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

AMPOXIN CV

1. Generic Name

Amoxycillin and Potassium Clavulanate Tablets I.P.

2. Qualitative and quantitative composition

AMPOXIN CV 375

Each film coated tablet contains:

Amoxycillin Trihydrate I.P. equivalent to Amoxycillin……..250 mg

Potassium Clavulanate Diluted I.P. equivalent to Clavulanic Acid….125 mg

Excipients …….q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Avicel, Polyplasdone XL, Syloid, Magnesium Stearate, Polyethylene Glycol, Isopropyl Alcohol, Dichloromethane, Hypromellose, Titanium Dioxide, Ethyl Cellulose and Triacetin.

AMPOXIN CV 625

Each film coated tablet contains:

Amoxycillin Trihydrate I.P. equivalent to Amoxycillin……..500 mg

Potassium Clavulanate Diluted I.P. equivalent to Clavulanic Acid….125 mg

Excipients …….q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Avicel, Crospovidone, Syloid, Magnesium Stearate, Polyethylene Glycol, Isopropyl Alcohol, Dichloromethane, Hypromellose, Titanium Dioxide, Ethyl Cellulose and Triacetin.

3. Dosage form and strength

Dosage form: Film Coated

Strebgth:

AMPOXIN CV 375

Amoxycillin……..250 mg

Potassium Clavulanate Diluted I.P. equivalent to Clavulanic Acid….125 mg

AMPOXIN CV 625

Amoxycillin……..500 mg

Potassium Clavulanate Diluted I.P. equivalent to Clavulanic Acid….125 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated in the treatment of acute bacterial sinusitis, acute otitis media, 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 Ampoxin CV that is selected to treat an individual infection should take into account:

• The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)

• 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 Ampoxin (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 (see section 4.4 regarding prolonged therapy).

Children may be treated with Ampoxin tablets, suspensions or paediatric sachets. Children aged 6 years and below should preferably be treated with suspension or paediatric sachets.

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.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals.

Method of administration

Ampoxin CV is for oral use.

Ampoxin CV should be administered with a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

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 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 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*.

This medicinal product contains potassium. To be taken into consideration in patients with reduced kidney function or patients on a controlled potassium diet.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

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) (see Section 4.8). This reaction requires Ampoxin CV 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 (see section 4.8). 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 Ampoxin CV 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.

4.5 Drugs 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 normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate

Penicillins 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.

4.6 Use in special populations

Pregnancy

Reported animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 6.1). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a reported 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 necrotising 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, diarrhoea 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.

4.7 Effects on ability to drive and use machines

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

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from reported clinical studies and post-marketing surveillance, 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	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
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
Convulsions[2]	Not known
Aeseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known

Acute generalised exanthemous pustulosis (AGEP)[9]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

[1] See section 4.4
[2] See section 4.4
[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.
[4] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See section 4.4
[10] See sections 4.3 and 4.4

- **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 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 (see section 4.4).

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 (see section 4.4).

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.

5. Pharmacological properties

5.1 Mechanism of Action

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 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.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

PK/PD 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.

Breakpoints

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Organism	Susceptibility Breakpoints (µg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae[1]	≤ 1	-	> 1
Moraxella catarrhalis[1]	≤ 1	-	> 1
Staphylococcus aureus [2]	≤ 2	-	> 2
Coagulase-negative staphylococci [2]	≤ 0.25		> 0.25
Enterococcus[1]	≤ 4	8	> 8
Streptococcus A, B, C, G[5]	≤ 0.25	-	> 0.25
Streptococcus pneumoniae[3]	≤ 0.5	1-2	> 2
Enterobacteriaceae[1,4]	-	-	> 8
Gram-negative Anaerobes[1]	≤ 4	8	> 8
Gram-positive Anaerobes[1]	≤ 4	8	> 8
Non-species related breakpoints[1]	≤ 2	4-8	> 8

[1] The reported values are for amoxicillin concentrations. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l.
[2] The reported values are oxacillin concentrations.
[3] Breakpoint values in the table are based on ampicillin breakpoints.

