SUMMARY OF PRODUCT CHARACTERISTICS

1. NAMEOFTHEMEDICINALPRODUCT

AmoxicillinandClavulanatePotassiumforOralsuspensionUSP312.5mg/5ml. (CLEDOMOX 312.5)

2. QUALITATIVEANDQUANTITATIVECOMPOSITION

Each 5 mL after reconstituted suspensioncontains:
AmoxicillintrihydrateBP Equivalent to Amoxicillin 250 mg
Diluted Potassium ClavulanateEquivalenttoClavulanicacid62.5mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICALFORM

A white to almost white powder with pleasant odour which gives white to almost white suspensiononreconstitution with water.

4. CLINICALPARTICULARS

4.1 Therapeuticindications

Amoxicillin and Clavulanate Potassium for Oralsuspension USP312.5mg/5ml (Cledomox312.5)isindicated forthetreatment ofthefollowinginfections in adults andchildren:

- Acutebacterialsinusitis(adequatelydiagnosed)
- Acuteotitismedia
- Acuteexacerbationsofchronicbronchitis(adequatelydiagnosed)
- Communityacquiredpneumonia
- Cystitis
- Pyelonephritis
- Skinandsofttissueinfectionsinparticularcellulitis,animalbites,severedentalabscesswithspreadingcellulitis
- Boneandjointinfections,inparticularosteomyelitis.

Considerationshouldbegiventoofficialguidanceontheappropriateuseofantibacterialagents

4.2 Posology and method of administration<u>Posology</u>

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except whendosesarestated in termsofan individualcomponent.

The dose of Cledomox 312.5 that is selected to treat an individual infection should take intoaccount:

- Theexpectedpathogensandtheirlikelysusceptibilitytoantibacterialagents
- Theseverityand thesiteoftheinfection

- Theage,weightandrenalfunctionofthepatientasshownbelow.

The use of alternative presentations of Amoxicillin and Clavulanate Potassium for Oralsuspension USP 312.5mg/5ml (Cledomox 312.5) (e.g. those that provide higher doses ofamoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered asnecessary

For adults and children ≥ 40 kg, this formulation of Amoxicillin and Clavulanate Potassiumfor Oral suspension USP 312.5mg/5ml provides a total daily dose of 1500 mgamoxicillin/375mgclavulanicacid,whenadministeredasrecommendedbelow.Forchildren < 40 kg, this formulation of Amoxicillin and Clavulanate Potassium for Oral suspension USP312.5mg/5ml (Cledomox 312.5) provides a maximum daily dose of 2400 mg amoxicillin/600mg clavulanic acid, when administered as recommended below. If it is considered that ahigher daily dose of amoxicillin is required, it is recommended that another preparation ofAmoxicillin and Clavulanate Potassium for Oral suspension USP 312.5mg/5ml (Cledomox312.5) is selected in order to avoid administration of unnecessarily high daily doses ofclavulanicacid.

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 extendedbeyond14 dayswithout review(seesection 4.4regardingprolonged therapy).

Adultsandchildren≥40kg

One500 mg/125mgdosetaken threetimes aday.

Children<40kg

20mg/5mg/kg/dayto60mg/15mg/kg/daygiven inthreedivideddoses.

Children may be treated with Amoxicillin and Clavulanate Potassium tablets, suspensions orpaediatric sachets. Children aged 6 years and below should preferably be treated withAmoxicillin and Clavulanate Potassium for Oral suspension USP 312.5mg/5ml (Cledomox312.5)suspension orpaediatricsachets.

No clinical data are available on doses of Amoxicillin and Clavulanate Potassium for Oralsuspension USP 312.5mg/5ml (Cledomox 312.5) 4:1 formulations higher than 40 mg/10mg/kgperdayin children under2years.

Elderly

Nodoseadjustmentisconsiderednecessary.

Renalimpairment

Doseadjustmentsarebasedonthemaximumrecommendedlevelofamoxicillin.

