# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

AMOKLAVIN-BID 200 mg + 28.5 mg Powder for Oral Suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active Substance:**
Each 5 ml suspension contains:
Amoxicillin (as amoxicillin trihydrate) (produced from bovine, sheep or goat milk) ..... 200 mg
Clavulanic acid (as potassium clavulanate) ..... 28.5 mg

**Excipient(s):**
Each 5 ml suspension contains:
Methylparaben ..... 2.5 mg

For full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for oral suspension.
White to creamy white, homogeneous, aromatic, flavored suspension, when reconstituted.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

AMOKLAVIN-BID is indicated for the short-term treatment of bacterial infections that are suspected to be caused by amoxicillin resistant beta-lactamase producing strains in the following systems. In other situations, amoxicillin alone should be considered.

- Upper respiratory tract infections (including ear, nose and throat): Recurrent tonsillitis, acute bacterial sinusitis, acute otitis media.
- Lower respiratory tract infections: Acute exacerbations of chronic bronchitis, lobar pneumonia and bronchopneumonia, community-acquired pneumonia.
- Urinary system infections: Cystitis, urethritis, pyelonephritis and female genital tract infections, gonorrhea.
- Skin and soft tissue infections: Especially cellulitis, animal bites.
- Dental infections: Severe dental abscess with spreading cellulitis.
- Bone and joint infections: Especially osteomyelitis.

Susceptibility to AMOKLAVIN-BID will vary with geography and time. Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

A list of susceptible organisms is provided in the section “Pharmacodynamic Properties” (see section 5.1).

Mixed infections caused by the combination of amoxicillin-susceptible organisms with β-lactamase producing microorganisms susceptible to AMOKLAVIN-BID, can be treated with AMOKLAVIN-

BID. They don't require the addition of another β-lactamase resistant antibiotic.

## 4.2 Posology and method of administration

**Posology/frequency and duration of administration:**

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 AMOKLAVIN that is selected to treat an individual infection should consider:

- Expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- Severity and the site of the infection
- Age, weight and renal function of the patient as shown below

The use of alternative presentations of AMOKLAVIN (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

For children < 40 kg, this formulation of AMOKLAVIN provides a total daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, when administered as advised below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of AMOKLAVIN is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

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).

Adults and children ≥ 40 kg should be treated with the adult formulations of AMOKLAVIN.

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).

Children may be treated with AMOKLAVIN tablets or suspensions. Children aged 6 years and below should preferably be treated with suspension.

No clinical data are available for AMOKLAVIN 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 AMOKLAVIN 7:1 formulations for patients under 2 months. Dosing recommendations in this population therefore should not be made.

**Frequency and duration of administration:**

Taken twice daily. The duration of treatment should be in accordance with the indication and should not exceed 14 days without treatment review.

**Method of administration:**

For oral use. It should be taken with a meal to minimize the potential for gastrointestinal intolerance.

Preparation of Suspension:

| Final Volume of Suspension | Filling Weight | Water to be added for reconstitution |
|---|---|---|
| 70 ml | 7.7 g | 64 ml |
| 100 ml | 11 g | 91 ml |

To prepare AMOKLAVIN-BID 200 mg + 28.5 mg/5 ml oral suspension, first shake the bottle until all the powder is dispersed and flows freely. Boiled and cooled water should be added gradually until it fills up to 2/3 of the mark on the bottle and the bottle should be shaken vigorously. When first reconstituted, allow to stand for 5 minutes to ensure full dispersion. Then, the remaining amount of water (1/3) should be filled up to the mark on the bottle and the bottle must be shaken again.

The dose recommended by the doctor is given to the patient using a 5 ml measuring spoon that is supplied with the bottle.

Dry powder for reconstitution should be stored at room temperature below 25°C, in a dry place. Reconstituted suspension should be stored in a refrigerator (2-8°C) and used within 7-10 days.

It should not be put into the freezer.

**Additional information on special populations:**

Renal impairment:

No dose adjustment is required in children with creatinine clearance (CrCl) is more than 30 ml/min. The use of AMOKLAVIN-BID is not recommended in children with creatinine clearance (CrCl) less than 30 ml/min because there are no recommendations for dose adjustment.

The use of AMOKLAVIN-BID 200 mg + 28.5 mg/5 ml oral suspension is not recommended in infants with undeveloped renal function.

Hepatic impairment:

Caution is advised in the dose adjustment of patients with hepatic impairment and hepatic functions should be monitored at regular intervals (see sections 4.3 and 4.4). There is insufficient data for dosage recommendations.

Pediatric population:

No clinical data are available regarding doses higher than 45 mg/6.4 mg/kg per day in children under 2 years.