[4] The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.
[5] Breakpoint values in the table are based on benzylpenicillin breakpoints.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

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 (see sections 4.2 and 4.4). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.3 **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. 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 reported 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(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC $_{(0-24h)}$ ((µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA 500/125 mg	500	7.19 ± 2.26	1.5 (1.0-2.5)	53.5 ± 8.87	1.15 ± 0.20
Clavulanic acid					
AMX/CA 500 mg/125 mg	125	2.40 ± 0.83	1.5 (1.0-2.0)	15.72 ± 3.86	0.98 ± 0.12
AMX – amoxicillin, CA – clavulanic acid * Median (range)					

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 reported 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 Ampoxin CV 250 mg/125 mg or 500 mg/125 mg tablets. Various reported 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

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid.

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Nonclinical data reveal no special hazard for humans based on reported studies of safety pharmacology, genotoxicity and toxicity to reproduction.

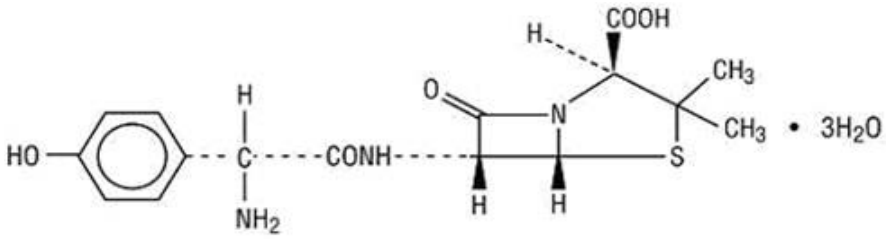
Reportedly, repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue**.**

Carcinogenicity studies have not been conducted.

7. Description

Amoxycillin Trihydrate

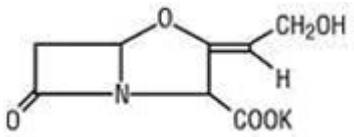
Amoxycillin Trihydrate is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. Chemically, Amoxycillin is (6R)-6-[(α-4-hydroxyphenyl)-D-glycylamino) penicillanic acid trihydrate and may be represented structurally as:



The molecular formula is $C_{16}H_{19}N_3O_5S.3H_2O$ and molecular weight is 419.45. It is white or almost white, crystalline powder which is slightly soluble in water, in ethanol (95%) and in methanol; soluble in dilute solutions of acids and of alkali hydroxides; practically insoluble in chloroform, in ether and in fixed oils.

Potassium Clavulanate

Potassium Clavulanate molecular formula is $C_8H_8KNO_5$, and the molecular weight is 237.25. Chemically, Potassium Clavulanate is potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate, and may be represented structurally as:



Potassium Clavulanate is white to off-white, crystalline hygroscopic powder which is freely soluble in water; slightly soluble in ethanol (95%); very slightly soluble in acetone.

AMPOXIN CV 375

Amoxycillin and Potassium Clavulanate Tablets are white to off-white, biconvex oval shaped plain film coated tablets. The excipients used are Avicel, Polyplasdone XL, Syloid, Magnesium Stearate, Polyethylene Glycol, Isopropyl Alcohol, Dichloromethane, Hypromellose, Titanium Dioxide, Ethyl Cellulose and Triacetin.

AMPOXIN CV 625

Amoxycillin and Potassium Clavulanate Tablets are white to off-white, biconvex oval shaped plain film coated tablets. The excipients used are Avicel, Crospovidone, Syloid, Magnesium Stearate, Polyethylene Glycol, Isopropyl Alcohol, Dichloromethane, Hypromellose, Titanium Dioxide, Ethyl Cellulose and Triacetin.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

AMPOXIN CV is available in Alu-Alu blister of 10 tablets

8.4 Storage and handing instructions

Store at a temperature not more than 25°C protected from light & moisture.

9. Patient Counselling Information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or your pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 WHAT AMPOXIN CV IS AND WHAT IT IS USED FOR

AMPOXIN CV is an antibiotic and works by killing bacteria that cause infections. It contains two different medicines called amoxicillin and clavulanic acid. Amoxicillin belongs to a group of medicines called "penicillins" that can sometimes be stopped from working (made inactive). The other active component (clavulanic acid) stops this from happening.

