SUMMARY OFPRODUCTCHARACTERISTICS

MEDOPHARM PRIVATE LIMITED, INDIA.

1. NAME OF THE MEDICINALPRODUCT

Co – Amoxiclav Tablets BP 625 mg (CLEDOMOX625)

2. QUALITATIVE ANDQUANTITATIVE

Each film-coated tablet contains

Amoxicillin trihydrate BP Equivalent to Amoxicillin500 mg

Diluted Potassium clavulanate BP Equivalent to Clavulanic acid 125 mg.

Refer Excipients section 6.1

3. PHARMACEUTICALFORM:

White or off white oval shaped film-coated tablets plain on both sides.

4. CLINICALPARTICULARS

4.1 Therapeuticindications:

It is indicated for the treatment diagnosed)of the following infections in adults andchildren

- Acute bacterial sinusitis(adequately
- Acute otitismedia
- Acute exacerbations of chronic bronchitis (adequatelydiagnosed)
- Community acquiredpneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dentalabscess with spreadingcellulitis.
- Bone and joint infections, in particularosteomyelitis.

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

4.2 Posology and Method ofAdministration:

Posology

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content exceptwhendoses are stated in terms of an individualcomponent.

ThedoseofCo-amoxiclavthatisselectedtotreatanindividualinfectionshouldtakeinto account:

- The expected pathogens and their likely susceptibility to antibacterialagents
- The severity and the site of theinfection
- The age, weight and renal function of the patient as shownbelow.

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

dosesof amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be consideredas necessary.

For adults and children ≥ 40 kg, this formulation of Co-amoxiclav provides a total dailydose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommendedbelow. Forchildren<40kg,thisformulationofCo-amoxiclavprovidesamaximumdailydoseof 2400 mg amoxicillin/600 mg clavulanic acid, when administered as recommended below. If itisconsideredthatahigherdailydoseofamoxicillinisrequired,itisrecommendedthat another preparation of Co-amoxiclav is selected in order to avoid administrationof unnecessarily high daily doses of clavulanicacid.

The duration of therapy should be determined by the response of the patient. Someinfections (e.g.osteomyelitis)requirelongerperiodsoftreatment.Treatmentshouldnotbeextended beyond 14 days withoutreview.

Adults and children ≥ 40kg

Recommended doses:

- Standard dose (for all indications): 500 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): 500 mg/125 mg three times a day.

Children < 40kg

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 500 mg/125 mg tablet.

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

Clavulanicacid[mg/kgbody weight] persingle dose (1film-coated tablet)	3.1	3.6	4.2	5.0	1.8 – 3.2 (up to 5)

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 considerednecessary.

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 amoxiclavpresentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

Hepaticimpairment

Dose with caution and monitor hepatic function at regularintervals.

Method ofadministration

Co-amoxiclav is for oraluse.

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

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

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of theexcipients.Historyofasevereimmediatehypersensitivityreaction(e.g.anaphylaxis)toanother beta- lactamagent(e.g.acephalosporin,carbapenemormonobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanicacid.

4.4 Special warnings and precautions for use

Beforeinitiatingtherapywithamoxicillin/clavulanicacid,carefulenquiryshouldbe made concerning previous hypersensitivity reactions to penicillins, cephalosporinsor other beta-lactamagents.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have beenreported 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 reactionoccurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternativetherapyinstituted.

Inthecasethataninfectionisproventobeduetoanamoxicillin-susceptibleorganisms(s) then consideration should be given to switching from amoxicillin/clavulanic acidto amoxicillin in accordance with officialguidance.

ThispresentationofCo-amoxiclavisnotsuitableforusewhenthereisahighriskthatthe presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents thatisnot mediated by beta-lactamases susceptible to inhibition by clavulanic acid.

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

Convulsionsmayoccurinpatientswithimpairedrenalfunctionorinthosereceivinghigh doses.

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspectedsince theoccurrenceofamorbilliformrashhasbeenassociatedwiththisconditionfollowingthe use ofamoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increasethe likelihood of allergic skinreactions.

Prolonged use may occasionally result in overgrowth of non-susceptibleorganisms.

