To be sold by retail on prescription of R.M.P. only

AMPOXIN-CV FORTE

1. Generic Name

Amoxycillin & Potassium Clavulanate Oral Suspension I.P.

2. Qualitative and quantitative composition

Each 5ml after reconstitution contains:

Amoxycillin Trihydrate I.P.

Equivalent to Amoxycillin …….400 mg

Potassium Clavulanate Diluted I.P.

Equivalent to Clavulanic Acid….57 mg

Excipients…….q.s.

The excipients used are Silicon Dioxide, Xanthum Gum, Hypromellose, Colloidal Anhydrous Silica, Succinic Acid Crystals, Aspartame, Orange Flavour Dry and Raspberry Flavour Dry.

3. Dosage form and strength

Dosage form: Dry Powder for Suspension

Strength: Amoxycillin Trihydrate I.P. Equivalent to Amoxycillin …….400 mg

Potassium Clavulanate Diluted I.P. Equivalent to Clavulanic Acid….57 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of LRTI infections (e.g. Pneumonia, bronchitis), acute otitis media, sinusitis, UTI, skin & soft tissue infections & bone & joint infections.

4.2 Posology and method 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 AMPOXIN CV FORTE 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.

For children < 40 kg, this formulation of AMPOXIN CV FORTE provides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, when administered as recommended below.

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.

Children < 40 kg

• 25 mg/3.6 mg/kg/day to 45 mg/6.4 mg/kg/day given as two divided doses;

• up to 70 mg/10 mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

No clinical data are available for Augmentin 7:1 formulations regarding doses higher than 45 mg/6.4 mg per kg per day in children under 2 years. There are no clinical data for Augmentin 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Elderly

No dose adjustment is considered necessary.

Renal impairment

No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

In patients with creatinine clearance less than 30 ml/min, the use of AMPOXIN CV FORTE presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals.

Method of administration

AMPOXIN CV FORTE is for oral use.

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

Shake to loosen powder, add water as directed, invert and shake.

Shake the bottle before each dose.

Reconstituted suspension should be used within seven days.

Do not freeze.

Store the reconstituted suspension in refrigerator when not in use.

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 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 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 AMPOXIN CV FORTE is not suitable for use when there is a high risk that the presumptive pathogens have 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 generalised exanthemous pustulosis (AGEP). This reaction requires AMPOXIN CV FORTE discontinuation and contraindicates 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 including amoxicillin 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 drugs are contraindicated 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 FORTE 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.

AMPOXIN CV FORTE 400 mg/57 mg/5 ml powder for oral suspension contains aspartame, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria.

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 (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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 necrotising 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, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. The possibility of sensitisation should be taken into account. 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 clinical studies and post-marketing surveillance with AMPOXIN CV FORTE, 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
Aseptic meningitis	Not known

Gastrointestinal disorders	
Diarrhoea	Common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Tooth discolouration[11]	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 (SJS)	Not known
Toxic epidermal necrolysis (TEN)	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 at the start of 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

[11] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

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.

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.

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.

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* <u>Other micro-organisms</u> *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

<u>Absorption</u>

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 optimised 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 (875 mg/125 mg tablets given twice daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose	C_{max}	T_{max} *	AUC $_{(0-24h)}$	T 1/2
	(mg)	(µg/ml)	(h)	(µg.h/ml)	(h)
Amoxicillin					
AMX/CA 875 mg/125 mg	875	11.64 ± 2.78	1.50 (1.0-2.5)	53.52 ± 12.31	1.19 ± 0.21

Clavulanic acid					
AMX/CA 875 mg/125 mg	125	2.18 ± 0.99	1.25 (1.0-2.0)	10.16 ± 3.04	0.96 ± 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 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 (see section 4.6).

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 FORTE 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.

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

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

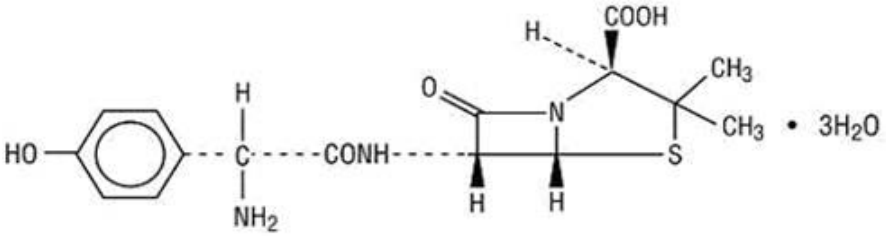
Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

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

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:

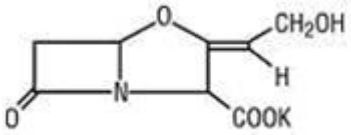


The molecular formula is $C_{16}H_{19}N_3O_5S.3H_2O$ and molecular weight is 419.45. It is white or almost white, crystalline powder which is slightly soluble in water, in ethanol (95%)

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.

