PRODUCT MONOGRAPH

PrNOVO-CLAVAMOXIN 125

PrNOVO-CLAVAMOXIN 250

(amoxicillin and clavulanate potassium)

Powder for Oral Suspension

USP

PrNOVO-CLAVAMOXIN 875

(amoxicillin and clavulanate potassium)

Tablets

USP

Antibiotic and β-Lactamase Inhibitor

Novopharm Limited
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Canada

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THERAPEUTIC CLASSIFICATION

Antibiotic and β-Lactamase Inhibitor

ACTION AND CLINICAL PHARMACOLOGY

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 ß-lactamases of some microorganisms and allows amoxicillin to inhibit amoxicillin (ampicillin) resistant organisms which produce clavulanic acid sensitive ß-lactamases.

A comparative, two-way, single-dose bioavailability study was performed on NOVO-CLAVAMOXIN 125 (amoxicillin 125 mg/clavulanic acid 31.25 mg per 5 mL) Suspension and CLAVULIN®-125F Suspension. The pharmacokinetic data calculated for the two amoxicillin/clavulanic acid formulations are tabulated below:

Pharmacokinetic Indices for Amoxicillin:

	Geometric Mean Arithmetic Mean (C.V.)		
	Novo-Clavamoxin 125 20 mL	Clavulin®-125F** 20 mL	Ratio of Geometric Means (%)
AUC_T (μg•hr/mL)	18.70 18.97 (16)	19.98 20.34 (17)	94
AUC_I (μg•hr/mL)	19.55 19.83 (16)	20.88 21.23 (16)	94
C_{max} (μg/mL)	7.60 7.78 (21)	7.70 7.99 (25)	99
T_{max}* (hr)	1.40 (0.41)	1.19 (0.32)	---
$T_{½}$* (hr)	1.13 (0.16)	1.12 (0.13)	---

*The T_{max} and T½ parameters are expressed as the arithmetic means (standard deviation).
**Clavulin® manufactured by SmithKline Beecham Pharma Inc., Oakville, Ontario, Canada.

Pharmacokinetic Indices for Clavulanic Acid:

	Geometric Mean Arithmetic Mean (C.V.)		
	Novo-Clavamoxin 125 20 mL	Clavulin®-125F** 20 mL	Ratio of Geometric Means (%)
AUC_T (μg•hr/mL)	5.31 5.61 (35)	5.02 5.28 (33)	106
AUC_I (μg•hr/mL)	5.89 6.23 (36)	5.58 5.87 (34)	106
C_{max} (μg/mL)	2.78 2.89 (27)	2.90 3.02 (28)	96
T_{max}* (hr)	0.92 (0.15)	0.93 (0.13)	---
$T_{½}$* (hr)	1.19 (0.72)	1.00 (0.38)	---

*The T_{max} and T½ parameters are expressed as the arithmetic means (standard deviation).
**Clavulin® manufactured by SmithKline Beecham Pharma Inc., Oakville, Ontario, Canada.

A comparative, two-way, single-dose bioavailability study was performed on NOVO-CLAVAMOXIN 250 (amoxicillin 250 mg/clavulanic acid 62.5 mg/5 mL) Suspension and CLAVULIN®-250F Suspension. The pharmacokinetic data calculated for the two amoxicillin/clavulanic acid formulations are tabulated below:

Pharmacokinetic Indices for Amoxicillin:

	Geometric Mean Arithmetic Mean (C.V.)		
	Novo-Clavamoxin 250 10 mL	Clavulin®-250F** 10 mL	Ratio of Geometric Means (%)
AUC_T (μg•hr/mL)	20.05 20.29 (16)	19.62 19.85 (15)	102
AUC_I (μg•hr/mL)	20.76 21.01 (15)	20.37 20.60 (15)	102
C_{max} (μg/mL)	8.77 8.98 (23)	8.46 8.67 (23)	104
T_{max}* (hr)	1.21 (0.25)	1.23 (0.30)	---
$T_{½}$* (hr)	1.21 (0.24)	1.28 (0.40)	---

*The T_{max} and T½ parameters are expressed as the arithmetic means (standard deviation).
**Clavulin® manufactured by SmithKline Beecham Pharma Inc., Oakville, Ontario, Canada.