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

Adultsandchildren≥40kg

CrCl:10-30ml/min	500 mg/125mgtwicedaily
CrCl<10 ml/min	500mg/125 mgoncedaily
Haemodialysis	500mg/125mgevery24hours,plus500mg/125mgduringdialysis,tobe repeatedattheendofdialysis(aserumconcentrationsofbothamoxicillinandclavulanicacidaredecreased)

Children< 40kg

CrCl:10-30ml/min	15mg/3.75mg/kgtwicedaily(maximum500mg/125mgtwicedaily).
CrCl<10 ml/min	15mg/3.75mg/kg asasingledailydose (maximum500mg/125mg).
Haemodialysis	15mg/3.75mg/kgperdayoncedaily. Priortohaemodialysis15mg/3.75mg/kg.Inordertorestorecirculating druglevels,15mg/3.75mgperkgshouldbeadministeredafterhaemodialysis.

Hepaticimpairment

Dosewithcautionandmonitorhepaticfunctionat regularintervals

Methodofadministration

Amoxicillin and Clavulanate Potassium for Oral suspension USP 312.5mg/5ml (Cledomox312.5)is fororal use.

Amoxicillin and Clavulanate Potassium for Oral suspension USP 312.5mg/5ml (Cledomox312.5) should be administered with a meal to minimise potential gastrointestinal intolerance.Therapy can be started parenterally according the SmPC of the IV-formulation and continuedwithan oral preparation.

Shake to loosen powder, add water as directed, invert and shake.Shakethebottlebeforeeach dose

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients.Historyofasevereimmediatehypersensitivityreaction(e.g.anaphylaxis)toanotherbetalactam agent (e.g.acephalosporin,carbapenem or monobactam). History ofjaundice/hepaticimpairment dueto amoxicillin/clavulanicacid

4.4 Specialwarningsandprecautionsforuse

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be madeconcerning previous hypersensitivityreactions to penicillins,cephalosporins or otherbetalactamagents

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severecutaneous adverse reactions) have been reported in patients on penicillin therapy. Thesereactions are more likely to occur in individuals with a history of penicillin hypersensitivityand in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapymustbediscontinued and appropriatealternativetherapyinstituted.

Inthe casethataninfectionisproventobedueto anamoxicillin-susceptibleorganisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin inaccordancewith officialguidance.

This presentation of Amoxicillin and Clavulanate Potassium for Oral suspension USP 312.5mg/5ml(Cledomox 312.5) is not suitable for use when there is a high risk that the presumptive pathogenshavereducedsusceptibilityorresistancetobeta-lactamagentsthatisnotmediatedbybeta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treatpenicillin-resistant S. pneumoniae. Convulsions may occur in patients with impaired renal functionorinthosereceivinghighdoses.Amoxicillin/clavulanicacidshouldbeavoidedifinfectiousmononucleosis is suspected since the occurrence of a morbilliform rash has been associated withthiscondition followingtheuseofamoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihoodofallergicskin reactions.

Prolongedusemayoccasionallyresultin overgrowthofnon-susceptibleorganisms.

Theoccurrenceatthetreatmentinitiationofafeverishgeneralisederythemaassociatedwithpustulamaybeasymptomofacutegeneralisedexanthemouspustulosis(AGEP).ThisreactionrequiresAmoxicillin and ClavulanatePotassium forOralsuspension USP 312.5mg/5ml(Cledomox312.5)discontinuationandcontraindicates anysubsequentadministrationofamoxicillin.Amoxicillin/clavulanicacidshouldbeusedwithcautionin patientswithevidenceofhepaticimpairment.

Hepatic events have been reported predominantly in males and elderly patients and may beassociated 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 insome cases may not become apparent until several weeks after treatment has ceased. Theseare usually reversible. Hepatic events may be severe and, in extremely rare circumstances,deaths have been reported. These have almost always occurred in patients with seriousunderlying disease or taking concomitant medications known to have the potential for hepaticeffects.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents includingamoxicillinand mayrangein severityfrom mild to lifethreatening.

