PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**Amoxicillin Sodium and Potassium Clavulanate for Injection**

Co-Amoxiclav for injection

Powder for Solution

500 mg amoxicillin (as amoxicillin sodium) and 100 mg clavulanic acid (as clavulanate potassium) per vial

1000 mg amoxicillin (as amoxicillin sodium) and 200 mg clavulanic acid (as clavulanate potassium) per vial

2000 mg amoxicillin (as amoxicillin sodium) and 200 mg clavulanic acid (as clavulanate potassium) per vial

Injection

House Standard

Antibiotic & β-Lactamase inhibitor

Sandoz Canada Inc.
110 rue de Lauzon
Boucherville, Quebec, Canada
J4B 1E6

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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.3 Reconstitution	01/2023
7 Warnings and Precautions, Immune	01/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Amoxicillin Sodium and Potassium Clavulanate for Injection (Co-Amoxiclav for injection) is indicated for the treatment of the following infections in adult and pediatric patients:

- Severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottitis, and sinusitis when accompanied by severe systemic signs and symptoms)
- 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
- Intra-abdominal infections
- Female genital infections.

Prophylaxis against infections associated with major surgical procedures in adults, such as those involving the:

- Gastrointestinal tract
- Pelvic cavity
- Head and neck
- Biliary tract surgery.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Amoxicillin Sodium and Potassium Clavulanate for Injection and other antibacterial drugs, Amoxicillin Sodium and Potassium Clavulanate for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology data, susceptibility patterns, and local official antibiotic prescribing guidelines, may contribute to the empiric selection of therapy (see 7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance and 10 CLINICAL PHARMACOLOGY).

1.1 Pediatrics

Pediatrics (< 18 years of age): See 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment.

Safety and efficacy of Amoxicillin Sodium and Potassium Clavulanate for Injection in pediatric patients with renal impairment have not been evaluated in clinical trials.

Pediatrics (3 months – 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Amoxicillin Sodium and Potassium Clavulanate for Injection in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): No dose adjustment is considered necessary, unless there is evidence of renal impairment (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Renal and 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

Amoxicillin Sodium and Potassium Clavulanate for Injection is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- patients with a history of hypersensitivity to beta-lactams, e.g., penicillins, carbapenems, monobactams, or cephalosporins.
- patients where infectious mononucleosis is either suspected or confirmed.
- patients with a previous history of amoxicillin/clavulanic acid associated jaundice/hepatic dysfunction.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving beta-lactam antibacterials, including Amoxicillin Sodium and Potassium Clavulanate for Injection.

- Before therapy with Amoxicillin Sodium and Potassium Clavulanate for Injection is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactam allergy, caution should be exercised, because cross sensitivity has been established.
- If an anaphylactic reaction to Amoxicillin Sodium and Potassium Clavulanate for Injection occurs, the drug should be discontinued and appropriate therapy instituted.

See 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The daily dose of Amoxicillin Sodium and Potassium Clavulanate for Injection is determined based on the indication, severity and site of the infection, susceptibility of the pathogen(s) to Amoxicillin Sodium and Potassium Clavulanate for Injection and renal function. In pediatric patients, it is also determined by age and body weight.

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content:

Amoxicillin Sodium and Potassium Clavulanate for Injection 500 mg/100 mg:

Amoxicillin Sodium and Potassium Clavulanate for injection (Co-Amoxiclav for injection) 500 mg/100 mg powder for solution consists of vials of sterile white to off-white powder providing amoxicillin sodium equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 100 mg clavulanic acid. Each vial contains 1.4 mmoL (31.4 mg) of sodium and 0.5 mmoL (19.6 mg) of potassium.

Amoxicillin Sodium and Potassium Clavulanate for Injection 1000 mg/200 mg:

Amoxicillin Sodium and Potassium Clavulanate for injection (Co-Amoxiclav for injection) 1000 mg/200 mg powder for solution consists of vials of sterile white to off-white powder providing amoxicillin sodium equivalent to 1 g amoxicillin and potassium clavulanate equivalent to 200 mg clavulanic acid. Each vial contains 2.7 mmoL (62.9 mg) of sodium and 1.0 mmoL (39.3 mg) of potassium.

Amoxicillin Sodium and Potassium Clavulanate for Injection 2000 mg/200 mg:

Amoxicillin Sodium and Potassium Clavulanate for injection (Co-Amoxiclav for injection) 2000 mg/200 mg powder for solution consists of vials of sterile white to off-white powder providing amoxicillin sodium equivalent to 2 g amoxicillin and potassium clavulanate equivalent to 200 mg clavulanic acid. Each vial contains 5.5 mmoL (125.9 mg) of sodium and 1.0 mmoL (39.3 mg) of potassium.

The dose that is selected to treat individual infections 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.

5:1 ratio (500 mg/100 mg and 1000 mg/200 mg)

Amoxicillin Sodium and Potassium Clavulanate powder for Injection (Co-Amoxiclav for injection) provides a total daily dose of 3000 mg amoxicillin and 600 mg clavulanic acid when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that an alternative intravenous formulation of Amoxicillin Sodium and Potassium Clavulanate for Injection is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

10:1 ratio (2000 mg/200 mg)

Amoxicillin Sodium and Potassium Clavulanate powder for Injection (Co-Amoxiclav for injection) provides a total daily dose of 6000 mg amoxicillin and 600 mg clavulanic acid when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, this must not be achieved by increasing the Amoxicillin Sodium and Potassium Clavulanate dose. This is in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

The duration of therapy should be determined by the response of the patient. Some infections (e.g., osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review.

Consideration should be given to local therapeutic guidelines on appropriate dosing frequencies for amoxicillin/clavulanic acid.

4.2 Recommended Dose and Dosage Adjustment

Treatment of infections

Adults and Pediatrics ≥ 40 kg

5:1 ratio (500 mg/100 mg and 1000 mg/200 mg): 1000 mg/200 mg every 8 hours.

10:1 ratio (2000 mg/200 mg): Usually 2000 mg/200 mg every 12 hours.

For very severe infections the dose may be increased to a maximum of 2000/200 mg every 8 hours.

Pediatrics < 40 kg

Aged ≥ 3 months
5:1 ratio (500 mg/100 mg and 1000 mg/200 mg): 25 mg/5 mg/kg every 8 hours.

10:1 ratio (2000 mg/200 mg): 50 mg/5 mg/kg every 8 hours.

Aged < 3 months or weighing < 4 kg
5:1 ratio (500 mg/100 mg and 1000 mg/200 mg): 25 mg/5 mg/kg every 12 hours.

10:1 ratio (2000 mg/200 mg): 50 mg/5 mg/kg every 12 hours.

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.

Geriatrics (> 65 years of age)

No adjustment needed, dose as for adults. If there is evidence of renal impairment, dose should be adjusted as for renally impaired adults (see 4.2 Recommended Dose and Dosage Adjustment, Renal impairment).