Pharmacokinetic Indices for Clavulanic Acid:

	Geometric Mean Arithmetic Mean (C.V.)		
	Novo-Clavamoxin 250 10 mL	Clavulin®-250F** 10 mL	Ratio of Geometric Means (%)
AUC_T (μg•hr/mL)	4.97 5.26 (32)	4.98 5.22 (30)	100

	Geometric Mean Arithmetic Mean (C.V.)		
AUC_I (μg•hr/mL)	5.51 5.79 (31)	5.57 5.83 (30)	99
C_{max} (μg/mL)	2.87 3.00 (30)	2.81 2.93 (27)	102
T_{max}* (hr)	0.94 (0.21)	0.98 (0.29)	---
$T_{½}$* (hr)	0.93 (0.20)	1.07 (0.45)	---

*The T_{max} and T½ parameters are expressed as the arithmetic means (standard deviation).
**Clavulin® manufactured by SmithKline Beecham Pharma Inc., Oakville, Ontario, Canada.

A comparative, two-way, single-dose bioavailability study was performed on NOVO-CLAVAMOXIN 875 (amoxicillin 875 mg/clavulanic acid 125 mg) Tablets and CLAVULIN®-875 Tablets. The pharmacokinetic data calculated for the two amoxicillin/clavulanic acid formulations are tabulated below:

Pharmacokinetic Indices for Amoxicillin:

Parameter	Geometric Mean Arithmetic Mean (CV)		% Ratio of Geometric Means
	Novo-Clavamoxin 875 1 tablet	CLAVULIN®-875** 1 tablet	
AUC_T (ng.h/mL)	31885 32523 (19.2%)	31201 31949 (21.0%)	102%
AUC_I (ng.h/mL)	32475 33117 (19.1%)	31769 32513 (20.8%)	102%
C_{MAX} (ng/mL)	9855 10205.4 (27.0%)	9940 10506.5 (32.8%)	99%
T_{MAX}* (h)	2.215 (46.3%)	2.078 (46.4%)	-
$T_{½}$* (h)	1.266 (23.4%)	1.200 (16.0%)	-

*The T_{max} and T½ parameters are expressed as the arithmetic means (CV%).
**Clavulin® manufactured by SmithKline Beecham Pharma Inc., Oakville, Ontario, Canada.

Pharmacokinetic Indices for Clavulanic Acid:

Parameter	Geometric Mean Arithmetic Mean (CV)		% Ratio of Geometric Means
	Novo-Clavamoxin 875 1 tablet	CLAVULIN®-875** 1 tablet	
AUC_T (ng.h/mL)	4220.8 4804.4 (45.8%)	4387.3 4941.5 (42.1%)	96%
AUC_I (ng.h/mL)	4337.6 4921.0 (44.9%)	4517.7 5054.0 (41.4%)	96%
C_{MAX} (ng/mL)	2002.1 2324.5 (47.4%)	2068.1 2329.2 (41.8%)	97%
T_{MAX}* (h)	1.341 (36.3%)	1.232 (35.1%)	-
$T_{½}$* (h)	1.096 (15.9%)	1.085 (17.2%)	-

*The T_{max} and T½ parameters are expressed as the arithmetic means (CV%).

**Clavulin® manufactured by SmithKline Beecham Pharma Inc., Oakville, Ontario, Canada.

INDICATIONS AND CLINICAL USE

NOVO-CLAVAMOXIN (amoxicillin:clavulanic acid) is indicated for the treatment of the following infections when caused by NOVO-CLAVAMOXIN-susceptible strains of the designated bacteria:

Sinusitis when caused by ß-lactamase producing strains of *H. influenzae* or *Moraxella (Branhamella) catarrhalis.*

Otitis Media when caused by ß-lactamase producing strains of *H. influenzae* or *Moraxella (Branhamella) catarrhalis.*

Lower Respiratory Tract Infections when caused by ß-lactamase producing strains of *H. influenzae, K. pneumoniae, S. aureus* or *Moraxella (Branhamella) catarrhalis*.

