

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrAG-Amoxi Clav Suspension

Amoxicillin and Clavulanate Potassium for Oral Suspension
Powder for Suspension

House Standard

AG-Amoxi Clav Suspension -200

200 mg amoxicillin (as trihydrate) and 28.5 mg clavulanic acid (as clavulanate potassium) / 5 mL

AG-Amoxi Clav Suspension -250

250 mg amoxicillin (as trihydrate) and 62.5 clavulanic acid (as clavulanate potassium) / 5 mL

AG-Amoxi Clav Suspension -400

400 mg amoxicillin (as trihydrate) and 57 mg clavulanic acid (as clavulanate potassium) / 5 mL

Combinations of penicillins, including beta-lactamase inhibitors
ATC code: J01CR02

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RECENT MAJOR LABEL CHANGES

Not Applicable

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

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AG-Amoxi Clav Suspension (amoxicillin / clavulanate potassium) is indicated for the treatment of the following infections when caused by AG-Amoxi Clav Suspension-susceptible strains of the designated bacteria:

- Sinusitis when caused by β -lactamase producing strains of *H. influenzae* or *Moraxella (Branhamella) catarrhalis*.
- Otitis Media when caused by β -lactamase producing strains of *H. influenzae* or *Moraxella (Branhamella) catarrhalis*.
- Lower Respiratory Tract Infections when caused by β -lactamase producing strains of *H. influenzae*, *K. pneumoniae*, *S. aureus* or *Moraxella (Branhamella) catarrhalis*.
- Skin and Soft Tissue Infections when caused by β -lactamase producing strains of *S. aureus*.
- Urinary Tract Infections when caused by β -lactamase producing strains of *E. coli*.

While AG-Amoxi Clav Suspension is indicated only for the conditions listed above, infections caused by ampicillin (amoxicillin) susceptible organisms are also amenable to AG-Amoxi Clav Suspension treatment due to its amoxicillin content. Furthermore, mixed infections caused by organisms susceptible to ampicillin (amoxicillin) and β -lactamase producing organisms susceptible to AG-Amoxi Clav Suspension should not require the addition of another antibiotic.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AG-Amoxi Clav Suspension and other antibacterial drugs, AG-Amoxi Clav Suspension should be used only to treat 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.

1.1 Pediatrics

Pediatrics (< 18): (See 4.2 Recommended Dose and Dosage Adjustment, Pediatrics, 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics: See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.

2 CONTRAINDICATIONS

AG-Amoxi Clav Suspension is contraindicated in patients with a history of hypersensitivity to the penicillin, or cephalosporin group of β -lactams, or to any ingredients contained in the preparation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING .

AG-Amoxi Clav Suspension is contraindicated in patients where infectious mononucleosis is either suspected or confirmed.

AG-Amoxi Clav Suspension is contraindicated in patients with a previous history of amoxicillin and clavulanate potassium-associated jaundice/hepatic dysfunction.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Pediatrics (3 months and older)

In infants 12 weeks (3 months) of age or older and in children, b.i.d. use of the AG-Amoxi Clav Suspension 200 mg and 400 mg formulations is recommended because of a significantly reduced incidence of diarrhea with the b.i.d. regimen (see 8 ADVERSE REACTIONS).

Based on the amoxicillin component, AG-Amoxi Clav Suspension should be dosed as follows in patients aged 12 weeks (3 months) and older:

Infection	Severity	Dosing Regimen	
		B.I.D.* AG-Amoxi Clav Suspension-200	T.I.D. 125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension***
Urinary tract	Mild to moderate	AG-Amoxi Clav Suspension-400 25 mg/kg/day in divided doses every 12 hours	AG-Amoxi Clav Suspension-250 20 mg/kg/day in divided doses every 8 hours
Skin and Soft Tissue	Severe	45 mg/kg/day in divided doses every 12 hours	40 mg/kg/day in divided doses every 8 hours
Lower Respiratory Tract Sinusitis		45 mg/kg/day in divided doses every 12 hours	40 mg/kg/day in divided doses every 8 hours

Infection	Severity	Dosing Regimen	
		B.I.D.* AG-Amoxi Clav Suspension-200	T.I.D. 125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension***
		AG-Amoxi Clav Suspension-400	AG-Amoxi Clav Suspension- 250
Otitis Media**			40 mg/kg/day in divided doses every 8 hours

* The bid regimen is recommended as it is associated with significantly less diarrhea.

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

***AG-Amoxi Clav Suspension is NOT available at the strength of 125 mg amoxicillin / 31.25 mg clavulanic acid.

The normal duration of treatment was 7 to 10 days. However, in general, treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days treatment for any infection caused by β -hemolytic streptococci to prevent the occurrence of acute rheumatic fever or glomerulonephritis.

The children's dosage should not exceed that recommended for adults. Children weighing more than 38 kg should be dosed according to the adult recommendations (*i.e., the usual adult dose is one (1) AG-Amoxi Clav 500 mg tablet every 12 hours. For more severe infections and infections of the lower respiratory tract, the dose should be one (1) AG-Amoxi Clav 875 mg tablet every 12 hours or one (1) AG-Amoxi Clav 500 mg tablet every 8 hours*).

Table 1 below may be used as a guide to determine the dosage of oral suspension (125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension or AG-Amoxi Clav Suspension-250) according to body weight.

Table 1 Pediatric Dosage Schedule for 125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension and AG-Amoxi Clav Suspension-250 Oral Suspensions^a

Body Weight	20 mg/kg/day dosing regimen ^a			40 mg/kg/day dosing regimen ^a		
	Total Daily Dose ^b	Volume (mL) of Reconstituted Oral Suspension Every 8 Hours		Total Daily Dose ^b	Volume (mL) of Reconstituted Oral Suspension Every 8 Hours	
(kg)	(mg)	125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension	AG-Amoxi Clav Suspension- 250	(mg)	125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension	AG-Amoxi Clav Suspension- 250
05	125	1.3	0.7	250	2.7	1.3

07	175	1.9	0.9	350	3.7	1.9
10	250	2.7	1.3	500	5.3	2.7
12	300	3.2	1.6	600	6.4	3.2
14	350	3.7	1.9	700	7.5	3.7
16	400	4.3	2.1	800	8.5	4.3
18	450	4.8	2.4	900	9.6	4.8
20	500	5.3	2.7	1000	10.7	5.3
25	625	6.7	3.3	1250	13.3	6.7
30	750	8.0	4.0	1500	16.0	8.0
35	875	9.3	4.7	1750	18.7	9.3
38	950	10.1	5.1	1900	20.3	10.1

^a Based on amoxicillin component

^b Dosages are expressed in terms of amoxicillin plus clavulanic acid. These two ingredients are in a ratio of 4:1 in both oral suspensions, 125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension and AG-Amoxi Clav Suspension-250.

Twenty (20) mL of reconstituted 125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension or ten (10) mL of reconstituted AG-Amoxi Clav Suspension-250 oral suspension are equivalent to one (1) amoxicillin and clavulanate potassium-500 mg /125 mg tablet.

