1. NAME OF THE MEDICINAL PRODUCT

Theoclav 375

GENERIC NAME: Amoxicillin & Clavulanate Potassium Tablets USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet Contains:

Amoxicillin USP----------250mg

Clavulanate Potassium BP-----125mg

Excipients----------q.s

3. PHARMACEUTICAL FORM

Solid Oral Dosage form, film coated tablets

4. Clinical particulars

4.1 Therapeutic indications

THEOCLAV 375 (Amoxicillin & Clavulanate Potassium Tablets USP 250 mg & 125 mg) 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

The dose of Amoxicillin & clavulanate potassium tablets (USP 250 mg & 125mg) that is selected to treat an individual infection should take into account:

• The expected pathogens and their likely susceptibility to antibacterial agents

• The severity and the site of the infection

• The age, weight and renal function of the patient as shown below.

The use of alternative presentations of amoxicillin/clavulanic acid (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review.

Adults and children ≥ 40 kg

One 500 mg/125 mg dose taken three times a day.

Children < 40 kg

20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.

No clinical data are available on doses of amoxicillin/clavulanic acid 4:1 formulations higher than 40 mg/ 10mg/kg per day in children under 2 years.

Elderly

No dose adjustment is considered necessary.

Renal impairment

Dose adjustments are based on the maximum recommended level of amoxicillin. No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min 500 mg/125 mg twice daily

CrCl < 10 ml/min 500 mg/125 mg once daily.

Haemodialysis

500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10-30 ml/min 15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily)

CrCl < 10 ml/min 15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg)

Haemodialysis 15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals.

Method of administration Amoxicillin & Clavulanate Potassium tablets USP 250 mg & 125 mg are for oral administration only. Administer at the start of a meal to minimize potential gastrointestinal intolerance and optimize absorption of amoxicillin/clavulanic acid.

Duration of treatment

The usual course of treatment is 7 days. In severe cases, this can be extended to 14 days.

Contraindications

4.3 Patients with known hypersensitivity to amoxicillin & Clavulanate Potassium Tablet USP 250 mg & 125 mg, other Cephalosporin antibiotics or to any of the excipients.

Amoxicillin & Clavulante Potassium Tablet USP (250mg & 125mg) are also contraindicated in paties with previous, immediate and/or severe hypersensitivity to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam). History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

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4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted. In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance. Convulsions may occur in patients with impaired renal function or in those receiving high doses Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin. Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully

monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Methotrexate Penicillin may reduce the excretion of methotrexate causing a potential increase in toxicity. Probenecid Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

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 and 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 and clavulanic acid may be associated with an increased risk of necrotizing 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 and clavulanic acid should only be used during breast feeding after benefit/risk assessment by the physician in charge.

PREGNANCY CATEGORY B

Reproduction studies performed in pregnant rats and mice give amoxicillin & clavulanate Potassium at oral dosage up to 1,200mg/kg/day, equivalent to 7,200 and 4,080 mg/m2/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to amoxicillin & clavulanate Potassium. There are, however, no adequate and well-controlled studies in pregnant women. Be case animal reproduction studies are not always predictive is human response, this drug should be used during pregnancy and if clearly needed.

LABOUR AND DELIVERY

Oral ampicillin-class antibiotics are generally pooly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of amoxicillin decreased the uterine tone, frequently of contraction, height of contractions, and duration of contractions; however, it is not known whether the use of amoxicillin & clavulanate Potassium in human during labour or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labour, or increases the likelihood that forceps delivery or other obstetrical intervention or resuciation of the newborn will be necessary in a single study in women with premature rupture of fetal membranes, it was reported that prophylates treatment with amoxicillin & clavulanate Potassium may be associated with an increased risk of necrotizing enerolitis in beonates.

NURSING MOTHERS

Amoxicillin-clav antibiotics are excreted in the milk, therefore, caution should be exercised when amoxicillin & clavulanate Potassium is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Theoclav 375 does not usually affect the ability to drive or operate machinery.

Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of amoxicillin & clavulanate and know how they will react to the medication.

HYPERSENSITIVITY REACTIONS

Skin rashes, pruritus, urticaria, angioedema, serum sickness - like reactions (urticaria or skin rash accompanied by arthritis, arthalgia, myalgia, and frequently fever), erythema multiforme (rarely stevens-johnson syndrome), acute generalized exanthematious pustulosis,

hypersensitivity vasculitis, and an occasional case of exfoliative dermattis (including toxic epidermal necrolysis)have been reported. These reactions maybe controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitive (anaphylactic) reactions can occur with oral penicillin.

HEMIC AND LYMPHATIC SYSTEMS

Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, cosinophilia, lckopena, and arganilocytosis has been reported during therapy with penicillin. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

CENTRAL NERVOUS SYSTEM

Agalation, anxiety, behavioural changes, confusion, conclusions, diseases, insonnia.

4.8 Undesirable effects

SIDE EFFECTS

Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue,

mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

ADVERSE REACTIONS

The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin/clavulanic acid, sorted by MedDRA System Organ Class are listed below.

The following terminologies have used in order to classify the occurrence of undesirable effects.