Therefore, it is important to consider this diagnosis in patients who present with diarrhoeaduring or subsequent to the administration of any antibiotics. Should antibiotic-associatedcolitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician beconsulted and an appropriate therapy initiated. Anti-peristaltic medicinal products arecontraindicatedin this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoieticfunctionis advisablduringprolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receivingamoxicillin/clavulanic acid. Appropriate monitoring should be undertaken whenanticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulantsmaybenecessaryto maintainthedesired level ofanticoagulation.

In patients with renal impairment, the dose should be adjusted according to the degree ofImpairment.

In patients with reduced urine output, crystalluria has been observed very rarely,predominantly with parenteral therapy. During the administration of high doses ofamoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order toreduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regularcheckofpatencyshouldbemaintained.

During treatment with amoxicillin, enzymatic glucose oxidase methods should be usedwhenever testing for the presence of glucose in urine because false positive results may occurwithnon-enzymaticmethods.

The presence of clavulanic acid in Amoxicillin and Clavulanate Potassium for Oral suspension USP312.5mg/5ml (Cledomox 312.5) may cause a non-specific binding of IgG and albumin by red cellmembranes leading to a false positive Coombs test. There have been reports of positive test resultsusingtheBio-RadLaboratoriesPlateliaAspergillusEIAtestinpatientsreceivingamoxicillin/clavulanic acid who were subsequently found to be free of Aspergillus infection. Cross-reactionswithnon-AspergilluspolysaccharidesandpolyfuranoseswithBio-RadLaboratoriesPlateliaAspergillusEIAtesthavebeenreported.Therefore,positivetestresultsinpatients receivingamoxicillin/clavulanicacidshouldbeinterpretedcautiouslyandconfirmedbyotherdiagnosticmethods.

Amoxicillin and Clavulanate Potassium for Oral suspension USP 250 mg/62.5 mg/5 ml powder fororal suspension contains 2.5 mg of aspartame (E951) per ml, a source of phenylalanine. Thismedicine should be used with caution in patients with phenylketonuria. Neither non-clinical

norclinicaldataareavailabletoassessaspartameusein infants below12weeksofage.

4.5 Interaction with other medicinal products and other forms of interaction

Oralanticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports ofinteraction. However, in the literature there are cases of increased international normalised ratio inpatients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administrationisnecessary,theprothrombintimeorinternationalnormalisedratioshouldbecarefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in thedoseoforal anticoagulants maybenecessary.

Methotrexate

Penicillinsmayreducetheexcretionofmethotrexatecausingapotentialincreaseintoxicity.

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubularsecretionofamoxicillin.Concomitantuseofprobenecidmayresultinincreasedandprolongedblood levels ofamoxicillin but not ofclavulanicacid.

Mycophenolatemofetil

In patients receiving mycophenolatemofetil, reduction in pre-dose concentration of the activemetabolitemycophenolicacid(MPA)ofapproximately50%hasbeenreportedfollowingcommencementoforalamoxicillinplusclavulanicacid.Thechangeinpre-doselevelmaynotaccuratelyrepresentchangesinoverallMPAexposure.Therefore,achangeinthedoseofmycophenolatemofetilshouldnotnormallybenecessaryintheabsenceofclinicalevidenceofgraft dysfunction. However, close clinical monitoring should be performed during the combinationandshortlyafterantibiotictreatment.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy,embryonal/foetaldevelopment, parturitionorpostnatal development.

Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do notindicateanincreasedriskofcongenitalmalformations.Inasinglestudyinwomenwith preterm, premature rupture of the foetal membrane it was reported that prophylactic treatmentwithamoxicillin/clavulanicacidmaybeassociatedwithanincreasedriskofnecrotizingenterocolitis in neonates.Use shouldbe avoidedduring pregnancy, unless considered essentialbythephysician.

