1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC) - Enclosed

ZANITIN DUO 625

(**Co-Amoxiclav Tablets BP**)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZANITIN DUO 625 (Co-Amoxiclav Tablets BP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Ingredients	Specification	% Overages	Qty /Tablet (mg)	Reason for inclusion
Part (A) Granulation:					
1.	* Amoxicillin Trihydrate	BP	1%	500.00 (579.65)	Antibiotic
2.	*Potassium Clavulanate Diluted	BP	1%	125.00 (300.730)	Antibiotic (Beta-lactamase Inhibitor)
3.	Crospovidone	BP	Nil	40.000	Disintegrants and binder
4.	Microcrystalline Cellulose PH-112	BP	Nil	39.949	Diluent & tablet disintegrant
5.	Silicon Dioxide	BP	Nil	10.000	Anticaking agent emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity increasing agent.
Part (A) Lubricants:					
6.	Colloidal Silicon Dioxide	BP	Nil	5.000	Anticaking agent emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity increasing agent.
7.	Magnesium stearate	BP	Nil	4.650	Lubricant

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Blending:					
8.	Crospovidone	BP	Nil	10.000	Disintegrants
9.	Microcrystalline Cellulose PH-112	BP	Nil	12.301	Diluent & tablet disintegrant
10.	Silicon Dioxide	BP	Nil	5.000	Anticaking agent emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity increasing
11.	Microcrystalline Cellulose	BP	Nil	10.000	Anticaking agent emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity increasing agent.
12.	**Microcrystalline Cellulose PH-112	BP	Nil	10.000	Diluent & tablet disintegrant
Lubricants:					
13.	Purified Talc	BP	Nil	1.000	Anti-caking agent; Glidant; tablet and capsule diluent; tablet and capsule lubricant
14.	Colloidal silicon dioxide	BP	Nil	5.000	Anticaking agent emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity increasing agent.
15.	Magnesium Stearate	BP	Nil	6.701	Lubricant
Film Coating Materials:					
16.	Hydroxy Propyl Methyl Cellulose (Any coat-C AN-6)	BP	Nil	1.328	Binder improves film flexibility, elongation, and adhesion to the tablet.
17.	Hydroxy Propyl Methyl Cellulose (Any coat-C AN-15)	BP	Nil	10.000	Binder improves film flexibility, elongation, and adhesion to the tablet.
18.	Ethyl cellulose N-20	BP	Nil	0.672	Stabiliser
19.	Purified talc	BP	Nil	0.672	Lubricant or glidant
20.	Titanium dioxide	BP	Nil	6.000	Colouring agent
21.	Dibutyl Phthalate	BP	Nil	1.328	Plasticizing agents
22.	Methylene Dichloride	BP	Nil	306.512	Solvent
23.	Iso Propyl Alcohol	BP	Nil	93.328	Solvent
24.	#Purified talc	BP	Nil	0.672	Lubricant or glidant

BP: British Pharmacopoeia

***** 1 % Overages added for Amoxicillin Trihydrate and Potassium Clavulanate.

**Quantity of Amoxicillin Trihydrate and Potassium Clavulanate will be compensated with Microcrystalline Cellulose PH-112.

Does not appear in final product

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zanitin Duo are indicated for short term treatment of bacterial infections at the following sites when caused by sensitive organisms

1. Urinary Tract Infections (uncomplicated and complicated)
2. Lower Respiratory Tract Infections, including community acquired pneumonia
3. Acute exacerbations of chronic bronchitis
4. Upper Respiratory Tract Infections, such as sinusitis, otitis media and recurrent tonsillitis.
5. Skin and Skin Structure Infection

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to Zanitin Duo whenever necessary.

4.2 Posology and method of administration

Zanitin Duo should be taken immediately before or with the first mouthful of food, to minimise potential gastrointestinal intolerance and to optimise absorption.

Adults: The usual adult dose is one Zanitin Duo tablet every 12 hours.

Treatment should usually be continued for 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. Treatment should not exceed 14 days without review.

