SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZANITIN DUO 457

(Amoxicillin and Clavulanate Potassium for Oral Suspension USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ingredient	**Quantity per 5 ml in mg**
Amoxicillin Trihydrate BP	482.08mg Equivalent to 400 mg of Amoxicillin
Clavulanate Potassium BP	149.35mg Equivalent to 57 mg of Clavulanic acid
Silicon Dioxide BP	188.57
Colloidal anhydrous silica (Collidal Silicon Dioxide) BP	25.00
Aspartame BP	10.00
Succinic acid NF	3.33
Xanthan Gum BP	11.67
Trusil Orange Flavour	22.00
Trusil Pineapple Flavour	18.00

3. PHARMACEUTICAL FORM

Powder for Oral Suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zanitin is indicated for the treatment of the following infections in adults and children:

• Acute bacterial sinusitis (adequately diagnosed)

• Acute otitis media

• Acute exacerbations of chronic bronchitis (adequately diagnosed)

• Community acquired pneumonia

• Cystitis

• Pyelonephritis

• Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.

• Bone and joint infections, in particular osteomyelitis.

4.2 Posology and method of administration

It is recommended that Zanitin DUO 457 suspensions be used for children weighing less than 40 kg. Pediatric Patients: Based on the amoxicillin component, Zanitin DUO 457 oral suspension should be dosed as follows: Zanitin DUO 457 oral suspension should be taken immediately before

or with the first mouthful of food, to minimize potential gastrointestinal intolerance and to optimize absorption. Children aged 2 months up to 12 years. For moderate to severe infections the dose should be 45mg/kg/day, based on the amoxicillin component, (or 6.4mg/kg/day Clavulanic acid) in two divided doses every 12 hours. The children's dosage is intended for individuals whose weight will not cause dosage to be calculated greater than that recommended for adults. Children weighing 40kg and more should be dosed according to the adult recommendations for other Zanitin DUO preparations. There are no clinical data available for Zanitin DUO 457 oral suspension in infants with immature renal function. The use of Zanitin DUO 457 oral suspension in this group cannot be recommended. Use in Hepatic Impairment. Data is currently insufficient for a dosage recommendation. Dose with caution and monitor hepatic function at regular intervals. Use in Renal Impairment Zanitin DUO 457 oral suspension is not recommended for use in children with renal impairment or in haemodialysis. In children with renal impairment, dosage should be adjusted according to degree of impairment.

Directions for Use: Zanitin DUO should be taken immediately before or with the first mouthful of food, to minimize potential gastrointestinal intolerance and to optimize absorption. Directions for re-constitution for Zanitin DUO 457 Oral Suspension: Add boiled & cooled water to the contents of the bottle up to the mark. Shake well until you obtain a homogenous suspension. If necessary, add some more water up to the mark and shake again. Use the reconstituted suspension within 7 days after reconstitution.

4.3 Contraindications

Zanitin DUO is contraindicated in patients with a history of allergic reactions to any penicillin.

It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Zanitin DUO.

4.4 Special warnings and precautions for use

General: History of allergy especially to penicillin’s & cephalosporins. Infectious mononucleosis. Severe renal impairment. Pregnancy & Nursing mothers: This drug should be used during pregnancy only if clearly needed under the supervision of a medical practitioner. Ampicillin-class antibiotics are excreted in the milk; therefore, caution should be exercised when Zanitin DUO is administered to a nursing woman.

4.5 Interaction with other medicinal products and other forms of interaction

Allopurinol may reduce renal tubular secretion of amoxicillin thus increasing the serum levels of amoxicillin. Concurrent use may reduce the efficacy of oral contraceptives.

4.6 Pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Lactation

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhea and fungus infection of the mucous

membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

4.8 Undesirable effects

The most frequently reported adverse effects were diarrhea/loose stools, nausea, skin rashes and urticaria, vomiting and vaginitis. Other less frequently reported reactions include: Abdominal discomfort, flatulence, and headache.

