CLAVULIN SUSPENSION 228 mg/5 mL and 457 mg/5 mL – Mixed fruit flavour

Amoxicillin trihydrate – Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

A white to off-white dry powder for reconstitution in water to form a white to tan mixed-fruit flavoured suspension.

CLAVULIN suspension 228 mg/5 mL: When reconstituted, each 5 mL contains 200 mg amoxicillin (as amoxicillin trihydrate) and 28.5 mg clavulanic acid (as potassium clavulanate).

CLAVULIN suspension 457 mg/5 mL: When reconstituted, each 5 mL contains 400 mg amoxicillin (as amoxicillin trihydrate) and 57 mg clavulanic acid (as potassium clavulanate).

CLINICAL INFORMATION

Indications

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

CLAVULIN suspension (228 mg/5 mL and 457 mg/5 mL), for twice daily oral dosing, is indicated for short term treatment of bacterial infections at the following sites when amoxicillin resistant beta-lactamase producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.

Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media.

Lower respiratory tract infections e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia.

Urinary tract infections e.g. cystitis, urethritis, pyelonephritis

Skin and soft tissue infections e.g. cellulitis, animal bites.

Dental infections e.g. severe dental abscess with spreading cellulitis.

Susceptibility to *CLAVULIN* will vary with geography and time (see *Pharmacological Properties, Pharmacodynamics* for further information). Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with *CLAVULIN* susceptible beta-lactamase-producing organisms may be treated with *CLAVULIN* suspension 228 mg/5 mL and 457 mg/5 mL. These infections should not require the addition of another antibiotic resistant to beta-lactamases.

Dosage and Administration

Dosage depends on the age, weight and renal function of the patient and the severity of the infection.

Dosages are expressed throughout in terms of amoxicillin/clavulanate content except when doses are stated in terms of an individual component.

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of *CLAVULIN* is optimised when taken at the start of a meal.

Treatment should not exceed 14 days without review.

Therapy can be started parenterally and continued with an oral preparation.

CLAVULIN bottle presentations for suspension may be supplied with a plastic dosing device. For preparation of the suspensions see *Instructions for Use/Handling*.

The usual recommended daily dosage is:

- *Lower dose*: 25/3.6 to 45/6.4 mg/kg/day in two divided doses for mild to moderate infections (upper respiratory tract infections e.g. recurrent tonsillitis, lower respiratory infections and skin and soft tissue infections).

- *Higher dose*: 45/6.4 to 70/10 mg/kg/day in two divided doses for the treatment of more serious infections (upper respiratory tract infections e.g. otitis media and sinusitis, lower respiratory tract infections e.g. bronchopneumonia and urinary tract infections).

No clinical data are available on doses above 45/6.4 mg/kg/day in children under 2 years.

There are no clinical data for *CLAVULIN* suspension 228 mg/5 mL and 457 mg/5 mL to make dosage recommendations for children under 2 months old.

The tables below give dosage guidance for children.

Children 2 years and over

***CLAVULIN* suspension 228 mg/5 mL**		
Body weight (kg)	For lower dose range (mL every 12 hours)	For higher dose range (mL every 12 hours)
12 to 16	5	10
17 to 26	10	15

***CLAVULIN* suspension 457 mg/5 mL**		
Body weight (kg)	For lower dose range (mL every 12 hours)	For higher dose range (mL every 12 hours)
12 to 16	2.5	5
17 to 26	5	7.5
27 to 35	7.5	10
36 to < 40	10	12.5

Children aged 2 months to under 2 years

***CLAVULIN* suspension 457 mg/5 mL**		
Body Weight (kg)	Lower dose at 25/3.6 mg/kg/day (mL every 12 hours)	Higher dose at 45/6.4 mg/kg/day (mL every 12 hours)
2	0.3	0.6
3	0.5	0.8
4	0.6	1.1
5	0.8	1.4
6	0.9	1.7
7	1.1	2.0
8	1.3	2.3
9	1.4	2.5
10	1.6	2.8
11	1.7	3.1
12	1.9	3.4
13	2.0	3.7
14	2.2	3.9
15	2.3	4.2

Renal Impairment

No adjustment in dose is required in patients with creatinine clearance greater than 30 mL/min.

