SUMMARY PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

1.1 Product Name: CLAVAMYN-625

1.2 Strength: Amoxicillin (as Amoxicillin Trihydrate BP) 500mg
Clavulanic acid (as Diluted Potassium Clavulanate BP) 125mg

1.3 Pharmaceutical Form: Tablets

2. Qualitative and Quantitative Composition

Qualitative declaration:

Each film-coated tablet contains:

Amoxicillin Trihydrate BP

Equivalent to Amoxicillin.....500 mg

Potassium Clavulanate BP (As Diluted Potassium Clavulanate BP)

Equivalent to Clavulanic Acid.....125 mg

3. Pharmaceutical form

Tablets

Description: White to off white caplet shape coated tablet, debossed AV 6 on one side and breakline on other side.

4 Clinical Particulars

4.1 Therapeutic indications-

CLAVAMYN is indicated for infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, genito-urinary and abdominal infections, cellulitis, animal bites, severe dental infection with spreading cellulitis or dental infection not responding to first-line antibacterial.

4.2 Posology and Method of Administration

ADULTS: One CLAVAMYN 250/125 strength tablet every 8 h, increased in severe infections to one 500/125 strength tablet every 8 h.

NEONATE: 0.25 mL/kg of 125/31 suspension every 8 h; CHILD 1 month-1 year: 0.25 mL/kg of 125/31 suspension every 8 h, dose doubled in severe infection; CHILD 1-6 years: 5 mL of 125/31 suspension every 8 h or 0.25 mL/kg of 125/31 suspension every 8 h; dose doubled in severe infection. CHILD 6-12 years: 5ml of 250/62 suspension every 8 h or 0.15mL/kg of 250/62 suspension every 8 h; dose doubled in severe infection. Severe dental infections, ADULT and CHILD over 12 years, one 250/125 strength tablet every 8 h for 5 days.

Renal impairment If eGFR 10-30ml per minute per 1.73m then, one 250/125 strength tablet every 12 h or one 500/125 strength tablet every 12 hr.

If eGFR <10ml per minute per 1.73m then, one 250/125 strength tablet every 24 h or one 500/125 strength tablet every 24 h.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients. History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam 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 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 (anaphylactoid) 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 patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. 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.The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP). This reaction requires CLAVAMYN discontinuation and contra-indicates any subsequent administration of amoxicillin. Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment. Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening. 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. In patients with bladder catheters, a regular check of potency should be maintained. Amoxicillin/clavulanic acid should be used with caution in patients with cytomegalovirus infection, acute or chronic lymphocytic leukemia.

4.5 Interactions with other medicinal products and other forms of interactions

Concurrent administration of Allopurinol during treatment with Amoxicillin can increase the likelihood of allergic skin reactions. In common with other broad-spectrum antibiotics, Amoxicillin may reduce the efficacy of oral contraceptives and patients should be warned accordingly. Prolongation of prothrombin time or alteration of INR may be possible in patients receiving anticoagulant therapy with amoxicillin. Probenecid decreases the renal tubular secretion of Amoxicillin. Concurrent use with Amoxicillin may result in increased and prolonged blood levels of Amoxicillin. Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Excretion of penicillin is reduced by sulfinpyrazole. Anti-bacterials may inactivate oral typhoid vaccine.

4.6 Pregnancy and Lactation

Use of CLAVAMYN should be avoided during pregnancy, unless considered essential by the physician.

CLAVAMYN should only be used during breast-feeding if benefits outweigh the risks involved.

4.7 Effects on ability to drive and use machine

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

Common: Nausea, vomiting, diarrhoea, rashes (discontinue treatment), hepatitis, cholestatic jaundice, Stevens Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitits, vaculitis. Rare: Prolongation of bleeding time, dizziness, headache, convulsions, antibiotic-associated colitis, Superficial staining of teeth with suspension.

4.9 Overdose

Symptoms: Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances. In patients with reduced urine output, over dosage may result in crystalluria with possibility of renal failure. 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 potency should be maintained. Treatment: Treat symptomatically with attention to the water/electrolyte balance. Amoxicillin / clavulanic acid can be removed from the circulation by hemodialysis.

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

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

ATC Code: J01CR02

Mechanism of action:

CLAVAMYN Tablets is a fixed dose combination of amoxicillin and potassium clavulanate. Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that exerts its bactericidal action by inhibiting 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. Amoxicillin exerts bactericidal action against many strains of Gram-positive and Gram-negative organisms. Potassium clavulanate has been shown in vitro to be an irreversible inhibitor of beta-lactamase produced by: Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris, Haemophilus influenzae, Neisseria gonorrhoea and Bacteroides fragilis. Potassium clavulanate does not inactivate the chromosomally mediated (Sykes Type 1 Cephalosporinase) beta-lactamases produced by Acinetobacter species, Citrobacter species, Enterobacter, Indole positive Proteus, Providencia species and Serratia marcescens. In vitro formulation shows synergism against amoxicillin-resistant organisms, with no evidence of antagonism and the activity was not reduced in the presence of serum. (In vitro activity does not necessarily imply in vivo efficacy.)

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimized when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid. Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk. Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms. Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Amoxicillin-clavulanic acid tablets 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration. Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

5.3 Pre-clinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections. Non-clinical data reveal no special hazards for humans based on conventional studies of safety, pharmacology, repeat–dose toxicity or genotoxicity.

6.0 Pharmaceutical Particulars

6.1 List of Excipients

Sr. No.	Ingredients	Specification
1.	Silicified microcrystalline cellulose	USP/NF
2.	Sodium starch glycolate (Primojel)	EP
3.	Magnesium Stearate	BP
4.	Hypromellose (HPMC E-15 premium LV DOW)	EP
5.	Ethocel (Std. 7 premium) Ethyl cellulose	EP
6.	Polyethylene glycol (Macrogol 400)	EP
7.	Opadry AMB II 88A180040 White	IH
8.	Isopropyl Alcohol***	BP

6.2 Incompatibilities

None

6.3 Shelf life-

24 Months (2 years)

Proposed shelf life (after first opening container): NA

Proposed shelf life (after reconstitution or dilution): NA

6.4 Special precautions for storage

Store below 25ºC in a dry place. Protect from light and moisture.

6.5 Nature and contents of container

Primary Packaging: Tablets are packed in Printed Aluminium foil/Plain aluminium Foil blisters.10 tablets are packed in 1 blister.

Secondary Packaging: 2 blisters are packed in 1 carton along with pack insert.

6.6 Instructions for use and handling

None

7. MARKETING AUTHORISATION HOLDER

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8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

04923/6338/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Jun 19, 2023

10. DATE OF REVISION OF THE TEXT

Jun 19, 2023