The occurrence at the treatment initiation of a feverish generalised erythema associatedwithpustula may be a symptom of acute generalisedexanthemouspustulosis (AGEP).This reaction requires Co-amoxiclav discontinuation and contra-indicates anysubsequent administration ofamoxicillin.

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

Hepaticeventshavebeenreportedpredominantlyinmalesandelderlypatientsandmaybe associated with prolonged treatment. These events have been very rarely reported inchildren. In all populations, signs and symptoms usually occur during or shortly after treatment butin somecasesmaynotbecomeapparentuntilseveralweeksaftertreatmenthasceased.Theseareusuallyreve rsible.Hepaticeventsmaybesevereand,inextremelyrarecircumstances,deaths have been reported. These have almost always occurred in patients withserious underlying disease or taking concomitant medications known to have the potential forhepaticeffects.

Antibiotic-associatedcolitishasbeenreportedwithnearlyallantibacterialagentsandmayrangeinseverityfrommild tolifethreatening.Therefore,itisimportanttoconsiderthis diagnosis in patients who present with diarrhoea during or subsequent to theadministrationof any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/

clavulanicacidshouldimmediatelybediscontinued,aphysicianbeconsultedandan appropriatetherapy initiated. Anti-peristaltic medicinal products are contra-indicated in thissituation.

Periodicassessmentoforgansystemfunctions,includingrenal,hepaticandhaematopoietic function is advisable during prolongedtherapy.

Prolongation of prothrombin time has been reported rarely in patientsreceiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertakenwhen anticoagulants are prescribed concomitantly. Adjustments in the dose of oralanticoagulants maybenecessarytomaintainthedesiredlevelofanticoagulation.

Inpatientswithrenalimpairment,thedoseshouldbeadjustedaccordingtothedegreeof impairment.

In patients with reduced urine output, crystalluria has been observed veryrarely, predominantly with parenteral therapy. During the administration of high dosesof amoxicillin,itisadvisabletomaintainadequatefluidintakeandurinaryoutputinorderto reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, aregularcheck ofpatency should be maintained. During treatmentwith amoxicillin, enzymaticglucose oxidase methods should be used whenever testing for the presence of glucose inurine becausefalsepositiveresultsmayoccurwithnon-enzymaticmethods.

ThepresenceofClavulanicacidinCo-amoxiclavmaycauseanon-specificbindingofIgG and albumin by red cell membranes leading to a false positive Coombstest.

There have been reports of positive test results using the Bio-Rad LaboratoriesPlateliaAspergillus EIA test in patients receiving amoxicillin/clavulanic acid whowere subsequently found to be free of Aspergillusinfection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories PlateliaAspergillusEIAtesthavebeenreported.Therefore,positivetest results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiouslyand confirmed by other diagnosticmethods.

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 ofinteraction

<u>Oralanticoagulants</u>

Oral anticoagulants and penicillin antibiotics have been widely used inpractice withoutreportsofinteraction.However,intheliteraturetherearecasesofincreasedinternational normalised ratio in patients maintained on acenocoumarol or warfarinand prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or

international normalised ratio should be carefully monitored withthe additionorwithdrawalofamoxicillin.Moreover, adjustments in thedoseoforal anticoagulants may be necessary.

Methotrexate

Penicillinsmayreducetheexcretionofmethotrexatecausingapotentialincreaseintoxicity.Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renaltubularsecretion of amoxicillin. Concomitant use of probenecid may result in increasedand prolonged blood levels of amoxicillin but not of clavulanicacid.

Mycophenolatemofetil

In patients receiving mycophenolatemofetil, reduction in pre-dose concentration of theactive metabolite mycophenolic acid of approximately 50% has been reportedfollowing commencementoforalamoxicillinplusclavulanicacid.Thechangeinpre-doselevelmay not accurately represent changes in overall MPA exposure. Therefore, a change in the doseof mycophenolatemofetil should not normally be necessary in the absence of clinical evidenceof graft dysfunction. However, close clinical monitoring should be performed duringthe combination and shortly after antibiotictreatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animalstudiesdonotindicatedirectorindirectharmfuleffectswithrespecttopregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on theuse of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk ofcongenitalmalformations.Inasinglestudyinwomenwithpreterm,prematureruptureof thefoetalmembraneitwasreportedthatprophylactictreatmentwithamoxicillin/ clavulanic acid may be associated with an increased risk of necrotisingenterocolitisin neonates. Use should be avoided during pregnancy, unless considered essential bythe physician.