Amoxycillin & Potassium Clavulanate Oral Suspension is white to off white free flowing powder, which on reconstitution gives white to off white coloured suspension. The excipients used are Silicon Dioxide, Xanthum Gum, Hypromellose, Colloidal Anhydrous Silica, Succinic Acid Crystals, Aspartame, Orange Flavour Dry and Raspberry Flavour Dry.

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 FORTE is available in bottle pack.

8.4 Storage and handing instructions

Store in a cool and dry place. Protect from light.

9. Patient Counselling Information

Package leaflet: Information for the user

AMPOXIN CV FORTE

(Amoxicillin/clavulanic acid)

Read all of this leaflet carefully before you start giving your child this medicine because it contains important information for them.

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

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

- This medicine is usually prescribed for a baby or child. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child's.

- If your child gets any side effects, talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

9.1 What AMPOXIN CV FORTE is and what it is used for

AMPOXIN CV FORTE 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.

AMPOXIN CV FORTE is used in babies and children to treat the following infections:

• Middle ear and sinus infections

• Respiratory tract infections

• Urinary tract infections

• Skin and soft tissue infections including dental infections

• Bone and joint infections.

9.2 What you need to know before you give AMPOXIN CV FORTE

Do not give your child AMPOXIN CV FORTE:

• If they are allergic to amoxicillin, clavulanic acid, penicillin or any of the other ingredients of this medicine.

• If they have ever had a severe allergic reaction to any other antibiotic. This can include a skin rash or swelling of the face or throat.

• If they have ever had liver problems or jaundice (yellowing of the skin) when taking an antibiotic.

Do not give AMPOXIN CV FORTE to your child if any of the above apply to your child. If you are not sure, talk to their doctor or pharmacist before giving AMPOXIN CV FORTE.

Warnings and precautions

Check with their doctor, pharmacist or nurse before giving your child AMPOXIN CV FORTE if they:

• 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 your child, talk to their doctor or pharmacist before giving AMPOXIN CV FORTE.

In some cases, your doctor may investigate the type of bacteria that is causing your child's infection.

Depending on the results, your child may be given a different strength of AMPOXIN CV FORTE or a different medicine.

Conditions you need to look out for

AMPOXIN CV FORTE 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 your child is taking AMPOXIN CV FORTE, to reduce the risk of any problems.

Blood and urine tests

If your child is 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 they are taking AMPOXIN CV FORTE. This is because

AMPOXIN CV FORTE can affect the results of these types of tests.

Other medicines and AMPOXIN CV FORTE

Tell your doctor or pharmacist if your child is taking, has recently taken or might take any other medicines.

If your child is taking allopurinol (used for gout) with AMPOXIN CV FORTE, it may be more likely that they will have an allergic skin reaction.

If your child is taking probenecid (used for gout), your doctor may decide to adjust the dose of AMPOXIN CV FORTE.

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

AMPOXIN CV FORTE can affect how methotrexate (a medicine used to treat cancer or rheumatic diseases) works. AMPOXIN CV FORTE can affect how mycophenolate mofetil (a medicine used to prevent the rejection or transplanted organs) works.

Pregnancy, breast-feeding and fertility

Ask your doctor or pharmacist for advice before taking this medicine, if the patient is pregnant or are planning to have a baby or is breast feeding.

Driving and using machines

AMPOXIN CV FORTE can have side effects and the symptoms may make you unfit to drive.

Do not drive or operate machinery unless you are feeling well.

AMPOXIN CV FORTE contains aspartame

• AMPOXIN CV FORTE contains aspartame (E951) which is a source of phenylalanine. This may be harmful for children born with a condition called ’phenylketonuria’

9.3 How to give AMPOXIN CV FORTE

Always give this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults and children weighing 40 kg or over

• This suspension is not usually recommended for adults and children weighing 40 kg and over. Ask your doctor or pharmacist for advice.