CLAVULIN suspension 228 mg/5 mL and 457 mg/5 mL are not recommended in patients with a creatinine clearance of less than 30 mL/min.

Hepatic Impairment

Administer with caution; monitor hepatic function at regular intervals. There are insufficient data on which to base a dosage recommendation.

Contraindications

CLAVULIN is contraindicated

- in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.

- in patients with a previous history of *CLAVULIN* -associated jaundice/hepatic dysfunction.

Warnings and Precautions

Before initiating therapy with *CLAVULIN*, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see *Contraindications*). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to *CLAVULIN* (see *Adverse Reactions*). Drug-induced enterocolitis syndrome has been reported mainly in children receiving *CLAVULIN* (see *Adverse Reactions*). Drug-induced enterocolitis syndrome is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicinal product administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, lethargy, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock. If an allergic reaction occurs, *CLAVULIN* therapy must be discontinued and appropriate alternative therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management (including intubation) may also be required.

CLAVULIN should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

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

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving *CLAVULIN* 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.

Changes in liver function tests have been observed in some patients receiving *CLAVULIN*. The clinical significance of these changes is uncertain but *CLAVULIN* should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

In patients with renal impairment *CLAVULIN* suspension 228 mg/5 mL and 457 mg/5 mL are not recommended.

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 *Overdose).*

CLAVULIN 228 mg/5 mL and 457 mg/5 mL suspensions contain aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria.

Interactions

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with *CLAVULIN* may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of *CLAVULIN* and allopurinol.

In common with other antibiotics, *CLAVULIN* may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

In the literature, there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of *CLAVULIN*.

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

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

Pregnancy and Lactation

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered *CLAVULIN* have shown no teratogenic effects. In a single study in women with pre-term, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with *CLAVULIN* may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, unless considered essential by the physician.

Lactation

CLAVULIN may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

Effects on Ability to Drive and Use Machines

Adverse effects on the ability to drive or operate machinery have not been observed.

Adverse Reactions

Data from large clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at < 1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency:

very common ≥ 1/10

common ≥ 1/100 to < 1/10

uncommon ≥ 1/1000 to < 1/100

rare ≥ 1/10,000 to < 1/1000

very rare < 1/10,000.

Infections and infestations

Common	Mucocutaneous candidiasis

Blood and lymphatic system disorders

Rare	Reversible leucopenia (including neutropenia) and thrombocytopenia
Very rare	Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time.

Immune system disorders

Very rare	Angioneurotic oedema, anaphylaxis (see *Warnings and Precautions*), serum sickness-like syndrome, hypersensitivity vasculitis (see also *Skin and subcutaneous tissue disorders*).

Nervous system disorders

Uncommon	Dizziness, headache
Very rare	Reversible hyperactivity, aseptic meningitis, convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Cardiac disorders

Very rare	Kounis syndrome (see *Warnings and Precautions*).

Gastrointestinal disorders

Adults

Very common	Diarrhoea
Common	Nausea, vomiting

Children

Common	Diarrhoea, nausea, vomiting

All populations

Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking *CLAVULIN* at the start of a meal.

Uncommon	Indigestion
Very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis, drug-induced enterocolitis syndrome (see *Warnings and Precautions*).
	Black hairy tongue
	Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

Hepatobiliary disorders

Uncommon	A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
Very Rare	Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children.

Signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

Skin and subcutaneous tissue disorders

Uncommon	Skin rash, pruritus, urticaria
Rare	Erythema multiforme
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) (see also *Immune system disorders*).
	If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

Linear IgA disease.

Renal and urinary disorders

Very rare Interstitial nephritis, crystalluria (see *Overdose*)

Overdose

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

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see *Warnings and Precautions*).