Skin and Soft Tissue Infections when caused by ß-lactamase producing strains of *S. aureus.*

Urinary Tract Infections when caused by ß-lactamase producing strains of *E. coli*.

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

Since susceptibility to amoxicillin-clavulanate will vary with geography and time, NOVO-CLAVAMOXIN (amoxicillin : clavulanic acid) should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data. Appropriate microbiological sampling and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to NOVO-CLAVAMOXIN. However, when there is reason to believe an infection may involve any of the β- lactamase producing organisms listed above, therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies. Once these results are known, therapy should be adjusted if appropriate.

CONTRAINDICATIONS

The use of NOVO-CLAVAMOXIN (amoxicillin:clavulanic acid) 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.

NOVO-CLAVAMOXIN is contraindicated in patients where infectious mononucleosis is either suspected or confirmed.

NOVO-CLAVAMOXIN is contraindicated in patients with a previous history of NOVO-CLAVAMOXIN-associated jaundice/hepatic dysfunction.

WARNINGS

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients on penicillin therapy, including amoxicillin:clavulanic acid. 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 NOVO-CLAVAMOXIN (amoxicillin:clavulanic acid), careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens.

If an allergic reaction occurs, the administration of NOVO-CLAVAMOXIN should be discontinued and appropriate therapy should be instituted. Serious 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:clavulanic acid 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.

NOVO-CLAVAMOXIN should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin:clavulanic acid 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**).

PRECAUTIONS

General

Periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy with NOVO-CLAVAMOXIN (amoxicillin : clavulanic acid).

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy with NOVO-CLAVAMOXIN. If superinfection should occur (usually involving *Aerobacter*, *Pseudomonas* or *Candida*), the administration of NOVO-CLAVAMOXIN 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 NOVO-CLAVAMOXIN.

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 : clavulanic acid. 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/clavulanic acid is excreted mostly by the kidney. There is insufficient data to make specific dosage recommendations for patients with renal dysfunction. However, either a reduction in dose level or an extension in dose interval in proportion to the degree of loss of renal function will be needed.

Pregnancy

In a single study in women with preterm, premature rupture of the fetal membranes (pPROM), it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with

an increased risk of necrotising enterocolitis in neonates. Use should be avoided 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 NOVO-CLAVAMOXIN 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 : clavulanic acid. If coadministration is necessary, the prothrombin time or INR should be carefully monitored upon antibiotic addition or withdrawal.

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

ADVERSE REACTIONS

The following adverse reactions have been observed during therapy with amoxicillin:clavulanic acid:

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

A U.S./Canadian clinical trial compared a 10-day amoxicillin/clavulanic acid b.i.d. regimen (45/6.4 mg/kg/day q12h) with a 10-day amoxicillin/clavulanic acid 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).

Data from two pivotal studies in 1,191 patients treated for either lower respiratory tract infections or complicated urinary tract infections compared a regimen of 875 mg amoxicillin/clavulanic acid tablets q12h with 500 mg amoxicillin/clavulanic acid tablets dosed q8h.

The most frequently reported adverse event was diarrhea; incidence rates were similar (14.9% and 14.3% respectively) for the 875 mg q12h and 500 mg q8h dosing regimens. However, there was a statistically significant difference in rates of moderate/severe diarrhea between the regimens: 3.4% for 875 mg q12h dosing versus 5.9% for the 500 mg q8h dosing.

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 have been reported. Other reactions including angioedema, toxic epidermal necrolysis and bullous exfoliative dermatitis, and acute generalised exanthematous pustulosis (AGEP) as in the case of other ß-lactam antibiotics, have been seen rarely. Interstitial nephritis can occur rarely.

Note
Urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and if necessary systemic corticosteroids. Whenever such reactions occur, NOVO -CLAVAMOXIN should be discontinued, unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to NOVO-CLAVAMOXIN therapy.