Surgical prophylaxis

Adults

For procedures less than 1 hour in duration, the recommended dose is 1000 mg/200 mg to 2000 mg/200 mg given at induction of anaesthesia.

For procedures greater than 1 hour in duration, the recommended dose is 1000 mg/200 mg to 2000 mg/200 mg given at induction of anaesthesia, with up to 3 doses of 1000 mg/200 mg in 24 hours.

Clear clinical signs of infection at operation will require a normal course of intravenous (IV) or oral therapy post-operatively.

Dosage adjustment in:

Renal impairment
Dosing adjustments are based on the maximum recommended level of amoxicillin.

Each 500 mg/100 mg vial contains 1.4 mmoL (31.4 mg) of sodium and 0.5 mmoL (19.6 mg) of potassium.

Each 1000 mg/200 mg vial contains 2.7 mmoL (62.9 mg) of sodium and 1.0 mmoL (39.3 mg) of potassium.

Each 2000 mg/200 mg vial contains 5.5 mmoL (125.9 mg) of sodium and 1.0 mmoL (39.3 mg) of potassium.

Adults and Pediatrics ≥ 40 kg

Creatinine Clearance	Dosage
>30 mL/min (mild impairment)	No change in dosage
10-30 mL/min (moderate impairment)	Initial dose of 1000 mg/200 mg followed by 500 mg/100 mg every 12 hours
<10 mL/min (severe impairment)	Initial dose of 1000 mg/200 mg followed by 500 mg/100 mg every 24 hours
Haemodialysis	Initial dose of 1000 mg/200 mg followed by 500 mg/100 mg 24 hourly, plus a dose of 500 mg/100 mg at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Pediatrics < 40 kg

Creatinine Clearance	Dosage
>30 mL/min (mild impairment)	No change in dosage
10-30 mL/min (moderate impairment)	25 mg/5 mg/kg every 12 hours
<10 mL/min (severe impairment)	25 mg/5 mg/kg every 24 hours
Haemodialysis	25 mg/5 mg/kg every 24 hours, plus a dose of 12.5/2.5 mg/kg at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

10:1 ratio (2000 mg/200 mg)
In patients with creatinine clearance less than 30 mL/min, the use of Amoxicillin Sodium and Potassium Clavulanate for Injection 10:1 is not recommended, as no dose adjustments are available. In such patients, Amoxicillin Sodium and Potassium Clavulanate for Injection formulations with an amoxicillin to clavulanic acid ratio of 5:1 are recommended.

Amoxicillin Sodium and Potassium Clavulanate for Injection should only be used in patients with creatinine clearance less than 30 mL/min for surgical prophylaxis when it should be used in one infusion.

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals for both adult and pediatric patients. See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.

There are as yet insufficient data on which to base a dosage recommendation.

4.3 Reconstitution

Reconstituted Amoxicillin Sodium and Potassium Clavulanate for Injection solutions are stable when stored at room temperature with the diluent sterile water for injection (WFI). The reconstituted solution should

be diluted within 15 minutes, or administered immediately (500 mg/100 mg and 1000 mg/200 mg strengths only) as per provided stability information in Table 1 below.

Table 1 – Reconstitution of powder and stability of reconstituted solutions

Strength	Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Stability of the reconstituted solution in WFI
500 mg/100 mg	20 mL	10 mL	10.25 mL	15 minutes
1000 mg/200 mg	20 mL	20 mL	20.50 mL	
2000 mg/200 mg	20 mL	20 mL	21.50 mL	

Preparation of infusion

Chemical and physical in-use stability has been demonstrated for 60 minutes at 25°C, or 4 hours at 5°C. From a microbiological point of view, the reconstituted and diluted solution (1 reconstituted vial in a minimum volume of 50 mL of infusion fluid) should be used immediately.

For storage and stability of the infusion solutions, please refer to Table 2 below.

Using aseptic technique, add without delay the 500 mg/100 mg reconstituted solution to 50 mL infusion fluid or the 1000 mg/200 mg and 2000 mg/200 mg reconstituted solutions to 100 mL infusion fluids (e.g., using a mini-bag or PVC perfusion bag).

Satisfactory antibiotic concentrations are retained at 5°C and at room temperature (25°C) in the recommended volumes of the following infusion fluids. If reconstituted and maintained at room temperature, infusions should be completed within the time stated in Table 2 below.

For storage at 5°C, the reconstituted solution should be added to pre-refrigerated infusion bags which may be stored up to the time recommended in Table 2. Thereafter, the infusion should be administered immediately after reaching room temperature.

Table 2 – Stability of the infusion

Intravenous Infusion	Stability at Room Temperature 20 - 25°C	Stability for Refrigeration 5 ± 3°C
Sterile Water for Injections	60 minutes	4 hours
Sodium Chloride Intravenous Infusion (0.9% w/v)	60 minutes	4 hours
Compound Sodium Chloride Injection (Ringer's Solution)	60 minutes	
Compound Sodium Lactate Intravenous Infusion (Hartmann's solution; Ringer-Lactate solution)	60 minutes	
Potassium Chloride and Sodium Chloride Intravenous Infusion	60 minutes	

Amoxicillin Sodium and Potassium Clavulanate for Injection vials are not suitable for multi-dose use. Product is for single use in one patient only. Discard any residue.

After dissolution in water for injection, a transient pink colour may occur; the solution will become clear again rapidly afterwards.

The solution is to be inspected visually for particulate matter prior to administration. The solution should only be used if the solution is clear and free from particles.

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

4.4 Administration

Amoxicillin Sodium and Potassium Clavulanate for Injection is for administration by intravenous route after reconstitution.

Amoxicillin Sodium and Potassium Clavulanate for Injection is not suitable for intramuscular administration.

5:1 ratio (500/100 mg and 1000/200 mg)
Amoxicillin Sodium and Potassium Clavulanate for Injection may be administered either by slow intravenous injection over a period of 3 to 4 minutes directly into a vein or via a drip tube or by infusion over 30 to 40 minutes.

10:1 ratio (2000/200 mg)
Amoxicillin Sodium and Potassium Clavulanate for Injection should be administered by intravenous infusion over 30 to 40 minutes.

Pediatric patients aged less than 3 months should be administered Amoxicillin Sodium and Potassium Clavulanate for Injection by infusion only.

Treatment with Amoxicillin Sodium and Potassium Clavulanate for Injection may be initiated by the use of an intravenous preparation and completed with an appropriate oral presentation as considered appropriate for the individual patient.

4.5 Missed Dose

If a dose is missed, it should be taken as soon as remembered, unless it is almost time for the next dose (less than 4 hours). The dose should not be doubled to make up for a missed dose.

5 OVERDOSAGE

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. They may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see 7 WARNINGS AND PRECAUTIONS, Genitourinary and 8 ADVERSE REACTIONS).

Amoxicillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained (see 7 WARNINGS AND PRECAUTIONS, Genitourinary).

