Brand Name: GORBACLAV 228.5

Generic Name: Amoxicillin & Clavulanate Potassium for Oral suspension U.S.P

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Invented Name of the Medicinal Product

GORBACLAV 228.5 (Amoxicillin + Clavulanic Acid) Powder for Oral Suspension

1.2 Strength

Amoxicillin (as trihydrate) USP eq.to. Amoxicillin -200 mg

Diluted Potassium Clavulanate BP eq.to Clavulanic acid -28.5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of Reconstituted Suspension Contains:

Amoxicillin (as trihydrate) USP eq.to. Amoxicillin -200 mg

Diluted Potassium Clavulanate BP eq.to Clavulanic acid -28.5mg

AMOXICILLIN (AS TRIHYDRATE) USP EQ.TO. AMOXICILLIN	200 mg
DILUTED POTASSIUM CLAVULANATE BP EQ.TO CLAVULANIC ACID	28.5mg
HYPROMELLOSE USP	22.00 mg
SUCCINIC ACID I.H.S	0.467 mg
XANTHAN GUM USP	5.333mg
ORANGE FLAVOUR I.H.S	22.67mg
NEOTAME USP	0.1320 mg
SYLOID AL -1FP I.H.S	32.122 mg
VANILLA FLAVOUR I.H.S	16.05mg

3. PHARMACEUTICAL FORM

Powder for oral suspension

An off-white colour granular powder filled in opaque white colour bottle.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the treatment of the following infections in adults and children:
- 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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Based on the amoxicillin component, amoxicillin and clavulanate potassium for oral suspension should be dosed as follows:

Neonates and infants aged < 12 weeks (3 months)

Due to incompletely developed renal function affecting elimination of amoxicillin in this age group, the recommended dose of amoxicillin and clavulanate potassium for oral suspension is 30 mg/kg/day divided q12h, based on the amoxicillin component. Clavulanate elimination is unaltered in this age group. Experience with the 200 mg/28.5 mg per 5 mL formulation in this age group is limited and, thus, use of the 125 mg/31.25 mg per 5 mL oral suspension is recommended.

Patients aged 12 weeks (3 months) and older

INFECTIONS	**DOSING REGIMEN**	
	q12h	q8h
	200 mg/28.5 mg per 5 mL or 400 mg/57 mg per 5 mL oral suspension	125 mg/31.25 mg per 5 mL or 250 mg/62.5 mg per 5 mL oral suspension
Otitis media sinusitis, lower respiratory tract infections, and more severe infections	45 mg/kg/day q12h	40 mg/kg/day q8h
Less severe infections	25 mg/kg/day q12h	20 mg/kg/day q8h

The q12h regimen is recommended as it is associated with significantly less diarrhea. However, the q12h formulations (200 mg and 400 mg) contain Neotame and should not be used by phenylketonurics.
Each strength of amoxicillin and clavulanate potassium for oral suspension is available as a chewable tablet for use by older children.

Duration of therapy studied and recommended for acute otitis media is 10 days.

Pediatric patients weighing 40 kg and more

Should be dosed according to the following adult recommendations: The usual adult dose is 1 amoxicillin 500 mg and clavulanate potassium tablet every 12 hours or 1 amoxicillin 250 mg and clavulanate potassium tablet every 8 hours. For more severe amoxicillin and clavulanate potassium oral suspension 312.5 infections and infections of the respiratory tract, the dose should be 1 amoxicillin 875 mg and clavulanate potassium tablet every 12 hours or 1 amoxicillin 500 mg and clavulanate potassium tablet every 8 hours. Among adults treated with 875 mg every 12 hours, significantly fewer experienced severe diarrhea or withdrawals with diarrhea vs. adults treated with 500 mg every 8 hours. For detailed adult dosage recommendations, please see complete prescribing information for amoxicillin and clavulanate potassium tablets.

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

Adults
Adults who have difficulty swallowing may be given the 125 mg/31.25 mg per 5 mL or 250 mg/62.5 mg per 5 mL suspension in place of the 500 mg tablet. The 200 mg/28.5 mg per 5 mL suspension or the 400 mg/57 mg per 5 mL suspension may be used in place of the 875 mg tablet. See dosage recommendations above for children weighing 40 kg or more.
The amoxicillin 250 mg and clavulanate potassium tablet and the 250 mg chewable tablet do not contain the same amount of clavulanic acid (as the potassium salt). The amoxicillin 250 mg and clavulanate potassium tablet contains 125 mg of clavulanic acid, whereas the 250 mg chewable tablet contains 62.5 mg of clavulanic acid. Therefore, the amoxicillin 250 mg and clavulanate potassium tablet and the 250 mg chewable tablet should not be substituted for each other, as they are not interchangeable.
Due to the different amoxicillin to clavulanic acid ratios in the amoxicillin 250 mg and clavulanate potassium tablet (250 mg/125 mg) versus the amoxicillin 250 mg and clavulanate potassium chewable tablet (250 mg/62.5 mg), the amoxicillin 250 mg and clavulanate potassium tablet should not be used until the child weighs at least 40 kg and more.

DIRECTIONS FOR RECONSTITUTION
Prepare a suspension at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

Each teaspoonful (5 mL) will contain 200 mg amoxicillin and 28.5 mg of clavulanic acid as the potassium salt.

Note: SHAKE ORAL SUSPENSION WELL BEFORE USING.

Reconstituted suspension must be stored under refrigeration and discarded after 10 days.

Administration

Reconstituted amoxicillin and clavulanate potassium for oral suspension may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when amoxicillin and clavulanate potassium for oral suspension is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, amoxicillin and clavulanate potassium for oral suspension should be taken at the start of a meal.

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 WARNING AND PRECAUTION

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 & Clavulanate 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 generalised exanthemous pustulosis (AGEP). This reaction requires Amoxicillin & Clavulanate 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 medicinal products 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 Amoxicillin & Clavulanate may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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 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 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 Amoxicillin & Clavulanate, 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
Immune system disorders	
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	Not known
Aeseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis	Not known
Black hairy tongue	Not known
Tooth discolouration	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT	Uncommon
Hepatitis	Not known
Cholestatic jaundice	Not known
Skin and subcutaneous tissue disorders	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Acute generalised exanthemous pustulosis (AGEP)	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

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
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

5.2 Pharmacokinetic properties

Absorption

The two components of Amoxicillin and Potassium Clavulanate suspension 228.5 mg/5 ml and 457 mg/5 ml, amoxicillin and clavulanate,are each fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of Amoxicillin and Potassium Clavulanate 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 (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 animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk.

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier

Biotransformation

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

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single amoxicillin & clavulanic 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 see.

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.

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5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

None

6.1 List of Excipients

Hypromellose

Succinic Acid

Xanthan Gum

Orange Flavour

Neotame

Syloid Al -1FP

Vanilla Flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Two years

6.4 Special precautions for storage

Do not store above 30ºC

6.5 Nature and contents of container

Gorbaclav 228.5 powder for oral suspension is provided as a dry, white to off-white, vamilla flavoured granule. When reconstituted as directed, it provides the Amoxicillin (as trihydrate) USP eq.to Amoxicillin -200 mg and Diluted Potassium Clavulanate BP eq.to Clavulanic acid
28.5 mg

It is supplied in plastic bottles of 100ml.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

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8. MARKETING AUTHORISATION NUMBER

Not Applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Not Applicable

10. DATE OF (PARTIAL) REVISION OF THE TEXT

To be given after approval of the product