SUMMARY OFPRODUCTCHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICALPRODUCT

Amoxicillin Tablets for Oral Suspension USP 250 MG (MEDOMOX 250 DT)

2. QUALITATIVE & QUANTITATIVECOMPOSITION:

Each dispersible tabletcontains:

AmoxicillinTrihydrateUSPEquivalenttoAmoxicillin250mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

- DispersibleTablet
- Whitetooffwhiteflatcirculartabletswithbeveledgesandscoredinthemiddleonone side and having a pleasantodour

4. CLINICALPARTICULARS

4.1 INDICATIONS

- Amoxicillinisindicatedforthetreatmentofthefollowingbacterialinfectionscaused by amoxicillin-sensitive gram-positive and gram-negativepathogens.
- Infectionsoftheupperrespiratorytract,includinginfectionsoftheears,noseandthroat: Acute otitis media, acute sinusitis and bacterialpharyngitis.
- Infectionsofthelowerrespiratorytract:Acuteexacerbationofchronicbronchitis,commu nity-acquiredpneumonia.
- Infections of the lower urinary tract:Cystitis
- Prophylaxisofendocarditisinpatientsatrisk-forexamplethoseundergoingdental procedures.
- Considerationshouldbegiventoofficialguidanceontheappropriateuseofantibacterial agents.
- Susceptibilityofthecausativeorganismtothetreatmentshouldbetested(ifpossible), although therapy may be initiated before the results areavailable.

4.2 POSOLOGY AND METHOD OFADMINISTRATION

Adultdosage(includingelderlypatients):Sta

ndarddosage:

- The usual dosage covers a range from 750 mg to 3g amoxicillin daily in divided doses. Insomeareas1500mgamoxicillindailyindivideddosesarerecommendedastheupperusualdose.

Special dosagerecommendation

- Acute exacerbation of chronic bronchitis in adults: 2 x 1 g

perdayChildren's dosage (under 40kg)

- Thedailydosageforchildrenis40-

90mg/kg/dayintwotothreedivideddoses*(notexceeding3g/day)dependingontheindication,theseverityofthediseaseandthesusceptibilityof thepathogen.

*PK/PDdataindicatethatdosingthreetimesdailyisassociatedwithenhancedefficacy,thustwice daily dosing is only recommended when the dose is in the upper range.

Childrenweighingmorethan40kgshouldbegiventheusualadultdosage.Special

dosagerecommendation

- Tonsillitis: 50 mg/kg/day in two divideddoses.
- Acute otitis media: In areas with high prevalence of pneumococci withreducedsusceptibility to penicillins, dosage regimens should be guided by national/localrecommendations.

Dosage in impaired renalfunction:

Thedoseshouldbereducedinpatientswithsevererenalfunctionimpairment.Inpatientswitharenalclearanceoflessthan30ml/minanincreaseinthedosageintervalandareductioninthetotal daily dose arerecommended.

Adults (including elderlypatients):

Creatinine clearanceml/	**Dose**	**Interval betweenadministration**
>30	No adjustmentnecessary.	
10 –30	500mg	12h
<10	500mg	24h

In case of hemo dialysis: 500 mg should be administered at the end of the procedure.

Renal impairment in children under 40kg:

Creatinine clearanceml/	**Dose**	**Interval betweenadministration**
>30	Usualdose	No adjustmentnecessary.
10 –30	Usualdose	12 h (corresponding to 2/3 of thedose)
<10	Usualdose	24 h (corresponding to 1/3 of thedose)

Dosage in impaired hepaticfunction

- No dose reduction is necessary as long as the renal function is

notimpaired.Method of administration:

- Thepreparationisadministeredorallywithameasuringspoon.Themeasuringspoonisincludedinthepackage.Theready-for-usesuspensionshouldbetakenwithaglassofwater.
- The absorption of amoxicillin is not reduced by foodintake.
- Administrationtobabies:Theprescribeddosageisadministeredundilutedtothebaby;milk or tea should be givenafterwards.

Prophylaxis forendocarditis:

- Forthepreventionofendocarditis,inpatientsnothavinggeneralanaesthetic,3gamoxicillinaregivenorallyinthehourprecedingthesurgicalprocedure,followedby(6hours later) a further 3 g dose, if consideredrnecessary.

- For children: 50 mg amoxicillin/kg body weight given as a single dose one hourpreceding the surgicalprocedure.
- Forfurtherdetailsanddescriptionofpatientsatrisklocalofficialguidelinesfortheprevention of endocarditis should be consulted.

Method ofadministration:

- Thepreparationisadministeredorallywithameasuringspoon.Themeasuringspoonisincludedinthepackage.Theready-for-usesuspensionshouldbetakenwithaglassofwater.
- The absorption of amoxicillin is not reduced by foodintake.
- Administrationtobabies:Theprescribeddosageisadministeredundilutedtothebaby;milk or tea should be givenafterwards.