Table 2 below may be used as a guide to determine the dosage of oral suspension (AG-Amoxi Clav Suspension-200 or AG-Amoxi Clav Suspension-400) according to body weight.

Table 2 Pediatric Dosage Schedule for AG-Amoxi Clav Suspension-200 and AG-Amoxi Clav Suspension -400 Oral Suspensions

Body Weight	25 mg/kg/day dosing regimen ^a			45 mg/kg/day dosing regimen ^a		
	Total Daily dose ^b	Volume (mL) of Reconstituted Oral Suspension Every 12 Hours		Total Daily dose ^b	Volume (mL) of Reconstituted Oral Suspension Every 12 Hours	
(kg)	(mg)	AG-Amoxi Clav Suspension-200	AG-Amoxi Clav Suspension-400	(mg)	AG-Amoxi Clav Suspension-200	AG-Amoxi Clav Suspension-400
05	143	1.6	0.8	257	2.8	1.4
07	200	2.2	1.1	360	3.9	2.0
10	286	3.1	1.6	514	5.6	2.8
12	343	3.8	1.9	617	6.8	3.4
14	400	4.4	2.2	720	7.9	3.9
16	458	5.0	2.5	822	9.0	4.5

18	515	5.6	2.8	925	10.1	5.1
20	572	6.3	3.1	1028	11.3	5.6
25	715	7.8	3.9	1285	14.1	7.0
30	858	9.4	4.7	1542	16.9	8.4
35	1001	11.0	5.5	1799	19.7	9.8
38	1087	11.9	5.9	1953	21.4	10.7

^a Based on amoxicillin component

^b Dosages are expressed in terms of amoxicillin plus clavulanic acid. These two ingredients are in a ratio of 7:1 in both oral suspensions, AG-Amoxi Clav Suspension-200 and AG-Amoxi Clav Suspension-400.

A calibrated dropper should be used to measure the appropriate volume for dosing.

Pediatrics (Neonates and children aged <12 weeks (3 months))

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

Renal Insufficiency

Dosage adjustment in renal impairment is based on the maximum recommended level of amoxicillin. AG-Amoxi Clav Suspension presentations with a 7:1 ratio of amoxicillin:clavulanate (i.e., the AG-Amoxi Clav Suspension-200 and -400 oral suspensions) should be used only in patients with a creatinine clearance of more than 30 ml/min.

Pediatrics

Creatinine clearance > 30 ml/min	No adjustment necessary.
Creatinine clearance 10 - 30 ml/min	15/3.75 mg/kg given twice daily (maximum 500/125 mg twice daily).
Creatinine clearance < 10 ml/min	15/3.75 mg/kg given as a single daily dose (maximum 500/125 mg).
Hemodialysis	15/3.75 mg/kg/day given as a single daily dose. Prior to hemodialysis one additional dose of 15/3.75 mg/kg should be administered. In order to restore circulating drug levels, another dose of 15/3.75 mg/kg should be administered after hemodialysis.

AG-Amoxi Clav Suspension-200 (200/28.5 mg) and AG-Amoxi Clav Suspension-400 (400/57 mg)

oral suspensions (7:1 ratio amoxicillin:clavanulate) should only be used in patients with a creatinine clearance of more than 30 ml/min.

4.3 Reconstitution

Reconstitute Powder for Oral Suspension with purified water.

AG-Amoxi Clav Suspension-200 Powder for Oral Suspension:

The approximate average concentration after reconstitution is 200 mg of amoxicillin (as the trihydrate) and 28.5 mg of clavulanic acid (as the potassium salt) per 5 mL.

Tap the bottle and then shake gently to loosen the dry powder. Transfer about 32 ml of purified water to the bottle, close the cap securely. Shake gently (Tilt the bottle up and down manually about 30 seconds). Hold for 1 minute. Again open the cap and add the 32 ml of purified water, close the cap securely. Shake vigorously, ensure the complete reconstitution by physical observation.

AG-Amoxi Clav Suspension-250 Powder for Oral Suspension

The approximate average concentration after reconstitution is 250 mg of amoxicillin (as the trihydrate) and 62.5 mg of clavulanic acid (as the potassium salt) per 5 mL.

Tap the bottle and then shake gently to loosen the dry powder. Transfer about 42 ml of purified water to the bottle, close the cap securely. Shake gently (Tilt the bottle up and down manually about 30 seconds). Hold for 1 minute. Again open the cap and add the 42 ml of purified water, close the cap securely. Shake vigorously, ensure the complete reconstitution by physical observation.

AG-Amoxi Clav Suspension-400 Powder for Oral Suspension

The approximate average concentration after reconstitution is 400 mg of amoxicillin (as the trihydrate) and 57 mg of clavulanic acid (as the potassium salt) per 5 mL.

Tap the bottle and then shake gently to loosen the dry powder. Transfer about 28.5 ml of purified water to the bottle, close the cap securely. Shake gently (Tilt the bottle up and down manually about 30 seconds). Hold for 1 minute. Again open the cap and add the 28.5 ml of purified water, close the cap securely. Shake vigorously, ensure the complete reconstitution by physical observation.

Shake vigorously until a homogenous, lump-free suspension is obtained.

The reconstituted AG-Amoxi Clav Suspension-250 oral suspension should be stored under refrigeration (2°C to 8°C) and should be used within 10 days. Discard unused suspension after 10 days. The reconstituted AG-Amoxi Clav Suspension-200 and AG-Amoxi Clav Suspension-400 oral suspension should be stored under refrigeration (2°C to 8°C) and should be used within 7 days. Discard unused suspension after 7 days. (see 11 STORAGE, STABILITY AND DISPOSAL).

4.4 Administration

While AG-Amoxi Clav Suspension can be given without regard to meals, absorption of clavulanic acid when taken with food is greater relative to the fasted state. Dosing in the fasted or fed

state has minimal effect on the pharmacokinetics of amoxicillin. The safety and efficacy of amoxicillin and clavulanate potassium have been established in clinical trials where amoxicillin and clavulanate potassium was taken without regard to meals.

To minimize potential gastrointestinal intolerance, administer at the start of a meal.

5 OVERDOSAGE

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supported measures are also recommended.

Many patients have been asymptomatic following overdose or have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity, or drowsiness have also been observed in a small number of patients. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see 7 WARNINGS AND PRECAUTIONS).