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

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

A prospective study of 51 pediatric patients at a poison control centre suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Drug abuse and dependence: Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Powder for solution ▪ 500 mg amoxicillin (as amoxicillin sodium)/100 mg clavulanic acid (as clavulanate potassium) per vial ▪ 1000 mg amoxicillin (as amoxicillin sodium)/200 mg clavulanic acid (as clavulanate potassium) per vial ▪ 2000 mg amoxicillin (as amoxicillin sodium)/200 mg clavulanic acid (as clavulanate potassium) per vial	None

Amoxicillin Sodium and Potassium Clavulanate for Injection is a white to off-white powder for solution. Once reconstituted it becomes a clear solution.

Container composition:
The powder is packed in clear 20 mL (Type II) glass vials with Bromobutyl latex-free rubber stoppers and polypropylene-aluminum bordered caps. The stopper contains no dry natural rubber.

Amoxicillin Sodium and Potassium Clavulanate for Injection is available in packs of 1 or 10 vials of powder for solution.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Avoid Amoxicillin Sodium and Potassium Clavulanate for Injection if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin (see 2 CONTRAINDICATIONS).

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.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions (see 9.4 Drug-Drug Interactions, Allopurinol).

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with beta-lactam treatment. When SCAR is suspected, Amoxicillin Sodium and Potassium Clavulanate for Injection should be discontinued and appropriate therapy and/or measures should be taken (see 8 ADVERSE REACTIONS).

Sodium and Potassium content
The 500 mg/100 mg powder for solution contains 31.4 mg (1.4 mmoL) of sodium per vial. This should be taken into consideration by patients on a controlled sodium diet. It also contains 19.6 mg (0.5 mmoL) of potassium per vial. This should be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

The 1000 mg/200 mg powder for solution contains 62.9 mg (2.7 mmoL) of sodium per vial. This should be taken into consideration by patients on a controlled sodium diet. It also contains 39.3 mg (1.0 mmoL) of potassium per vial. This should be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

The 2000 mg/200 mg powder for solution contains 125.9 mg (5.5 mmoL) of sodium per vial. This should be taken into consideration by patients on a controlled sodium diet. It also contains 39.3 mg (1.0 mmoL) of potassium per vial. This should be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

5:1 ratio (500 mg/100 mg and 1000 mg/200 mg)
This presentation of amoxicillin/clavulanic acid may not be 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. As no specific data for T>MIC are available and the data for comparable oral presentations are borderline, this presentation (without additional amoxicillin) may not be suitable for the treatment of penicillin-resistant *S. pneumoniae*.

10:1 ratio (2000 mg/200 mg)
This presentation of amoxicillin/clavulanic acid may not be 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. At recommended doses of up to 1000 mg/100 mg every 8 hours,

this presentation may not be suitable for treatment of penicillin-resistant *S. pneumoniae*. For coverage of this pathogen, a dose of at least 2000 mg/200 mg every 12 hours is required.

Cardiovascular

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving amoxicillin-clavulanate and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation. See 8 ADVERSE REACTIONS and 9.4 Drug-Drug Interactions, Oral anticoagulants.

Kounis syndrome (see 7 WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions and 8 ADVERSE REACTIONS).

Driving and Operating Machinery

Amoxicillin Sodium and Potassium Clavulanate for Injection can have side effects and the symptoms may make you unfit to drive. Don't drive or operate machinery unless you are feeling well.

Gastrointestinal

***Clostridium difficile*-associated disease**

Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including Amoxicillin Sodium and Potassium Clavulanate for Injection. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see 8 ADVERSE REACTIONS).

Genitourinary

In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During 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 5 OVERDOSAGE.

Hepatic/Biliary/Pancreatic

Hepatitis and cholestatic jaundice have been reported with penicillins and cephalosporins. 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 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS).

Amoxicillin Sodium and Potassium Clavulanate for Injection should be used with caution in patients with evidence of hepatic dysfunction.

Immune

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving beta-lactam antibacterials, including the combination of amoxicillin sodium and potassium clavulanate for injection. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Serious anaphylactic/anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management, including intubation should also be used as indicated (see 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS, and 8 ADVERSE REACTIONS).

Kounis syndrome is a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to amoxicillin-clavulanate (see 8 ADVERSE REACTIONS).

Monitoring and Laboratory Tests

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

As administration of amoxicillin will result in high amoxicillin concentrations in the urine, false positive reactions may be elicited when testing the urine for glucose with Clinitest, Benedict's solution or Fehling's solution. Tests based on enzymatic glucose oxidase reactions such as Testape or Clinistix should be used instead.

The presence of clavulanic acid in Amoxicillin Sodium and Potassium Clavulanate for Injection may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Neurologic

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see 8 ADVERSE REACTIONS).

Renal

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see 4.2 Recommended Dose and Dosage Adjustment, Renal impairment).

Amoxicillin Sodium and Potassium Clavulanate for Injection is primarily excreted via the kidneys.

The total serum clearance of Amoxicillin Sodium and Potassium Clavulanate for Injection 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.

Reproductive Health: Female and Male Potential

Fertility
Amoxicillin Sodium and Potassium Clavulanate for Injection at oral doses of up to 1200 mg/kg/day had no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin and clavulanate.

Sensitivity/Resistance

Development of Drug Resistant Bacteria
Prescribing Amoxicillin Sodium and Potassium Clavulanate for Injection in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Skin

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see 8 ADVERSE REACTIONS). This reaction requires amoxicillin/clavulanic acid discontinuation and contraindicates any subsequent administration of amoxicillin. See 7 WARNINGS AND PRECAUTIONS, General.

7.1 Special Populations

7.1.1 Pregnant Women

No clinical studies of Amoxicillin Sodium and Potassium Clavulanate for Injection use in pregnant women are available. Both amoxicillin and clavulanic acid have been shown to cross the placental barrier. Amoxicillin Sodium and Potassium Clavulanate for Injection should therefore not be prescribed to pregnant women unless the benefit to the mother outweighs the risk to the fetus.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see 16 NON-CLINICAL TOXICOLOGY). 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.

7.1.2 Breast-feeding

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

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Amoxicillin Sodium and Potassium Clavulanate for Injection and any potential adverse effects on the breast-fed child from Amoxicillin Sodium and Potassium Clavulanate for Injection or from the underlying maternal condition.

7.1.3 Pediatrics

No data available.

7.1.4 Geriatrics

Because geriatric 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 (see 4.2 Recommended Dose and Dosage Adjustment, Renal impairment).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

8.5 Post-Market Adverse Reactions

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

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Table 4 - ADRs derived from clinical studies and post-marketing surveillance

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
Kounis syndrome	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Convulsions[2]	Not known
Aseptic meningitis	Not known
Vascular disorders	
Thrombophlebitis[3]	Rare
Gastrointestinal disorders	
Diarrhea	Common
Nausea	Uncommon
Vomiting	Uncommon
Indigestion	Uncommon
Antibiotic-associated colitis[4]	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)[9]	Not known
Toxic epidermal necrolysis (TEN)[9]	Not known
Bullous exfoliative-dermatitis	Not known

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

1 See 7 WARNINGS AND PRECAUTIONS.
2 See 7 WARNINGS AND PRECAUTIONS.
3 At the site of injection.
4 Including pseudomembranous colitis and haemorrhagic colitis (see 7 WARNINGS AND PRECAUTIONS).
5 A moderate rise in aspartate aminotransferase (AST) and/or alanine aminotransferase (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 7 WARNINGS AND PRECAUTIONS).
7 If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see 7 WARNINGS AND PRECAUTIONS).
8 See 5 OVERDOSAGE.
9 See 7 WARNINGS AND PRECAUTIONS.
10 See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS.