4.3 CONTRAINDICATIONS

Amoxicillin is contraindicated in patientswith:

• Hypersensitivity to penicillin; a cross-allergy to other beta-lactams such ascephalosporin'sshould be taken into account.

• Hypersensitivity to any of theexcipients.

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FORUSE

- Beforeinitiatingtherapywithamoxicillin,carefulenquiryshouldbemadeconcerningprevioushypersensitivityreactionstopenicillinsandcephalosporins.Thepossibilityofcross-hypersensitivity (10 % - 15 %) with cephalosporins should be taken intoaccount.
- Seriousandoccasionallyfatalhypersensitivity(anaphylactoid)reactionshavebeenreportedinpatientsonpenicillintherapy.Thesereactionsaremorelikelytooccurinindividuals with a history of hypersensitivity to beta-lactamantibiotics.
- Inpatientswithrenalfunctionimpairmenttheexcretionofamoxicillinwillbedelayedand,dependingonthedegreeoftheimpairment,itmaybenecessarytoreducethetotaldailydosage.
- Precautionshouldbetakeninprematurechildrenandduringneonatalperiod: renal,hepatic and

haematological functions should bemonitored.

- Theprolongeduseof amoxicillinmayoccasionallyresultinanovergrowthofnon-susceptible bacteria or yeasts. Patients should therefore carefully be watchedforsuperinfections.
- Theoccurrenceofanaphylacticshockandothersevereallergicreactionsisrarefollowingtheoraladministrationofamoxicillin.However,ifsuchreactionsoccur,appropriateemergency treatment measures must betaken.
- Thepresenceofhighurinaryconcentrationsofamoxicillincancauseprecipitationoftheproduct in urinary catheters. Therefore, catheters should be visually inspected atintervals.
- Athighdoses,adequatefluidintakeandurinaryoutputmustbemaintainedtominimisethe possibility of amoxicillincrystalluria.
- Amoxicillinshouldnotbeusedforthetreatmentofbacterialinfectionsinpatientswithviralinfections,acutelymphaticleukaemia,orinfectiousmononucleosisaserythematous(morbilliform)rashe shavebeenassociatedwithglandularfeverinpatientsreceivingamoxicillin.
- Antibiotic-associatedcolitishasbeenreportedwithnearlyallantibacterialagentsandmayrangeinseverityfrommildtolifethreatening(seesection4.8).Therefore,itisimportanttoconsiderthisdiagnosisinpatientswhopresentwithdiarrhoeaduringorsubsequenttotheadministrationofanyantibiotics.Shouldantibiotic-associatedcolitisoccur,amoxicillinshouldimmediatelybediscontinued,aphysicianbeconsultedandanappropriatetherapyinitiated.Anti-peristalticmedicinalproductsarecontra-indicatedinthis situation.
- Aswithotherbeta-lactams,thebloodformulashouldbecheckedregularlyduringhigh-dose therapy.
- Periodic assessment of organ system functions, including renal, hepaticandhaematopoietic function is advisable during prolongedtherapy.
- Highdosetherapywithbeta-lactamsforpatientswithrenalinsufficiencyorseizureshistory, treated epilepsy and meningeal affection, could exceptionally lead toseizures.
- Theoccurrenceofageneralizederythemawithfeverandpustulesatthebeginningoftreatmentshouldmakesuspectageneralizedacuteexanthematicpustulosis;thisnecessitatestheinterruptionoftherapyandcontraindicatedanyfurtheradministrationofamoxicillin.
- AllAmoxicillinpowdersfororalsuspensioncontainaspartame(E951)andshouldbeusedwithcareinpatientswithphenylketonuria.Inhomozygoticpatientswithphenylketonuria,theamountofphenylalaninethat issuppliedbyaspartamemustbeincluded in the calculation for the dietaryregulations

4.5 DRUGINTERACTION

Concomitant use notrecommended

Allopurinol

Concomitantadministrationofallopurinolmaypromotetheoccurrenceofallergiccutaneousreactions and is therefore notadvised.

Digoxin

An increase in the absorption of digoxin is possible on concurrent administrationwithamoxicillin. A dose adjustment of digoxin may be necessary.