In the case of overdose, discontinue AG-Amoxi Clav Suspension, treat symptomatically, and institute supportive measures as required. If gastrointestinal symptoms and disturbance of the fluid and electrolyte balances are evident, they may be treated symptomatically. AG-Amoxi Clav Suspension can be removed from the circulation by hemodialysis. A prospective study of 51 pediatric patients at a poison center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdose with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 **Route of Administration, Dosage Forms, Strengths and Non-medicinal Ingredients**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Powder for oral suspension AG-Amoxi Clav Suspension-200: Each 5 mL of reconstituted suspension contains 200 mg of amoxicillin as the trihydrate and 28.5 mg of clavulanic acid as the potassium salt (in a ratio of 7:1) AG-Amoxi Clav Suspension-250: Each 5 mL of reconstituted suspension contains 250 mg of amoxicillin as the trihydrate and 62.5 mg of clavulanic acid as the potassium salt (in a ratio of 4:1) AG-Amoxi Clav Suspension-400: Each 5 mL of reconstituted suspension contains 400 mg of amoxicillin as the trihydrate and 57 mg of clavulanic acid as the potassium salt (in a ratio of 7:1)	Citric acid, golden syrup flavour, hypromellose, magnesium stearate, orange flavour, raspberry flavour, silica hydrophobic colloid, silicon dioxide, sodium benzoate, sucralose and xanthan gum.

Availability of Dosage Forms

AG-Amoxi Clav Suspension-250 is available in bottles of 100 mL. AG-Amoxi Clav Suspension-200 and 400 are available in bottles of 70 mL.

7 WARNINGS AND PRECAUTIONS

General

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy with AG-Amoxi Clav Suspension. If superinfection should occur (usually involving *Aerobacter*, *Pseudomonas* or *Candida*), the administration of AG-Amoxi Clav Suspension should be discontinued and appropriate therapy instituted.

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

The occurrence of a morbilliform rash following the use of ampicillin in patients with infectious mononucleosis is well documented. This reaction has also been reported following the use of amoxicillin. A similar reaction would also be expected with AG-Amoxi Clav Suspension.

***Clostridium difficile*-associated disease**

Clostridium difficile -associated disease (CDAD) has been reported with the use of many antibacterial agents, including amoxicillin and clavulanate potassium. 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](#)).

Cardiovascular

Abnormal prolongation of prothrombin time (increased international normalized ratio (INR)) has been reported in patients receiving amoxicillin and clavulanate potassium 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.

Kounis syndrome (see [7 WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions](#)).

Hepatic/Biliary/Pancreatic

Transient hepatitis and cholestatic jaundice have been reported rarely. These events have been noted with other penicillins and cephalosporins. Hepatic injury events associated with amoxicillin and clavulanate potassium may be severe, and occur predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. 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. Hepatic toxicity associated with the use of amoxicillin and clavulanate potassium is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications (see [2 CONTRAINDICATIONS](#) and [8.5 Post-Market Adverse Reactions, Liver](#)).

AG-Amoxi Clav Suspension should be used with caution in patients with evidence of hepatic dysfunction.

Immune

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity reactions, including:

- angioedema
- anaphylactic/anaphylactoid reactions

- severe cutaneous adverse reactions (SCAR) (e.g., acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS)). These have been reported in patients on penicillin therapy, including amoxicillin / clavulanate potassium.
- Kounis syndrome, 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 [8.5 Post-Market Adverse Reactions](#))

Although these reactions are more frequent following parenteral therapy, they have occurred in patients receiving penicillins orally. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of cephalosporin hypersensitivity who have experienced severe reactions when treated with penicillins. Before initiating therapy with AG-Amoxi Clav Suspension, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens (see [2 CONTRAINDICATIONS](#)).

If an allergic reaction occurs, the administration of AG-Amoxi Clav Suspension should be discontinued and appropriate alternative therapy should be instituted. Serious anaphylactic/anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management, including intubation should also be used as indicated.

Monitoring and Laboratory Tests

Periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy with AG-Amoxi Clav Suspension.

Renal

AG-Amoxi Clav Suspension is excreted mostly by the kidney. In renal impairment, dosage adjustments should be made based on the maximum recommended level of amoxicillin (see [4.2 Recommended Dose and Dosage Adjustment, Renal Insufficiency](#)).

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see [5 OVERDOSAGE](#)).

Sensitivity/Resistance

Prescribing AG-Amoxi Clav Suspension 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.

Skin

Severe cutaneous adverse reactions (SCAR) have been reported with amoxicillin and clavulanate

potassium (see [7 WARNINGS and PRECAUTIONS, Hypersensitivity Reactions](#)).

7.1 Special Populations

7.1.1 Pregnant Women

In a single study in women with preterm, premature rupture of the fetal membranes (pPROM), it was reported that prophylactic treatment with amoxicillin and clavulanate potassium may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided in pregnancy, unless considered essential by the physician.

7.1.2 Breast-feeding

Penicillins (including ampicillin) have been shown to be excreted in human breast milk. It is not known whether clavulanic acid is excreted in breast milk. Caution should be exercised if AG-Amoxi Clav Suspension is to be administered to a nursing mother.

7.1.3 Pediatrics

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of AG-Amoxi Clav Suspension should be modified in pediatric patients younger than 12 weeks (3 months), see [4.2 Recommended Dose and Dosage Adjustment, Pediatrics \(Neonates and children aged <12 weeks \(3 months\)\)](#).

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

A U.S./Canadian clinical trial compared a 10-day amoxicillin and clavulanate potassium b.i.d. regimen (45/6.4 mg/kg/day q12h) with a 10-day amoxicillin and clavulanate potassium t.i.d. regimen (40/10 mg/kg/day q8h) in 575 patients with acute otitis media, aged 2 months to 12 years. The incidence of diarrhea was significantly lower in patients who received the b.i.d. regimen compared to patients who received the t.i.d. regimen (9.6% vs. 26.7%; $p < 0.001$). Significantly fewer patients who received the b.i.d. regimen withdrew due to diarrhea compared to patients receiving the t.i.d. regimen (2.8% vs. 7.6%; $p = 0.009$). The incidence of related/possibly related diaper rash was also lower in patients who received the b.i.d. regimen compared to patients who received the t.i.d. regimen (3.1% vs. 6.6%; $p = 0.054$).

8.5 Post-Market Adverse Reactions

The following adverse reactions have been observed during therapy with amoxicillin and clavulanate potassium.

Black hairy tongue has been reported very rarely. Tooth discolouration has been reported very rarely in children and adults. Good oral hygiene may help to prevent tooth discolouration as it can often be removed by brushing.

Central Nervous System Effects

Aseptic meningitis.

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

Gastrointestinal

Diarrhea has been reported very commonly in adults and commonly in children. Nausea and vomiting have been reported commonly in adults and children. Mucocutaneous candidiasis has been reported commonly. Abdominal cramps, flatulence, constipation, anorexia, colic pain, acid stomach, intestinal candidiasis, antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) have been reported rarely. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin and clavulanate potassium at the start of the meal.

Hemic and Lymphatic Systems

As with other β -lactams, anemia, hemolytic anemia thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, lymphocytopenia, basophilia, slight increase in platelets, neutropenia and agranulocytosis have been reported rarely during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Prolongation of bleeding time and prolongation of prothrombin time have also been reported.

Immune

Note: If any hypersensitivity dermatitis reaction occurs, treatment with AG-Amoxi Clav Suspension should be discontinued (see [7 WARNINGS and PRECAUTIONS, Hypersensitivity Reactions](#)).

