides. Therefore, do not mix parenteral aminoglycosides and penicillins in the same IV solution. Monitor aminoglycoside serum concentrations and renal function and adjust dose accordingly. Penicillins and aminoglycosides are often used together to achieve synergistic action.

**Penicillins/Live Typhoid Vaccine:** Penicillins may interfere with the immunologic response to the vaccine. Therefore, administer oral live typhoid vaccine at least 24 hours from the last dose of the antibiotic.
**Penicillins/Oral Contraceptives:** Antibacterial agents may suppress intestinal flora that provide hydrolytic enzymes essential for enterohepatic recirculation of estrogens resulting in decreased contraceptive effectives. There is a possibility of contraceptive failure. Concurrent use may therefore warrant an additional form of birth control to avoid slight increased risk of pregnancy.

*Penicillins/Chloramphenicol/Erythromycin/Tetracyclines/Sulfonamides:* Pharmacologic and therapeutic action of penicillins could be reduced. Since bacteriostatic drugs may interfere with the bactericidal effect of penicillins in the treatment of meningitis or other conditions where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

*Penicillins/Probenecid:* Probenecid may decrease renal tubular secretion of penicillin-type drugs, resulting in increased blood levels of cloxacillin. Thus there may be an increase in the effect of cloxacillin; this effect has been utilized clinically to prolong the excretion and enhance the efficacy of penicillins.

**Drug/Food Interactions (for oral cloxacillin):** Food decreases the extent of absorption of cloxacillin and therefore may reduce its antimicrobial effectiveness. Administer cloxacillin on an empty stomach 1 hour before or 2 hours after meals to enhance its absorption.

**Diagnostic Interference**
Treatment with penicillins may result in false positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution. Tests based on enzymatic glucose oxidase reactions such as Clinistix or Tes-Tape are not affected.

**Dosage and Administration**

*Parenteral drug products should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.*

Orbenil injection is intended for intramuscular, intravenous, intrapleural and intra-articular use.

The recommended dosages are given below. In severe, stubborn infections, a higher dosage may be administered.

**Adults**

**Intramuscular Use**
250 mg every 4-6 hours.

**Intravenous Use**
500 mg every 4-6 hours, administered into a vein either directly or via a drip-tube over a period of 3-4 min. More rapid administration may result in convulsive seizures.

**Intrapleural Use**
500 mg administered once daily as a single injection.

**Intra-articular Use**
500 mg administered once daily as a single injection.

**Infants and Children**
In infants up to 2 years of age, one-quarter of the adult dosage.
In children 2-10 years of age, half the adult dosage.
**Overdosage**
Overdosage of penicillin drugs may cause neuromuscular hyperirritability or convulsive seizures.
Discontinue medication, treat symptomatically, and institute supportive measures as required. In patients with renal function impairment, the antibiotic may be removed from the circulation by hemodialysis, not by peritoneal dialysis.

**Preparation of the Solution**
Prior to reconstitution, Orbenil vials should be stored in a cool dry place. Solutions for injections should be freshly prepared.

If Orbenil is prescribed concurrently with an aminoglycoside, the two antibiotics should not be mixed in the same syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

Orbenil injection should not be mixed with proteinaceous fluids such as protein hydrolysates, blood or plasma, or with intravenous lipid emulsions.

**Reconstitution**

**Intramuscular Use**
To reconstitute the 500 mg vial, add 1.6 ml Water for Injection to provide a concentration of 250 mg/ml.
To reconstitute the 2g vial, add 6.4 ml Water for Injection to provide a concentration of 250 mg/ml.

**Intravenous Use**
To reconstitute the 500 mg vial, add 10 ml Water for Injection.

**Intrapleural Use**
To reconstitute the 500 mg vial, add 5-10 ml Water for Injection.

**Intra-articular Use**
To reconstitute the 500 mg vial, add 5 ml Water for Injection or 5 ml 0.5% Lidocaine HCl Solution.

**Stability of the Reconstituted Solution**
Orbenil injection is unstable in concentrated solution and, when prepared for intramuscular or direct intravenous injection, should be used within 30 minutes of preparation. Orbenil injection is compatible with most commonly-used intravenous fluids.
The periods of stability at room temperature in various intravenous solutions are shown below:

**Stability of Reconstituted Orbenil at 23°C**

<table>
<thead>
<tr>
<th>Intravenous Solution</th>
<th>Stability Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride Injection</td>
<td>24 hours</td>
</tr>
<tr>
<td>Compound Sodium Chloride Injection (Ringer's Injection)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Dextrose Injection (5%)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Sodium Chloride and Dextrose Injection (4%)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Sodium Lactate Injection</td>
<td>6 hours</td>
</tr>
<tr>
<td>Sodium Bicarbonate Injection (1.4%)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Rheomacrodex 10% in normal saline</td>
<td>24 hours</td>
</tr>
<tr>
<td>Rheomacrodex 10% in 5% dextrose</td>
<td>24 hours</td>
</tr>
</tbody>
</table>
Drug Reg. No.:  
500 g: 052 57 24630 00  
2 g: 102 73 27338 00

Storage  
Store below 25°C.

Manufacturer  
Sandoz GmbH  
Kundl, Austria

Licence Holder  
Salomon Levin & Elstein Ltd  
P.O. Box: 3696, Petach-Tikva 49133  
Teva Group.

Marketed by:  
Teva Pharmaceutical Industries Ltd.,  
P.O.Box 3190, Petach-Tikva

ירצוי:  
טנדוז בך"מ,  
קונדל, אוסטריה.

בעל הרישיון:  
סלומון, לין ואלטשטיין בך"מ  
תינ"ד 8077, מנהל 42504,  
מ抨וג תונב.

משווק ב"י:  
טב אופטימי מרצבטים בך"מ  
תינ"ד 3190, מנהל תוקא.