

# **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Co – Amoxiclav Tablets BP 1000 mg (CLEDOMOX-1000)

## 2. QUALITATIVE AND QUANTITATIVE

Each film-coated tablet contains

Amoxicillin trihydrate BP Equivalent to Amoxicillin 875 mg

Diluted Potassium clavulanate BP Equivalent to Clavulanic acid 125 mg.

Refer Excipients section 6.1

## 3. PHARMACEUTICAL FORM:

White capsule shape film coated tablets with score in the middle on both sides.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications:

It is indicated for the treatment (diagnosed) of the following infections in adults and children

- Acute bacterial sinusitis (adequately)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### 4.2 Posology and Method of Administration:

#### Posology

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Co-amoxiclav that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

The use of alternative presentations of Co-amoxiclav (e.g. those that provide higher

doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.

For adults and children  $\geq 40$  kg, this formulation of Co-amoxiclav provides a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below.

For children  $< 40$  kg, this formulation of Co-amoxiclav provides a maximum daily dose of 2400 mg amoxicillin/600 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Co-amoxiclav is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

The duration of therapy should be determined by the response of the patient.

Some infections

(e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review.

**Adults and children  $\geq 40$  kg**

**Recommended doses:**

- Standard dose (for all indications): 875 mg/125 mg two times a day;
- Higher dose (particularly for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): 875 mg/125 mg three times a day.

Children  $< 40$  kg

Children may be treated with Augmentin tablets, suspensions or paediatric sachets.

Recommended doses:

- 25 mg/3.6 mg/kg/day to 45 mg/6.4 mg/kg/day given as two divided doses;
- Up to 70 mg/10 mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

As the tablets cannot be divided children weighing less than 25 kg must not be treated with Co amoxiclav tablets.

The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 875 mg/125 mg tablet.

Body weight [kg]	40	35	30	25	Singledose recommended [mg/kg body weight] (see above)
Amoxicillin [mg/kg body weight] per singledose (1 film-coated tablet)	21.9	25.0	29.2	35.0	12.5 – 22.5 (up to 35)

Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.8 – 3.2 (up to 5)
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Children weighing less than 25 kg should preferably be treated with Augmentin suspension or paediatric sachets.

No clinical data are available for Co-Amoxiclav 7:1 formulations regarding doses higher than 45 mg/6.4 mg per kg per day in children under 2 years

There are no clinical data for Co-Amoxiclav 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

#### Elderly

No dose adjustment is

considered necessary. Renal

#### impairment

No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

In patients with creatinine clearance less than 30 ml/min, the use of Co amoxiclav presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

#### Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals. Method of administration

Co-amoxiclav is for oral use.

Co-Amoxiclav should be administered with a meal to minimise potential gastrointestinal intolerance.

Therapy can be started parenterally according to the SMPC of the IV formulation and continued with an oral preparation.

### **4.3 Contraindications**

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients. History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

### **4.4 Special warnings and precautions for use**

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a

history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organism(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Co-amoxiclav is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid.

This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin/clavulanic acid 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.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

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

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP). This reaction requires Co-amoxiclav discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment.

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. In all populations, 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.

Antibiotic-

associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/

clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

In patients with renal impairment, the doses should be adjusted according to the degree of impairment.

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. In patients with bladder catheters, a regular check of patency should be maintained. During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of Clavulanic acid in Co-amoxiclav may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad

Laboratories Platelia Aspergillus EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of

Aspergillus infection. Cross-reactions with non-Aspergillus polysaccharides

and polyfuranoses with

Bio-Rad Laboratories

Platelia Aspergillus EIA test have been reported. Therefore, positive test results in

patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are 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 amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

#### Methotrexate

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

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

#### Mycophenolatemofetil

In patients receiving mycophenolatemofetil, 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. Therefore, a change in the dose of mycophenolatemofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane 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 during pregnancy, unless considered essential by the physician.

### **Breast-feeding**

Both substances are excreted into breast milk (nothing is known of the effect of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

#### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

#### 4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Co-amoxiclav, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

<u>Infections and infestations</u>	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
<u>Blood and lymphatic system disorders</u>	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time <sup>1</sup>	Not known
<u>Immune system disorders<sup>10</sup></u>	
Angioneurotic oedema	Not known



Anaphylaxis	Notknown
Serum sickness-like syndrome	Notknown
Hypersensitivity vasculitis	Notknown
<u>Nervous system disorders</u>	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Notknown
Convulsions <sup>2</sup>	Notknown
Aseptic meningitis	Notknown
<u>Gastrointestinal disorders</u>	
Diarrhoea	Very common
Nausea <sup>3</sup>	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis <sup>4</sup>	Notknown
Black hairy tongue	Notknown
Tooth discoloration <sup>11</sup>	Notknown
<u>Hepatobiliary disorders</u>	
Rises in AST and/or ALT <sup>5</sup>	Uncommon
Hepatitis <sup>6</sup>	Notknown
Cholestatic jaundice <sup>6</sup>	Notknown
<u>Skin and subcutaneous tissue disorders</u> <sup>7</sup>	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Notknown
Toxic epidermal necrolysis	Notknown
Bullous exfoliative dermatitis	Notknown