General hypersensitivity reactions: Erythematous macropapular rash, urticaria, anaphylaxis, hypersensitivity vasculitis and pruritus.

Severe cutaneous adverse reactions (SCAR): Rarely erythema multiforme and Stevens-Johnson syndrome (SJS) have been reported. Other reactions including angioedema, toxic epidermal necrolysis (TEN), bullous exfoliative dermatitis, and acute generalised exanthematous pustulosis (AGEP) as in the case of other β -lactam antibiotics, have been seen rarely. Drug reaction with eosinophilia and systemic symptoms (DRESS) has also been reported.

Other immune system disorders: A morbilliform rash in patients with mononucleosis. Interstitial nephritis can occur rarely, Kounis syndrome, Serum sickness-like syndrome.

Liver

Transient hepatitis and cholestatic jaundice have been reported rarely. These events have been noted with other penicillins and cephalosporins. Moderate rises in AST (SGOT), alkaline phosphatase, lactic dehydrogenase, and/or ALT (SGPT) have been noted in patients treated with ampicillin class antibiotics. The significance of these findings is unknown.

Other

Vaginitis, headache, bad taste, dizziness, malaise, glossitis, and stomatitis.

Renal and Urinary Tract Disorders

Very rare: crystalluria and interstitial nephritis (see 5 OVERDOSAGE).

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

In common with other broad spectrum antibiotics, amoxicillin-clavulanate may reduce the efficacy of combined oral contraceptives by altering the gut-flora to result in lower estrogen reabsorption. Concomitant use of probenecid is not recommended, and may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

Increases in prothrombin time, INR or bleeding have been reported in patients maintained on coumarin anticoagulants, such as acenocoumarol and warfarin and then coadministered amoxicillin or amoxicillin and clavulanate potassium. If coadministration is necessary, the prothrombin time or INR should be carefully monitored upon antibiotic addition or withdrawal.

Reduction in the median pre-dose concentration of the mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil, of approximately 54% has been reported in renal transplant recipients in the days immediately following the commencement of oral amoxicillin-clavulanic acid.

These reductions in pre-dose MPA concentrations from baseline (mycophenolate mofetil alone) tended to diminish with continued antibiotic use and cease after discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.

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

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Amoxicillin exerts a bactericidal action against sensitive organisms during the stage of active multiplication through the inhibition of the biosynthesis of bacterial cell wall mucopeptides. Clavulanic acid inhibits specific β -lactamases of some microorganisms and allows amoxicillin to inhibit amoxicillin (ampicillin) resistant organisms which produce clavulanic acid sensitive β -lactamases.

10.3 Pharmacokinetics

There is no significant difference between the absorptions of amoxicillin and clavulanic acid, whether administered separately or as a combination in amoxicillin and clavulanate potassium.

The half-life of amoxicillin when given alone is 1.2 hours and 1.3 hours when given in the form of amoxicillin and clavulanate potassium. The half-life of clavulanic acid alone is 1.0 hour. Time above the minimum inhibitory concentration of 1.0 mcg/mL for amoxicillin has been shown to be similar after corresponding b.i.d. and t.i.d. dosing regimens of amoxicillin and clavulanate potassium in adults and children.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Neither component of amoxicillin and clavulanate potassium is highly protein-bound; clavulanic acid has been found to be approximately 30% bound to human serum protein and amoxicillin approximately 20% bound.

Special Populations and Conditions

Pediatrics

The plasma concentrations of amoxicillin and clavulanic acid following single doses of an oral suspension containing amoxicillin and clavulanic acid in a ratio of 4:1 are given in Table 4 below.

Table 4 Mean Plasma Concentrations of Amoxicillin and Clavulanic Acid

No. of	Mean Age	Drug	Dose*	Mean Plasma Concentrations (mg/mL) at Indicated Time (h) After Dosing					
				1/3	2/3	1	2	3	4
Children	(Years)		(mg/kg)						
17	3.5	amoxicillin	6.6	0.91	1.58	2.11	2.16	1.23	0.71
		clavulanic acid	1.7	0.29	0.72	0.67	0.47	0.20	0.04
17	4.1	amoxicillin	13.3	1.80	3.56	4.67	3.31	1.95	1.14

		clavulanic acid	3.3	0.42	1.12	1.45	1.02	0.52	0.25
--	--	-----------------	-----	------	------	------	------	------	------

* A single dose of 6.6 mg/kg of amoxicillin plus 1.7 mg/kg of clavulanic acid is equivalent to one third of the daily dose of 25 mg/kg of amoxicillin and clavulanate potassium oral suspension (4:1 ratio). A single dose of 13.3 mg/kg of amoxicillin plus 3.3 mg/kg of clavulanic acid is equivalent to one third of the daily dose of 50 mg/kg of amoxicillin and clavulanate potassium oral suspension (4:1 ratio).

Some pharmacokinetic parameters for these children are given in Table 5 below.

Table 5 Pharmacokinetic Parameters

No. of Children	Drug	Dose (mg/kg)	Plasma Half-life (h)	AUC (mg/mL-h)	Volume of Distribution (mL/kg)	Volume of Distribution (mL/min/1.73m ²)
17	amoxicillin	6.6	1.25	6.11	1950	504
	clavulanic acid	1.7	1.10	1.66	1622	478
17	amoxicillin	13.3	1.46	12.90	2172	481
	clavulanic acid	3.3	1.17	3.54	1575	435

The steady state pharmacokinetic profiles of amoxicillin and clavulanic acid were compared after dosing amoxicillin and clavulanate potassium oral suspension at a dose of 45/6.4 mg/kg/day (7:1 ratio) q12h and 40/10 mg/kg/day (4:1 ratio) q8h in pediatric patients with age ranges from 1 month to 12 years. The elimination kinetics of amoxicillin and clavulanic acid in b.i.d. or t.i.d. regimens to pediatric patients aged 4 months or greater were similar to those of adults. However, in infants younger than 4 months, half-lives were delayed due to the relative immaturity of renal function in these infants.

11 STORAGE, STABILITY AND DISPOSAL

Store powder in a dry place at room temperature (15°C – 25°C). Use the powder only if its appearance is white to off-white.

The reconstituted AG-Amoxi Clav Suspension-250 oral suspension should be stored under refrigeration (2°C to 8°C) and should be used within 10 days. Discard unused suspension after 10 days.

The reconstituted AG-Amoxi Clav Suspension-200 and AG-Amoxi Clav Suspension-400 oral suspension should be stored under refrigeration (2°C to 8°C) and should be used within 7 days. Discard unused suspension after 7 days.