It is Indicated in the treatment of acute bacterial sinusitis, acute otitis media, 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.

9.2 BEFORE YOU TAKE YOUR MEDICINE

Do not take your medicine:

- if you are allergic (hypersensitive) to amoxicillin, clavulanic acid, penicillin or any of the other ingredients of your medicine.
- if you have ever had a severe allergic (hypersensitive) reaction to any other antibiotic. This can include a skin rash or swelling of the face or neck
- if you have ever had liver problems or jaundice (yellowing of the skin) when taking an antibiotic.

Do not take your medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking your medicine.

Take special care with your medicine

Talk to your doctor or pharmacist before taking this medicine if you: Have glandular fever are being treated for liver or kidney problems are not passing water regularly.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking your medicine.

In some cases, your doctor may investigate the type of bacteria that is causing your infection. Depending on the results, you may be given a different strength of Ampoxin CV or a different medicine.

Important information about some of the ingredients in your medicine

This medicine contains 0.63mmol (24.5mg) potassium per tablet, therefore, it may not be suitable if you are on a controlled potassium diet or you have reduced kidney function. Check with your doctor if you are unsure about this.

Conditions you need to look out for

Your medicine can make some existing conditions worse, or cause serious side effects. These include allergic reactions, convulsions (fits) and inflammation of the large intestine. You must look out for certain symptoms while you are taking your medicine, to reduce the risk of any problems. See 'Conditions you need to look out for' in **Section 9.4.**

Blood and urine tests

If you are having blood tests (such as red blood cell status tests or liver function tests) or urine tests (for glucose), let the doctor or nurse know that you are taking your medicine. This is because your medicine can affect the results of these types of tests.

Using other medicines

Please tell your doctor or pharmacist if you are using or have recently used any other medicines. This includes medicines that can be bought without a prescription and herbal medicines.

If you are taking allopurinol (used for gout) with your medicine, it may be more likely that you'll have an allergic skin reaction.

If you are taking probenecid (used for gout), your doctor may decide to adjust your dose of your medicine.

If medicines to help stop blood clots (such as warfarin) are taken with your medicine, then extra blood tests may be needed.

Your medicine can affect how methotrexate (a medicine used to treat cancer or rheumatic diseases) works.

Pregnancy and breast-feeding

If you are pregnant, you think you might be pregnant or if you are breast-feeding, please tell your doctor or pharmacist.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Your medicine can have side effects and the symptoms may make you unfit to drive.

Don't drive or operate machinery unless you are feeling well.

9.3 HOW TO TAKE YOUR MEDICINE

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults and children weighing 40 kg and over

The usual dose is: 1 tablet three times a day

Children weighing less than 40 kg

Children aged 6 years or less should preferably be treated with **Ampoxin CV** oral suspension.

Ask your doctor or pharmacist for advice when giving Ampoxin CV tablets to children weighing less than 40 kg.

Patients with kidney and liver problems

If you have kidney problems the dose might be changed. A different strength or a different medicine may be chosen by your doctor.

If you have liver problems, you may have more frequent blood tests to check how your liver is working.

How to take your medicine?

Swallow the tablets whole with a glass of water at the start of a meal or slightly before.

Space the doses evenly during the day, at least 4 hours apart. Do not take 2 doses in 1 hour.

Do not take your medicine for more than 2 weeks. If you still feel unwell you should go back to see the doctor.

If you take more of your medicine than you should

If you take too much of your medicine, signs might include an upset stomach (feeling sick, being sick or diarrhoea) or convulsions. Talk to your doctor as soon as possible. Take the medicine carton or bottle to show the doctor.

If you forget to take your medicine

If you forget to take a dose, take it as soon as you remember. You should not take the next dose too soon, but wait about 4 hours before taking the next dose.

If you stop taking your medicine

Keep taking your medicine until the treatment is finished, even if you feel better. You need every dose to help fight the infection. If some bacteria survive they can cause the infection to come back.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4 POSSIBLE SIDE EFFECTS

Like all medicines, your medicine can cause side effects, although not everybody gets them.