CLAVULIN can be removed from the circulation by haemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

Anatomical Therapeutic Chemical (ATC) code: J01CR02.
Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors.

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in *CLAVULIN* suspension anticipates this defence mechanism by blocking the beta-lactamase enzymes, thus rendering the organisms sensitive to amoxicillin's rapid bactericidal effect at concentrations readily attainable in the body.

Clavulanate by itself has little antibacterial activity; however, in association with amoxicillin as *CLAVULIN* it produces an antibiotic agent of broad-spectrum with wide application in hospital and general practice.

Pharmacodynamic Effects

In the list below, organisms are categorised according to their *in vitro* susceptibility to *CLAVULIN*.

In vitro* susceptibility of micro-organisms to *CLAVULIN
Where clinical efficacy of Clavulin 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 *CLAVULIN*.
Commonly susceptible species

Gram-positive aerobes:
Bacillius anthracis
Enterococcus faecalis
Listeria monocytogenes
Nocardia asteroides
*Streptococcus pyogenes**†
*Streptococcus agalactiae**†
Streptococcus spp. (other beta-hemolytic)*†
Staphylococcus aureus (methicillin susceptible)*
Staphylococcus saprophyticus (methicillin susceptible)
Coagulase negative staphylococcus (methicillin susceptible)
Gram-negative aerobes:
Bordetella pertussis
*Haemophilus influenzae**
Haemophilus parainfluenzae
Helicobacter pylori
*Moraxella catarrhalis**
Neisseria gonorrhoeae
Pasteurella multocida
Vibrio cholerae
Other:
Borrelia burgdorferi
Leptospira ictterohaemorrhagiae
Treponema pallidum
Gram positive anaerobes:
Clostridium spp.
Peptococcus niger
Peptostreptococcus magnus
Peptostreptococcus micros
Peptostreptococcus spp.
Gram-negative anaerobes:
Bacteroides fragilis

Bacteroides spp.
Capnocytophaga spp.
Eikenella corrodens
Fusobacterium nucleatum
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp.
Species for which acquired resistance may be a problem
Gram-negative aerobes:
*Escherichia coli**
Klebsiella oxytoca
*Klebsiella pneumoniae**
Klebsiella spp.
Proteus mirabilis
Proteus vulgaris
Proteus spp.
Salmonella spp.
Shigella spp.
Gram-positive aerobes:
Corynebacterium spp.
Enterococcus faecium
*Streptococcus pneumoniae**[†]
Viridans group streptococcus

Inherently resistant organisms
Gram-negative aerobes:
Acinetobacter spp.
Citrobacter freundii
Enterobacter spp.
Hafnia alvei
Legionella pneumophila
Morganella morganii
Providencia spp.
Pseudomonas spp.
Serratia spp.
Stenotrophomas maltophilia
Yersinia enterolitica
Others:
Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia spp.
Coxiella burnetti
Mycoplasma spp.

Infections caused by amoxicillin-susceptible organisms are amenable to *CLAVULIN* treatment due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms in conjunction with *CLAVULIN* -susceptible beta-lactamase producing organisms may therefore be treated with *CLAVULIN*.

Pharmacokinetics

Absorption

The two components of *CLAVULIN* suspension 228 mg/5 mL and 457 mg/5 mL, amoxicillin and clavulanate, are each fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of *CLAVULIN* is optimised when taken at the start of a meal.

The mean AUC values for amoxicillin are essentially the same following twice a day dosing with the *CLAVULIN* 875/125 mg tablet or three times a day dosing with the *CLAVULIN* 500/125 mg tablet, in adults. No differences between the 875 mg twice daily and 500 mg three times daily dosing regimes are seen when comparing the amoxicillin $T_{1/2}$, or C_{max} after normalisation for the different doses of amoxicillin administered.

Similarly, no differences are seen for the clavulanate $T_{1/2}$, C_{max} or AUC values after appropriate dose normalisation.