Adults with Impaired Renal Function: Both amoxycillin and clavulanic acid are excreted by the kidneys and the serum half life of each increases in patients with renal failure. No adjustment to the initial Zanitin Duo dose is necessary, but the dosing interval should be extended according to the degree of renal impairment.

The following schedule is proposed for Zanitin Duo: Mild Impairment: No change in dosage.

(Creatinine clearance > 30mL/min)

Moderate Impairment: One Zanitin Duo tablet 12

(Creatinine clearance 10 - 30mL/min) hourly

Severe Impairment: One Zanitin Duo tablet (Creatinine

clearance < 10mL/min) every 24 hours

Haemodialysis decreases serum concentrations of both amoxycillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

Adults with Impaired Hepatic Function: Data is currently insufficient for a dosage recommendation. Dose with caution, and monitor hepatic function at regular intervals.

Children: Children weighing 40 Kg and more should be dosed according to the adult recommendations. It is recommended that Zanitin Duo suspensions be used for children weighing less than 40 kg.

Method of administration: Oral

4.3 Contraindications

Zanitin Duo 625 is contraindicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins. Zanitin Duo 625 is contraindicated in patients with a previous history of associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Warnings & precautions for use in special populations: Warnings serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, Zanitin duo should be discontinued and the 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.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including amoxycillin. A toxin produced with Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases

appropriate therapy with a suitable oral antibiotic agent effective against Clostridium difficile should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, eg. opiates and diphenoxylate with atropine may prolong and/or worsen the condition and should not be used.

PRECAUTIONS: General: As with any potent drug, periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Since Zanitin Duo contain amoxycillin, an aminopenicillin, these are not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of rash if amoxycillin is used.

Zanitin Duo should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxycillin induced skin rashes.

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Aerobacter, Pseudomonas or Candida), the drug should be discontinued and/or appropriate therapy instituted.

Hepatitis and cholestatic jaundice have been reported rarely. These events have been noted with other penicillins and cephalosporins. Hepatic events subsequent to amoxycillin/ clavulanic acid have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

Cholestatic hepatitis, which may be severe but is usually reversible, has been reported. Signs and symptoms may not become apparent until several weeks after treatment has ceased. In most cases resolution has occurred with time. However, in extremely rare circumstances, deaths have been reported. These have almost always been cases associated with serious underlying disease or concomitant medications. Hepatic events subsequent to Zanitin Duo have occurred predominantly in males and elderly patients and may be associated with prolonged treatment. Zanitin Duo should be used with care in patients with evidence of hepatic dysfunction. Zanitin Duo tablets should be used with care in patients with moderate or severe renal impairment. The dosage of Zanitin duo should be adjusted as recommended in the “DOSAGE AND ADMINISTRATION” section.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Use in Pregnancy: (Category B1). Animal studies with orally and parenterally administered Zanitin Duo have shown no teratogenic effects. There is limited experience of the use of

Zanitin Duo in human pregnancy. In women with preterm, premature rupture of the foetal mebrane (pPROM), prophylactic treatment with Zanitin Duo may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician. Use in Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labour. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of Zanitin Duo in humans during labour or delivery has immediate or delayed adverse effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Use in Lactation: Amoxycillin is excreted in the milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when Zanitin Duo are administered to a nursing woman.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid decreases the renal tubular secretion of amoxycillin but does not affect clavulanic acid excretion. Concurrent use with Zanitin Duo may result in increased and prolonged blood levels of amoxycillin but not of clavulanic acid.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with Zanitin Duo and allopurinol administered concurrently.

No information is available about the concurrent use of Zanitin Duo and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram (Antabuse) like reaction in some patients. Therefore the ingestion of alcohol should be avoided during and for several days after treatment with Zanitin Duo.

In common with other antibiotics, Zanitin Duo may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Oral administration of Zanitin Duo will result in high urine concentrations of amoxycillin. Since high urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution, it is recommended that glucose tests based on enzymatic glucose oxidase reactions.