Conditions you need to look out for

Allergic reactions:

- skin rash
- inflammation of blood vessels (vasculitis) which may be visible as red or purple raised spots on the skin, but can affect other parts of the body
- fever, joint pain, swollen glands in the neck, armpit or groin
- swelling, sometimes of the face or mouth (angioedema), causing difficulty in breathing
- Collapse.

Contact a doctor immediately if you get any of these symptoms. **Stop taking your medicine.**

Inflammation of large intestine

Inflammation of the large intestine, causing watery diarrhoea usually with blood and mucus, stomach pain and/or fever.

Contact your doctor as soon as possible for advice if you get these symptoms.

Very common side effects

These may affect more than 1 in 10 people

- Diarrhoea (in adults).

Common side effects

These may affect up to 1 in 10 people

- thrush (candida - a yeast infection of the vagina, mouth or skin folds)
- feeling sick (nausea), especially when taking high doses
- if affected take your medicine before food
- vomiting diarrhoea (in children).

Uncommon side effects

These may affect up to 1 to 100 people

- skin rash, itching
- raised itchy rash (hives)
- indigestion
- dizziness
- Headache.

Uncommon side effects that may show up in your blood tests:

- Increase in some substances (enzymes) produced by the liver.

Rare side effects

These may affect up to 1 in 1000 people

- skin rash, which may blister, and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge - erythema multiforme)

If you notice any of these symptoms contact a doctor urgently.

Rare side effects that may show up in your blood tests:

Low number of cells involved in blood clotting

Low number of white blood cells.

Other side effects

Other side effects have occurred in a very small number of people but their exact frequency is unknown.

- Allergic reactions (see above)
- Inflammation of the large intestine (see above)
- Serious skin reaction: a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome), and a more severe form,

causing extensive peeling of the skin (more than 30% of the body surface - toxic epidermal necrolysis)

- widespread red skin rash with small pus-containing blisters (bullous exfoliative dermatitis)
- a red, scaly rash with bumps under the skin and blisters (exanthemous pustulosis)

Contact a doctor immediately if you get any of these symptoms.

- inflammation of the liver (hepatitis)
- Jaundice, caused by increases in the blood of bilirubin (a substance produced in the liver) which may make your skin and whites of the eyes appear yellow.
- inflammation of tubes in the kidney
- blood takes longer to clot
- hyperactivity
- Convulsions (in people taking high doses of this medicine or who have kidney problems)
- Black tongue which looks hairy
- stained teeth (in children), usually removed by brushing

Side effects that may show up in your blood or urine tests:

- severe reduction in the number of white blood cells
- low number of red blood cells (haemolytic anaemia) crystals in urine.

If you get side effects

Tell your doctor or pharmacist if any of the side effects become **severe or troublesome**, or if you notice any side effects not listed in this leaflet.

9.5 HOW TO STORE YOUR MEDICINE

Store at a temperature not more than 25°C protected from light & moisture.

9.6 FURTHER INFORMATION

What your medicine contains

The active substances are: amoxicillin (as trihydrate) 500mg/250 mg; clavulanic acid (as potassium Clavulanate) 125mg.

AMPOXIN CV 375
The excipients used are Avicel, Polyplasdone XL, Syloid, Magnesium Stearate, Polyethylene Glycol, Isopropyl Alcohol, Dichloromethane, Hypromellose, Titanium Dioxide, Ethyl Cellulose and Triacetin.

AMPOXIN CV 625
The excipients used are Avicel, Crospovidone, Syloid, Magnesium Stearate, Polyethylene Glycol, Isopropyl Alcohol, Dichloromethane, Hypromellose, Titanium Dioxide, Ethyl Cellulose and Triacetin.

AMPOXIN CV is available in Alu-Alu blister of 10 tablets

10. Details of manufacturer

Manufactured by:

Uni Medicolabs

21-22, Pharmacity, Selaqui, Distt. Dehradun – 248011, Uttarakhand.

11. Details of permission or licence number with date

AMPOXIN CV 375

Mfg Lic No. 55/UA/SC/P-2008 issued on 16.12.2013

AMPOXIN CV 625

Mfg Lic No. 55/UA/SC/P-2008 issued on 16.12.2013

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/AMPOXIN CV 250mg+125mg, 500+125mg/APR-20/01/PI