There are no clinical data for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Geriatric population:

No dose adjustment is considered necessary.

## 4.3 Contraindications

Contraindicated in patients with hypersensitivity to the active substances, any of the penicillins or any of the excipients listed in section 6.1.

AMOKLAVIN-BID is contraindicated in patients with a history of hypersensitivity (e.g.

anaphylaxis) to other beta-lactam agents (e.g. cephalosporin, carbapenem or monobactam).

Contraindicated in patients with a history of jaundice/hepatic dysfunction due to AMOKLAVIN-BID (see section 4.8).

**4.4 Special warnings and precautions for use**

Before initiating therapy with AMOKLAVIN-BID, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Other symptoms could comprise abdominal pain, diarrhea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock. If an allergic reaction occurs, AMOKLAVIN 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 AMOKLAVIN 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 (see section 4.8).

AMOKLAVIN should be avoided if infectious mononucleosis is suspected since a morbilliform rash occurrence has been associated with this condition after amoxicillin use.

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.

Occurrence at treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires AMOKLAVIN discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

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 (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin 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 diarrhea 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 hematopoietic 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 (see sections 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

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 AMOKLAVIN-BID 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.

AMOKLAVIN-BID contains methylparaben which may cause allergic reactions (possibly delayed).

## 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 normalized ratio (INR) in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate:
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid:
Concomitant use with probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of probenecid with AMOKLAVIN-BID 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 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 mycophenolic acid 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.

Allopurinol:
Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. No data is available regarding the concomitant use of allopurinol and amoxicillin/clavulanic acid.

Oral contraceptives:
As with other antibiotics, AMOKLAVIN-BID may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

**Additional information on special populations**
Data is not available.

**Pediatric population**
The information given above is applicable for the pediatric population.

## 4.6 Fertility, pregnancy and lactation

**General recommendation**
Pregnancy category: B

**Women of child-bearing potential/Contraception**
As with other antibiotics, AMOKLAVIN-BID may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives. Therefore, an effective, reliable

and alternative method of contraception should be applied during treatment.

**Pregnancy**
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy/ embryonal/fetal development/parturition or postnatal development (see section 5.3).

Caution is advised when prescribing to pregnant women.

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 fetal membrane (pPROM) it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotizing enterocolitis in neonates. It should not be used during pregnancy, unless considered essential by the doctor.

**Breast-feeding**
Both drug substances of AMOKLAVIN-BID are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. The possibility of sensitization should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the doctor in charge.

**Fertility**
Reproduction studies in animals (mice and rats) with orally and parenterally administered amoxicillin/clavulanic acid have shown no teratogenic effects.

## 4.7 Effects on ability to drive and use machines
No studies on the effects of amoxicillin/clavulanic acid on the ability to drive and use machines have been performed. However, undesirable effects (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines may occur (see section 4.8).

## 4.8 Undesirable effects
The most commonly reported adverse drug reactions are diarrhea, nausea and vomiting.

The adverse drug reactions derived from clinical studies and post-marketing surveillance with amoxicillin/clavulanic acid, sorted by MedDRA System Organ Class are listed below.

Following terminologies have been used in order to classify 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 (frequency cannot be estimated from the available data).

| | |
|---|---|
| **Infections and infestations** | |
| *Common* | Mucocutaneous candidiasis |
| *Unknown* | Overgrowth of non-susceptible organisms |
| **Blood and lymphatic system disorders** | |
| *Rare* | Reversible leucopenia (including neutropenia) and thrombocytopenia |

| | |
|---|---|
| *Unknown* | Reversible agranulocytosis, hemolytic anemia, prolongation of bleeding and prothrombin time[1] |
| **Immunity system disorders[8]** | |
| *Unknown* | Angioneurotic edema, anaphylaxis, serum disease-like syndrome, hypersensitivity vasculitis |
| **Nervous system disorders** | |
| *Uncommon* | Headache, dizziness |
| *Unknown* | Reversible hyperactivity and convulsions[1], aseptic meningitis |
| **Cardiac disorders** | |
| *Not known* | Kounis syndrome |
| **Gastrointestinal disorders** | |
| *Common* | Diarrhea, nausea[2], vomiting |
| *Uncommon* | Indigestion |
| *Unknown* | Antibiotic-associated colitis[3]<br>Drug-induced enterocolitis syndrome (DIES)<br>Pancreatitis acute<br>Black hairy tongue (papillae on the tongue become more prominent and turn black)<br>Tooth discoloration[9] |
| **Hepatobiliary disorders** | |
| *Uncommon* | Rises in AST and/or ALT[4] |
| *Unknown* | Hepatitis[5] and cholestatic jaundice[5] |
| **Skin and subcutaneous tissue disorders[6]** | |
| *Uncommon* | Skin rash, itching, urticaria |
| *Rare* | Erythema multiforme |
| *Unknown* | Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalized exanthematous pustulosis (AGEP)[1], Drug reaction with eosinophilia and systemic symptoms (DRESS), linear IgA disease |
| **Renal and urinary disorders** | |
| *Not known* | Interstitial nephritis, crystalluria (including acute renal impairment)[7] |

