SUMMARY OF PRODUCT CHARACTERISTICS
KOACT 1000
Co-amoxiclav Tablets 875-125 mg
Rx Only

QUALITATIVE AND QUANTITATIVE COMPOSITION

Co-amoxiclav Tablets 875-125 mg is White colored capsule shaped film coated tablets, debossed with 'A' on one side and with a score line in between '6' and '5' on the other side.

Each film-coated tablet contains: Amoxicillin Trihydrate equivalent to Amoxicillin 875 mg and Potassium Clavulanate, diluted equivalent to Clavulanic Acid 125 mg.

This score-line is non-functional and is only for ease of swallowing and is not intended to divide the tablet in two equal halves.

CLINICAL INFORMATION

Indications

Co-amoxiclav Tablets 875-125 mg 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.

Co-amoxiclav Tablets 875-125 mg should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

Co-amoxiclav Tablets 875-125 mg 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 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, pericoronitis, acute periodontitis.

Other infections e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis.

Susceptibility to *Co-amoxiclav* 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

Pharmaceutical form: Film-coated tablets

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 Co-amoxiclav Tablets 875-125 mg 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.
Co-amoxiclav Tablets 875-125 mg 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 *Co-amoxiclav Tablets 500-125* mg tablet every 12 hours.
Severe infections	One Co-amoxiclav Tablets 875-125 mg tablet every 12 hours.

Renal Impairment

No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 mL/min. The *Co-amoxiclav Tablets 875-125 mg* 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 Co-amoxiclav Tablets 500-125 mg tablet every 12 hours.
CrCl <10 mL/min	One Co-amoxiclav Tablets 500-125 mg tablet every 24 hours.
Haemodialysis	One *Co-amoxiclav Tablets 500-125 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

Dose with caution; monitor hepatic function at regular intervals.

Contraindications

Co-amoxiclav Tablets 875-125 mg is contraindicated in patients with a history of hypersensitivity to betalactams, e.g. penicillins and cephalosporins.

Co-amoxiclav Tablets 875-125 mg is contraindicated in patients with a previous history of Co-amoxiclav Tablets 875-125 mg associated jaundice/hepatic dysfunction.

Warnings and Precautions

Before initiating therapy with Co-amoxiclav, 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 Co-amoxiclav (see *Adverse Reactions*). If an allergic reaction occurs, Co-amoxiclav 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.
Co-amoxiclav 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) have been reported rarely in patients receiving Co-amoxiclav 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 Co-amoxiclav. The clinical significance of these changes is uncertain. Co-amoxiclav 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, Co-amoxiclav 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 Co-amoxiclav 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 Co-amoxiclav and allopurinol.
In common with other antibiotics, Co-amoxiclav 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 Co-amoxiclav.
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

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered Co-amoxiclav have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with Co-amoxiclav 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

Co-amoxiclav 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 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 ≥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, serum sickness-like syndrome, hypersensitivity vasculitis.

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 Co-amoxiclav Tablets 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 exanthematous 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*).
Co-amoxiclav can be removed from the circulation by haemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics
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 Co-amoxiclav 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 Co-amoxiclav 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 Co-amoxiclav.

***In vitro* susceptibility of micro-organisms to Co-amoxiclav.** Where clinical efficacy of Co-amoxiclav 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 Co-amoxiclav.
Commonly susceptible species
<u>Gram-positive aerobes:</u> *Bacillius anthracis* *Enterococcus faecalis* *Gardnerella vaginalis* *Listeria monocytogenes* *Streptococcus pneumoniae**†* *Streptococcus pyogenes**†* *Streptococcus agalactiae**†* *Viridans group streptococcus†* *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**
Helicobacter pylori
*Moraxella catarrhalis**
Neisseria gonorrhoeae
Pasteurella multocida
Vibrio cholerae

Gram-positive anaerobes:

Clostridium spp.
Peptococcus niger
Peptostreptococcus magnus
Peptostreptococcus micros
Peptostreptococcus spp.

Gram-negative anaerobes:

Bacteroides fragilis
Bacteroides spp.
Fusobacterium nucleatum
Fusobacterium 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

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 Co-amoxiclav are closely matched. Peak serum levels of both occur about 1 hour after oral administration. Absorption of Co-amoxiclav is optimised at the start of a meal.
Doubling the dosage of Co-amoxiclav approximately doubles the serum levels achieved.
Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Non-Clinical Information
No further information of relevance.

PHARMACEUTICAL INFORMATION
List of Excipients
Co-amoxiclav Tablets contain Microcrystalline Cellulose, Sodium Starch Glycolate, Colloidal anhydrous Silica, Magnesium Stearate and Opadry white (Hypromellose 5 cP, Titanium dioxide, Macrogol/PEG 400, Hypromellose 15 cP).

Shelf Life
24 Months.

Storage
Store in a dry place at or below 30°C. Protect from moisture.
Keep out of the reach of children.

Nature and Contents of Container
KOACT 1000: 3 blisters x 5 tablets.

Incompatibilities
None known.

PRODUCT OWNER:

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DATE OF PREPARATION OF THIS LEAFLET
August 2022