Children weighing less than 40 kg

All doses are worked out depending on the child's bodyweight in kilograms.

• Your doctor will advise you how much AMPOXIN CV FORTE you should give to your baby or child.

• You may be provided with a plastic measuring cup, spoon or syringe. Instructions on how to use the dosing syringe are provided at the end of this leaflet. You should use this to give the correct dose to your baby or child.

• Recommended dose – 25 mg/3.6 mg to 45 mg/6.4 mg for each kilogram of body weight a day, given in two divided doses

• Higher dose – up to 70 mg/10 mg for each kilogram of body weight a day, given in two divided doses.

Patients with kidney and liver problems

• If your child has kidney problems the dose might be lowered. A different strength or a different medicine may be chosen by your doctor.

• If your child has liver problems they may have more frequent blood tests to see how their liver is working.

How to give AMPOXIN CV FORTE

• Always shake the bottle well before each dose

• Give 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 give your child AMPOXIN CV FORTE for more than 2 weeks. If your child still feels unwell they should go back to see the doctor.

If you give more AMPOXIN CV FORTE than you should

If you give your child too much AMPOXIN CV FORTE, signs might include an upset stomach (feeling sick, being sick or diarrhoea) or convulsions. Talk to their doctor as soon as possible. Take the medicine bottle to show the doctor.

If you forget to give AMPOXIN CV FORTE

If you forget to give your child a dose, give it as soon as you remember. You should not give your child the next dose too soon, but wait about 4 hours before giving the next dose. Do not take a double dose to make up for a forgotten dose.

If your child stops taking AMPOXIN CV FORTE

Keep giving your child AMPOXIN CV FORTE until the treatment is finished, even if they feel better. Your child needs 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 medicine, ask your doctor, pharmacist or nurse.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects below may happen with this medicine.

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 throat (angioedema), causing difficulty in breathing

• Collapse.

Contact a doctor immediately if your child gets any of these symptoms. Stop taking AMPOXIN CV FORTE.

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 your child gets these symptoms.

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 AMPOXIN CV FORTE before food

• vomiting

• Diarrhoea (in children).

Uncommon side effects

These may affect up to 1 in 100 people

• Skin rash, itching

• raised itchy rash (hives)

• Indigestion

• Dizziness

• Headache.

Uncommon side effects that may show up in 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 blood tests:

• Low number of cells involved in blood clotting

• Low number of white blood cells.

Frequency not known

Frequency cannot be estimated from the available data.

• Allergic reactions (see above)

• Inflammation of the large intestine (see above)

• Inflammation of the protective membrane surrounding the brain (aseptic meningitis)

• Serious skin reactions:

- 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)

- Flu-like symptoms with a rash, fever, swollen glands, and abnormal blood test results (Including increased white blood cells (eosinophilia) and liver enzymes) (Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)).

Contact a doctor immediately if your child gets 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 child's 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 AMPOXIN CV FORTE 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 blood or urine tests:

• Severe reduction in the number of white blood cells

• Low number of red blood cells (haemolytic anaemia)

• Crystals in urine.

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.

9.5 How to store AMPOXIN CV FORTE

Store in a cool and dry place. Protect from light.

9.6 Contents of the pack and other information

What AMPOXIN CV FORTE contains

• The active substances are amoxicillin and clavulanic acid. Each 5ml after reconstitution contains: Amoxycillin Trihydrate I.P. Equivalent to Amoxycillin …….400 mg

Potassium Clavulanate Diluted I.P. Equivalent to Clavulanic Acid….57 mg

• The other ingredients Silicon Dioxide, Xanthum Gum, Hypromellose, Colloidal Anhydrous Silica, Succinic Acid Crystals, Aspartame, Orange Flavour Dry and Raspberry Flavour Dry.

• See also "AMPOXIN CV FORTE contains aspartame"

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd.

Indrad-382721, Dist. Mehsana, INDIA.

At: Plot No. 16, Vardhman Industrial Estate,

Vill – Bahadarpur Saini, N.H. 58, Haridwar – 247667 (Uttarakhand)

11. Details of permission or licence number with date

Mfg Lic No. 24/UA/LL/SC/P/2015 issued on 01.01.2018.

12. Date of revision

Not applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ AMPOXIN CV FORTE 400 and 57 mg/APR-2020/PI