CLAVULIN BD TABLETS

Amoxicillin trihydrate - Potassium clavulanate

QUALITATIVE AND QUANTITATIVE COMPOSITION

**CLAVULIN** 625 mg tablets: Each tablet contains 500 mg amoxicillin (as amoxicillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).

**CLAVULIN** 1 g tablets: Each tablet contains 875 mg amoxicillin (as amoxicillin trihydrate) and 125 mg clavulanic acid (as potassium clavulanate).

PHARMACEUTICAL FORM

**CLAVULIN** 625 mg tablets: A white to off-white oval-shaped film-coated debossed tablet, with a score line on one side and plain on the other side.

**CLAVULIN** 1 g tablets: A white to off-white oval-shaped film-coated debossed tablet, with a score line on one side and plain on the other side.

CLINICAL PARTICULARS

Indications

**CLAVULIN** is an antibiotic agent with a notably broad spectrum of activity against the commonly occurring bacterial pathogens in general practice and hospital. The β-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other β-lactam antibiotics.

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

**CLAVULIN** oral presentations for twice daily dosing, are indicated for short-term treatment of bacterial infections at the following sites:

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

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

*Genito-urinary tract infections* e.g. cystitis, urethritis, pyelonephritis.

*Skin and soft tissue infections*, e.g. boils, abscesses, cellulitis, wound infections.

*Bone and joint infections* e.g. osteomyelitis.

*Dental infections* e.g. dentoalveolar abscess
Other infections e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis.

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.

**Dosage and Administration**

**Usual dosages for the treatment of infection**

*Adults and children over 12 years*+

- **Mild - Moderate infections**
  - One CLAVULIN 625 mg tablet twice daily
- **Severe infections**
  - One CLAVULIN 1 g tablet twice daily

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

+ CLAVULIN 625 mg and 1 g tablets are not recommended in children of 12 years and under

**Dosage in renal impairment**

*Adults:*

The CLAVULIN 1g tablet should only be used in patients with a glomerular filtration rate of >30 ml/min.

<table>
<thead>
<tr>
<th>Mild impairment (Creatinine clearance &gt;30 ml/min)</th>
<th>Moderate impairment (Creatinine clearance 10-30 ml/min)</th>
<th>Severe impairment (Creatinine clearance &lt;10 ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in dosage (i.e. either one 625 mg tablet twice daily or one 1 g tablet twice daily)</td>
<td>One 625 mg tablet twice daily.</td>
<td>Not more than one 625 mg tablet every 24 hours.</td>
</tr>
<tr>
<td>The 1 g tablet should not be administered.</td>
<td></td>
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</tr>
</tbody>
</table>

**Dosage in hepatic impairment**

Dose with caution; monitor hepatic function at regular intervals.

**Administration**

Tablets should be swallowed whole without chewing. If required, tablets may be broken in half and swallowed without chewing.

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 be extended beyond 14 days without review.

*CLAVULIN* is also available as *CLAVULIN* intravenous for the short-term treatment of bacterial infections and for prophylaxis against infection which may be associated with major surgical procedures. *CLAVULIN* intravenous is described in a separate Pack Insert.

*CLAVULIN* is also available as a suspension for three times daily dosing for administration to children under the age of 12 years for the treatment of bacterial infections. *CLAVULIN* suspension three times daily is described in a separate Pack Insert.

**Contraindications**

*CLAVULIN* is contra-indicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.

*CLAVULIN* is contra-indicated 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). 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. 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 dosage should be adjusted as recommended in the Dosage and Administration section.

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).

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 clavulanate.

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.

Pregnancy and Lactation

Reproduction studies in animals (mice and rats) 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, especially during the first trimester, unless considered essential by the physician.