[1] See section 4.4
[2] 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.
[3] Including pseudomembranous colitis and hemorrhagic colitis (see section 4.4)
[4] 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.
[5] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[6] If any hypersensitivity dermatitis reaction occurs, treatment should be stopped (see section 4.4).
[7] See section 4.9
[8] See sections 4.3 and 4.4
[9] Superficial tooth discoloration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discoloration as it can usually be removed by brushing.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

## 4.9 Overdose

Signs and symptoms of overdose
Gastrointestinal symptoms and disturbance of water and electrolyte balance may be evident. Amoxicillin crystalluria, in some cases causing renal failure, was observed (see section 4.4).

Convulsions may occur in patients with renal dysfunction or in those receiving high doses.

Amoxicillin was reported to precipitate in bladder catheters, mostly after intravenous administration of large doses. Regular patency checks should be maintained (see section 4.4).

Treatment of intoxication
Gastrointestinal symptoms may be treated symptomatically, with attention to the balance for water/electrolyte.

AMOKLAVIN-BID can be removed from the circulation by hemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, including 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 classes 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 (mcg/ml) | |
|---|---|---|
| | Susceptible | Resistant |
| *Haemophilus influenzae* | ≤ 0.001[1] | > 2[1] |
| *Moraxella catarrhalis* | ≤ 1[1] | > 1[1] |
| *Staphylococcus* spp. | See footnotes 2a,3a,3b,4 | See footnotes 2a,3a,3b,4 |
| *Enterococcus* spp.[7] | ≤ 4[1,5] | > 8[1,5] |
| Streptococcus group A, B, C, G[2b,8] (indications other than meningitis) | See footnotes 2b | See footnotes 2b |
| *Streptococcus pneumoniae*[8] | ≤ 0.5[1,6] | > 1[1,6] |
| Enterobacter Infections in Uncomplicated Urinary System | ≤ 32[1] | > 32[1] |
| Gram-negative Anaerobes | ≤ 4[1] | > 8[1] |
| Gram-positive Anaerobes *(*except *Clostridioide difficile)* | ≤ 4[1] | > 8[1] |
| Non-species-related breakpoints | ≤ 2[1] | > 8[1] |
| Viridans group streptococci[8] | See footnotes 2a,9 | See footnotes 2a,9 |
| *Pasteurella multocida* | ≤ 1[1] | > 1[1] |
| *Burkholderia pseudomallei* | ≤ 0.001[1] | > 8[1] |

[1] For the purpose of susceptibility testing, the clavulanic acid concentration has been fixed at 2 mg/l.

[2a] The breakpoint values in the table are based on the benzylpenicillin breakpoints. Susceptibility interpretation is made based on susceptibility to benzylpenicillin.

[2b] In the interpretation of penicillin susceptibility for Streptococcus groups A, B, C, and G (in non-meningitis indications), susceptibility to benzylpenicillin is used as a reference, but phenoxymethylpenicillin and isoxazolylpenicillins are exceptions for group B streptococci.

[3a] Most staphylococci produce penicillinase and some are resistant to methicillin. Both mechanisms make them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci found susceptible to benzylpenicillin and cefoxitin in the test may be reported as susceptible to all penicillins. Staphylococci resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to combinations of beta-lactamase inhibitors, isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For oral agents, care should be taken to ensure adequate exposure at the site of infection. Staphylococci resistant to cefoxitin are resistant to all penicillins.

[3b] Most coagulase-negative staphylococci produce penicillinase, and some are resistant to methicillin. Both mechanisms make them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin, and ticarcillin. Currently, no method reliably detects penicillinase production in coagulase-negative staphylococci, but resistance to methicillin can be detected with cefoxitin, as mentioned above.

[4] Ampicillin-susceptible *S. saprophyticus* is *mec*A-negative and is susceptible to ampicillin, amoxicillin, and piperacillin (with or without a beta-lactamase inhibitor).

[5] Susceptibility to ampicillin, amoxicillin, and piperacillin (with or without a beta-lactamase inhibitor) can be interpreted based on ampicillin. Resistance to ampicillin is uncommon in *E. faecalis* (verify with MIC), but it is common in *E. faecium*.