Breastfeeding

Bothsubstancesareexcretedintobreastmilk(nothingisknownoftheeffectsofclavulanicacid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucousmembranesarepossibleinthe breast-fedinfant,sothatbreast-feedingmighthave tobediscontinued. The possibility of sensitisation should be taken into account.Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/riskassessmentbythephysician incharge.

4.7 Effectsonabilitytodriveandusemachines

Nostudiesontheeffectsontheability todriveandusemachineshavebeenperformed.However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), whichmayinfluencetheabilityto driveand usemachines.

4.8 Undesirableeffects

The ADRs derived from clinical studies and post-marketing surveillance with Amoxicillin andClavulanate Potassium for Oral suspension USP 312.5mg/5ml, sorted by MedDRA System OrganClassarelisted below.

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

Verycommon (≥1/10)
Common (≥1/100 to

<1/10)Uncommon (≥1/1,000 to

<1/100)Rare (≥1/10,000 to

<1/1,000)Veryrare(<1/10,000)

Notknown(cannotbeestimatedfromtheavailabledata)

Infectionsandinfestations	
Mucocutaneouscandidosis	Common
Overgrowthofnon-susceptibleorganisms	Notknown
Bloodandlymphaticsystemdisorders	
Reversible leucopenia (includingneutropenia)	Rare
Thrombocytopenia	Rare
Reversibleagranulocytosis	Notknown

Haemolyticanaemia	Notknown
Prolongationofbleedingtimeandprothrombintime[1]	Notknown
Immunesystemdisorders[10]	
Angioneuroticoedema	Notknown
Anaphylaxis	Notknown
Serumsickness-likesyndrome	Notknown
Hypersensitivityvasculitis	Notknown
Nervoussystemdisorders	
Dizziness	Uncommon
Headache	Uncommon
Reversiblehyperactivity	Notknown
Convulsions[2]	Notknown
Aesepticmeningitis	Notknown
Gastrointestinaldisorders	
Diarrhoea	Common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associatedcolitis[4]	Notknown
Black hairytongue	Notknown
Toothdiscolouration[11]	Notknown
Hepatobiliarydisorders	
RisesinASTand/orALT[5]	Uncommon
Hepatitis[6]	Notknown
Cholestaticjaundice[6]	Notknown
Skinandsubcutaneoustissuedisorders[7]	
Skinrash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon

Erythemamultiforme	Rare
Stevens-Johnsonsyndrome	Notknown
Toxicepidermalnecrolysis	Notknown
Bullousexfoliative-dermatitis	Notknown
Acutegeneralised exanthemouspustulosis(AGEP)9	Notknown
Drugreactionwitheosinophiliaandsystemicsymptoms(DRESS)	Notknown
Renalandurinarydisorders	
Interstitialnephritis	Notknown
Crystalluria[8]	Notknown

[1]See section4.4

[2]Seesection4.4

[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactionsare evident,theymaybereducedbytaking amoxicillin/clavulanic acid withameal.

[4]Including pseudomembranouscolitisandhaemorrhagiccolitis

[5]AmoderateriseinASTand/orALThasbeennotedinpatientstreatedwithbeta-lactamclassantibiotics,butthesignificanceofthesefindingsisunknown.

[6]These eventshave beennoted withotherpenicillins andcephalosporins.

[7]Ifanyhypersensitivitydermatitisreactionoccurs, treatmentshouldbediscontinued

[8]Seesection4.9

[9]Seesection4.4

[10]Seesections 4.3 and4.4

[11] Superficial tooth discolouration has been reported very rarely inchildren. Goodoral hygiene may help to prevent tooth discolouration as it can usually be removed

Reportingofsuspectedadversereactions

Reportingsuspectedadversereactionsafterauthorisationofthemedicinalproductisimportant.It allows continued monitoring of the benefit/risk balance of the medicinal product.Healthcareprofessionalsare askedto reportany suspectedadverse reactions via theYellow CardSchemeat:www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptomsandsignsofoverdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may beevident. 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 highdoses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly afterintravenous administration of large doses. A regular check of patency should be maintained**Treatmentofintoxication**

Gastrointestinal symptoms may be treated symptomatically, with attention to thewater/electrolytebalance.