Keep bottle tightly closed at all times.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

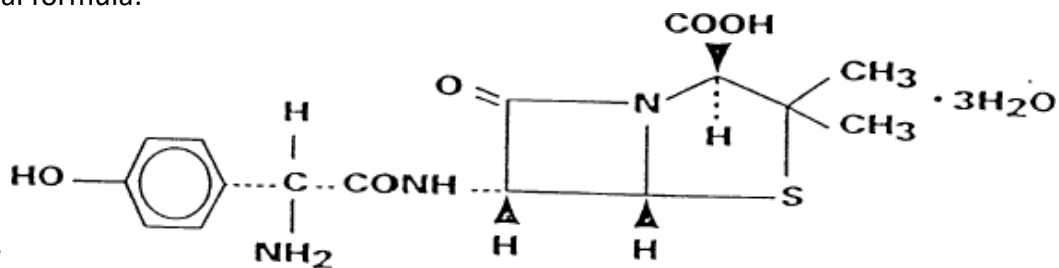
Proper name: amoxicillin / clavulanate potassium

Amoxicillin

Chemical name: Trihydrate of 6-[-(α)-amino-4-hydroxy-phenylacetamido]-penicillanic acid]

Molecular formula and molecular mass: $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ / 419.47 g/mol (trihydrate) and 365.41 g/mol (anhydrous)

Structural formula:



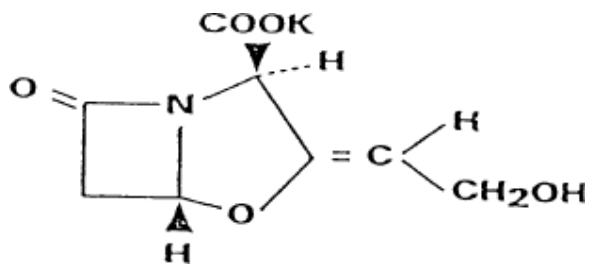
Physicochemical properties: Amoxicillin trihydrate is a white or almost white crystalline powder.

Clavulanate Potassium

Chemical name: Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3,2,0]-heptane-2-carboxylate

Molecular formula and molecular mass: $C_8H_8NO_5K$ / 199.16 g/mol (free acid) and 237.25 g/mol (potassium salt)

Structural formula:



Physicochemical properties: white or almost white powder, hygroscopic.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

AG-Amoxi Clav Suspension-400

A double blinded, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study of 5 mL of AG-Amoxi Clav Suspension-400 (400 mg amoxicillin/57 mg clavulanate potassium per 5 mL) (Angita Pharma Inc.) and 5 mL of PrCLAVULIN®-400 Oral Suspension (400 mg amoxicillin/57 mg clavulanate potassium per 5 mL) (GlaxoSmithKline Inc.) was conducted in 56 healthy, adult, Asian male subjects under fasting conditions. A summary of the comparative bioavailability data for Amoxicillin and Clavulanic acid from the 50 subjects who completed the study are presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amoxicillin (5 mL X 400 mg amoxicillin/57 mg clavulanate potassium per 5 mL) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng•h/mL)	29927.57 30651.71 (21.8)	28506.28 29164.60 (21.0)	105.0	101.7 - 108.4
AUC _I (ng•h/mL)	30208.87 30946.70 (22.0)	28754.89 29424.94 (21.1)	105.1	101.8-108.5
C _{max} (ng/mL)	8769.99 9096.83 (26.8)	8732.73 9073.08 (28.0)	100.4	96.1 - 105.0
T _{max} ³ (h)	1.63 (0.75 - 3.00)	1.63 (0.75 - 3.50)		
T _½ ⁴ (h)	1.65 (18.8)	1.62 (14.9)		

¹ AG-Amoxi Clav Suspension-400 (400 mg amoxicillin/57 mg clavulanate potassium per 5 mL) (Angita Pharma Inc.)

² PrCLAVULIN®- 400 Oral Suspension (400 mg amoxicillin/57 mg clavulanate potassium per 5 mL) (GlaxoSmithKline Inc.), purchased in Canada.

³ Expressed as the median (range) only

⁴ Expressed as the arithmetic mean (CV%) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Clavulanic acid (5 mL X 400 mg amoxicillin/57 mg clavulanate potassium per 5 mL) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng•h/mL)	3345.64 3495.31 (28.3)	3206.88 3354.82 (28.5)	104.3	98.1 - 110.9
AUC _I (ng•h/mL)	3353.82 3503.58 (28.3)	3215.0497 3362.68 (28.5)	104.3	98.1 - 110.9
C _{max} (ng/mL)	1390.84 1477.32 (35.1)	1375.9988 1444.20 (32.5)	101.1	94.1 - 108.5
T _{max} ³ (h)	1.13 (0.50 - 4.00)	1.00 (0.75 - 4.00)		
T _½ ⁴ (h)	1.21 (12.3)	1.20 (12.6)		

¹ AG-Amoxi Clav Suspension-400 (400 mg amoxicillin/57 mg clavulanate potassium per 5 mL) (Angita Pharma Inc., Canada)

² PrCLAVULIN®- 400 Oral Suspension (400 mg amoxicillin/57 mg clavulanate potassium per 5 mL) (GlaxoSmithKline Inc.), purchased in Canada.

³ Expressed as the median (range) only

⁴ Expressed as the arithmetic mean (CV%) only

AG-Amoxi Clav Suspension-250

A double blinded, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study of 5 mL of AG-Amoxi Clav Suspension-250 (250 mg amoxicillin/62.5 mg clavulanate potassium per 5 mL) (Angita Pharma Inc.) and 5 mL of PrCLAVULIN®-250F Oral Suspension (250 mg amoxicillin/62.5 mg clavulanate potassium per 5 mL) (GlaxoSmithKline Inc.) was conducted in 56 healthy, adult, Asian male subjects under fasting conditions. A summary of the comparative bioavailability data for Amoxicillin and Clavulanic acid from the 53 subjects who completed the study are presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amoxicillin (5 mL X 250 mg amoxicillin/62.5 mg clavulanate potassium per 5 mL) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng•h/mL)	19999.99 20435.43 (19.8)	20473.16 20810.51 (17.9)	97.7	95.7 - 99.7
AUC _I (ng•h/mL)	20169.70 20606.99 (19.7)	20637.11 20977.36 (17.9)	97.7	95.8 - 99.7
C _{max} (ng/mL)	6735.53 6967.15 (26.7)	7003.76 7195.28 (23.2)	96.2	91.9 - 100.6
T _{max} ³ (h)	1.25 (0.75-3.00)	1.25 (0.50-3.00)		
T _½ ⁴ (h)	1.55 (19.8)	1.55 (21.8)		

¹ AG-Amoxi Clav Suspension-250 (250 mg amoxicillin/62.5 mg clavulanate potassium per 5 mL) (Angita Pharma Inc.)