9 DRUG INTERACTIONS

9.3 Drug-Behavioral Interactions

Alcohol
No information is available about the concurrent use of intravenous amoxicillin-clavulanic acid and alcohol. However, the ingestion of alcohol whilst being treated with the beta-lactam antibiotics has precipitated a disulfiram (Antabuse) like reaction in some patients. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with Amoxicillin Sodium and Potassium Clavulanate for Injection.

9.4 Drug-Drug Interactions

Allopurinol
Concurrent administration of allopurinol and amoxicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving amoxicillin alone. It is not known whether this potentiation of amoxicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with Amoxicillin Sodium and Potassium Clavulanate for Injection and allopurinol administered concurrently (see 7 WARNINGS AND PRECAUTIONS, General).

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.

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

Oral contraceptives
In common with other antibiotics, amoxicillin/clavulanic acid may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are rare 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 (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 8 ADVERSE REACTIONS).

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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

As administration of amoxicillin will result in high amoxicillin concentrations in the urine, false positive reactions may be elicited when testing the urine for glucose with Clinitest, Benedict's solution or Fehling's solution. Tests based on enzymatic glucose oxidase reactions such as Testape or Clinistix should be used instead.

The presence of clavulanic acid in Amoxicillin Sodium and Potassium Clavulanate for Injection may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often

referred to as penicillin-binding proteins, PBP's) 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. Beta-lactamase related resistance can be constitutive or acquired (plasmid mediated beta-lactamases).

Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of beta-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferable drug resistance. It is generally less effective against chromosomally-mediated type 1 beta-lactamases, such as found in *Enterobacter*, *Serratia* and *Citrobacter* species.

The presence of clavulanic acid in Amoxicillin Sodium and Potassium Clavulanate for Injection formulations protects amoxicillin from degradation by beta-lactamase enzymes and effectively extends the antibacterial spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other penicillins and cephalosporins.

For information related to microbiology, see 15 MICROBIOLOGY.

10.2 Pharmacodynamics

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

10.3 Pharmacokinetics

Table 5 - Summary of Amoxicillin/Clavulanic Acid Pharmacokinetic Parameters in Healthy Volunteers

Mean (±SD) pharmacokinetic parameters					
Dose administered	**Amoxicillin**				
	Dose	Mean peak serum conc (µg/mL)	T 1/2 (h)	AUC (h.mg/L)	Urinary recovery (%, 0 to 6 h)
AMX/CA 500 mg/100 mg*	500 mg	32.2	1.07	25.5	66.5
AMX/CA 1000 mg/200 mg*	1000 mg	105.4	0.9	76.3	77.4
AMX/CA 2000 mg/200 mg#	2000 mg	108	-	119	74.7
	Clavulanic acid				
AMX/CA 500 mg/100 mg*	100 mg	10.5	1.12	9.2	46.0
AMX/CA 1000 mg/200 mg*	200 mg	28.5	0.9	27.9	63.8

Mean (±SD) pharmacokinetic parameters					
Dose administered	**Amoxicillin**				
	Dose	Mean peak serum conc (µg/mL)	T 1/2 (h)	AUC (h.mg/L)	Urinary recovery (%, 0 to 6 h)
AMX/CA 2000 mg/200 mg#	200 mg	13.9	-	18.2	51.4
AMX – amoxicillin, CA – clavulanic acid.					

* Given as bolus intravenous injection.

Given as intravenous infusion over 30 minutes.

Absorption

The pharmacokinetic results for studies in which amoxicillin/clavulanic acid was administered to groups of healthy volunteers as either 500 mg/100 mg, 1000 mg/200 mg or 2000/200 mg are presented below.

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 gallbladder, 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.

Metabolism

Amoxicillin is partly excreted in the kidneys 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 humans, 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 hours after administration of a single 500/100 mg or a single 1000/200 mg bolus intravenous injection. 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 9.4 Drug-Drug Interactions, Probenecid).

Special Populations and Conditions

- **Pediatrics:**
  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.

- **Geriatrics:**
  Because geriatric 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.

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

- **Renal Insufficiency:**
  The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function.

11 STORAGE, STABILITY AND DISPOSAL

Store Amoxicillin Sodium and Potassium Clavulanate for Injection powder at room temperature (15°C to 30°C).

Once reconstituted in water for injection, the stability of the reconstituted solution is 15 minutes at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

The reconstitution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter prior to administration. The solution should only be used if the solution is clear and free from particles. Any unused solution should be discarded.

For single use only. Any unused product or waste material should be disposed as biohazardous waste.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

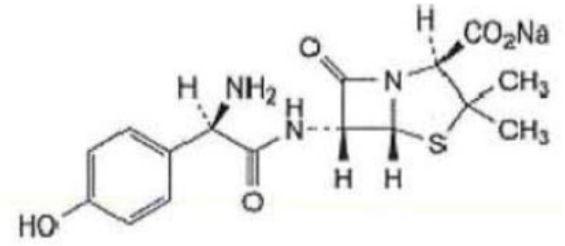
Drug Substance 1

Proper name: Amoxicillin

Chemical name: Amoxicillin sodium

Molecular formula and molecular mass: $C_{16}H_{18}N_3NaO_5S$, MW: 387.4 g/mol

Structural formula:



Physicochemical properties: Amoxicillin sodium is a white or almost white, crystalline powder, very hygroscopic, very soluble in water. A 1% solution in water has a pH of 8.0 to 10.0.

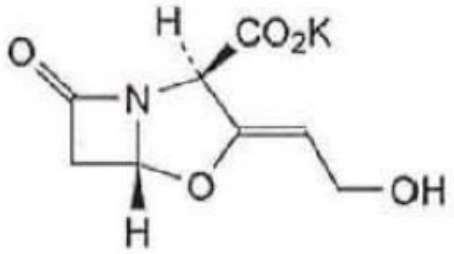
Drug Substance 2

Proper name: Potassium clavulanate

Chemical name: Potassium clavulanate

Molecular formula and molecular mass: $C_8H_8KNO_5$, MW: 237.3 g/mol

Structural formula:



Physicochemical properties: Potassium clavulanate is a white or almost white, crystalline powder. A 1% solution in water has a pH of 5.5 to 8.0.

14 CLINICAL TRIALS

Clinical trial information is not available.

15 MICROBIOLOGY

In the list below, organisms are categorised according to their *in vitro* susceptibility to amoxicillin-clavulanate based mainly on studies published during 2001-2011.