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/clavulanic acid 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 ß-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
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, black hairy tongue and stomatitis. 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.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect**.**

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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 NOVO-CLAVAMOXIN, 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. NOVO-CLAVAMOXIN can be removed from the circulation by haemodialysis. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. 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].

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

DOSAGE AND ADMINISTRATION

While NOVO-CLAVAMOXIN 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/clavulanic acid have been established in clinical trials where amoxicillin/clavulanic acid was taken without regard to meals.

Adults

For severe infections and infections of the lower respiratory tract, the dose should be 1 NOVO-CLAVAMOXIN 875 mg tablet every 12 hours.

Children

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

Infection	Severity	Dosing Regimen	
		B.I.D.*	T.I.D.
Urinary Tract	Mild to moderate	25 mg/kg/day in divided doses every 12 hours	20 mg/kg/day in divided doses every 8 hours

		Dosing Regimen	
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
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.

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 NOVO-CLAVAMOXIN is 30 mg/kg/day divided q12h, based on the amoxicillin component. Clavulanate elimination is unaltered in this age group. Use of 125 mg/5 mL oral suspension is recommended for this age group.

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 NOVO-CLAVAMOXIN 125 or NOVO-CLAVAMOXIN 250 oral suspension according to body weight**.**

Table 1: Pediatric Dosage Schedule for NOVO-CLAVAMOXIN 125 and NOVO-CLAVAMOXIN 250 Oral Suspensions

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)	NOVO-CLAVAMOXIN 125	NOVO-CLAVAMOXIN 250	(mg)	NOVO-CLAVAMOXIN 125	NOVO-CLAVAMOXIN 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

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)	NOVO-CLAVAMOXIN 125	NOVO-CLAVAMOXIN 250	(mg)	NOVO-CLAVAMOXIN 125	NOVO-CLAVAMOXIN 250
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, NOVO-CLAVAMOXIN 125 and NOVO-CLAVAMOXIN 250.*

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

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

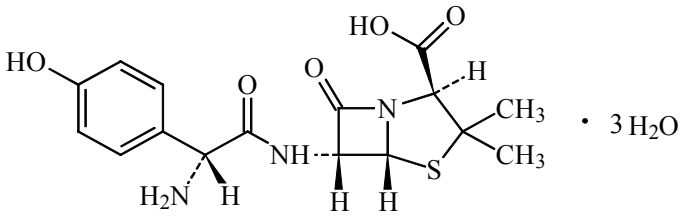
Tradename: NOVO-CLAVAMOXIN

Proper Name: Amoxicillin: Clavulanate Potassium

Amoxicillin Trihydrate:

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

Structural Formula:



Molecular Formula: $C_{16}H_{19}N_3O_5S \cdot 3H_2O$

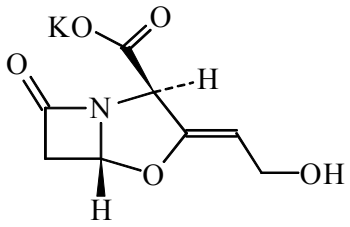
Molecular Weight: 419.46 (trihydrate)

Description: Amoxicillin trihydrate is a white to almost white crystalline powder, slightly soluble in water and in alcohol, practically insoluble in ether and in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Clavulanate Potassium:

Chemical Name: 4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt, [2R-(2α,3Z,5α)]

Structural Formula:



Molecular Formula: $C_8H_8KNO_5$

Molecular Weight: 237.25 (potassium salt)

Description: A white to almost white crystalline powder, hygroscopic. Freely soluble in water; slightly soluble in ethanol (96%); very slightly soluble in acetone.