² PrCLAVULIN®-250F Oral Suspension (250 mg amoxicillin/62.5 mg clavulanate potassium per 5 mL) (GlaxoSmithKline Inc.), purchased in Canada

³ Expressed as the median (range) only

⁴ Expressed as the arithmetic mean (CV%) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Clavulanic acid (5 mL X 250 mg amoxicillin/62.5 mg clavulanate potassium per 5 mL) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng•h/mL)	4385.52 4568.77 (30.5)	4461.36 4689.17 (31.8)	98.3	92.9 - 104.0
AUC _I (ng•h/mL)	4392.81 4576.44 (30.5)	4468.51 4696.61 (31.9)	98.3	92.9 - 104.0
C _{max} (ng/mL)	1932.46 2055.56 (34.0)	1920.04 2036.63 (32.6)	100.6	94.7 - 107.0
T _{max} ³ (h)	1.00 (0.50 – 3.00)	1.00 (0.50 – 3.50)		
T _½ ⁴ (h)	1.16 (11.4)	1.15 (11.5)		

¹ AG-Amoxi Clav Suspension-250 (250 mg amoxicillin/62.5 mg clavulanate potassium per 5 mL) (Angita Pharma Inc.)

² PrCLAVULIN®- 250F Oral Suspension (250 mg amoxicillin/62.5 mg clavulanate potassium per 5 mL) (GlaxoSmithKline Inc.), purchased in Canada

³ Expressed as the median (range) only

⁴ Expressed as the arithmetic mean (CV%) only

AG-Amoxi Clav Suspension-200

A double blinded, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study of 5 mL of AG-Amoxi Clav Suspension-200 (200 mg amoxicillin/28.5 mg clavulanate potassium per 5 mL) (Angita Pharma Inc.) and 5 mL of PrCLAVULIN®-200 Oral Suspension (200 mg amoxicillin/28.5 mg clavulanate potassium per 5 mL) (GlaxoSmithKline Inc.) in 56 healthy, adult, Asian male subjects under fasting conditions. A summary of the comparative bioavailability data for Amoxicillin and Clavulanic acid from 52 and 53 subjects, respectively are presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amoxicillin (5 mL x 200 mg amoxicillin/28.5 mg clavulanate potassium per 5 mL) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng•h/mL)	14607.62 14869.90 (18.5)	15198.71 15531.63 (19.7)	96.1	93.7 - 98.5
AUC _I (ng•h/mL)	14760.15 15021.84 (18.4)	15349.82 15685.35 (19.7)	96.2	93.8 - 98.6
C _{max} (ng/mL)	5193.66 5374.73 (26.5)	5530.23 5770.91 (31.6)	93.9	90.0 - 98.0
T _{max} ³ (h)	1.25 (0.75 - 2.67)	1.00 (0.50 - 3.00)		
T _½ ⁴ (h)	1.42 (15.9)	1.47 (18.7)		

¹ AG-Amoxi Clav Suspension-200 (200 mg amoxicillin/28.5 mg clavulanate potassium per 5 mL) (Angita Pharma Inc.)

² PrCLAVULIN®-200 Oral Suspension (200 mg amoxicillin/28.5 mg clavulanate potassium per 5 mL) (GlaxoSmithKline Inc.), purchased in Canada

³ Expressed as the median (range) only

⁴ Expressed as the arithmetic mean (CV%) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Clavulanic acid (5 mL x 200 mg amoxicillin/28.5 mg clavulanate potassium per 5 mL) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng•h/mL)	1514.04 1605.11 (33.5)	1656.21 1751.83 (33.2)	91.4	86.1 - 97.1
AUC _I (ng•h/mL)	1520.49 1611.09 (33.3)	1663.02 1758.08 (33.1)	91.4	86.2 - 97.0
C _{max} (ng/mL)	697.43 757.87 (40.4)	765.34 825.91 (38.3)	91.1	85.3 - 97.4
T _{max} ³ (h)	1.00 (0.75 - 4.00)	1.00 (0.50 - 3.50)		
T _½ ⁴ (h)	1.13 (11.9)	1.14 (12.1)		

¹ AG-Amoxi Clav Suspension-200 (200 mg amoxicillin/28.5 mg clavulanate potassium per 5 mL) (Angita Pharma Inc.)

² PrCLAVULIN®-200 Oral Suspension (200 mg amoxicillin/28.5 mg clavulanate potassium per 5 mL) (GlaxoSmithKline Inc.), purchased in Canada

³ Expressed as the median (range) only

⁴ Expressed as the arithmetic mean (CV%) only

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.

Table 6 In vitro susceptibility of micro-organisms to amoxicillin-clavulanate

<p>Where clinical efficacy of amoxicillin-clavulanate has been demonstrated in clinical trials this is indicated with an asterisk (*).</p> <p>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.</p>
<p>Commonly susceptible species</p> <p>Gram-positive aerobes: <i>Enterococcus faecalis</i> <i>Streptococcus bovis</i> <i>Streptococcus pyogenes</i>[†] <i>Streptococcus agalactiae</i>[†] <i>Streptococcus spp.</i> (other β-hemolytic) [†] <i>Staphylococcus aureus</i> (methicillin susceptible)* <i>Staphylococcus saprophyticus</i> (methicillin susceptible) <i>Coagulase negative staphylococcus</i> (methicillin susceptible)</p>

<p><u>Gram-negative aerobes:</u> <i>Haemophilus influenzae*</i> <i>Haemophilus parainfluenzae</i> <i>Moraxella catarrhalis*</i> <i>Pasteurella multocida</i> <i>Proteus mirabilis</i></p>
<p><u>Gram positive anaerobes:</u> <i>Clostridium spp.</i> <i>Peptostreptococcus spp.</i></p>
<p><u>Gram-negative anaerobes:</u> <i>Eikenella corrodens</i> <i>Fusobacterium spp.</i> <i>Porphyromonas spp.</i> <i>Prevotella spp.</i></p>
<p>Species for which acquired resistance may be a problem</p>
<p><u>Gram-positive aerobes:</u> <i>Streptococcus pneumoniae</i>[†] <i>Viridans group streptococcus</i></p>
<p><u>Gram-negative aerobes:</u> <i>Escherichia coli*</i> <i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae*</i> <i>Klebsiella spp.</i> <i>Proteus vulgaris Salmonella spp. Shigella spp.</i></p>
<p><u>Gram-negative anaerobes:</u> <i>Bacteroides fragilis</i> <i>Bacteroides spp.</i> <i>Bacteroides thetiotamicron</i></p>
<p>Inherently resistant organisms</p>
<p><u>Gram-positive aerobes:</u> <i>Enterococcus faecium</i></p>
<p><u>Gram-negative aerobes:</u> <i>Acinetobacter spp.</i> <i>Aeromonas spp.</i> <i>Citrobacter spp.</i> <i>Enterobacter spp.</i> <i>Hafnia alvei</i> <i>Morganella morganii</i> <i>Providencia rettgeri</i> <i>Providencia stuartii</i> <i>Pseudomonas spp.</i> <i>Serratia marcescens</i></p>

Susceptibility Testing

Interpretive Criteria for Dilution and Disk Diffusion Testing

MIC and disk diffusion results should be interpreted according to Table 7 and are based on 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 7 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
<i>Haemophilus influenzae</i> (Note 1)	≤ 4/2	Not applicable (NA)	≥ 8/4	≥ 20	NA	≤ 19
<i>Enterobacteriaceae</i>	≤ 8/4	16/8	≥ 32/16	≥ 18	14 to 17	≤ 13
<i>Staphylococcus aureus</i> (Note 2)	≤ 4/2	NA	≥ 8/4	≥ 20	NA	≤ 19
<i>Streptococcus pneumoniae</i> (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 8 (CLSI M100-S21).