Where clinical efficacy of amoxicillin-clavulanate has been demonstrated in clinical trials this is indicated with an asterisk (*). Organisms that do not produce beta-lactamase are identified (with †). If an isolate is susceptible to amoxicillin, it can be considered susceptible to amoxicillin-clavulanate.
Commonly susceptible species
Gram-positive aerobes: *Enterococcus faecalis* *Streptococcus bovis* *Streptococcus pyogenes* † *Streptococcus agalactiae* † *Streptococcus spp. (*other β-hemolytic*)* † *Staphylococcus aureus* (methicillin susceptible)* *Staphylococcus saprophyticus* (methicillin susceptible) *Coagulase negative staphylococcus* (methicillin susceptible)
Gram-negative aerobes: *Haemophilus influenzae** *Haemophilus parainfluenzae* *Moraxella catarrhalis** *Pasteurella multocida* *Proteus mirabilis*
Gram-positive anaerobes: *Clostridium spp.* *Peptostreptococcus spp.*
Gram-negative anaerobes: *Eikenella corrodens* *Fusobacterium spp.* *Porphyromonas spp.* *Prevotella spp.*
Species for which acquired resistance may be a problem

Gram-positive aerobes: *Streptococcus pneumoniae* † *Viridans group streptococcus*
Gram-negative aerobes: *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Klebsiella spp.* *Proteus vulgaris* *Salmonella spp.* *Shigella spp.*
Gram-negative anaerobes: *Bacteroides fragilis* *Bacteroides spp.* *Bacteroides thetiotamicron*
Inherently resistant organisms
Gram-positive aerobes: *Enterococcus faecium*
Gram-negative aerobes: *Acinetobacter spp.* *Aeromonas spp.* *Citrobacter spp.* *Enterobacter spp.* *Hafnia alvei* *Morganella morganii* *Providencia rettgeri* *Providencia stuartii* *Pseudomonas spp.* *Serratia marcescens*

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.

Susceptibility testing

Interpretive Criteria for Dilution and Disk Diffusion Testing

Minimum inhibitory concentration (MIC) and disk diffusion results should be interpreted according to Table 6 and are based on Clinical and Laboratory Standards Institute (CLSI) methodologies (CLSI M7-A910 and M2-A1011). The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The disk procedure uses paper disks impregnated with 30 mcg amoxicillin/clavulanate potassium (20 mcg amoxicillin plus 10 mcg clavulanate potassium).

A report of S ("Susceptible") indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of I ("Intermediate") indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible antimicrobials, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high doses of antimicrobial can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of R ("Resistant") indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Table 6 - Susceptibility Test Result Interpretive Criteria for Amoxicillin/Clavulanate Potassium

Pathogen	**Minimum Inhibitory Concentration (mcg/mL)**			**Disk Diffusion (Zone Diameter in mm)**		
	S	**I**	**R**	**S**	**I**	**R**
Haemophilus influenzae (Note 1)	≤ 4/2	Not applicable (NA)	≥ 8/4	≥ 20	NA	≤ 19
Enterobacteriaceae	≤ 8/4	16/8	≥ 32/16	≥ 18	14 to 17	≤ 13
Staphylococcus aureus (Note 2)	≤ 4/2	NA	≥ 8/4	≥ 20	NA	≤ 19
Streptococcus pneumoniae (nonmeningitis isolates)	≤ 2/1	4/2	≥ 8/4	(Note 3)		

Note 1: β-lactamase–negative, ampicillin-resistant *H. influenzae* isolates must be considered resistant to amoxicillin/clavulanate potassium.

Note 2: *Staphylococci* which are susceptible to amoxicillin/clavulanate potassium but resistant to methicillin or oxacillin must be considered as resistant.

Note 3: Susceptibility of *S. pneumoniae* should be determined using a 1-mcg oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible to amoxicillin/clavulanate potassium. An amoxicillin/clavulanate potassium MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤ 19 mm.

Quality Control Reference Ranges

Standardized susceptibility test procedures require the use of quality control microorganisms to determine the performance of the test procedures. The expected quality control results based on CLSI MIC and disk diffusion methods are shown in Table 7 (CLSI M100-S21).

Table 7 - Acceptable Quality Control Ranges for Amoxicillin/Clavulanate Potassium

Quality Control Organism	Minimum Inhibitory Concentration Range (mcg/mL)	Disk Diffusion (Zone Diameter Range in mm)
Escherichia coli ATCC® 35218 [*H. influenzae* quality control (Note 1)]	4/2 to 16/8	17 to 22
Escherichia coli ATCC 25922	2/1 to 8/4	18 to 24
Haemophilus influenzae ATCC 49247	2/1 to 16/8	15 to 23
Staphylococcus aureus ATCC 29213	0.12/0.06 to 0.5/0.25	Not applicable (NA)
Staphylococcus aureus ATCC 25923	NA	28 to 36
Streptococcus pneumoniae ATCC 49619	0.03/0.015 to 0.12/0.06	NA

® ATCC is a trademark of the American Type Culture Collection.

Note 1: When using *Haemophilus* Test Medium (HTM).

16 NON-CLINICAL TOXICOLOGY

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

General Toxicology:

Acute Toxicity

The acute toxicity of amoxicillin trihydrate and potassium clavulanate, formulated in a 2:1 and 4:1 ratio, was determined in mice and rats dosed orally and intravenously. LD_{50}'s are shown in Table 8.

Table 8 – Acute Toxicity

Species	Route	Sex	Drug Ratio	LD_{50} (mg/kg)**
Rats	Oral	M	2:1	>5000
		F	2:1	>5000
Mice	Oral	M	2:1	>5000
		F	2:1	>5000
Rats	Oral	M	4:1	>5000
		F	4:1	>5000
	i.v.	M	4:1	1850
		F	4:1	1960
Mice	Oral	M	4:1	>5000
		F	4:1	>5000
	i.v.	M	4:1	1715-2450*
		F	4:1	1715-2450*

M: male, F: female, i.v.: intravenous.
* Estimated.
** Calculated in terms of amoxicillin and clavulanic acid.

All animals were observed for 14 days. Soft faeces which were observed in rats at the beginning of the observation period regained good general condition by the end of the observation period. All mice showed a slight dose-related loss of condition for up to 72 hours after dosing, thereafter remaining in good condition for the duration of the study. Animals, dosed by the intravenous route, which survived were observed to have mild convulsions and abnormal gait 2-3 minutes after dosing. Those which did not survive convulsed immediately on dosing and died within 1 minute.

The LD_{50} of clavulanate potassium administered orally to 4 day old rats was determined to be 1360 mg/kg. This compares with an oral LD_{50} of greater than 10,000 mg/kg for adult rats. In these neonates, weight loss, diarrhea and abdominal distension were frequently observed following dosing.