COMPOSITION:

NOVO-CLAVAMOXIN powders for oral suspension contain amoxicillin as the trihydrate and clavulanic acid as the potassium salt in a ratio of 4:1 for the NOVO-CLAVAMOXIN 125 and NOVO-CLAVAMOXIN 250 oral suspensions. The suspensions also contain the following non-medicinal ingredients: citric acid, xanthan gum, silica, sodium benzoate, strawberry flavour (for NOVO-CLAVAMOXIN 125) and wild cherry flavour (for NOVO-CLAVAMOXIN 250), silicon dioxide, sodium citrate, saccharin, microcrystalline cellulose, carboxymethylcellulose, and mannitol.

NOVO-CLAVAMOXIN 875 Tablets: Each white capsule-shaped tablet contains 875 mg amoxicillin as the trihydrate and 125 mg of clavulanic acid as the potassium salt (in the ratio of 7:1) and the following non-medicinal ingredients: microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, titanium dioxide, polydextrose, hydroxypropylmethyl cellulose, triacetin and macrogol.

Reconstitution: Reconstitute Powder for Oral Suspension with purified water.

NOVO-CLAVAMOXIN 125 powder for oral suspension: The approximate average concentration after reconstitution is 125 mg of amoxicillin (as the trihydrate) and 31.25 mg of clavulanic acid (as the potassium salt) per 5 mL.

Bottle size	Volume to be added
100 mL	86 mL
150 mL	129 mL

NOVO-CLAVAMOXIN 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.

Bottle size	Volume to be added
100 mL	85 mL
150 mL	127.5 mL

Shake vigorously and keep bottle tightly closed.

Stability and Storage Recommendations

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

The reconstituted NOVO-CLAVAMOXIN 125 and NOVO-CLAVAMOXIN 250 oral suspension should be stored under refrigeration and should be used within 10 days.

Keep bottle tightly closed at all times.

Tablets:
Store in a dry place at room temperature (15°C – 30°C).

AVAILABILITY OF DOSAGE FORMS

NOVO-CLAVAMOXIN (amoxicillin/clavulanic acid) is available as a powder for oral suspension. Each 5 mL of reconstituted NOVO-CLAVAMOXIN 125 suspension contains 125 mg of amoxicillin as the trihydrate and 31.25 mg of clavulanic acid as the potassium salt (in a ratio of 4:1) and each 5 mL of reconstituted NOVO-CLAVAMOXIN 250 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).

Supplied in bottles of 100 mL and 150 mL.

NOVO-CLAVAMOXIN (amoxicillin/clavulanic acid) is available as white to off-white, capsule shaped, single-scored film-coated tablets, engraved N vertical scoreline N on one side and 875 on the other side. Each white capsule-shaped tablet contains 875 mg amoxicillin as the trihydrate and 125 mg of clavulanic acid as the potassium salt (in a ratio of 7:1).

Supplied in bottles of 20 tablets.

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 3 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
Gram-positive aerobes: *Enterococcus faecalis* *Streptococcus bovis* *Streptococcus pyogenes*† *Streptococcus agalactiae*† *Streptococcus spp. (other β-hemolytic)* † *Staphylococcus aureus (methicillin susceptible)** *Staphylococcus saprophyticus (methicillin susceptible)* *Coagulase negative staphylococcus (methicillin susceptible)*
Gram-negative aerobes: *Haemophilus influenzae** *Haemophilus parainfluenzae* *Moraxella catarrhalis** *Pasteurella multocida* *Proteus mirabilis*
Gram positive anaerobes: *Clostridium spp.* *Peptostreptococcus spp.*
Gram-negative anaerobes: *Eikenella corrodens* *Fusobacterium spp.* *Porphyromonas spp.* *Prevotella spp.*

Species for which acquired resistance may be a problem
Gram-positive aerobes: *Streptococcus pneumoniae*† *Viridans group streptococcus*
Gram-negative aerobes: *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae**

Klebsiella spp. *Proteus vulgaris* *Salmonella spp.* *Shigella spp.*
Gram-negative anaerobes: *Bacteroides fragilis* *Bacteroides spp.* *Bacteroides thetiotamicron*

Inherently resistant organisms
Gram-positive aerobes: *Enterococcus faecium*
Gram-negative aerobes: *Acinetobacter spp.* *Aeromonas spp.* *Citrobacter spp.* *Enterobacter spp.* *Hafnia alvei* *Morganella morganii* *Providencia rettgeri* *Providencia stuartii* *Pseudomonas spp.* *Serratia marcescens*

Susceptibility Testing

Interpretive Criteria for Dilution and Disk Diffusion Testing

MIC and disk diffusion results should be interpreted according to Table 4 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 4 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 5 (CLSI M100-S2112).