Breast-feeding

Bothsubstancesareexcretedintobreastmilk(nothingisknownoftheeffectsof clavulanicacidonthebreast-fedinfant).Consequently,diarrhoeaandfungusinfectionof the mucous membranes are possible in the breast-fed infant, so thatbreast-feeding mighthavetobediscontinued.Amoxicillin/clavulanicacidshouldonlybeusedduring breast-feeding after benefit/risk assessment by the physician incharge.

4.7 Effects on ability to drive and usemachines

Nostudiesontheeffectsontheabilitytodriveandusemachineshavebeenperformed. However, undesirable effects may occur (e.g. allergic reactions, dizziness,convulsions), which may influence the ability to drive and usemachines.

4.8 Undesirableeffects

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

The ADRs derived from clinical studies and post-marketing surveillance withCo-amoxiclav,sortedbyMedDRASystemOrganClassarelistedbelow.

Thefollowingterminologieshavebeenusedinordertoclassifytheoccurrenceofundesirableeffects.

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to<1/100)

Rare (≥1/10,000 to<1/1,000) Very rare(<1/10,000)

Not known (cannot be estimated from the availabledata)

Infections andinfestations	
Mucocutaneouscandidosis	Common
Overgrowth ofnon-susceptible organisms	Notknown
Blood and lymphatic systemdisorders	
Reversible leucopenia(including neutropenia)	Rare
Thrombocytopenia	Rare
Reversibleagranulocytosis	Notknown
Haemolyticanaemia	Notknown
Prolongation of bleeding timeand prothrombintime[1]	Notknown
Immune systemdisorders[10]	
Angioneuroticoedema	Notknown

Anaphylaxis	Notknown
Serum sickness-likesyndrome	Notknown
Hypersensitivityvasculitis	Notknown
Nervous systemdisorders	
Dizziness	Uncommon
Headache	Uncommon
Reversiblehyperactivity	Notknown
Convulsions[2]	Notknown
Aesepticmeningitis	Notknown
Gastrointestinaldisorders	
Diarrhoea	Verycommon
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associatedcolitis[4]	Notknown
Black hairytongue	Notknown
Toothdiscolouration[11]	Notknown
Hepatobiliarydisorders	
Rises in AST and/orALT[5]	Uncommon
Hepatitis[6]	Notknown
Cholestaticjaundice[6]	Notknown
Skin and subcutaneous tissuedisorders[7]	
Skinrash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythemamultiforme	Rare
Stevens-Johnsonsyndrome	Notknown
Toxic epidermalnecrolysis	Notknown
Bullousexfoliative-dermatitis	Notknown

Acute generalisedexanthemouspustulosi (AGEP)[9]	Notknown
Renal and urinarydisorders	
Interstitialnephritis	Notknown
Crystalluria[8]	Notknown

[1] See section4.4

[2] See section4.4

[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactionsare evident, they may be reduced by taking Co-Amoxiclav at the start of ameal.

[4] Including pseudomembranous colitis and haemorrhagic colitis (see section4.4)

[5]AmoderateriseinASTand/orALThasbeennotedinpatientstreatedwithbeta-lactam classantibiotics, but thesignificanceofthese findings is unknown.

[6]These events havebeennoted with otherpenicillinsand cephalosporins(seesection 4.4).

[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).

[8]Seesection 4.9

[9]Seesection 4.4

[10]Seesections 4.3 and 4.4

[11]Superficial tooth discolourationhas been reported very rarely in children. Good oralhygienemayhelp to prevent tooth discolourationas it can usuallybe removed bybrushing.