[6] An oxacillin 1 µg disk screening test or benzylpenicillin MIC test should be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥20 mm or benzylpenicillin MIC ≤0.06 mg/L), all beta-lactam agents with clinical breakpoints available can be reported as susceptible without further testing.

[7] Aminopenicillin breakpoints for enterococci are based on intravenous administration. Oral administration is valid only for urinary tract infections.

[8] Addition of a beta-lactamase inhibitor provides no additional clinical benefit.

[9] Benzylpenicillin (MIC or disk diffusion) can be used to screen for beta-lactam resistance in viridans group streptococci. Isolates classified as negative in the screening can be reported as susceptible to all beta-lactam agents listed with clinical breakpoints. Isolates classified as positive in the screening should be tested for susceptibility to each agent. For isolates that are negative in the benzylpenicillin screening (MIC ≤0.25 mg/L), susceptibility interpretation can be made based on benzylpenicillin or ampicillin. For isolates that are positive in the benzylpenicillin screening (MIC >0.25 mg/L), susceptibility interpretation should be based on ampicillin.

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%.

## 5.2 Pharmacokinetic properties

**General properties**

Absorption:

Both components of AMOKLAVIN-BID, 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 of a study conducted in a group of healthy volunteers given 875 mg/125 mg amoxicillin/clavulanic acid tablets twice daily in the fasting state are given below:

| **Mean (±SD) Pharmacokinetic Parameters** | | | | | |
|---|---|---|---|---|---|
| Active substance(s) administered | Dose (mg) | $C_{max}$ (mcg/ml) | $T_{max}$* (h) | AUC (0-24h) (mcg.h/ml) | $T_{1/2}$ (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 (1-2) | 10.16 ±3.04 | 0.96 ±0.12 |
| AMX: Amoxicillin, CA: Clavulanic acid<br>* Median | | | | | |

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 (see section 4.6).

Both amoxicillin and clavulanic acid were shown to cross 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 feces 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 around one hour and a mean total clearance of around 25 l/h in healthy subjects. About 60 to 70% of the amoxicillin and about 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single amoxicillin/clavulanic acid 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

**Characteristics in patients**
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 sustaining adequate clavulanic acid levels (see section 4.2).

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

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.

Linearity/Non-linearity:
Amoxicillin has linear pharmacokinetics over therapeutic dose range.

## 5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity, and reproductive toxicity.

Repeat dose toxicity studies with amoxicillin/clavulanic acid in dogs showed gastric irritation, vomiting, and tongue discoloration.

No carcinogenicity studies have been conducted with AMOKLAVIN-BID or its components.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Silicon dioxide
Xantan gum
Hydroxypropylmethylcellulose
Colloidal silicon dioxide
Sodium saccharin
Methylparaben
Succinic acid
Golden syrup flavor
Powder orange flavor

### 6.2 Incompatibilities

There is no known incompatibility.

### 6.3 Shelf life

48 months

### 6.4 Special precautions for storage

Dry powder for reconstitution should be stored at room temperature below 25°C, in a dry place. Reconstituted suspension should be stored in a refrigerator (2-8°C). The 70 ml presentation of AMOKLAVIN-BID suspension should be used in 7 days, the 100 ml presentation of AMOKLAVIN-BID suspension should be used in 10 days.

Protect from moisture. Bottle should be closed tightly right after administration. Should not be put into freezer.

### 6.5 Nature and contents of container

The dry powder, which yields 70 ml or 100 ml of suspension when diluted, is available in a honey-colored glass bottle with a 28/16 mm PE/PP child-resistant plastic cap. The presentations are supplied with a 5 ml measuring spoon.

### 6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

Preparation of AMOKLAVIN-BID suspension:

1. To prepare AMOKLAVIN-BID 200 mg + 28.5 mg Powder for Oral Suspension, first shake the bottle until all the powder is dispersed and flows freely.
2. Add water gradually until it fills up to 2/3 of the mark on the bottle and shake vigorously (Boiled and cooled water should be preferred for preparing a suspension).

3. Allow to stand for 5 minutes to ensure full dispersion.

4. Add water up to the mark on the bottle (remaining 1/3) and shake well again (Boiled and cooled water should be preferred for preparing a suspension).
5. The dose recommended by your doctor is given to the patient using a 5 ml measuring spoon that is supplied with the bottle.

## 7. MARKETING AUTHORIZATION HOLDER

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## 8. MARKETING AUTHORIZATION NUMBER(S)

184/69

## 9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization : 06.10.1997
Date of latest renewal : 03.01.2013

## 10. DATE OF REVISION OF THE TEXT