430

Clavicin

COMPOSITION:

600 mg - Vial
Each vial contains: Amoxicillin sodium equivalent to Amoxicillin 500 mg and Potassium clavulanate USP equivalent to Clavulanic acid 100 mg.

1.2 g - Vial
Each vial contains: Amoxicillin sodium equivalent to Amoxicillin 1 g and Potassium clavulanate USP equivalent to Clavulanic acid 200 mg.

ACTIONS: Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in Amoxicillin and Clavulanic acid anticipates this defence mechanism by blocking the organisms sensitive to amoxicillin's rapid bactericidal effect at concentrations rapidly attainable in the body.

Clavulanate by itself has little antibacterial activity; however in association with amoxicillin as Amoxicillin and Clavulanic acid, it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice.

DESCRIPTION:

White to off white powder.

PHARMACOLOGY:

Pharmacodynamics
Amoxicillin and Clavulanic acid combination is bactericidal to a wide range of organisms including:

Gram-positive
Aerobes: *Enterococcus faecalis*, Enterococcus faecium*, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Staphylococcus aureus*,* Coagulase negative *staphylococci** (including *Staphylococcus epidermidis**), *Corynebacterium* sp, *Bacillus anthracis**, *Listeria monocytogenes.*
Anaerobes: *Clostridium* sp, *Peptococcus* sp, *Peptostreptococcus.*

Gram-negative
Aerobes: *Haemophilus influenzae*, Moraxella catarrhalis* (Branhamella catarrhalis), Escherichia coli*, Proteus mirabilis*, Proteus vulgaris*, Klebsiella sp*, Salmonella sp*, Shigella sp*, Bordetella pertussis, Brucella sp, Neisseria gonorrhoeae*, Neiserria meningitidis*, Vibrio cholerae, Pasteurella multocida.*
Anaerobes: *Bacteroides sp** including *B. fragilis.*
* Some members of these species of bacteria produce β-lactamase, rendering them insensitive to amoxicillin alone.

Pharmacokinetics
The pharmacokinetics of the 2 components of Amoxicillin and Clavulanic acid are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum. Doubling the dosage of the Amoxicillin and Clavulanic acid approximately doubles the serum levels achieved.

When taken together with amoxicillin (500 mg), absorption of clavulanic acid (250 mg) is approximately the same, with a serum peak of around 6 $mg.1^{-1}$ and a peak amoxicillin level of 10 $mg.1^{-1}$, both after 1h. The urinary recovery is about 27-32% after a 250mg dose of clavulanic acid in combination with amoxicillin. The plasma half-life is 0.8-1h and plasma protein binding is 22-30%.

The activity of clavulanic acid is dependent upon the drug achieving concentrations at the site of action above the minimum inhibitory concentration (MIC).

INDICATIONS:

CLAVICIN should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

CLAVICIN is indicated for short-term treatment of bacterial infections at the following sites:

Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media.

Lower respiratory tract infections e.g. acute exacerbation of chronic bronchitis, lobar and bronchopneumonia.

Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis.

Skin and soft tissue infections, e.g. boils, abscesses, cellulitis, wound infections.

Bone and joint infections e.g. osteomyelitis.

Other infections e.g. intra-abdominal sepsis.

CLAVICIN intravenous is also indicated for prophylaxis against infection which may be associated with major surgical procedures such as gastrointestinal, pelvic, head and neck, cardiac, renal, joint replacement and biliary tract.

Susceptibility to CLAVICIN will vary with geography and time (see Pharmacological Properties, Pharmacodynamics for further information). Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

CONTRAINDICATIONS:

Penicillin hypersensitivity. Attention should be paid to possible sensitivity with other β-lactam antibiotics, e.g. Cephalosporin. A previous history of Amoxicillin and Clavulanic acid or penicillin associated jaundice / hepatic dysfunction.

