Product Monograph, including Patient Medication Information

PrM-AMOXI CLAV

Amoxicillin and clavulanate potassium for oral suspension,
House Std.

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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Product Monograph

PrM-AMOXI CLAV

Amoxicillin and clavulanate potassium for oral suspension, House Std.
400 mg amoxicillin and 57 mg clavulanic acid / 5 mL
(as Amoxicillin Trihydrate and Clavulanate Potassium)

Antibiotic and β-Lactamase Inhibitor

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.

Indications and Clinical Use

M-AMOXI CLAV (amoxicillin / clavulanate potassium) is indicated for the treatment of the following infections when caused by M-AMOXI CLAV-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 M-AMOXI CLAV is indicated only for the conditions listed above, infections caused by ampicillin (amoxicillin) susceptible organisms are also amenable to M-AMOXI CLAV treatment due to its amoxicillin content. Furthermore, mixed infections caused by organisms susceptible to ampicillin (amoxicillin) and β-lactamase producing organisms susceptible to M-AMOXI CLAV should not require the addition of another antibiotic.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of M-AMOXI CLAV and other antibacterial drugs, M-AMOXI CLAV 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.

Contraindications

The use of M-AMOXI CLAV (amoxicillin / clavulanate potassium) 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 **COMPOSITION** and **AVAILABILITY OF DOSAGE FORMS**.

M-AMOXI CLAV is contraindicated in patients where infectious mononucleosis is either suspected or confirmed.

M-AMOXI CLAV is contraindicated in patients with a previous history of amoxicillin and clavulanate potassium -associated jaundice/hepatic dysfunction.

Warnings

Serious and occasionally fatal hypersensitivity reactions, including angioedema, anaphylactic/anaphylactoid and 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) have been reported in patients on penicillin therapy, including M-AMOXI CLAV (amoxicillin / clavulanate potassium) (see **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 M-AMOXI CLAV, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens (see **CONTRAINDICATIONS**).

If an allergic reaction occurs, the administration of M-AMOXI CLAV 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.

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.

M-AMOXI CLAV should be used with caution in patients with evidence of hepatic dysfunction. 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 **CONTRAINDICATIONS** and **ADVERSE REACTIONS - Liver**).

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 **OVERDOSAGE**).

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing M-AMOXI CLAV 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.

Precautions

General

Periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy with M-AMOXI CLAV (amoxicillin / clavulanate potassium).

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

The occurrence of a morbilliform rash following the use of ampicillin in patients with infectious mononucleosis is well documented[5]. This reaction has also been reported following the use of amoxicillin[4]. A similar reaction would also be expected with M-AMOXI CLAV.

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

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 **ADVERSE REACTIONS**).

Renal

Amoxicillin and clavulanate potassium is excreted mostly by the kidney. In renal impairment, dosage adjustments should be made based on the maximum recommended level of amoxicillin (see **DOSAGE AND ADMINISTRATION**).

Pregnancy

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.

Nursing Mothers

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 M-AMOXI CLAV is to be administered to a nursing mother.

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.

Pediatric Use

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of M-AMOXI CLAV should be modified in pediatric patients younger than 12 weeks (3 months) (see **DOSAGE AND ADMINISTRATION, Children)**.

In infants 12 weeks (3 months) of age or older and in children, b.i.d. use of the M-AMOXI CLAV 400 mg formulation is recommended because of a significantly reduced incidence of diarrhea with the b.i.d. regimen (see **ADVERSE REACTIONS**).

Adverse Reactions

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

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 M-AMOXI CLAV (amoxicillin and clavulanate potassium) at the start of the meal.

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%; $p =0.054$).

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.

Hypersensitivity Reactions

Erythematous macropapular rash, urticaria, anaphylaxis, hypersensitivity vasculitis and pruritus. A morbilliform rash in patients with mononucleosis. 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. Interstitial nephritis can occur rarely. Drug reaction with eosinophilia and systemic symptoms (DRESS) has also been reported (see **WARNINGS**).

Note

If any hypersensitivity dermatitis reaction occurs, treatment with M-AMOXI CLAV should be discontinued.