The time of dosing of *CLAVULIN* relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the *CLAVULIN* 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and C_{max}, the highest mean values and smallest inter-subject variabilities were achieved by administering *CLAVULIN* at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean Cmax, Tmax, T1/2 and AUC values for amoxicillin and clavulanate are given below for an 875 mg/125 mg dose of amoxicillin /clavulanic acid administered at the start of a meal.

Mean Pharmacokinetic Parameters

Drug Administration	Dose (mg)	Cmax (mg/L)	Tmax* (hours)	AUC (mg.h/L)	T1/2 (hours)
CLAVULIN 1 g					
Amoxicillin	875	12.4	1.5	29.9	1.36
Clavulanate	125	3.3	1.3	6.88	0.92

*Median values

Amoxicillin serum concentrations achieved with *CLAVULIN* are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

Distribution

The pharmacokinetics of the two components of *CLAVULIN* are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Doubling the dosage of *CLAVULIN* approximately doubles the serum levels achieved.

Non-Clinical Information

No further information of relevance.

PHARMACEUTICAL INFORMATION

List of Excipients

CLAVULIN dry powder for suspension contains xanthan gum, hydroxypropyl methylcellulose, colloidal silica, succinic acid, silicon dioxide, aspartame and dry flavours (raspberry, orange “1”, orange “2” and golden syrup).

For important information about some of these excipients see *Warnings and Precautions.*

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Do not take after the expiry date shown on the pack.

Store in a dry place in the original packaging to protect from moisture.

Once reconstituted, the suspension must be stored in a refrigerator (2°C to 8°C) and used within 7 days. Do not freeze. (see also *Use and Handling*).

KEEP OUT OF THE SITE AND REACH OF CHILDREN.

Nature and Contents of Container

CLAVULIN for suspension in bottles

Clear glass bottles containing powder for reconstitution. Bottles may be supplied with either an aluminium screw cap with a ring seal or a plastic child-resistant cap with a removable foil-backed seal on the bottle. Fill-lines are indicated on the bottle label. Bottles may be supplied with a plastic dosing device.

CLAVULIN for suspension from sachets (*457 mg presentation only*)

Single-use paper/aluminium/polyethylene laminate sachets containing powder for reconstitution.

Incompatibilities

None known.

Use and Handling

CLAVULIN suspension in bottles

For bottles with aluminium screw caps, check the cap ring seal is intact before using. Alternatively, for bottles with a plastic child-resistant cap, check the foil-backed bottle seal is intact before using.

At time of use, the dry powder should be reconstituted to form an oral suspension, as detailed below:

- Invert and shake bottle to loosen powder.
- Add volume of water (indicated below). Invert and shake well.

- Alternatively, fill the bottle with water to just below the mark on bottle label. Invert and shake well, then top up with water to the mark. Invert and shake again.
- Allow to stand for 5 minutes to ensure full dispersion.
- Shake well before taking each dose.

***CLAVULIN* suspension 228 mg/5 mL**		
Fill Weight (g)	Volume of water to be added to reconstitute (mL)	Final volume of reconstituted oral suspension (mL)
7.7	64	70
15.4	128	140

***CLAVULIN* suspension 457 mg/5 mL**		
Fill Weight (g)	Volume of water to be added to reconstitute (mL)	Final volume of reconstituted oral suspension (mL)
6.3	31	35
12.6	62	70
25.2	124	140

A plastic dosing device may be supplied with the pack which can be used to measure the dose accurately.

Discard any unused suspension after 7 days.

CLAVULIN suspension in sachets

Each single-use sachet contains powder for a 2.5 mL dose of *CLAVULIN* suspension 457 mg/5 mL. At time of use, the dry powder should be reconstituted to form an oral suspension, as detailed below:

- Check that the sachet is intact before use.
- Cut sachet along dotted line.
- Empty contents into a glass.
- Half fill sachet with water.
- Pour into glass, stir to mix.
- Drink immediately upon reconstitution.

If more than one sachet needs to be taken at once then they can be mixed in the same glass.

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

Not all presentations are available in every country.

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Zone Industrielle de la

Peyenniere

53100 Mayenne - France