4.9 Overdose

Following over dosage, patients have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity or drowsiness have also been observed in a small number of patients. Treatment is supportive and symptomatic and as directed by the physician.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors;
ATC code: J01CR02.

Mode of action: Amoxicillin is semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death. Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

PK/PD relationship:

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance: The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

•Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.

• Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

5.2 Pharmacokinetic properties

For Zanitin DUO 457 oral suspension (45mg/kg/day) taken every 12 hours: peak plasma concentration (Cmax) is 12.0 µg/mL, area under the plasma concentration-time curve between 0 and 24 hours after the first dose (AUC(0-24 hours)) is 35.2 µg.h/mL, half-life (t½) is 1.22 hours,

median time to peak plasma concentration (Tmax) is 1.0 hours and the mean predicted time above the minimum inhibitory concentration (TMIC 24 hours) is 12.3 hours. The following pharmacokinetic parameters were observed for Clavulanic acid for Zanitin DUO 457 oral suspension (45mg/kg/day) taken every 12 hours: Cmax of 5.49 µg/mL, AUC (0-24 hours) of 13.3 µg.h/mL, t½ of 0.99 hours and median Tmax of 1.0 hours, and mean predicted TMIC 24 hours of 9.80 hours. Distribution: Following oral administration, both Amoxicillin and Clavulanic acid have been shown to diffuse in significant concentrations into pus, bile, and pleural, synovial and peritoneal fluids. Both penetrate poorly into the CSF when the meninges are normal. Amoxicillin penetrates into the CSF better through inflamed meninges, but the maximum concentrations are still much lower than the peak serum levels. There are no data at present on the CSF penetration of Clavulanic acid in patients with meningeal inflammation. Neither amoxicillin nor Clavulanic acid is highly protein bound. Clavulanic acid has been variously reported to be bound to human serum in the range of 9 - 30% and amoxicillin approximately 20% bound. From animal studies, there is no evidence to suggest either component accumulates in any organ. Elimination: As with other penicillin's, renal excretion is the major route of amoxicillin clearance, while clavulanate elimination is via both renal and non-renal mechanisms. Approximately 70% of the dose of amoxicillin is excreted in urine as amoxicillin. For Clavulanic acid, following the administration of 125mg of radiolabelled potassium clavulanate orally to normal volunteers 68% of the administered Radioactivity was recovered in the urine in 24 hours. Of this 34% (i.e. 23% of the administered dose) represented unchanged Clavulanic acid. 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3-carboxylic acid (the major metabolite) and 1-amino-4-hydroxy-butan-2-one accounted for a further 23% and 12% (i.e. 16% and 8% respectively of the administered dose). Small amounts of other yet unidentified metabolites were also present. These metabolites were also present in the urine of rat and dog. The extent of urinary excretion of Clavulanic acid and its metabolites is lower in rat urine than in dog and human urine. Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of Clavulanic acid.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discolored tongue.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal Silicon Dioxide, Silicon dioxide, Aspartame, Succinic Acid, Xanthan Gum, Flavor Orange, Flavor Pineapple.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

The dry powder: Do not store above 25°C. Protect from sunlight moisture.

Reconstituted suspension: Store reconstituted suspension in a refrigerator. Do not freeze.

6.5 Nature and contents of container

70 ml HDPE bottle with 10ml Polypropylene measuring cup.

6.6 Special precautions for disposal and other handling

Check cup seal is intact before using. Shake bottle to loosen powder.
Shake the bottle well before each dose.

7. MARKETING AUTHORISATION HOLDER

SHALINA HEALTHCARE DMCC
30th Floor, Almas Towers,
Jumeirah Lakes Towers Dubai-UAE
E-mail regulatory@shalina.com
Website: www.shalina.com.

8. MARKETING AUTHORISATION IN OTHER COUNTRIES

Product is registered in D R Congo, Central African republic with brand name Moxyclav DUO 457 Suspension. Product registeredin Ghana, Nigeria & Zambia. with brand name Zanitin DUO 457 Suspension