Liver

Transient hepatitis and cholestatic jaundice have been reported rarely. These events have been noted with other penicillins and cephalosporins. The hepatic 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. The hepatic events are usually reversible. However, in extremely rare circumstances, deaths have been reported. These have almost always been cases associated with serious underlying

disease or concomitant medications. 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.

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.

CNS Effects

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

Renal and Urinary Tract Disorders

Very rare: crystalluria and interstitial nephritis (see **SYMPTOMS and TREATMENT OF OVERDOSAGE**).

Other

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

Symptoms and Treatment of Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 overdosage 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 **WARNINGS** for use).

In the case of overdosage, discontinue M-AMOXI CLAV (amoxicillin and clavulanate potassium) 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. Amoxicillin and clavulanate potassium can be removed from the circulation by haemodialysis. 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 overdosage 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[9].

Dosage and Administration

While M-AMOXI CLAV (amoxicillin and clavulanate potassium) 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.

Dosage adjustment in renal impairment is based on the maximum recommended level of amoxicillin. M-AMOXI CLAV presentations with a 7:1 ratio of amoxicillin: clavanulate (i.e. the M-AMOXI CLAV 400 mg / 57 mg per 5 mL oral suspension) should be used only in patients with a creatinine clearance of more than 30 ml/min (see **Renal Impairment and Hemodialysis**).

Children

Based on the amoxicillin component, M-AMOXI CLAV should be dosed as follows in patients aged 12 weeks (3 months) and older:

Infection	Severity	**Dosing Regimen**	
		B.I.D.* 200 mg amoxicillin / 28.5 mg Clavulanic Acid*** 400 mg amoxicillin / 57 mg Clavulanic Acid	**T.I.D.** 125 mg amoxicillin / 31.25 mg clavulanic acid*** 250 mg amoxicillin / 62.5 mg clavulanic acid***
Urinary tract Skin and Soft Tissue	Mild to moderate	25 mg/kg/day in divided doses every 12 hours	
	Severe	45 mg/kg/day in divided doses every 12 hours	
Lower Respiratory Tract Sinusitis		45 mg/kg/day in divided doses every 12 hours	
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.
***M-AMOXI-CLAV is only available at the strength of 400 mg amoxicillin / 57 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.

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 M-AMOXI CLAV 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.

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.

Table 1 below may be used as a guide to determine the dosage of oral suspension (M-AMOXI CLAV (400 mg / 57 mg pr 5 mL)) according to body weight.

Table 1 Pediatric Dosage Schedule for M-AMOXI CLAV 400 mg / 57 mg per 5 mL (in a ration of 7:1) Oral Suspension

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)	M-AMOXI CLAV (400 mg / 57 mg)	(mg)	M-AMOXI CLAV (400 mg / 57 mg)
05	143	0.8	257	1.4
07	200	1.1	360	2.0
10	286	1.6	514	2.8
12	343	1.9	617	3.4
14	400	2.2	720	3.9
16	458	2.5	822	4.5
18	515	2.8	925	5.1
20	572	3.1	1028	5.6
25	715	3.9	1285	7.0
30	858	4.7	1542	8.4
35	1001	5.5	1799	9.8
38	1087	5.9	1953	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 the oral suspension.

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

Renal Impairment

Children

Creatinine clearance greater than 30 ml/min	No adjustment necessary.
Creatinine clearance 10 to 30 ml/min	15/3.75 mg/kg given twice daily (maximum 500/125 mg twice daily).
Creatinine clearance less than 10 ml/min	15/3.75 mg/kg given as a single daily dose (maximum 500/125 mg).

In the majority of cases, parenteral therapy, where available, may be preferred.

Haemodialysis

Children

15/3.75 mg/kg/day given as a single daily dose.

Prior to haemodialysis 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 haemodialysis.

M-AMOXI CLAV (400 mg/57 mg per 5 mL) oral suspension (7:1 ratio amoxicillin:clavanulate) should only be used in patients with a creatinine clearance of more than 30 ml/min.