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 ofoverdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances maybe evident. Amoxicillin crystalluria, in some cases leading to renal failure, has beenobserved. Convulsionsmayoccurinpatientswithimpairedrenalfunctionorinthosereceivinghigh doses. Amoxicillin has been reported to precipitate in bladder catheters, predominantlyafterintravenous administration of large doses. A regular check of patency

should bemaintained. **Treatment ofintoxication**

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolytebalance.Amoxicillin/clavulanic acid can be removed from the circulation byhaemodialysis.

5. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:Combinations of penicillin's, incl. beta-lactamase inhibitorsATC code:J01CR02.

Mechanism of action

Amoxicillinissemisyntheticpenicillin(beta-lactamantibiotic)thatinhibitsoneormore enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosyntheticpathway ofbacterialpeptidoglycan,whichisanintegralstructuralcomponentofthebacterialcell wall.Inhibitionofpeptidoglycansynthesisleadstoweakeningofthecellwall,whichis usually followed by cell lysis anddeath.

Amoxicillinissusceptibletodegradationbybeta-lactamasesproducedbyresistantbacteria and therefore the spectrum of activity of amoxicillin alone does not include organismswhich produce theseenzymes.

Clavulanicacidisabeta-lactamstructurallyrelatedtopenicillins.Itinactivatessomebeta- lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alonedoes not exert a clinically useful antibacterialeffect.

PK/PDrelationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be themajor determinant of efficacy foramoxicillin.

Mechanisms ofresistance

The two main mechanisms of resistance to amoxicillin/clavulanic acidare:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibitedby clavulanic acid, including class B, C andD.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for thetarget. Impermeabilityofbacteriaoreffluxpumpmechanismsmaycauseorcontributetobacterial resistance, particularly in Gram-negativebacteria.

Breakpoints

MICbreakpointsforamoxicillin/clavulanicacidarethoseoftheEuropeanCommitteeon

Antimicrobial Susceptibility Testing(EUCAST)

Organism	**Susceptibility Breakpoints(□g/ml)**	
	Susceptible	**Resistant**
Haemophilusinfluenzae	≤0.001[1]	>2[1]
Moraxellacatarrhalis	≤1[1]	>1[1]
Staphylococcus spp.	Note[2a,3a,3b,4]	Note[2a,3a,3b,4]
Enterococcus spp.[7]	<4[1,5]	> 8[1,5]
Streptococcus groups A, B, C,G[2b,8](indications other	Note[2b]	Note[2b]
Streptococcus pneumoniae[8]	≤0.5[1,6]	> 1[1,6]
Enterobacterales in uncomplicatedUTIs	≤ 32[1]	> 32[1]
Gram-negativeAnaerobes	≤4[1]	>8[1]
Gram-positiveAnaerobes (except	≤4[1]	>8[1]
Non-species relatedbreakpoints	≤2[1]	>8[1]
Viridans groupstreptococci[8]	Note[2a,9]	Note[2a,9]
Pasteurellamultocida	≤1[1]	>1[1]
Burkholderiapseudomallei	≤ 0.001[1]	>8[1]

1For 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 isoxazolylpenicillins 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 isoxazolylpenicillins (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 ≥20 mm, or benzylpenicillin MIC ≤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 ≤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 dvice 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-negativemicro-organisms Acinetobactersp.

Citrobacterfreundii

Enterobactersp.

Legionellapneumophila

MorganellamorganiiProvidenciaspp.

Pseudomonassp.

Serratiasp.

Stenotrophomonasmaltophilia

Othermicro-organisms Chlamydophilapneumoniae

Chlamydophilapsittaci

Coxiellaburnetti

$ Natural intermediate susceptibility in the absence of acquired mechanism ofresistance.
£All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanicacid
[1]Streptococcus pneumoniae that are resistant to penicillin should not be treated withthis presentation of amoxicillin/clavulanic acid (see sections 4.2 and4.4).
[2] Strains with decreased susceptibility have been reported in some countries in the EU witha frequency higher than10%.