Table 5 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

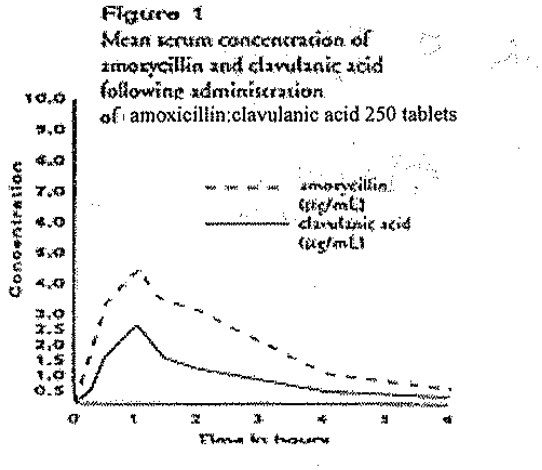
®ATCC is a trademark of the American Type Culture Collection.
Note 1: When using Haemophilus Test Medium (HTM)

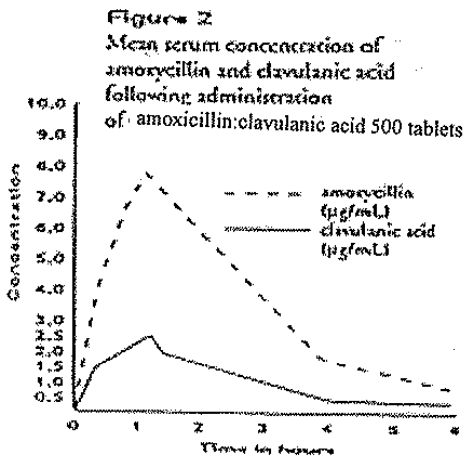
PHARMACOLOGY

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

Adults

Serum profiles of amoxicillin and clavulanic acid following single oral doses of amoxicillin:clavulanic acid 250 tablets (250 mg of amoxicillin and 125 mg of clavulanic acid; a 2:1 ratio preparation) or amoxicillin:clavulanic acid 500 tablets (500 mg of amoxicillin and 125 mg of clavulanic acid; a 4:1 ratio preparation) are shown in Figures 1 and 2 below.





Some pharmacokinetic parameters and the urinary excretion for these two preparations are given in Table 6 and 7.

Table 6 Pharmacokinetic Parameters

Parameter*	**Amoxicillin:Clavulanic acid 250mg Tablets**		**Amoxicillin:Clavulanic acid 500mg Tablets**	
	Amoxicillin	**Clavulanic acid**	**Amoxicillin**	**Clavulanic acid**
C_{max} (μg/mL)	4.45 ± 0.91	2.27 ± 0.76	7.66 ± 1.65	2.33 ± 0.73
T_{max}	1.39 ± 40.65	1.08 ± 0.32	1.35 ± 0.31	1.22 ± 0.40

AUC (μg/mL.h)	11.39 ± 1.60	4.73 ± 1.67	20.15 ± 3.31	5.24 ± 1.63

* Cmax - maximum serum concentration ± SD
Tmax - time to reach the maximum serum concentration ± SD
AUC - area under the curve ± SD

Table 7 Urinary Excretion of Amoxicillin (mg) and of Clavulanic Acid (mg)

Collection Period	**Amoxicillin:Clavulanic acid 250mg Tablets**		**Amoxicillin:Clavulanic acid 500mg Tablets**	
	Amoxicillin	**Clavulanic acid**	**Amoxicillin**	**Clavulanic acid**
0 to 2 hours	77.72 ± 44.69	19.71 ± 15.00	228.84 ± 141.87	18.07 ± 8.47
2 to 4 hours	65.00 ± 40.65	11.22 ± 7.77	131.41 ± 63.93	11.76 ± 5.99
4 to 6 hours	15.80 ± 11.82	2.24 ± 1.40	40.17 ± 22.81	4.19 ± 3.75
Total Excreted	158.72 ± 54.48	33.18 ± 16.61	391.30 ± 194.01	33.27 ± 13.68
% Excreted	63.5%	26.5%	78.3%	26.6%

N.B. Excretion is in terms of active drug.