Amoxicillin/clavulanicacidcanberemovedfrom thecirculationbyhaemodialysis.

5. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamicproperties

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

Mechanismof action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or moreenzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathwayof bacterial peptidoglycan, which is an integral structural component of the bacterial cellwall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which isusuallyfollowed bycell lysisand death.

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

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamaseenzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert aclinicallyuseful antibacterialeffect.

Pharmacokinetic/pharmacodynamicrelationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the majordeterminantofefficacyfor amoxicillin.

Mechanismsofresistance

Thetwomainmechanismsofresistancetoamoxicillin/clavulanicacidare:

•Inactivation by those bacterial beta-lactamases that are not themselves inhibited byclavulanic acid,includingclassB, C andD.

•AlterationofPBPs,whichreducethe affinityoftheantibacterialagentforthetarget.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance,particularlyin Gram-negativebacteria.

Breakpoints

MIC breakpoints foramoxicillin/clavulanic acid are thoseoftheEuropeanCommitteeonAntimicrobialSusceptibilityTesting (EUCAST)Organism	SusceptibilityBreakpoints(µg/ml)		
	Susceptible		Resistant
Haemophilusinfluenzae	$\leq 2^1$		$>2^1$
Moraxellacatarrhalis	$\leq 1^1$		$>1^1$

Staphylococcusspp	≤0.125[2,3,4]		>0.125[2,3,4]
Enterococcus	≤ 4[1]		>8[1]
StreptococcusA,B,C,G	≤ 0.25[2]		>0.25[2]
Streptococcuspneumoniae	≤0.5[1,5]		>1[1,5]
Enterobacterales	≤8[1,6]		>8[6]
Enterobacterales in	≤32[1,6]		>32[6]
Gram-negativeAnaerobes	≤ 4[1]		>8[1]
Gram-positiveAnaerobes(except	≤ 4[1]		>8[1]
Non-species related	≤ 2[1]		>8[1]

The reported values are for amoxicillin concentrations. For susceptibility testingpurposes, theconcentrationofclavulanicacid is fixed at 2mg/l.

[2]Breakpointvalues inthetableare based on benzylpenicillinbreakpoints.

[3]Moststaphylococciarepenicillinaseproducers,whichmakethemresistanttobenzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin.When staphylococci test as susceptible to benzylpenicillin and cefoxitin theycan be reportedas susceptible to the above agents. However, the efficacy of oral formulations, particularlyphenoxymethylpenicillin, is uncertain. Isolates that test as resistantto benzylpenicillin butsusceptibletocefoxitinaresusceptibletoβ-lactamaseinhibitorcombinations,theisoxazolylpenicillins(oxacillin,cloxacillin,dicloxacillinandflucloxacillin),nafcillinandmany cephalosporins. With the exception of ceftaroline and ceftobiprole, cefoxitin-resistantisolatesareresistant to all beta-lactamagents.

[4] Ampicillin susceptible S. saprophyticus are mecA-negative and susceptible toampicillin,amoxicillinandpiperacillin (withoutorwith abeta-lactamaseinhibitor).

[5] Theoxacillin1unitdiskscreentestshallbeusedtoexcludebeta-lactamresistancemechanisms. When the screen is negative (inhibition zone ≥20 mm) all beta-lactamagents forwhichclinicalbreakpointsareavailable,canbereportedsusceptiblewithoutfurthertesting.