4.6 Pregnancy and lactation

Use in Pregnancy: (Category B1). Animal studies with orally and parenterally administered Zanitin Duo have shown no teratogenic effects. There is limited experience of the use of Zanitin Duo in human pregnancy. In women with preterm, premature rupture of the foetal mebrane (pPROM), prophylactic treatment with Zanitin Duo may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician. Use in Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labour. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of Zanitin Duo in humans during labour or delivery has immediate or delayed adverse effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Use in Lactation: Amoxycillin is excreted in the milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when Zanitin Duo are administered to a nursing woman.

4.7 Adverse Reactions

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

4.8 Symptoms of Overdosage & Treatment

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Gastrointestinal symptoms may be treated symptomatically with attention to the water electrolyte balance.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Zanitin Duo 625 can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Zanitin is a broad spectrum antibiotic which is a combination of betalactam penicillin Amoxycillin & betalactamase inhibitor clavulanic acid.

ATC code: J01CR02.

Pharmacological action: Amoxicillin is a 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.

Microbiology of Zanitin Duo: Commonly susceptible species: Aerobic Gram-positive micro-organisms, Enterococcus faecalis, Gardnerella vaginalis, Staphylococcus aureus (methicillin-susceptible), Streptococcus agalactiae, Streptococcus pneumoniae1, Streptococcus pyogenes and other beta-haemolytic streptococci, Streptococcus viridans group.

Aerobic Gram-negative micro-organisms: Capnocytophaga spp., Eikenella corrodens, Haemophilus influenzae2, Moraxella catarrhalis, Pasteurella multocida, Anaerobic micro-organisms, Bacteroides fragilis, Fusobacterium nucleatum, Prevotella spp.

Species for which acquired resistance may be a problem: Aerobic Gram-positive micro-organisms: Enterococcus faecium $.

Aerobic Gram-negative micro-organisms: Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris.

Inherently resistant organisms: Aerobic Gram-negative micro-organisms: Acinetobacter sp., Citrobacter freundii, Enterobacter sp., Legionella pneumophila, Morganella morganii, Providencia spp., Pseudomonas sp., Serratia sp., Stenotrophomonas maltophilia.

Other micro-organisms: Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetti, Mycoplasma pneumonia

$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

£ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid

1. Streptococcus pneumoniae that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid.

2. Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption: It is rapid if given before or with the meals.

Distribution: Following oral administration, both amoxycillin 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. Amoxycillin 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.

Protein binding: About 25% (Clavulanic acid); about 18% (Amoxicillin). Amoxicillin distributes readily into most body tissues and fluids except the brain and spinal fluid.

Excretion: Half-life after oral administration is 1.3 hr (Amoxicillin); 1 hr (Clavulanic acid). About 50-70% of amoxicillin and 25-40% of clavulanic acid are excreted unchanged in urine during the first 6 hours after administration.

5.3 Preclinical safety data

Non-clinical 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 discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone	BP
Microcrystalline Cellulose PH-112	BP
Silicon Dioxide	BP
Colloidal Silicon Dioxide	BP
Magnesium stearate	BP
Microcrystalline Cellulose	BP
Purified Talc	BP
Hydroxy Propyl Methyl Cellulose (Any coat-C AN-6)	BP
Hydroxy Propyl Methyl Cellulose (Any coat-C AN-15)	BP
Ethyl cellulose N-20	BP
Titanium dioxide	BP
Dibutyl Phthalate	BP
Methylene Dichloride	BP
Iso Propyl Alcohol	BP

6.2 Incompatibilities

None.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C. Protect from sunlight and moisture. Keep out of reach of children.

6.5 Nature and contents of container

7 tablets Alu-Alu blister. 2 such blister packed in Printed carton with pack insert.

7. MARKETING AUTHORISATION HOLDER

SHALINA HEALTHCARE DMCC

30th Floor, Almas Towers,

Jumeirah Lakes Towers Dubai-UAE.

Country: UAE.

8. MARKETING AUTHORISATION IN OTHER COUNTRIES

Product is registered in Nigeria & Ghana.