The 24-hour pharmacokinetic profile of amoxicillin and clavulanic acid following a dosing regimen of amoxicillin : clavulanic acid 875 tablets every 12 hours, amoxicillin : clavulanic acid 500 tablets every 8 hours, amoxicillin : clavulanic acid 500 tablets every 12 hours and amoxicillin : clavulanic acid 250 every 8 hours, with a light meal was compared in healthy volunteers. Some pharmacokinetic parameters for these preparations are provided in Table 8.

Table 8 Amoxicillin and Clavulanic Acid Plasma Concentrations

Dose* and Regimen	$AUC_{0\text{-}24\ hr}$ (mcg/mL.hr) ± SD		Mean † Maximum Plasma Concentration (mcg/mL) ± SD	
(amoxicillin/clavulanic acid)	**Amoxicillin**	**Clavulanic acid**	**Amoxicillin**	**Clavulanic acid**
250/125 mg t.i.d.	26.77 ± 4.56	12.63 ± 3.25	3.32 ± 1.12	1.47 ± 0.70
500/125 mg b.i.d.	33.43 ± 6.76	8.60 ± 1.95	6.51 ± 1.41	1.75 ± 0.61
500/125 mg t.i.d.	53.35 ± 8.87	15.72 ± 3.86	7.19 ± 2.26	2.40 ± 0.83
875/125 mg b.i.d.	53.52 ± 12.31	10.16 ± 3.04	11.64 ± 2.78	2.18 ± 0.99

* Administered at the start of a light meal.
† Mean values of 16 normal volunteers. Peak concentrations occurred approximately 1.5 hours after the dose

The AUC (0-24h) for amoxicillin was comparable between the amoxicillin : clavulanic acid 875 b.i.d. and amoxicillin : clavulanic acid 500 t.i.d. regimens and between the amoxicillin : clavulanic acid 500 b.i.d. and amoxicillin : clavulanic acid 250 t.i.d. regimens. Although the T_{MIC} values (time above MIC of 1 mcg/mL) were slightly reduced for the b.i.d. regimen, no differences were observed for half-life or C_{max} after normalization for doses of amoxicillin and clavulanic acid.

The half-life of amoxicillin when given alone is 1.2 hours and 1.3 hours when given in the form of amoxicillin/clavulanic acid. 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/clavulanic acid in adults and children.

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

Neither component of amoxicillin/clavulanic acid 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 9 below.

Table 9 Mean Plasma Concentrations of Amoxicillin and Clavulanic Acid

No. of Children	Mean Age (Years)	Drug	Dose* (mg/kg)	Mean Plasma Concentrations (μg/mL) at Indicated Time (h) after Dosing					
				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:clavulanic acid 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:clavulanic acid oral suspension (4:1 ratio).

Some pharmacokinetic parameters for these children are given in Table 10 below.

Table 10 Pharmacokinetic Parameters

No. of Children	Drug	Dose (mg/kg)	Plasma half-life (h)	AUC (μg/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/clavulanic acid 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 11.

Table 11 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 1360 mg/kg. This compares with an oral LD_{50} of greater than 10,000 mg/kg for adult rats. In these neonates, weight loss, diarrhea and abdominal distension were frequently observed following dosing.

Subacute Toxicity

Rats:

Amoxicillin trihydrate and clavulanate potassium formulated in a 2:1 ratio were administered orally by gavage to 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 2-½ 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 postmortem 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 (1mL) 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 affect 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.

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