[6]WildtypeEnterobacteralesarecategorisedassusceptibletoaminopenicillins. Some countries prefer to categorise wild-type isolates of E. coli and P. mirabilis as "Susceptible,increasedexposure".Whenthisisthecase,usetheMICbreakpointS≤0.5mg/Landthe

Theprevalenceofresistancemayvarygeographicallyandwithtimeforselectedspecies,andlocalinformationonresistanceisdesirable,particularlywhentreatingsevereinfections.Asnecessary,

expertadviceshouldbesoughtwhenthelocalprevalenceofresistanceissuchthattheutilityoftheagentin at least sometypes ofinfections isquestionable.

Commonlysusceptiblespecies
AerobicGram-positivemicro-organisms *Enterococcus* *faecalisGardnerellav* *aginalis* *Staphylococcusaureus*(methicillin- susceptible)£Coagulase-negative staphylococci (methicillin-susceptible)*Streptococcusagalactiae* *Streptococcuspneumoniae*[1] *Streptococcuspyogenes*andotherbeta-haemolyticstreptococci *Streptococcusviridans*group AerobicGram-negativemicro-organisms *Capnocytophaga*spp.*Eik* *enellacorrodensHaemop* *hilus* *influenzae*[2]*Moraxellacat* *arrhalis* *Pasteurellamultocida*Anaer obic micro- organisms*Bacteroidesfragil* *isFusobacteriumnucleatum* *Prevotella*spp.
Species forwhich acquired resistance maybeaproblem
AerobicGram-positivemicro-organisms *Enterococcusfaecium*$
AerobicGram-negativemicro-organisms *Escherichiacoli*
Inherentlyresistantorganisms

AerobicGram-negativemicro-organisms *Acinetobacter*sp.*Cit* *robacterfreundii**Ent* *erobacter*sp. *Legionellapneumophila* *Morganellamorganii**Pr* *ovidencia*spp. *Pseudomonas*sp. *Serratia*sp.*Stenotrophomonas* *maltophilia*Other micro- organisms*Chlamydophilapneu* *moniae**Chlamydophilapsittaci* *Coxiellaburnetti* *Mycoplasmapneumonia*
$Naturalintermediate susceptibilityintheabsence of acquired mechanismofresistance. £ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid[1]*Streptococcuspneumoniae*thatareresistanttopenicillinshouldnotbetreatedwiththispresentationofamoxicillin/clavulanicacid(seesections 4.2 and4.4). [2]StrainswithdecreasedsusceptibilityhavebeenreportedinsomecountriesintheEUwithafrequencyhigherthan10%.

5.2 Pharmacokineticproperties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH.Bothcomponentsarerapidlyandwellabsorbedbytheoralrouteofadministration.Followingoraladministration,amoxicillinandclavulanicacidareapproximately70%bioavailable. The plasma profiles of both components are similar and the time to peak plasmaconcentration (T_{max})ineachcaseis approximatelyonehour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mgtabletsthreetimesdaily)wasadministeredinthefastingstatetogroupsofhealthyvolunteersarepresentedbelow.

Mean(±SD)pharmacokineticparameters					
Activesubstance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max}* (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 500mg/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 ofequivalentdosesofamoxicillinorclavulanicacidalone.

Distribution

About25%oftotalplasmaclavulanicacidand18%oftotalplasmaamoxicillinisboundto protein.Theapparent volumeofdistribution is around0.3-0.4 l/kgforamoxicillinandaround

0.2l/kgfor clavulanicacid

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid inquantitiesequivalenttoupto10to25%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 clavulanicacidit is byboth renal and non-renalmechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hourand a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60to 70% of theamoxicillinandapproximately40to65%oftheclavulanicacidareexcretedunchangedinurineduringt hefirst6hafteradministrationofsingleAmoxicillinand Clavulanate PotassiumforOralsuspensionUSP250mg/125mgor500mg/125mgtablets.Variousstudieshavefoundt heurinaryexcretiontobe50-85%foramoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case ofclavulanic acid, the largest amountof drug is excreted during the first 2

hours afteradministration.