Table 8 Acceptable Quality Control Ranges for Amoxicillin/Clavulanate Potassium

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

General Toxicology

Single Dose

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. LD₅₀'s are shown in Table 9.

Table 9 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*

* 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 LD₅₀ of clavulanate potassium administered orally to 4 day old rats was determined to be 1,360 mg/kg. This compares with an oral LD₅₀ of greater than 10,000 mg/kg for adult rats. In these neonates, weight loss, diarrhea and abdominal distension were frequently observed following dosing.

Repeat Dose

Rats

Amoxicillin trihydrate and clavulanate potassium formulated in a 2:1 ratio were administered orally by gavage to 3 groups of rats each comprising 10 males and 10 females at doses of 20/10, 60/30 or 180/90 mg/kg/day for 4 weeks. A fourth group served as a control. Clinical condition and laboratory determinations were monitored and post-mortem and histopathologic determinations were carried out. There were no deaths during the study. Apart from the passage of slightly soft faeces in all treated groups, there were no adverse clinical signs. Body weight gain and food intake were comparable with controls. Water intake was increased in the male high dose group (8%, 16.3%, 16.8% and 12.2% for weeks 1, 2, 3 and 4, respectively). Female rats showed an overall increase in water consumption of 22%, 11% and 13% for low, intermediate and high dose groups, respectively.

Hematology and blood chemistry parameters were comparable to controls and within accepted normal limits. There was a statistically significant increase in urine output in the low and high dose male groups compared to controls. Macroscopic examination revealed an increased incidence of caecal enlargement in all treated groups and was marginally greatest at the high dose level. There was a statistically significant decrease in relative liver weights in both sexes (-9%, -14% and -9% for high, intermediate and low dose male groups, respectively and -12%, -16% and -6% for equivalent female groups). The mean relative thymus weight in the high dose male group was also significantly decreased by 21% and the relative heart weight in the intermediate dose female group was significantly reduced by 12% compared with control. Histological examination of the kidneys revealed minimal chronic inflammatory cell infiltration in a proportion of animals from all groups and was associated with occasional distended tubules and tubules characterized by basophilic staining of the cells of the epithelium.

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 3 groups of beagle dogs, each comprising 2 males and 2 females, at doses of 20/10, 60/30 or 180/90 mg/kg/day for 28 days. A fourth group served as a control. Clinical condition and laboratory determinations were monitored and post-mortem and histopathologic determinations were carried out. There were no deaths during the study. The high dose animals showed immediate signs of excessive salivation and severe vomiting was seen up to 2-1/2 hours after dosing. Vomiting was present but less severe in the female intermediate dose group. Body weight gain, food and water consumption and hematology were unaffected by treatment. The blood glucose level of the 60/30 mg/kg dosed male dogs was raised 25% on day 13 and 11% on day 27. These two dogs also showed increases in mean BUN (70%), total protein (5%) and albumin (10%) concentrations at the terminal bleed. The high dose group had reduced total protein (11%) and albumin (10%) levels on day 27. Female dogs dosed at 180/90 mg/kg had total protein levels reduced by 4% and total albumin levels reduced by 12% and 10% at interim and terminal bleeds.

All dose groups had SGOT activity slightly reduced on days 13 and 27. A pronounced enzymuria and minor proteinuria was seen in one male dog of the low dose group. All dosed groups had slight elevation in osmolality and electrolyte excretion. The low dose female group had a slight elevation in urinary alkaline phosphatase (UAP) activity while the urine concentration capacity of test animals was marginally raised. Macroscopic post-mortem examinations did not reveal any treatment-related changes. Histological examination revealed that in the colon of two female dogs in the high dose group, distended glands were prominent and were associated with chronic inflammatory changes both in the colon and in the mucosa of the duodenum in one instance. No other changes were observed that would be considered to be related to the administration of the test compound.

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 GI 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 GI 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.

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, foetal 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.

Perinatal 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. ^{Pr}CLAVULIN (Oral suspension, 125/31.25 mg per 5 mL, 200/28.5 mg per 5 mL, 250/62.5 mg per 5 mL, 400/57 mg per 5 mL), submission control 235606, Product Monograph, GlaxoSmithKline Inc. November 28, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAG-Amoxi Clav Suspension

Amoxicillin and Clavulanate Potassium for Oral Suspension House Standard

Read this carefully before you start taking **AG-Amoxi Clav Suspension** 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 **AG-Amoxi Clav Suspension**.

What is AG-Amoxi Clav Suspension used for?

AG-Amoxi Clav Suspension is an antibiotic used to treat bacterial infections.

How does AG-Amoxi Clav Suspension work?

AG-Amoxi Clav Suspension's ingredients work in 2 ways. Amoxicillin causes bacterial death. Clavulanic acid helps amoxicillin kill bacteria.

What are the ingredients in AG-Amoxi Clav Suspension?

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

Non-medicinal ingredients: Citric acid, golden syrup flavour, hypromellose, magnesium stearate, orange flavour, raspberry flavour, silica hydrophobic colloid, silicon dioxide, sodium benzoate, sucralose and xanthan gum.

AG-Amoxi Clav Suspension comes in the following dosage forms:

AG-Amoxi Clav Suspension Powder for Oral Suspension: 200 / 28.5 mg, 250 / 62.5 mg and 400 / 57 mg of amoxicillin / clavulanic acid per 5 mL (when reconstituted with purified water).

Do not use AG-Amoxi Clav Suspension if:

- You or your child are allergic to:
 - Amoxicillin
 - Beta-lactam antibiotics (such as penicillins and cephalosporins)
 - Any of the other ingredients of AG-Amoxi Clav Suspension (see **What are the ingredients in AG-Amoxi Clav Suspension**)
- You or your child have had a history of:
 - Jaundice (yellowing of the skin and/or eyes) or liver disease, after taking AG-Amoxi Clav Suspension
- You have mononucleosis

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AG-Amoxi Clav Suspension. Talk about any health conditions or problems you may

have, including if you:

- Have had an allergic reaction (such as a rash) when taking an antibiotic.
- Start to have a skin rash while taking AG-Amoxi Clav Suspension then:
 - stop taking AG-Amoxi Clav Suspension.
 - tell your healthcare professional right away.
- Have mononucleosis.
- Have liver or kidney problems.
- Are pregnant or planning to become pregnant.
- Are breastfeeding or planning to breastfeed:
 - The amoxicillin in AG-Amoxi Clav Suspension is passed into human breast milk. Talk about this with your healthcare professional.
- Are taking a birth control pill. Birth control pills may not work as well if you take AG-Amoxi Clav Suspension.

