

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

CLAVULIN 625 MG AND 1 G

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clavulin 625 mg and 1 g contain amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate) 500mg/125mg & 875mg/125mg respectively.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL form

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

Clavulin 1 g tablets: A white to off-white capsule-shaped film-coated tablet, debossed with 'AC' on both sides and a score line on one side.

4. Clinical particulars

4.1 Therapeutic 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 beta-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrace a wider range of organisms, including many resistant to other beta-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. recurrent tonsillitis, sinusitis, otitis media.

Lower respiratory tract infections e.g. acute exacerbation of chronic obstructive pulmonary disease (AECOPD)/ acute exacerbation of chronic bronchitis (AECB), 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.

4.2 Posology and method of administration

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

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.

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

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

Clavulin tablets are not recommended in children of 12 years and under.

Adults and Children over 12 years

The usual recommended daily dosage is:

Mild - Moderate infections	One Clavulin 625 mg tablet every 12 hours
Severe infections	One Clavulin 1 g tablet every 12 hours.

Renal Impairment

No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 mL/min. The Clavulin 1g tablet should only be used in patients with a creatinine clearance (CrCl) rate of more than 30 mL/min.

CrCl 10-30 mL/min	One Clavulin 625 mg tablet every 12 hours.
CrCl < 10 mL/min	One Clavulin 625 mg tablet every 24 hours.
Haemodialysis	One Clavulin 625 mg tablet every 24 hours, plus a further one tablet during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased).

Hepatic Impairment

Administer with caution; monitor hepatic function at regular intervals.

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

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 *Undesirable effects*). 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 should 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).

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Pregnancy and lactation

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, 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 known detrimental effects for the breast-fed infant.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Data from large clinical trials was 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 $\geq 1/10$

common $\geq 1/100$ to $< 1/10$

uncommon $\geq 1/1000$ to $< 1/100$

rare $\geq 1/10,000$ 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 Special warnings and precautions for use), 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 Special warnings and precautions for use).

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 Special warnings and precautions for use).

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), drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) (see also <i>Immune system disorders</i>).

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

Linear IgA disease.

Renal and urinary disorders

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

4.9 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 Special warnings and precautions for use).

Clavulin can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 anticipates this defence mechanism by blocking the beta-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.

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:

Bacillus 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 icterohaemorrhagiae

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 enterocolitica

Others:

Chlamydia pneumoniae

Chlamydia psittaci

Chlamydia spp.

Coxiella burnetti

Mycoplasma spp.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

No further information of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Clavulin tablets contain;
sodium starch glycolate,
magnesium stearate (E572),
colloidal silica,
microcrystalline cellulose,
titanium dioxide (E171),
hydroxypropyl methylcellulose,
polyethylene glycol,
dimeticone (silicone oil).

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

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

Refer to pack for storage temperature.

For Clavulin tablet packs with a storage temperature up to 25°C, use tablets within 30 days of opening (see also Instructions for Special precautions for disposal and other handling).

Clavulin tablet packs contain desiccant sachets. Do not remove or eat.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Clavulin tablets are supplied in a carton containing blister packs. Each blister pack is stored within a sealed pouch, with a desiccant sachet.

6.6 Special precautions for disposal and other handling

Blister pouches contain a desiccant sachet; do not remove or eat. Discard any opened and unused tablets after storing as directed in the Special Precautions for Storage section.

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

7. APPLICANT/SUPPLIER

GlaxoSmithKline Export Ltd.
980 Great West Road, Brentford, Middlesex,
TW89GS, United Kingdom
T +44 2080 475 000

8. FDA APPLICATION NUMBER

Clavulin 625mg; FDA/SD.203-06284

Clavulin 1g; FDA/SD.203-06283

9. DATE OF RENEWAL OF REGISTRATION

23/5/2017

10. DATE OF REVISION OF THE TEXT

07/09/2023