5.2 Pharmacokineticpropertie

sAbsorption

Amoxicillinandclavulanicacid,arefullydissociatedinaqueoussolutionatphysiological pH.Bothcomponentsarerapidlyandwellabsorbedbytheoralrouteofadministration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of ameal. Following oral administration, amoxicillin and clavulanic acid are approximately70% bioavailable. The plasma profiles of both components are similar and the time to peakplasma concentration (Tmax) in each case is approximately onehour.

Thepharmacokineticresultsforastudy,inwhichamoxicillin/clavulanicacid(500mg/125 mgtabletsthreetimesdaily)wasadministeredinthefastingstatetogroupsofhealthy volunteers are presentedbelow.

Mean (+/- SD) pharmacokineticparameters					
Active substance(s)	Dose (mg)	Cmax (Mg /ml)	Tmax * (h)	AUC(0-24h) ((µg.h/ml)	T1/2 (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 withamoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent dosesof amoxicillin or clavulanic acidalone.

Distribution

About25%oftotalplasmaclavulanicacidand18%oftotalplasmaamoxicillinisboundto protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin andaround 0.2 l/kg for clavulanicacid.

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

From animal studies there is no evidence for significant tissue retention ofdrug-derivedmaterialforeithercomponent.Amoxicillin,likemostpenicillins,canbedetectedinbreast milk. Trace quantities of clavulanic acid can also be detected in breastmilk.

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

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid inquantities equivalenttoupto10to25%oftheinitialdose.Clavulanicacidisextensivelymetabolized in man and eliminated in urine and faeces and as carbon dioxide in expiredair.

Elimination

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

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 to70% oftheamoxicillinandapproximately40to65%oftheclavulanicacidareexcreted unchangedinurineduringthefirst6hafteradministrationofsingleCo-amoxiclav250 mg/125mgor500mg/125mgtablets.Variousstudieshavefoundtheurinaryexcretionto be50-85%foramoxicillinandbetween27-60%forclavulanicacidovera24hour 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 delayrenal excretion of clavulanicacid.

Age

Theeliminationhalf-lifeofamoxicillinissimilarforchildrenagedaround3monthsto 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 betaken in dose selection, and it may be useful to monitor renalfunction.

Gender

Followingoraladministrationofamoxicillin/clavulanicacidtohealthymalesandfemalesubjects,gender hasnosignificantimpactonthepharmacokineticsofeitheramoxicillinor clavulanicacid.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionatelywithdecreasing renal function. The reduction in drug clearance is more pronouncedfor amoxicillinthanforclavulanicacid,asahigherproportionofamoxicillinisexcretedviatherenal route. Doses inrenal impairment must therefore prevent undueaccumulation of amoxicillin while maintaining adequate levels of clavulanicacid.

Hepaticimpairment

Hepatically impaired patients should be dosed with caution and hepatic function monitoredat regularintervals.

5.3 Preclinical safetydata

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

Repeat dosetoxicitystudies performed in dogs with amoxicillin/clavulanic acid demonstrategastricirritancy 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 625 are available as 2 x 7's Aluminum strippack.

Primary Container(s):

Cledomox 625are available as strip pack. Each strip of 2 x 7'sAluminum strip pack contains 7 tabletsrespectively.

SecondaryContainer:

Suchstrippacksarepackedinaprintedcarton.PrintedCartonsareprintedwithrelevant batchdetails.

OuterContainer:

Such cartons are packed in Export Worthy 5/7 Ply Shippers. These shippers are labeled 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 specialrequirements.

7. Marketing authorizationholder

NameandPermanentaddressoftheMarketingauthorizationholder:

Medopharm, Private limited

"MEDOHOUSE"

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

Tamil Nadu,India.

PH: +9144-30149992/30149955

Fax: 260211286283

Manufacturing Siteaddress:

Medopharm Private Limited,

No. 50, KayarambeduVillage,

Guduvanchery- 603 202, Tamil Nadu,India.

8. Number (s) in the National register of finished pharmaceuticalproducts

First Registration No.: MEDOP/IND/001 Certificate No. : R058/09

Renewal registration - 05360/07550/REN/2020

9. Date of first authorization/renewal of theauthorization

First authorization - 18/10/2016.

Renewal authorization - 25.09.2020

10. Date of revision of thetext

12.07.2023