National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) MAXICLAV 625

1. NAME OF THE MEDICINAL PRODUCT

(Maxiclav 625) Amoxicillin and Clavulanate potassium Tablets USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains:

Amoxicillin USP (as Trihydrate)	
Eq.to Amoxicillin Anhydrous	500mg
Diluted Potassium Clavulanate BP	
Eq.to. Clavulanic acid 125 mg	125mg
Excipients	Q.S
Colour: Titanium Dioxide BP	

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

White coloured oval shape film coated tablet with both sides plain

4. Clinical particulars

4.1 Therapeutic indications

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.
- Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method ofadministration

Posology

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Amoxicillin/Clavulanic acid 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

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

For adults and children ≥ 40 kg, this formulation of Amoxicillin /Clavulanic acid provides a total daily dose of 1500 mg amoxicillin and 375 mg clavulanic acid, when administered as recommended below. For children < 40 kg, this formulation of Amoxicillin /Clavulanic acid provides a maximum daily dose of 2400 mg amoxicillin and 600 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily doseof amoxicillin is required, it is recommended that another preparation of Amoxicillin/Clavulanic acid is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

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 (see section 4.4 regarding "prolonged therapy").

Adults and children ≥ 40 kg

One Maxiclav 500/125mg tablet 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

Children may be treated with Maxiclav tablets or Amoxicillin /Clavulanic acid suspension (powder for oral suspension in bottles or sachets).

As the tablets cannot be divided, children weighing less than 25 kg must not be treated with Amoxicillin / Clavulanic acid tablets.

The table below presents the received dose (mg/kg body weight) in children weighing 25kg to 40 kg upon administering a single 500/125 mg tablet

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight] (see above}
Amoxicillin [mg/kg body weight] per single dose (1film-coated tablet)	12.5	14.3	16.7	20.0	6.67-20
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.67-5

Children aged 6 years and below or weighing less than 25kg should preferably be treated with Amoxicillin /Clavulanic acid suspension (powder for oral suspension in bottles or sachets).

No clinical data are available on doses of Amoxicillin /Clavulanic acid 4:1 formulations higher than 40 mg/10 mg/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 30ml/min.

Method of administration

For oral administration

Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

Therapy can be started parenterally according to the SmPC of Amoxicillin/Clavulanic acid

IV formulations and continued with an oral preparation

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients includes in the formulation.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another betalactam agent (e.g. a cephalosporin, carbapenem or monobactam)

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid

4.4 Special warnings and precautions for use

Before initiating therapy, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy.

These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. If an allergic reaction occurs, Maxiclav 228.5 therapy must be discontinued and appropriate alternative therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management (including intubation) may also be required.

Formulation 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. Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately

and the patient investigated further.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving formulation and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Changes in liver function tests have been observed in some patients receiving formulation. The clinicalsignificance of these changes is uncertain but formulation should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

In patients with renal impairment Maxiclav 228.5 mg/5 ml is not recommended.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria.

Maxiclav 228.5 mg/5 ml suspension contain aspartame per 5 ml dose and therefore care should be taken in patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with formulation may result in increased and prolonged blood levels of amoxicillin but not of clavulanate.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of formulation and allopurinol.

In common with other antibiotics, formulation may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If coadministration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of formulation.

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

4.6 Pregnancy and Lactation

Pregnancy

Reproduction studies in animals (mice and rats) with orally and parenterally administered formulation have shown no teratogenic effects. In a single study in women with pre-term, premature rupture of the foetal

membrane (pPROM), it was reported that prophylactic treatment with formulation may be associated with an increased risk of necrotizing enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Breast-feeding

Formulation may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no detrimental effects for the infant.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

Data from large clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency: very common ≥1/10, common ≥1/100 and <1/10

uncommon ≥1/1000 and <1/100

rare ≥1/10,000 and <1/1000

very rare <1/10,000

Infections and Infestations	
Mucocutaneous candidosis	Common
Blood and Lymphatic System disorders	
Reversible leucopenia (including neutropenia) and thrombocytopenia	Very rare
Immune System Disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses	Very rare
Gastrointestinal Disorders	
Adults:	Common

Diarrhoea, Nausea, Vomiting	
Children: Diarrhoea, Nausea, Vomiting	Common

4.9 Overdose

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.
Formulation can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic Group: Combinations of penicillin, incl. beta-lactamase inhibitors;
ATC code: J01CR02

Pharmacodynamics

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 isan 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 betalactamase 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(time)>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

Absorption:

The two components amoxicillin and clavulanate, are each fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption offormulation is optimized when taken at the start of a meal.

Distribution

The pharmacokinetics of the two components of formulation are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Doubling the dosage of formulation approximately doubles the serum levels achieved.

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 discoloured tongue.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Raw Material
Magnesium stearate
Sodium starch glycolate
Croscarmellose sodium
Purified Talc
Titanium Dioxide Moisture Protect
Isopropyl alcohol anhydrous
Methylene Chloride Anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C, protect from light

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Alu-Alu 2 strips of 7 Tablets in a carton along with a Leaflet.

6.6 Special precautions for disposal <and other handling>

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT

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