Other warnings you should know about:

- AG-Amoxi Clav Suspension treats only bacterial infections, not viral infections like the common cold.
- Although you may feel better early in treatment, use AG-Amoxi Clav Suspension exactly as directed.
- Using too much AG-Amoxi Clav Suspension 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).

Do not share your medicine.

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 AG-Amoxi Clav Suspension:

- Allopurinol or probenecid (for treatment of gout)
- Anticoagulants (used to prevent blood clots) such as warfarin
- Mycophenolate mofetil (suppressed the immune system)

How to take AG-Amoxi Clav Suspension:

You must use the medicine as instructed by your healthcare professional. Your healthcare professional will decide how much medicine you or your child need each day, and how many days you should take it for.

Treatment normally lasts 7 to 10 days. Your healthcare professional may ask you to take AG-Amoxi Clav Suspension for 48 to 72 hours more depending on how it works for you.

It is better to take AG-Amoxi Clav Suspension at the same time as a meal, but it still works without food. For the oral suspension:

- Shake before use.
- An accurate measuring device (like a measuring spoon) should be used to deliver the dose.

If there is anything you do not understand please ask your healthcare professional.

Usual dose:

Children:

For children aged 12 weeks (3 months) and older as directed by a healthcare professional:

Infection	Severity	Dosing Regimen	
		Twice a day* AG-Amoxi Clav Suspension-200 AG-Amoxi Clav Suspension-400	Three times a day 125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension*** AG-Amoxi Clav Suspension-250
Urinary tract	Mild to moderate	25mg per kg per day in divided doses every 12 hours	20mg per kg per day in divided doses every 8 hours
Skin and Soft Tissue	Severe	45mg per kg per day in divided doses every 12 hours	40mg per kg per day in divided doses every 8 hours
Lower Respiratory Tract, Sinusitis		45mg per kg per day in divided doses every 12 hours	40mg per kg per day in divided doses every 8 hours
Otitis Media (inner ear infection)**			40mg per kg per day in divided doses every 8 hours

*The twice a day regimen is recommended as it is associated with significantly less diarrhea.

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

***AG-Amoxi Clav Suspension is NOT available at the strength of 125 mg amoxicillin / 31.25 mg clavulanic acid.

Infants and children less than 12 weeks (3 months):

The recommended dose of AG-Amoxi Clav Suspension is 30 mg per kg per day in divided doses every 12 hours as directed by a healthcare professional. 125 mg amoxicillin / 31.25 mg clavulanic acid per 5 mL for oral suspension is recommended. AG-Amoxi Clav Suspension is NOT available at the strength of 125 mg amoxicillin / 31.25 mg clavulanic acid.

The children’s dosage should not exceed that recommended for adults. Children weighing more than 38 kg should be dosed according to the adult recommendations (*i.e., the usual adult dose is one (1) AG-Amoxi Clav 500 mg tablet every 12 hours. For more severe infections and infections*

of the lower respiratory tract, the dose should be one (1) AG-Amoxi Clav 875 mg tablet every 12 hours or one (1) AG-Amoxi Clav 500 mg tablet every 8 hours).

Patients with kidney problems:

If you have kidney problems, your doctor may adjust your dose.

Overdose:

If you think you, or a person you are caring for, have taken too much AG-Amoxi Clav Suspension, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you or your child miss a dose of AG-Amoxi Clav Suspension, take it as soon as you remember. However, if it is almost time for the next dose, do not take the missed dose. Instead, continue with your next scheduled dose. Do not try to make up for the missed dose by taking double the dose next time.

What are possible side effects from using AG-Amoxi Clav Suspension?

These are not all the possible side effects you may have when taking AG-Amoxi Clav Suspension. If you experience any side effects not listed here, tell your healthcare professional.

- very common side effect in adults can be diarrhea (loose, or watery bowel movements)
- common side effects can be:
 - A yeast infection of the nails, skin, mouth, vagina, stomach or urinary tract
 - Nausea (feeling sick) or vomiting
 - Diarrhea (loose, or watery bowel movements) in children
- uncommon side effects can be:
 - Indigestion and headache
 - Mild skin rash or itching
- very rare side effects can be:
 - Your tongue may change colour to yellow, brown or black, or look “hairy”
 - Your teeth may discolour
 - To reduce or prevent discolouring, brush your teeth thoroughly
 - Talk to your dentist or doctor if this does not go away

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			
Blood problems , with symptoms such as bleeding, or bruising, more easily than usual			✓

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	
Erythema multiforme (allergic skin reaction): skin reaction which results in itchy reddish-purple patches especially on the palms of the hands or soles of the feet			✓
VERY RARE			
Allergic reactions: difficulty breathing, fever, hives (itchy and red bumps on skin), itching, rash, swelling of your tongue or throat			✓
Central Nervous System (fits or seizures) problems such as convulsions (aseptic meningitis) inflammation of the protective membrane surrounding the brain			✓
<i>Clostridium difficile</i> colitis (bowel inflammation): with symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness			✓
Drug reaction with eosinophilia and systemic symptoms (DRESS) (severe life-threatening reaction): flu-like symptoms with fever, rash, swelling of the face or glands			✓
Kidney problems with symptoms such as blood in the urine which may be associated with a rash, fever, joint pain, or a reduction in passing water (urination)			✓
Liver problems with symptoms such as yellowing of the skin and/or eyes, or dark-coloured urine, nausea, vomiting, abdominal pain, fever or unusual tiredness			✓
Severe skin reactions: (Steven-Johnson syndrome and toxic epidermal necrolysis) blisters and peeling skin, particularly around the mouth, nose, eyes, and genitals; or more severely, blisters and peeling skin on a lot of the			

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	
body; body aches or fever (bullous exfoliative dermatitis) red itchy scaly rash with blisters and bumps under the skin (exanthemous pustulosis) widespread red skin rash with small blisters containing pus			✓
Vasculitis (blood vessel inflammation): red or purple raised spots on the skin, fatigue, fever, numbness or weakness			✓
UNKNOWN FREQUENCY			
Cardiovascular Kounis syndrome: chest pain which can be a sign of a potentially serious allergic reaction			✓

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/adverse-reaction-reporting.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:

Store powder in a dry place at room temperature (15-25°C). Use the powder only if its colour is white to off-white.

The reconstituted AG-Amoxi Clav Suspension-250 oral suspension should be stored under refrigeration (2-8°C) and should be used within 10 days. Dispose of any unused suspension 10

days after it is first made up.

The reconstituted AG-Amoxi Clav Suspension-200 and AG-Amoxi Clav Suspension-400 oral suspensions should be stored under refrigeration (2-8°C) and should be used within 7 days. Dispose of any unused suspension 7 days after it is first made up.

Keep bottle tightly closed at all times.

Keep out of reach and sight of children.

If you want more information about AG-Amoxi Clav Suspension:

- 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>); or by calling 1-450-449-9272.

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