Pharmaceutical Information

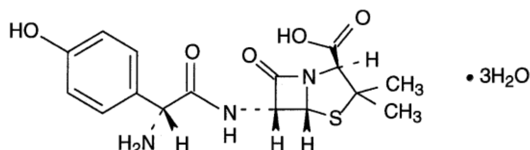
Drug Substance

Amoxicillin

Proper Name: Amoxicillin Trihydrate

Chemical Name: (2S,5R,6R)-6-[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

Structural Formula:



Molecular Formula: $C_{16}H_{19}N_3O_5S.3H_20$

Molecular Weight: 419.47 g/mol (trihydrate)
365.41 g/mol (anhydrous)

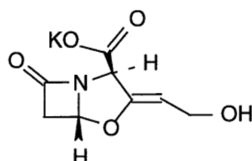
Description: Amoxicillin trihydrate is a white or almost white highly hydroscopic crystalline powder. Amoxicillin trihydrate is slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Clavulanate Potassium

Proper Name: Clavulanate Potassium

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

Structural Formula:



Molecular Formula: $C_8H_8NO_5K$

Molecular Weight: 199.16 g/mol (free acid)
237.25 g/mol (potassium salt)

Description: A white or almost white powder. Clavulanante Potassium is freely soluble in water, slightly soluble in ethanol (96 per cent) and very slightly soluble in acetone.

Composition

M-AMOXI CLAV powder for oral suspension contain amoxicillin as the trihydrate and clavulanic acid as the potassium salt in a ratio of 7:1 (400 mg / 57 mg).

M-AMOXI CLAV 400 mg/57 mg per 5 mL:
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) and the following non-medicinal ingredients (in alphabetical order): carmellose sodium, citric acid anhydrous, colloidal silica, mannitol, microcrystalline cellulose, silicon dioxide, sodium citrate anhydrous, sucralose, tutti frutti flavour, vanilla flavour and, xanthan gum.

Reconstitution:

Reconstitute Powder for Oral Suspension with purified water. Measure 62 mL of water and add to the bottle in two portions (31 mL each). Shake vigorously after each addition.

M-AMOXI CLAV (400 mg / 57 mg):
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.

Package size	*Reconstituted volume*	*Amount of water required for the strength of 400 mg / 57 mg*
100 mL bottle	70 mL	62 mL

Stability and Storage Recommendations

Powder: Store in the original carton to protect from light and moisture at room temperature (15°C – 30°C). Use the powder only if its appearance is white to off-white.

Reconstituted 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.

Availability of Dosage Forms

M-AMOXI CLAV is available as a powder for oral suspension.

M-AMOXI CLAV (400 mg / 57 mg)
Each 5 mL of white to creamy white reconstituted suspension with vanilla odour contains 400 mg of amoxicillin as the trihydrate and 57 mg of clavulanic acid as the potassium salt (in a ratio of 7:1). Bottles of 70 mL (reconstitution volume).

Clinical Trials

Comparative Bioavailability Studies

A double blind, randomized, two-treatment, two-period, two-sequence, cross-over, single-dose oral comparative bioequivalence study of M-AMOXI CLAV 400 mg and 57 mg /5 mL powder for oral suspension (Mantra Pharma Inc.) and PrCLAVULIN-400 powder for oral suspension (GlaxoSmithKline Inc.) was conducted in 36 healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from 33 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amoxicillin (5 mL × 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)	24134.76 24601.45 (19.85)	23918.43 24376.25 (20.47)	100.9	98.5 – 103.4
AUC_I (ng·h/mL)	24449.07 24914.62 (19.69)	24248.10 24699.05 (20.21)	100.8	98.5 – 103.2
C_{max} (ng/mL)	7539.47 7782.98 (25.40)	7704.11 7962.79 (26.87)	97.9	93.8 – 102.0
T_{max}[3] (h)	1.75 (0.75 - 3.00)	1.75 (0.75 - 2.50)		
$T_{½}$[4] (h)	1.42 (16.22)	1.40 (14.14)		