Acute generalised exanthematous pustulosis <sup>9</sup>	Not known
<u>Renal and urinary disorders</u>	
Interstitial nephritis	Not known
Crystalluria <sup>8</sup>	Not known
<sup>1</sup> See section 4.4 <sup>2</sup> See section 4.4 <sup>3</sup> Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking Co-Amoxiclav at the start of a meal. <sup>4</sup> Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4) <sup>5</sup> 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. <sup>6</sup> These events have been noted with other penicillins and cephalosporins (see section 4.4). <sup>7</sup> If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4). <sup>8</sup> See section 4.9 <sup>9</sup> See section 4.4 <sup>10</sup> See sections 4.3 and 4.4 <sup>11</sup> 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.	

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare

professionals are asked to report any suspected adverse reactions via HPRA

Pharmacovigilance

### **4.9 Overdose**

#### **Symptoms and signs of overdose**

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed.

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency

should be maintained. **Treatment of intoxication**

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors ATC code: J01CR02.

#### **Mechanism of action**

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

#### **PK/PD relationship**

The time above the minimum inhibitory concentration ( $T > MIC$ ) is considered to be the major determinant of efficacy for amoxicillin.

#### **Mechanisms of resistance**

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target. Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

#### **Breakpoints**

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on

Antimicrobial Susceptibility Testing(EUCAST)

Organism	Susceptibility Breakpoints( $\mu$ g/ml)	
	Susceptible	Resistant
<i>Haemophilus influenzae</i>	$\leq 0.001^1$	$> 2^1$
<i>Moraxella catarrhalis</i>	$\leq 1^1$	$> 1^1$
<i>Staphylococcus spp.</i>	Note <sup>2a,3a,3b,4</sup>	Note <sup>2a,3a,3b,4</sup>
<i>Enterococcus spp.</i> <sup>1</sup>	$< 4^{1,5}$	$> 8^{1,5}$
Streptococcus groups A, B, C,G <sup>2b,8</sup> (indications other	Note <sup>2b</sup>	Note <sup>2b</sup>
<i>Streptococcus pneumoniae</i> <sup>8</sup>	$\leq 0.5^{1,6}$	$> 1^{1,6}$
Enterobacterales in uncomplicated UTIs	$\leq 32^1$	$> 32^1$
Gram-negative Anaerobes	$\leq 4^1$	$> 8^1$
Gram-positive Anaerobes (except	$\leq 4^1$	$> 8^1$
Non-species related breakpoints	$\leq 2^1$	$> 8^1$
Viridans group streptococci <sup>8</sup>	Note <sup>2a,9</sup>	Note <sup>2a,9</sup>
<i>Pasteurella multocida</i>	$\leq 1^1$	$> 1^1$
<i>Burkholderia pseudomallei</i>	$\leq 0.001^1$	$> 8^1$

1 For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l.

2a Breakpoint values in the table are based on benzylpenicillin breakpoints. The susceptibility is inferred from the benzylpenicillin susceptibility.

2b The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility (indications other than meningitis) with the exception of phenoxymethylpenicillin and isoxazolympenicillins for streptococcus group B.

3a Most staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to beta-lactamase inhibitor combinations, the isoxazolympenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Staphylococci that test resistant to cefoxitin are resistant to all penicillins.

3b Most coagulase-negative staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. No currently available method can reliably detect penicillinase production in coagulase-negative staphylococci but methicillin resistance can be detected with cefoxitin as described.

4 Ampicillin susceptible *S. saprophyticus* are *mecA*-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).

5 Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in *E. faecalis* (confirm with MIC) but common in *E. faecium*.

6 The oxacillin 1 µg disk screen test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone  $\geq 20$  mm, or benzylpenicillin MIC  $\leq 0.06$  mg/L) all beta-lactam agents for which clinical breakpoints are available, can be reported susceptible without further testing.

7 Aminopenicillin breakpoints in enterococci are based on intravenous administration. Oral administration is relevant for urinary tract infections only.

8 The addition of a beta-lactamase inhibitor does not add clinical benefit.

9 Benzylpenicillin (MIC or disk diffusion) can be used to screen for beta-lactam resistance in viridans group streptococci. Isolates categorised as screen negative can be reported susceptible to beta-lactam agents for which clinical breakpoints are listed. Isolates categorised as screen positive should be tested for susceptibility to individual agents. For benzylpenicillin screen negative isolates (MIC  $\leq 0.25$  mg/L), susceptibility can be inferred from benzylpenicillin or ampicillin. For benzylpenicillin screen positive isolates (MIC  $> 0.25$  mg/L), susceptibility is inferred from ampicillin.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Commonly susceptible species

**Aerobic Gram-positive micro-organisms**

Enterococcus faecalis

Gardnerellavaginalis

Staphylococcus aureus (methicillin-susceptible)£

Coagulase-negative staphylococci (methicillin-susceptible)

Streptococcus agalactiae

Streptococcus pneumoniae1

Streptococcus pyogenes and other beta-haemolytic streptococci

Streptococcus viridans group

**Aerobic Gram-negative micro-organisms**

Capnocytophaga spp.

