Size : (150x300)
Paper : White
GSM : 58

For the use of Registered Medical Practitioner of Hospital or a Laboratory only

NOVAMENTIN 625
Amoxicillin & Clavulanate Potassium Tablets USP 625 mg

COMPOSITION
Each film coated Tablets contains:
Amoxicillin Trihydrate USP
eq. to Amoxicillin …….500 mg
Diluted Potassium Clavulanate BP
Eq. to Clavulanic acid ……. 125 mg
Excipients ……..q.s
Colour : Titanium Dioxide USP

CLINICAL PHARMACOLOGY
Pharmacotherapeutic group: Combinations of penicillin's, incl. beta-lactamase inhibitors
ATC Code: J01CR02
Mechanism of action: Amoxicillin is semi-synthetic 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's. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.
Pharmacokinetic/pharmacodynamic relationship
The time above the minimum inhibitory concentration (T>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.
Commonly susceptible species
Aerobic Gram-positive micro-organisms
Enterococcus faecalis, *Gardnerella vaginalis*, *Staphylococcus aureus (*methicillin-susceptible) £,
Coagulase-negative staphylococci (methicillin-susceptible), *Streptococcus agalactiae, Streptococcus pneumoniae*[1], *Streptococcus pyogenes* and other beta-haemolytic streptococci, *Streptococcus viridans* group
Aerobic Gram-negative micro-organisms
Capnocytophaga spp., *Eikenella corrodens, Haemophilus influenzae,*[2],*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 pneumoniae
$ 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%.
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 (T_{max}) in each case is approximately one hour.
The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers, are presented below.
Mean (± SD) pharmacokinetic parameters:
Active substance Amoxicillin 500 mg when administered C_{max} is 7.19± 2.26 µg/ml, T_{max} is 1.5 (1.0-2.5) h, $AUC_{(0-24h)}$ is 53.5 ± 8.87 µg.h/ml & T ½1.15 ± 0.20 h. Similarly, Active substance Clavulanic acid 125 mg when administered C_{max} is 2.40 ± 0.83 µg/ml, T_{maxi} 1.5 (1.0-2.0) h, $AUC_{(0-24h)}$ is 15.72 ± 3.86 µg.h/ml & T ½ 0.98± 0.12 h.
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 penicillin's, 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.
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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 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

INDICATION AND USAGE
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.

CONTRA-INDICATION
Hypersensitivity to the active substances, to any of the penicillin's 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

DRUG INTERACTIONS
Oral anticoagulants: 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's 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.
Mycophenolate mofetil: In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) 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. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

WARNINGS AND PRECAUTIONS
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 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.
This presentation of amoxicillin/clavulanic acid is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.
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.
The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP). This reaction requires Amoxicillin/clavulanic acid discontinuation and contra-indicates any subsequent administration of amoxicillin.
Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment.
Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.
Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.
Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.
Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.
In patients with renal impairment, the dose should be adjusted according to the degree of impairment.
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. In patients with bladder catheters, a regular check of patency should be maintained.
During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.
The presence of Clavulanic acid in amoxicillin/clavulanic acid may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.
There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

SIDE EFFECTS
The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting. 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 been 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
Common: Overgrowth of non-susceptible organisms
Not known: Mucocutaneous candidosis
Blood and lymphatic system disorders
Rare: Reversible leucopenia (including neutropenia), Thrombocytopenia
Not known: Reversible agranulocytosis, Hemolytic anemia and Prolongation of bleeding time and prothrombin time
Immune system disorders
Not known: Angioneurotic oedema, Anaphylaxis, Serum sickness-like syndrome and Hypersensitivity vasculitis
Nervous system disorders
Uncommon: Dizziness, Headache
Not known: Reversible hyperactivity, Convulsions, Aseptic meningitis
Gastrointestinal disorders
Very common: Diarrhea
Common: Nausea, Vomiting
Uncommon: Indigestion
Not known: Antibiotic-associated colitis, Black hairy tongue
Hepatobiliary disorders
Uncommon: Rises in AST and/or ALT, Hepatitis, Cholestatic jaundice
Skin and subcutaneous tissue disorders
Uncommon: Skin rash, Pruritus, Urticaria
Rare: Erythema multiforme
Not known: Stevens-Johnson syndrome, Toxic epidermal necrolysis, Bullous exfoliative-dermatitis, Acute generalized exanthemous pustulosis (AGEP)
Renal and urinary disorders
Not known: Interstitial nephritis, Crystalluria

OVERDOSE
Symptoms and signs of 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 haemodialysis

POSOLOGY & MODE OF ADMINISTRATION
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 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.
For adults and children ≥ 40 kg, this formulation of amoxicillin/clavulanic acid provides a total daily dose of 1500 mg amoxicillin/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/600 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of 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.
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
Children may be treated with amoxicillin/clavulanic acid tablets, suspensions or paediatric sachets.
As the tablets cannot be divided, children weighing less than 25 kg must not be treated with amoxicillin/clavulanic acid tablets.
Below presenting the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 500/125 mg tablet.
For children with body weight 40 kg: the received dose will be 12.5 mg of Amoxicillin & 3.1 mg of Clavulanic acid per single dose; with body weight of 35 kg: the received dose will be 14.3 mg of Amoxicillin & 3.6 mg of Clavulanic acid per single dose; with body weight of 30 kg: the received dose will be 16.7 mg of Amoxicillin & 4.2 mg of Clavulanic acid per single dose; with body weight of 25 kg: the received dose will be 20.0 mg of Amoxicillin & 5.0 mg of Clavulanic acid per single dose.
Children aged 6 years and below or weighing less than 25 kg should preferably be treated with Augmentin suspension or pediatric sachets.
No clinical data are available on doses of Augmentin 4:1 formulation 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 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 twice 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/clavulanic acid is for oral use. Administer at the start of a meal to minimize potential gastrointestinal intolerance and optimize absorption of amoxicillin/clavulanic acid.

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/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/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.
Breastfeeding: 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/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

STORAGE CONDITION
Store protected from light at a temperature not exceeding 30°C

KEEP OUT OF REACH OF CHILDREN

PRESENTATION
2 Alu-Alu blisters of 10 tablets are packed in carton along with leaflet.

MANUFACTURED BY
Scott-Edil Advance Research Laboratories & Education Limited.
Hill Top Ind. Area, Bhatoli Kalan,
Baddi-173205, Himachal Pradesh, INDIA

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