Subacute Toxicity

Rats

Amoxicillin trihydrate and clavulanate potassium formulated in a 2:1 ratio were administered orally by gavage to five groups of Sprague-Dawley rats, each comprising 10 males and 10 females, at doses of 30/15, 60/30, 300/150, 1000/500 or 3000/1500 mg/kg/day for 30 days. A sixth group served as control. Mortality due to gastrointestinal irritations and debilitation were observed in rats receiving 3000/1500 mg/kg/day. Gastrointestinal irritations were noted at all doses. Signs of toxicity included vomiting, soft to diarrhoeic stools, weight loss, and enlargement of hepatocytes with PAS-positive infiltrations and occasional irritation of the gastric and intestinal mucosa. Erosions or flat ulcers of the gastric mucosa which frequently bled were observed as from doses of 1000/500 mg/kg/day.

Dogs

Amoxicillin trihydrate and clavulanate potassium formulated in a 2:1 ratio were administered by gavage to

three groups of Beagle dogs, each comprising 3 males and 3 females, at doses of 30/15, 60/30, or 120/60 mg/kg/day for 35 days. A fourth group served as control. There were no death during the study. Mild symptoms of vomiting and diarrhoea were observed during study period. There were no other marked changed in gross behavioural manifestation. Histopathological examination revealed a slight hepatocyte enlargement accompanied by a pale granular appearance in animals administered 120/60 mg/kg/day. No other hepatotoxic changes were observed in the study.

Chronic Toxicity

Rats

Amoxicillin trihydrate and clavulanate potassium formulated in a 2:1 ratio were administered orally by gavage to four groups of Sprague-Dawley rats, each comprising 15 males and 15 females, at doses of 20/10, 40/20, 100/50 or 800/400 mg/kg/day for 26 weeks. A fifth group served as a control. Five male and 5 female rats were added to each of the high dose and control groups to determine the effect of drug withdrawal. At the end of the treatment period, these two groups were left undosed for a period of four weeks before sacrificing. Clinical condition and laboratory determinations were monitored and post-mortem and histopathologic determinations were carried out.

There were 4 deaths during the treatment period: one male and two females in the 20/10 mg/kg/day group and one female in the 40/20 mg/kg/day group. There were no deaths during the withdrawal period. Salivation immediately after dosing was noted in both male and female high dose groups. For males receiving 800/400 mg/kg/day, 21% lower body weight gains were recorded from week 3 onwards and 10% lower body weight gains were recorded in the 100/50 mg/kg/day group. Females receiving 800/400 mg/kg/day had lower body weight gains of 62% recorded from week 13.

Decreased urine volumes (males - 30%, females - 54%) were recorded in the 800/400 mg/kg/day group. A statistically significant increase in osmolality was noted in the female high dose group compared to controls.

There was an increase in total white blood cell count associated with an increase in lymphocytes in male rats from the high dose group. This group also had shorter APTT (Activated Partial Thromboplastin Time) while a non-dose related shortened PT (Prothrombin Time) was observed for males receiving 800/400, 100/50, or 40/20 mg/kg at various intervals during treatment, and for all treated males after 24 weeks. At the end of the withdrawal period, values for all parameters were similar to controls. Blood chemistry investigations revealed lower serum albumin (5 to 16%) and higher globulin levels (16 to 30%) during weeks 12 and 24 for male animals receiving 800/400 mg/kg, with an associated decrease in A/G ratios.

A similar effect was seen at week 24 for males receiving 100/50 mg/kg. High dose female rats had globulin levels and A/G ratios similar to controls. However, total protein levels were lower than controls, with an associated decrease in serum albumin levels. At the end of the withdrawal period the only difference from controls was a reduction in total serum protein in females.

At post-mortem examination, a prominent limiting ridge was seen in the stomachs of nearly all the high dose group rats and 1 male dosed at 100/50 mg/kg. Distension of the caecum was seen at all dose levels in a dose-related fashion. At the end of the withdrawal period these findings were no longer observed. Significantly increased liver weights (males - 40%; females - 22%), spleen weights (females - 23%) and kidney weights (males - 10%) were recorded for the high dose group. There was an increase of 30% in liver weights in high dose females and an increase of 26% in kidney weights of high dose males at the end of the withdrawal period. Treatment-related microscopic effects were seen in high dose rats of both sexes.

These were hepatocyte enlargement in centrilobular and mid-zonal areas of the liver, hyperplasia of the non-glandular epithelium of the stomach in the region of the limiting ridge and distension of the lumen of the caecum. The only persistent change present after the withdrawal period was hepatocyte enlargement in all previously dosed males.

A study of similar design was carried out in which identical doses of only the clavulanic acid component of the combination described above were administered. In general, the results were similar to those reported above for the combination.

Dogs

Amoxicillin trihydrate and clavulanate potassium formulated in a 2:1 ratio were administered orally by gavage to four groups of Beagle dogs, each comprising 4 females and 4 males, at doses of 10/5, 20/10, 40/20 or 100/50 mg/kg/day for 26 weeks. A fifth group served as a control. Three male and 3 female dogs were added to each of the high dose and control groups to determine the effect of drug withdrawal. At the end of the treatment period, these two groups were left undosed for a period of 30 days before sacrificing. Clinical condition and laboratory determinations were monitored and post-mortem and histopathologic determinations were carried out.

There were no deaths during the study. Salivation and emesis including the occasional presence of blood streaks (1 mL) in the vomitus were observed in the high dose groups. A low incidence of fecal occult blood was observed in both treated and control animals but the highest incidence occurred in the high dose group after 3 months of treatment. Abnormal granulations in segmented neutrophils were observed most frequently in animals from the high dose group.

Serum glucose levels in males from all treated groups and females from the low and high dose groups were found to be 8 - 29% greater than in controls on some of the assessment occasions during treatment. Similarly, high dose males and females had decreased total protein levels of 9 - 13% on various occasions during treatment. In both cases the absolute magnitude of the change was small with the observed values not falling outside of normal ranges for Beagle dogs.

Focal reddening and petechiation of the mucosa of the pyloric antrum, the presence of white patchy areas in the liver and the presence of white streaks along the cortico-medullary junctions of the kidneys were recorded more frequently for animals of the treated groups than for control animals. At the end of the recovery period kidney changes and some gastrointestinal effects remained. Histopathological studies revealed hepatic and renal changes in the form of cytoplasmic glycogen diminution or disappearance and tubular vacuolization. The kidney and liver changes identified in dogs killed after 6 months of treatment were not observed in dogs of the regression group. Histopathological examination of the gastrointestinal tract revealed capillary congestion and some extravasation of erythrocytes in the superficial mucosa of the fundus and pylorus in both treated and control dogs.

A study of similar design was carried out in which identical doses of only the clavulanic acid component of the combination described above were administered. In general, the results were similar to those reported above for the combination.

Carcinogenicity:

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

Genotoxicity:

The genotoxic potential of amoxicillin/clavulanic acid was investigated in assays for chromosomal damage (mouse micronucleus test and a dominant lethal test) and gene conversion. All were negative.