Drug interactions:
Prolongation of bleeding time and prothrombin time have been reported in some patients receiving Amoxicillin and Clavulanic acid. It should be used with care in patients on anticoagulation therapy. In common with other broad-spectrum antibiotics, Amoxicillin and Clavulanic acid may reduce the efficacy of oral contraceptives and patients should be warned accordingly. Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with Amoxicillin and Clavulanic acid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

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 Amoxicillin and Clavulanic acid and allopurinol.

SIDE EFFECTS/ADVERSE REACTIONS:

Side effects are uncommon and mainly of a mild and transitory nature.

Gastrointestinal reactions:
Side effects include diarrhoea, indigestion, nausea, vomiting, and mucocutaneous candidiasis have been reported. Antibiotic associated colitis (including pseudomembranous colitis and haemorrhagic colitis) has been reported rarely. Nausea, although uncommon, is more often associated with higher oral dosages.

Gastrointestinal disorders:
Gastrointestinal disorders, with a frequency 'not known': Drug-induced enterocolitis syndrome.

Renal and urinary tract disorders:
Crystalluria has been reported very rarely.

Genito-urinary effects:
Vaginal itching, soreness and discharge may occur.

Hepatic effects:
Moderate and asymptomatic rises in AST and/or ALT and alkaline phosphatase have been reported occasionally. Hepatitis and cholestatic jaundice have been reported rarely. It has been reported more commonly in the elderly, in males, or in patients with duration of treatment longer than 14 days.

Signs and symptoms usually occur during or shortly after treatment but in some cases may not occur until several weeks after treatment has ended. Hepatic reactions are usually reversible but they may be severe and, very rarely, deaths have been reported.

Hypersensitivity reactions:
Urticarial and erythematous skin rashes sometimes occur. Rarely erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP), serum sickness-like syndrome and hypersensitivity vasculitis have been reported. Whenever such disorders occur, treatment should be discontinued. In common with other β-lactam antibiotics angioedema and anaphylaxis have been reported. Intestinal nephritis can occur rarely.

Hematological effects:
As with other β-lactams transient leucopenia (including neutropenia and agranulocytosis), thrombocytopenia and haemolytic anaemia have been reported rarely. Prolongation of bleeding time and prothrombin time has also been reported rarely.

CNS effects:
CNS effects have been very rarely. These include reversible hyperactivity, dizziness, headache and convulsions. Convulsions may occur with impaired renal function or in those receiving high doses. Aseptic meningitis with frequency not known.

Skin and subcutaneous tissue disorders:
Frequency 'very rare'. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Local:
Thrombophlebitis at the site of injection has been reported occasionally.

Cardiac disorders:
Cardiac disorders, with a frequency 'not known': Kounis syndrome.

PRECAUTIONS/WARNINGS:

Changes in liver function tests have been observed in some patients receiving Amoxicillin and Clavulanic acid. The clinical significance of these changes is uncertain but Amoxicillin and Clavulanic acid should be used with caution in patients with evidence of severe hepatic dysfunction.

FRONT SIDE

ARTWORK DETAIL LABEL

Product	**Clavicin**				
Buyer/Country	Mylan / Malaysia	Component	Pack Insert		
Dimension	300 x 160 mm			Pack	--
New Item Code	**1034936 (1200007672)**	Old Item Code	1033214 (1200006192)		
Colour Shades	Black			No. of Colours	1

Change Control No.	PR# 3332920
Design/Style	Front & Back Printing. To be supplied in folded size of 35 x 55 mm. Brand name facing front after final folding.
Substrate	40/45 GSM Paper.
Special Instructions	Printing clarity to be clear & sharp.
Autocartonator Requirements	NA
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Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for several weeks after treatment has ceased.

Dosage should be adjusted in patients with renal impairment.

The sodium content must be taken into account in patients on a sodium restricted diet if the parenteral administration of high doses is necessary.

Crystalluria has been observed very rarely in patients with reduced urine output, predominantly with parenteral therapy. During 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. Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of potency should be maintained.