Very Common (≥ 1/10)

Common (≥1/100 to < 1/10)

Uncommon (≥1/1,000 to < 1/100)

Rare (≥1/10,000 to <1/1,000)

Very Rare (<1/10,000)

Not known (Cannot be estimated from the available data)

INFECTIONS AND INFESTATIONS	
Mucocutaneous Candidosis Common	Common
Overgrowth of non-susceptible organisms	Not Known
Aseptic meningitis	Not Known
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Reversible leucopenia (Including Neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not Known
Haenolytic anemia	Not Known
CARDIAC DISORDERS	
Kounis Syndrome	Not Known
Angioneurotic Oedema	Not Known
Anaphylaxis	Not Known
Serum sickness-like syndrome	Not Known
Hypersensitivity vasculitis	Not Known
NERVOUS SYSTEM DISORDERS	
Dizziness	Uncommon
Headache	Uncommon
Reversible Hyperactivity	Not Known
GASTROINTESTINAL DISORDERS	
Diarrhea	Very common
Vomiting	Common
Indigestion	Uncommon
Black Hairy Tongue	Not known
HEPATOBILIARY DISORDERS	

Cholangitis	Not known
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Skin Rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema Multiforme	Rare
Toxic Epidermal Necrolysis	Not known
Bullous Exfoliative-Dermatitis	Not known
Acute Generalised Exanthemous Pustulosis (AGEP)	Not known
RENAL AND URINARY DISORDERS	
Interstitial Nephritis	Not known
Crystalluria	Not known

4.9 Overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed.

Convulsions may occur in patients with impaired renal function or in those receiving high doses

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. a regular check of patency should be maintained.

TREATMENT OF INTOXICATION

Gastrointestinal symptoms may be treated symptomatically, with attention to the water electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemdialysis.

No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Combinations of penicillin, incl. beta-lactamase inhibitors;

ATC code J01CR 02.

Mechanism 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 penicillin. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

5.2 Pharmacokinetic properties

Oral administration of 5 mL of amoxicillin and clavulanate potassium 250 mg/62.5 mg per 5 mL suspension or the equivalent dose of 10 mL of amoxicillin and clavulanate potassium 125 mg/31.25 mg per 5 mL suspension provides average peak serum concentrations approximately 1 hour after dosing of 6.9 mcg/mL for amoxicillin and 1.6 mcg/mL for clavulanic acid. The areas under the serum concentration curves obtained during the first 4 hours after dosing were 12.6 mcg*h/mL for amoxicillin and 2.9 mcg*h/mL for clavulanic acid when 5 mL of amoxicillin and clavulanate potassium 250 mg/62.5 mg per 5 mL suspension or equivalent dose of 10 mL of amoxicillin and clavulanate potassium 125 mg/31.25 mg per 5 mL suspension were administered to normal adults. Amoxicillin serum concentrations achieved with amoxicillin and clavulanate potassium are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. Time above the minimum inhibitory concentration of 1 mcg/mL for amoxicillin has been shown to be similar after corresponding every 12 hour and every 8 hour dosing regimens of amoxicillin and clavulanate potassium in adults and children.

Absorption:

Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin and clavulanate potassium can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In one study, the relative bioavailability of clavulanate was reduced when amoxicillin and clavulanate potassium was dosed at 30 and 150 minutes after the start of a high-fat breakfast.

Distribution:

Neither component in amoxicillin and clavulanate potassium is highly protein-bound; clavulanic acid is approximately 25% bound to human serum and amoxicillin approximately 18% bound. Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. Two hours after oral administration of a single 35 mg/kg dose of suspension of amoxicillin and clavulanate potassium to fasting children, average concentrations of 3 mcg/mL of amoxicillin and 0.5 mcg/mL of clavulanic acid were detected in middle ear effusions.

Metabolism and Excretion:

The half-life of amoxicillin after the oral administration of amoxicillin and clavulanate potassium is 1.3 hours and that of clavulanic acid is 1 hour. Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single amoxicillin and clavulanate potassium tablet 250 mg/125 mg or 500 mg/125 mg.

5.3 Preclinical safety data

Reproduction toxicity Reproduction toxicity studies in rats did not show any adverse effects of the combination on fertility and no teratogenic effects were evident. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions,

strength of contractions and duration of contractions. The relevance of these findings in humans is unknown.

Acute toxicity

The LD50 of clavulanic acid (potassium salt) is determined by the potassium content. Administration of clavulanic acid (potassium salt) together with amoxicillin does not result in any unexpected or synergistic toxicity.

Chronic toxicity/subchronic toxicity

The animal species used in chronic toxicity studies were rats and dogs. Solely after high doses (corresponding to 20- to 50-fold the maximal human dose) were mild haematological and blood-chemical changes observed, which regressed completely following discontinuation of therapy.

Mutagenic and tumorigenic potential

In-vitro and in-vivo studies did not reveal any signs of any mutagenic effects of the combination of amoxicillin and clavulanic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose Sodium BP
Colloidal Anhydrous Silica BP
Purified Talc BP
Magnesium Stearate BP
Hypromellose (Hydroxypropylmet hylcellulose E-5) BP
Ethly cellulose BP
Titanium Dioxide Bp
Diethyl Phthalate BP
Isopropyl Alcohol BP
Dichloromethane BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months from the date of manufacturing.

Special precautions for storage.

Store in a cool & dry place below 30°C. Protect from Light.

Keep all medicines out of the reach of children.

6.4 Nature and contents of container

1 X 10 Alu Alu Strip packed in a carton along with pack insert.

6.5 Special precautions for disposal and other handling

Any unused portion should be discarded as per local regulations

7. APPLICANT

Synermed Nig LTD, no 3 Abike jokogbola street, Solebo Estate, Aga Ikorodu, Lagos

8. MANUFACTURER

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