Reproductive and Developmental Toxicology:

Fertility and general reproductive performance
Amoxicillin trihydrate and clavulanate potassium in a 2:1 ratio were administered orally by gavage to 3 groups of rats, each comprising 24 males and 24 females, at doses of 20/10, 100/50 or 800/400 mg/kg/day. A fourth group served as a control. Male rats were dosed daily for a minimum of 63 days prior to mating and continuing until weaning of offspring on day 21. Female rats were treated for 15 days prior to mating until weaning or until selected for caesarean section at the end of gestation. On gestation day 20, 10 females/group were sacrificed, a caesarean section was carried out and the remaining 14 females/group were allowed to litter normally. Two high dose males died, one each during study week 11 and 15. Necropsy indicated impaction of the caecal content for one while the other showed pulmonary hemorrhage. Treatment-related effects in the high dose males included a slight increase in wheezing and hair loss, decrease in mean body weight gain (21%) and a moderate increase in soft stools.

A slight increase in hair loss was noted in the 100/50 and 800/400 mg/kg/day females. Fertility and general reproductive performance was not affected by treatment as assessed by pregnancy rate and duration of gestation. Male and female mean pup body weights were statistically significantly higher in the 100/50 mg/kg/day group when compared to control. Although not statistically significant, a decrease which tended to be dose related, was observed with respect to viable fetuses, total implantations and corpora lutea per dam. Two F1 fetuses, from the 800/400 mg/kg dose group, had malformations (one had a malformed scapula and the other a thread-like tail and small anus). Litter size, foetal loss and development and behaviour of pups were not adversely affected by treatment.

A study of similar design was carried out in which identical doses of only the clavulanic acid component of the combination described above were administered. The results were generally similar to those reported above for the combination with the addition that 2 fetuses from the 400 mg/kg/day dose group exhibited scoliosis.

Teratology
Three groups of 30 female rats were mated and amoxicillin trihydrate and clavulanate potassium in a 2:1 ratio were then administered from day 6 to day 15 of gestation at doses of 20/10, 100/50 or 800/400 mg/kg/day. A fourth group served as a control. On day 20 of gestation, 20 females/group were sacrificed and a caesarean section was carried out while the remaining 10/group were allowed to litter normally. One dam in the 100/50 mg/kg/day group died; however, the dam was normal internally. Maternal observations revealed a dose related loss of hair, a reduction (11 to 23%) in mean maternal body weight gain for gestation days 6 to 20 and a decrease in food consumption. Slight increases in post-implantation losses were seen in the treated groups, but these were neither dose-related nor statistically significant. Pregnancy rate, litter size, fetal loss and mean pup weights were not affected by the treatment.

The incidence of bent ribs was dose-related and scoliosis was observed in three offspring of dams dosed at 100/50 and 800/400 mg/kg/day. Other offspring abnormalities included extra sternebrae (1 pup), numerous petechiae on the stomach and misplaced sternebrae (1 pup) and cleft lip with several skeletal anomalies involving the vertebrae, ribs, skull and sternum (1 pup).

A study of similar design was carried out in which identical doses of only the clavulanic acid component of the combination described above were administered. The results were generally similar to those reported above for the combination with the addition that a dose-related reduction in ossification and a statistically significant decrease in mean pup body weight were also observed.

Peri- and postnatal studies

Amoxicillin trihydrate and clavulanate potassium in a ratio of 2:1 were administered orally by gavage to 3 groups, each comprising 20 pregnant rats, at doses of 20/10, 100/50 or 800/400 mg/kg/day from day 15 of gestation, through lactation to 21 days post-partum. A fourth group served as a control. Among parent animals, no deaths were observed but there was a slight decrease (17%) of mean body weight in the 800/400 mg/kg/day group on gestation days 15 to 20 and lactation days 0 to 4. Among the litters, 6 deaths were observed; 5 in the 100/50 mg/kg/day group and 1 in the 800/400 mg/kg/day group. A statistically significant decrease in mean number of viable pups per litter in the high dose group was observed.

There was a statistically significant decrease in pup survival in the 100/50 mg/kg/day dose group on lactation days 4, 8, 12 and 21 and a small statistically insignificant decrease in the 800/400 mg/kg/day group. In the F1 generation animals, which were mated, a statistically significant decrease in total implantations per dam and corpora lutea was observed for animals in dams of the 800/400 mg/kg/day group compared to control. The F1 generation parameters revealed no other biologically meaningful differences or dose-related trends in litter observations, behavioural and developmental indices, neuropharmacological responses or reproductive capability of any treatment group when compared with control.

A study of similar design was carried out in which identical doses of only the clavulanic acid component of the combination described above were administered. The maternal effects observed were, in general, similar to those reported above for the combination preparation. In the F1 generation, 1 pup from each of the 50 and 400 mg/kg dosage groups had bilateral rudimentary ribs and 1 pup from the 400 mg/kg dosage group had hydrocephaly in addition to bilateral rudimentary ribs.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Amoxicillin Sodium and Potassium Clavulanate for Injection

Powder for Solution

Read this carefully before you start taking **Amoxicillin Sodium and Potassium Clavulanate for Injection** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Amoxicillin Sodium and Potassium Clavulanate for Injection**.

Serious Warnings and Precautions

- Some people taking beta-lactam antibiotics like Amoxicillin Sodium and Potassium Clavulanate for Injection have reported serious allergic reactions, including death.
- If you have had an allergic reaction to cephalosporins, penicillins, or other beta-lactam antibiotics, tell your healthcare professional before you start treatment with Amoxicillin Sodium and Potassium Clavulanate for Injection.
- For further information and symptoms see:
  - the "To help avoid side effects and ensure proper use…" section
  - the "What are possible side effects from using…"section

What is Amoxicillin Sodium and Potassium Clavulanate for Injection used for?

- Amoxicillin Sodium and Potassium Clavulanate for Injection is used to treat certain bacterial infections including infections of the:
  - Nose, ear, and throat
  - Respiratory tract
  - Genitals and urinary tract
  - Skin and soft tissue
  - Bone and joints
  - Abdominal organs

- Amoxicillin Sodium and Potassium Clavulanate for Injection is also used to help stop infections in patients having surgery.

How does Amoxicillin Sodium and Potassium Clavulanate for Injection work?

Amoxicillin Sodium and Potassium Clavulanate for Injection is an antibiotic. It belongs to a group of antibiotics called penicillins. Amoxicillin works by killing bacteria that cause infections. It does this by preventing them from making their cell walls. Clavulanic Acid helps stop amoxicillin kill bacteria.

Antibacterial drugs like Amoxicillin Sodium and Potassium Clavulanate for Injection treat only bacterial infections. They do not treat viral infections such as the common cold.

What are the ingredients in Amoxicillin Sodium and Potassium Clavulanate for Injection?

Medicinal ingredients: Amoxicillin (as amoxicillin sodium) and clavulanic acid (as clavulanate potassium)

Non-medicinal ingredients: None

Amoxicillin Sodium and Potassium Clavulanate for Injection comes in the following dosage forms:

500 mg / 100 mg Powder for solution
1000 mg / 200 mg Powder for solution
2000 mg / 200 mg Powder for solution

Container composition:
Clear 20 mL (Type II) glass vials with Bromobutyl latex-free rubber stoppers and polypropylene-aluminum bordered caps**.** The stopper contains no dry natural rubber.