*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 detrimental effects for the 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:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>common</td>
<td>≥1/100 and &lt;1/10</td>
</tr>
<tr>
<td>uncommon</td>
<td>≥1/1000 and &lt;1/100</td>
</tr>
<tr>
<td>rare</td>
<td>≥1/10,000 and &lt;1/1000</td>
</tr>
<tr>
<td>very rare</td>
<td>&lt;1/10,000</td>
</tr>
</tbody>
</table>

**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, serum sickness-like syndrome, hypersensitivity vasculitis

**Nervous system disorders**

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

**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 – see Warnings and Precautions).

Black hairy tongue

**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), and drug reaction with eosinophilia and systemic symptoms (DRESS)

If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

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

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in CLAVULIN anticipates this defence mechanism by blocking the β-lactamase enzymes, thus rendering the organisms susceptible 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.

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

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive aerobes:</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Gram-positive bacilli:</th>
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<tbody>
<tr>
<td>Bacillus anthracis</td>
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<tr>
<td>Enterococcus faecalis</td>
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<tr>
<td>Listeria monocytogenes</td>
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<tr>
<td>Nocardia asteroides</td>
</tr>
<tr>
<td>Streptococcus pyogenes*†</td>
</tr>
<tr>
<td>Streptococcus agalactiae*†</td>
</tr>
<tr>
<td>Streptococcus spp. (other β-hemolytic) *†</td>
</tr>
<tr>
<td>Streptococcus pyogenes (methicillin susceptible)*</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin susceptible)</td>
</tr>
<tr>
<td>Staphylococcus agalactiae (methicillin susceptible)</td>
</tr>
<tr>
<td>Coagulase negative staphylococcus (methicillin susceptible)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-negative aerobes:</th>
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<tbody>
<tr>
<td>Bordetella pertussis</td>
</tr>
<tr>
<td>Haemophilus influenzae*</td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>Moraxella catarrhalis*</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
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<table>
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<tr>
<th>Other:</th>
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<tbody>
<tr>
<td>Borrelia burgdorferi</td>
</tr>
<tr>
<td>Leptospira icterohaemorrhagiae</td>
</tr>
<tr>
<td>Treponema pallidum</td>
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<table>
<thead>
<tr>
<th>Gram positive anaerobes:</th>
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<tbody>
<tr>
<td>Clostridium spp.</td>
</tr>
<tr>
<td>Gram-negative anaerobes:</td>
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<tr>
<td>----------------------------------------------</td>
</tr>
<tr>
<td><em>Peptococcus niger</em></td>
</tr>
<tr>
<td><em>Peptostreptococcus magnus</em></td>
</tr>
<tr>
<td><em>Peptostreptococcus micros</em></td>
</tr>
<tr>
<td><em>Peptostreptococcus spp.</em></td>
</tr>
</tbody>
</table>

**Species for which acquired resistance may be a problem**

<table>
<thead>
<tr>
<th>Gram-negative aerobes:</th>
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<tbody>
<tr>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td><em>Klebsiella spp.</em></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
</tr>
<tr>
<td><em>Proteus spp.</em></td>
</tr>
<tr>
<td><em>Salmonella spp.</em></td>
</tr>
<tr>
<td><em>Shigella spp.</em></td>
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<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
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</table>
### 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.
Pharmacokinetics

The pharmacokinetics of the two components of CLAVULIN are closely matched. Peak serum levels of both occur about 1 hour after oral administration. Absorption of CLAVULIN is optimised at the start of a meal.

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

Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Pre-clinical Safety Data

No further information of relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients

CLAVULIN 625 mg and 1 g tablets contain the following inactive ingredients: colloidal silicon dioxide, sodium starch glycolate, magnesium stearate (E572), microcrystalline cellulose, titanium dioxide (E171), hydroxypropyl methylcellulose, polyethylene glycol, dimethicone (silicon oil).

Incompatibilities

None known.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

CLAVULIN 1 g tablets should be stored in un-opened, original packs in a dry place at below 30°C.

CLAVULIN 625 mg tablets should be stored in un-opened, original packs in a dry place at below 25°C

Not all presentations are available in every country.

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