[1] M-AMOXI CLAV (amoxicillin as amoxicillin trihydrate and clavulanic acid as clavulanate potassium) powder for oral suspension, 400 mg/57 mg per 5 mL (Mantra Pharma Inc.)
[2] PrClavulin-400 (amoxicillin as amoxicillin trihydrate and clavulanic acid as clavulanate potassium) powder for oral suspension, 400 mg/57 mg per 5 mL (GlaxoSmithKline Inc.)
[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 × 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)	4063.06 4386.21 (33.61)	3854.98 4190.57 (37.94)	105.4	95.4 – 116.4
AUC_I (ng·h/mL)	4136.59 4455.46 (33.15)	3931.91 4261.46 (37.39)	105.2	95.6 – 115.8
C_{max} (ng/mL)	1613.55 1726.74 (32.29)	1590.19 1692.52 (34.49)	101.5	92.4 – 111.5

Clavulanic acid (5 mL × 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
T_{max}[3] (h)	1.75 (0.75 - 3.00)	1.75 (0.75 - 2.50)		
$T_{½}$[4] (h)	1.42 (16.22)	1.40 (14.14)		

[1] M-AMOXI CLAV (amoxicillin as amoxicillin trihydrate and clavulanic acid as clavulanate potassium) powder for oral suspension, 400 mg/57 mg per 5 mL (Mantra Pharma Inc.)
[2] [Pr]Clavulin-400 (amoxicillin as amoxicillin trihydrate and clavulanic acid as clavulanate potassium) powder for oral suspension, 400 mg/57 mg per 5 mL (GlaxoSmithKline Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

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 2 *In vitro* susceptibility of micro-organisms to amoxicillin-clavulanate

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
<u>Gram-positive aerobes:</u> *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)
<u>Gram-negative aerobes:</u> *Haemophilus influenzae** *Haemophilus parainfluenzae* *Moraxella catarrhalis** *Pasteurella multocida* *Proteus mirabilis*
<u>Gram positive anaerobes:</u> *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*

Susceptibility Testing

Interpretive Criteria for Dilution and Disk Diffusion Testing

MIC and disk diffusion results should be interpreted according to Table 3 and are based on CLSI methodologies (CLSI M7-A9[10] and M2-A10[11]). 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 3 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 4 (CLSI M100-S21[12]).

Table 4 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)

PHARMACOLOGY

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 M-AMOXI CLAV is highly protein-bound; clavulanic acid has been found to be approximately 30% bound to human serum protein and amoxicillin approximately 20% bound.

Children

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 5 below.

Table 5 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					
Children	(Years)		(mg/kg)	1/3	2/3	1	2	3	4
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 6 below.

Table 6 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.

TOXICOLOGY

Acute Toxicology

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 7.

Table 7 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 LD_{50} of clavulanate potassium administered orally to 4 day old rats was determined to be 1,360 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 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.

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 21/2 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.

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 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 Studies

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 F_1 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 misplace 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 F_1 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 F_1 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 F_1 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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrM-AMOXI CLAV
Amoxicillin and clavulanate potassium for oral suspension, House Std.

Read this carefully before you start taking **M-AMOXI CLAV** (amoxicillin / clavulanate potassium) 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 M-AMOXI CLAV.

What is M-AMOXI CLAV used for?

M-AMOXI CLAV is an antibiotic used to treat bacterial infections.

How does M-AMOXI CLAV work?

M-AMOXI CLAV's ingredients work in 2 ways. Amoxicillin causes bacterial death. Clavulanic acid helps amoxicillin kill bacteria.

What are the ingredients in M-AMOXI CLAV?

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

Non-medicinal ingredients: carmellose sodium, citric acid anhydrous, colloidal silica, mannitol, microcrystalline cellulose, silicon dioxide, sodium citrate anhydrous, sucralose, tutti frutti flavour, vanilla flavour and, xanthan gum.

M-AMOXI CLAV comes in the following dosage forms:
M-AMOXI CLAV Powder for Oral Suspension: 400/57mg of amoxicillin / clavulanic acid per 5mL (when reconstituted with purified water).