Do not use Amoxicillin Sodium and Potassium Clavulanate for Injection if:

- you are allergic to amoxicillin or clavulanic acid or any ingredients in this drug , including the components of the container.
- you are allergic to beta-lactam antibiotics such as medications from the following:
    - penicillins
    - carbapenems
    - monobactams
    - cephalosporins
- you have a previous history of amoxicillin/ clavulanic acid associated jaundice (yellowing of the skin and/or eyes) and / or liver disease.
- you have a disease called mononucleosis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Amoxicillin Sodium and Potassium Clavulanate for Injection. Talk about any health conditions or problems you may have, including if you:

- have allergies to:
    - other antibiotics, in particular penicillins and cephalosporines. If you are allergic to any of these antibiotics you may be allergic to Amoxicillin Sodium and Potassium Clavulanate for Injection.
    - any other drugs or any other substances such as foods, preservatives or dyes.
- have any medical conditions, especially:
    - kidney problems
    - liver problems
    - controlled potassium intake
    - mononucleosis (glandular fever)
- are pregnant or intend to become pregnant.
- are breast-feeding or plan to breast-feed.

Other warnings you should know about:

- If you develop severe diarrhea (very loose or watery stool), tell your healthcare professional right away. Do this even if it occurs several weeks after you stopped taking Amoxicillin Sodium and

Potassium Clavulanate for Injection. Diarrhea may mean that you have a serious condition affecting your bowel (colitis). You may need urgent medical care. Do not try to treat loose stools without first checking with your healthcare professional (see the "Serious side effects and what to do about them" table below).

- If you develop the following while receiving Amoxicillin Sodium and Potassium Clavulanate for Injection:
    - itching with swelling
    - skin rash
    - difficulty breathing

  Tell your healthcare professional immediately.
- Amoxicillin Sodium and Potassium Clavulanate for Injection can have side effects that make you unable to drive. Before driving a vehicle or using machinery wait to see how you feel after taking Amoxicillin Sodium and Potassium Clavulanate for Injection.
- If you have to have any blood or urine tests, tell your healthcare professional you are being given Amoxicillin Sodium and Potassium Clavulanate for Injection. It may affect the results of some blood and urine tests.
- Using too much Amoxicillin Sodium and Potassium Clavulanate for Injection or using it in the wrong way may cause:
    - more bacteria to grow
    - bacteria that will not be killed (resistance).
    - it not to work for you in the future (resistance).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Amoxicillin Sodium and Potassium Clavulanate for Injection:

- medicines to treat gout and stone formations (including allopurinol and probenecid)
- medicines to suppress the immune system (including methotrexate and mycophenolate mofetil)
- medicines used for birth control (contraceptive pills). You may need to use extra birth control methods such as condoms.
- Medicines to prevent blood clots (including warfarin)

Avoid drinking alcohol during treatment and several days after treatment.

How to take Amoxicillin Sodium and Potassium Clavulanate for Injection:

Your healthcare professional will give you Amoxicillin Sodium and Potassium Clavulanate for Injection by:

- Intravenous injection (shot into the vein or by drip tube)
- Intravenous infusion (injected slowly into a vein)

Usual dose:

Your healthcare professional will decide how much, how often and how long you will receive Amoxicillin Sodium and Potassium Clavulanate for Injection**.** This will be based on the severity and type of infection and your body weight.

Overdose:

If you think you, or a person you are caring for, have taken too much Amoxicillin Sodium and Potassium Clavulanate for Injection, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

The injection will be given to you by your healthcare professional. They will monitor your response and condition to decide what treatment is needed. If you miss an appointment, call your doctor or nurse for instructions.

What are possible side effects from using Amoxicillin Sodium and Potassium Clavulanate for Injection?

These are not all the possible side effects you may have when taking Amoxicillin Sodium and Potassium Clavulanate for Injection. If you experience any side effects not listed here, tell your healthcare professional.

- Headache
- Nausea
- Vomiting
- Diarrhea
- Indigestion
- Dizziness
- Itching
- Hives
- Soreness of the mouth or tongue
- Yeast infections (thrush) of the mouth, scalp, skin, and nails.
- During treatment, you may also have side effects of abnormal blood test results including:
    - low number of white blood cells
    - low number of cells involved in blood clotting
    - blood takes longer to clot
    - high level of enzymes related to the liver
    - crystals in urine

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Severe stomach cramps or abdominal cramps			**X**
Watery and severe diarrhea, which may also be bloody			**X**
Fever, in combination with one or both of the above			**X**
Thrombophlebitis (blood clot of the vein): swelling and redness along a vein, tender to the touch			**X**
Erythema multiforme (an allergic skin reaction): raised red or purple			**X**

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning			
Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs): • Skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish) • Swelling and redness of eyes or face • Flu-like feeling, fever, chills, body aches, swollen glands, cough Shortness of breath, chest pain or discomfort			**X**
NOT KNOWN			
Anaphylaxis (Allergic reaction): wheezing, swelling of the lips/mouth, difficulty in breathing, hay fever, lumpy rash (hives) or fainting			**X**
Kounis syndrome (heart problems caused by an allergic reaction): Symptoms of anaphylaxis (see above), chest pain, chest pressure or discomfort, heart palpitations, nausea or vomiting, sweating, shortness of breath, fatigue, clammy skin, feeling anxious or faint, disorientation, upset stomach.			**X**
Hypersensitivity vasculitis (Inflammation of the blood vessels)**:** rash, red spots, hives, and blisters on the lower part of the body			**X**

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Convulsions			X
Aseptic meningitis (inflammation of the brain lining): fever, headache, body aches, vomiting, fatigue			X
Antibiotic-associated colitis (inflammation of the colon): severe diarrhea, passing of blood with stool, fatigue, fever			X
Hepatitis (inflammation of the liver): fatigue, fever, body ache, dark urine or pale stools, difficulty to urinate.		X	
Jaundice: yellowing of the skin or eyeballs		X	
Stevens-Johnson syndrome (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			X
Toxic Epidermal Necrolysis (severe skin reaction): redness, blistering and/or peeling of large areas of the skin			X
Bullous exfoliative Dermatitis: widespread red skin rash with small pus-containing blisters			X
Acute Generalised Exanthemous Pustulosis (AGEP): a red, scaly rash with bumps under the skin and blisters			X
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect more than one or more organs): fever, severe rash, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of			X

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
breath, dry cough, chest pain or discomfort, feel thirsty, urinate less often, less urine			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Amoxicillin Sodium and Potassium Clavulanate for Injection should be stored at room temperature between 15°C to 30°C.

It should be used within 15 minutes after reconstitution.

Keep out of reach and sight of children.

If you want more information about Amoxicillin Sodium and Potassium Clavulanate for Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sandoz.ca, or by calling 1-800-361-3062.

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