Erythematous rashes have been associated with glandular fever in patients receiving amoxicillin.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin (see section Adverse effects). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug <intake> <administration> <use>) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction *(see section Adverse effects).*

In patients with reduced urine output, crystalluria (including acute renal injury) 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. In patients with bladder catheters, a regular check of patency should be maintained *(see sections Adverse effects and Overdosage).*

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, the amoxicillin and clavulanic acid combination should be discontinued and the appropriate therapy instituted.

Pregnancy
Reproduction studies in animals (mice and rats) with orally and parenterally administered Amoxicillin and Clavulanic acid have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with Amoxicillin and Clavulanic acid 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 1st trimester, unless considered essential by the physician.

Nursing mothers
Amoxicillin and Clavulanic acid 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 known detrimental effects on the breast-fed infant.

Geriatric use
No special precautions have to be taken when prescribing for the elderly.

Effects on ability to drive and use machines
None known.

DOSAGE AND ADMINISTRATION:

Dosages for the treatment of infection
Adults and children over 12 years: Usually 1.2 g 8 hourly. In more serious infections increase frequency to 6-hourly intervals.
Children 3 months-12 years:
30 mg/kg Amoxicillin and Clavulanic acid 8 hourly. In more serious infections, increase frequency to 6-hourly intervals.
Children 0-3 months:
30 mg/kg Amoxicillin and Clavulanic acid 12 hours in premature infants and in full-term infants during the perinatal period, increasing to 8 hours thereafter.

Dosage in renal impairment
Adults:

Mild impairment (creatinine clearance >30 ml/min)	Moderate impairment (creatinine clearance 10-30 ml/min)	Severe impairment (creatinine clearance <10 ml/min)
No change in dosage.	1.2g IV stat., followed by 600mg IV 12 hourly.	1.2g IV stat., followed by 600mg IV 24 hourly. Dialysis decreases serum concentrations of Amoxicillin and Clavulanic acid combination and an additional 600mg IV dose may need to be given during dialysis and at the end of dialysis.

Children:
Similar reductions in dosage should be made for children.

Dosage in hepatic impairment
Dose with caution; monitor hepatic function at regular intervals.
There are, as yet, insufficient data on which to base a dosage recommendation.
Each 1.2g vial of Amoxicillin and Clavulanic acid contains 1.0 mmol of potassium and 2.7 mmol of sodium (approx).

Route of administration:
Intravenous route only.
Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

Incompatibilities
Amoxicillin and Clavulanic acid should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.
If Amoxicillin and Clavulanic acid combination is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

Instructions for use and handling
600mg vial: To reconstitute dissolve in 10ml Water for Injections.
(Final volume 10.5ml)

1.2g vial: To reconstitute dissolve in 20ml Water for Injections.
(Final volume 20.9ml)

The solution should be given by slow intravenous injection over a period of three to four minutes and used within 20 minutes of reconstitution. It may be injected directly into a vein or via drip tube. Any residual antibiotic solutions should be discarded.

SYMPTOMS AND TREATMENT FOR OVERDOSAGE:

Symptoms: Cases of overdosage with Amoxicillin and Clavulanic acid are usually asymptomatic. If encountered gastrointestinal symptoms and disturbances of the fluid and electrolyte balances may be evident.

Treatment: They may be treated symptomatically with attention to the water electrolyte balance. Amoxicillin and Clavulanic acid can be removed from the circulation by haemodialysis. During the administration of high doses of Amoxicillin and Clavulanic acid adequate fluid intake and urinary output should be maintained to minimize the possibility of amoxicillin crystalluria.

PRESENTATION:

1 vial in a carton.
10/50 vials in a carton.

STORAGE:

Store at controlled room temperature not exceeding 30°C. Protect from light.

Shelf-life: 2 years

Date of revision: January, 2024

Mylan

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Product Owner:
Mylan Laboratories Limited
Plot No. 564/A/22, Road No.92, Jubilee Hills,
Hyderabad-500096, Telangana, India.

Manufactured by:
M/S Steriscience Specialties Private Limited
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Importer and Product Registration Holder in Malaysia:
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52200, Kuala Lumpur, Malaysia.

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