Do not use if:

- you or your child are allergic to:
  - amoxicillin.
  - beta-lactam antibiotics (such as penicillins and cephalosporins).
  - any of the other ingredients of M-AMOXI CLAV. See **What are the ingredients in M-AMOXI CLAV**.
- you or your child have had a history of:
  - jaundice (yellowing of the skin and/or eyes) or liver disease, after taking M-AMOXI CLAV.
- you have mononucleosis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take M-AMOXI CLAV. Talk about any health conditions or problems you may have, including if you or your child:

- have had an allergic reaction (such as a rash) when taking an antibiotic.

- start to have a skin rash while taking M-AMOXI CLAV then:
  - stop taking M-AMOXI CLAV.
  - 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 M-AMOXI CLAV 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 M-AMOXI CLAV.

Other warnings you should know about:

- M-AMOXI CLAV treats only bacterial infections, not viral infections like the common cold.
- Although you may feel better early in treatment, use M-AMOXI CLAV exactly as directed.
- Using too much M-AMOXI CLAV 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 or your child are taking, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with M-AMOXI CLAV:

- 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 M-AMOXI CLAV:

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 M-AMOXI CLAV for 48 to 72 hours more depending on how it works for you.

It is better to take M-AMOXI CLAV at the same time as a meal, but it still works without food.

For the oral suspension:

- shake before use.
- Please administer using the syringe provided by your pharmacist to ensure the correct dose is given.

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* 200 mg amoxicillin / 28.5 mg Clavulanic Acid*** 400 mg amoxicillin / 57 mg Clavulanic Acid	Three times a day 125 mg amoxicillin and 31.25 mg clavulanic acid*** 250 mg amoxicillin and 62.5 mg clavulanic acid***
Urinary tract	Mild to moderate	25 mg per kg per day in divided doses every 12 hours	
Skin and Soft Tissue	Severe	45 mg per kg per day in divided doses every 12 hours	
Lower Respiratory Tract, Sinusitis		45 mg per kg per day in divided doses every 12 hours	
Otitis Media (inner ear infection)**			40 mg 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.
***M-AMOXI-CLAV is only available at the strength of 400 mg amoxicillin / 57 mg clavulanic acid.

Infants and children less than 12 weeks (3 months):
The recommended dose of M-AMOXI CLAV is 30mg per kg per day in divided doses every 12 hours as directed by a healthcare professional.

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.

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

Overdose:

If you think you have taken too much M-AMOXI CLAV, contact your 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 M-AMOXI CLAV, 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 M-AMOXI CLAV?

Using M-AMOXI CLAV may cause side effects:
- that are not all listed here. If not listed here, contact your healthcare professional. Side effects may also be explained in Warnings and Precautions, or if they are serious they will be listed in the Serious Side Effects Table below.

While taking M-AMOXI CLAV a very common side effect in adults can be diarrhea (loose, or watery bowel movements).

While taking M-AMOXI CLAV 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.

While taking M-AMOXI CLAV uncommon side effects can be:
- indigestion and headache
- mild skin rash or itching

While taking M-AMOXI CLAV, 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			
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			✓
Blood problems, with symptoms such as bleeding, or bruising, more easily than usual			✓
VERY RARE			
Allergic reactions: difficulty breathing, fever, hives (itchy and red bumps on skin), itching, rash, swelling of your tongue or throat			✓

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	
Drug reaction with eosinophilia and systemic symptoms (DRESS) (severe life-threatening reaction): flulike symptoms with fever, rash, swelling of the face or glands			✓
Vasculitis (blood vessel inflammation): red or purple raised spots on the skin, fatigue, fever, numbness or weakness			✓
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 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			✓
Central Nervous System (fits or seizures) problems such as convulsions **(aseptic meningitis)** inflammation of the protective membrane surrounding the brain			✓
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			✓
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)			✓
Clostridium difficile colitis (bowel inflammation): with symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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 more 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:

Powder: Store at room temperature (15-30°C) in its original carton to protect from light and moisture. Use the powder only if its colour is white to off-white.

The reconstituted M-AMOXI CLAV oral suspension should be stored under refrigeration (2°C to 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 M-AMOXI CLAV:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the latest available 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 contacting Mantra Pharma Inc., at: 1-833-248-7326 or medinfo@mantrapharma.ca.

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