Concomitant use of probenecid delays amoxicillin excretion but does not delayrenalexcretionofclavulanicacid

Age

Theeliminationhalf-lifeofamoxicillinissimilarforchildrenagedaround3monthsto2 years and older children and adults. For very young children (including pretermnewborns)in thefirstweekoflifetheinterval of administration should notexceedtwicedaily

administration due to immaturity of the renal pathway of elimination. Becauseelderlypatientsaremorelikelytohavedecreasedrenalfunction,careshouldbetakenindoseselection, and it maybeuseful to monitorrenalfunction.

Gender

Followingoraladministrationofamoxicillin/clavulanicacidtohealthymalesandfemale subjects,genderhasnosignificantimpactonthepharmacokineticsofeitheramoxicillinorclavulanicacid.

Renalimpairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionatelywithdecreasingrenalfunction.Thereductionindrugclearanceismorepronouncedforamoxicillin 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 ofamoxicillinwhilemaintainingadequatelevels ofclavulanicacid.

Hepaticimpairment

Hepaticallyimpairedpatientsshouldbedosedwithcautionandhepaticfunctionmonitoredat regularintervals

5.3Preclinicalsafetydata

Non-clinicaldatarevealnospecialhazardforhumansbasedonstudiesofsafetypharmacology,genotoxicityandtoxicitytoreproduction.

Repeatdosetoxicitystudiesperformedindogswithamoxicillin/clavulanicaciddemonstrate gastricirritancyandvomiting, and discolouredtongue.

Carcinogenicitystudieshavenotbeenconductedwithamoxicillin/clavulanicacidoritscomponents

6. PHARMACEUTICALPARTICULARS

6.1 Listof excipients

- Colloidalsilicondioxide(Heavy)
- ColloidalSilicondioxide(Aerosil)
- Hypromellose–E5
- Aspartame
- Succinicacid
- Xanthangum
- Orange drypowder
- RasberryDC 107
- Pineappledrypowder

6.2 Incompatibilities

Notapplicable

6.3 Shelf life

24months.

6.4 Specialprecautionsforstorage

Storeinacooldryplace,between15-30°C.Protectfrom light.

6.5 Natureandcontents ofcontainer

PrimaryContainer(s): AmoxicillinandClavulanatePotassiumfororalsuspensionUSP 312.5mg/5ml(Cledomox312.5) isavailable in 100mlHDPEbottle.

SecondaryContainer:

Each bottle is labelled and packed in a Printed Carton with relevant batch details along withleaflet.

- Carton: ITCCyber XLwithaquavarnishsideopenwith300GSMmulti-colours.
- Leaflet:60GSMMaplithopaper.

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.

6.6Specialprecautionsfordisposalandotherhandling

Bottlesmaybesuppliedwitharing-sealontheneckofthecaporwitharemovablefoil-backed seal

on themouth ofthebottle.

Checkcaporbottle sealisintactbefore using.The capring-sealisbrokenoncethecapis opened. Alternatively, ifa foil-backed seal on the mouth of the bottle is present,thisshould beremoved at thetimeofpreparation.

Shake bottle to loosen powder. Add volume of water (as indicated below). Close, invertandshakewell.

Alternatively, shake thebottle to loosen powder then fill the bottle withwater to justbelow the line on the label. Close, invert and shake well, then top up with water exactly totheline. Close, invert and again shakewell.

Strength	Volumeofwatertobeaddedatreconstitution(ml)	Finalvolumeofreconstitutedoralsuspension(ml)
250mg/62.5mg/5ml	59.78	70

Shakethebottlewellbeforeeachdose.

Anyunusedmedicinalproductorwastematerialshouldbedisposedofinaccordancewithlocalrequirements.

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 – MEDO/IND/005 certificate No.: RV/242/09

Renewal registration - 05819/07752/REN/2020

9. Date of first authorization/renewal of theauthorization

First authorization – 21/02/2017

Renewal authorization - 30.03.2021

10. Date of revision of thetext

12.07.2023