Eikenellacorrodens

Haemophilus influenzae2

Moraxella catarrhalis

Pasteurellamultocida

Anaerobic micro-organisms

Bacteroidesfragilis

Fusobacteriumnucleatum

Prevotella spp.

**Species for which acquired resistance may be a problem****Aerobic Gram-positive micro-organisms**

Enterococcus faecium \$

**Aerobic Gram-negative micro-organisms**

Escherichia coli

Klebsiellaoxytoca

Klebsiellapneumoniae

Proteus mirabilis

Proteus vulgaris

**Inherently resistant organisms**

### **Aerobic Gram-negative micro-**

**organisms** Acinetobacter sp.

Citrobacter freundii

Enterobacter sp.

Legionella pneumophila

Morganella morganii

Proteus spp.

Pseudomonas sp.

Serratia sp.

Stenotrophomonas maltophilia

### **Other micro-**

**organisms** Chlamydia pneumoniae

Chlamydia psittaci

Coxiella burnetii

Mycoplasma pneumoniae

§ Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

£ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid

<sup>1</sup> Streptococcus pneumoniae that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4).

<sup>2</sup> Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

## **5.2 Pharmacokinetic properties**

### **Absorption**

Amoxicillin and clavulanic acid are fully dissociated in an aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T<sub>max</sub>) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablet three times daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (+/- SD) pharmacokinetic parameters					
Active substance(s)	Dose	Cmax	Tmax *	AUC(0-24h)	T1/2
	(mg)	(Mg /ml)	(h)	((µg.h/ml)	(h)
Amoxicillin					
AMX/CA 500/125 mg	500	7.19 +/-2.26	1.5 (1.0-2.5)	53.5 +/-8.87	1.15 +/-0.20
Clavulanicacid					
AMX/CA 500 mg / 125mg	125	2.40 +/-0.83	1.5 (1.0-2.0)	15.72 +/-3.86	0.98 +/-0.12
AMX – amoxicillin, CA – clavulanicacid * Median(range)					

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

### Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk.

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.

### Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

### Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.



Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of single Co-amoxiclav 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24-hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

### **Age**

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

### **Gender**

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

### **Renal impairment**

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid.

### **Hepatic impairment**

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

## **5.3 Preclinical safety data**

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate

gastricirritancy and vomiting, and discolouredtongue.

Carcinogenicity studies have not been conducted with Co-amoxiclav or itscomponents.

## **6. Pharmaceuticalparticulars**

### **6.1 List ofexcipients**

- Microcrystalline Cellulose(pH112)
- MagnesiumStearate
- Colloidal anhydrous silica(Aerosil)
- Sodium Starch Glycolate
- Hydroxypropyl methyl cellulose E5 (HPMC E5)
- Hydroxypropyl methyl cellulose E15 (HPMC E15)
- Titanium Dioxide
- Polyethylene glycol 6000 (PEG6000)
- Simethicone
- PurifiedWater

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelflife**

24 months from the date ofmanufacturing

### **6.4 Special precautions forstorage**

Not applicable

### **6.5 Nature and contents ofcontainer**

**Presentation:** Cledomox 1000 are available as 1x10's ,10 x10 's and 2 x 7's Aluminium strippack. Primary Container(s):

Cledomox 1000 are available as strip pack. Each strip of1x10's 10 x10 's and 2 x 7'sAluminum strip pack contains 10 and 7 tabletsrespectively.

#### **SecondaryContainer:**

Suchstrippacksarepackedinaprintedcarton.PrintedCartonsareprintedwithrelevant batchdetails.

#### **OuterContainer:**

Such cartons are packed in Export Worthy 5/7 Ply Shippers. These shippers are labelled with product name and relevant batch details and sealed with BOPP tape. Shippersare then strapped with Polypropylenetapes.

### **6.6 Special precautions for disposal and otherhandling**

No special requirements.

**7. Marketing authorization holder**

**Name and Permanent address of the Marketing authorization holder:**

Medopharm, Private limited

“MEDOHOUSE”

25, Puliur II Mainroad, Trustpuram, Chennai-600024,

Tamil Nadu, India.

PH: +9144-30149992/30149955

Fax: 260211286283

**Manufacturing Site address:**

Medopharm Private Limited,

No. 50, Kayarambedu Village,

Guduvanchery- 603 202, Tamil Nadu, India.

**8. Number (s) in the National register of finished pharmaceutical products**

08671/09890/NMR/2022

**9. Date of first authorization/renewal of the authorization**

23.05.2023

**10. Date of revision of the text**

12.07.2023