Anticoagulants

Concomitantadministrationofamoxicillinandanticoagulantsfromthecoumarinclass,mayprolong the bleeding time. A dose adjustment of anticoagulants may be necessary. A largenumberofcasesshowinganincreaseoforalanticoagulantactivityhasbeenreportedinpatientsreceivingantibiotics.Theinfectiousandinflammatorycontext,ageandthegeneralstatusofthepatientappearasriskfactors.Inthesecircumstances,itisdifficulttoknowthepartoftheresponsibility between the infectious disease and its treatment in the occurrence of INRdisorders.However,someclassesofantibioticsaremoreinvolved,notablyfluoroquinolones,macrolides, cyclines, cotrimoxazole and somecephalosporins

Methotrexate

Interactionbetweenamoxicillinandmethotrexateleadingtomethotrexatetoxicityhasbeenreported.Serummethotrexatelevelsshouldbecloselymonitoredinpatientswhoreceiveamoxicillinandmethotrexatesimultaneously.Amoxicillindecreasestherenalclearanceofmethotrexate, probably by competition at the common tubular secretion system.

Cautionisrecommendedwhenamoxicillinisgivenconcomitantlywith:Oral hormonalcontraceptives

Administrationofamoxicillincantransientlydecreasetheplasmalevelofestrogensandprogesterone,and mayreducetheefficacyoforalcontraceptives.Itisthereforerecommendedtotake supplemental non-hormonal contraceptive measures.

Other forms ofinteractions:

- Forceddiuresisleadstoareductioninbloodconcentrationsbyincreasedeliminationofamoxicillin.
- It is recommended that when testing for the presence of glucose in urine duringamoxicillintreatment,enzymaticglucoseoxidasemethodsshouldbeused.Duetothehighurinaryconcentrationsofamoxicillin,falsepositivereadingsarecommonwithchemicalmethods.
- Amoxicillin may decrease the amount of urinary estriol in pregnantwomen.
- At high concentrations, amoxicillin may diminish the results of serum glycemialevels
- Amoxicillin may interfere with protein testing when colormetric methods areused

4.6 Uses during Pregnancy &Lactation

Use inpregnancy

AmoxicillinhasbeenassignedtopregnancycategoryBbytheFDA.Animalstudiesusing10times the human dose have failed to reveal any evidence of teratogenicity. Although no controlleddatainhumanpregnancyareavailable,literaturereportsofadversefetaleffectsarelacking. Amoxicillin is only recommended during pregnancy when benefit outweighs risk.

IntheCollaborativePerinatalProjectinvolving50,282mother-childpairs,therewere3,546mother-childpairsexposedtopenicillinderivativesinthefirsttrimester.Asagroup,therewasnosignificantincreaseintheriskofmalformations.IntheMichiganMedicaidBirthDefectsStudyinvolving229,101pregnanciesfrom1985to1992,therewere8,538firsttrimesterexposurestoamoxicillin.Overall,317casesofbirthdefectswereobserved(363expected).Therewasnoevidenceofanassociationbetweenfirsttrimesteruseofamoxicillinandmajorgroupsofmalformations.ADanishstudyof401womenexposedtoamoxicillinduringpregnancyfrom1991to2000didnotfindanincreasedriskofbirthdefectsoradverseoutcomescomparedtowomenwhohadtakennomedication.Transientdecreasesin totalconjugatedestriol,estriol-glucuronide,conjugatedestrone,andestradiolplasmaconcentrationshavebeenreported in pregnant women who received ampicillin and this may also occur with amoxicillin.

Inonestudy,sixwomenwereadministeredasingle1000mgdoseofamoxicillinonthethirdpostpartumday. Amoxicillinmilkconcentrationsrangedfrom0.10to0.81mcg/mL,withapeakconcentrationmeasuredat 5hourspost-

dose.Themilktomaternalserumconcentrationratiorangedfrom0.013to0.043.Amoxicillinisexcretedintohumanmilkinsmallamounts.SensitizationoftheinfantmayoccurTheAmericanAcademyofPediatricsconsiderstheuseofamoxicillintobecompatiblewithbreast-

feeding.Themanufacturerrecommendsthatcautionbeused when administering amoxicillin to nursingwomen.

4.7 EFFECTS ON ABILITY TO DRIVE AND TO USEMACHINES

No studies on the effects on the ability to drive and use machines have been performed.However,undesirableeffectsmayoccur(e.g.allergicreactions,dizziness,convulsions),whichmay influence the ability to drive and usemachines.

4.8 SIDE EFFECTS / ADVERSEREACTIONS

In this section undesirable effects are defined as follows:

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,

Infections andinfestations

Uncommon

- Superinfections and colonization with resistant organisms or yeasts such as oral andvaginal candidiasis after prolonged and repeated use ofamoxicillin.

Blood and the lymphatic systemdisorders

- *Rare*

  Eosinophilia and haemolyticanaemia.

- *Veryrare*

  Leucopenia, neutropenia, granulocytopenia, thrombocytopenia, pancytopenia, anaemia,myelosuppression,agranulocytosis,prolongationofbleedingtime,andprolongationof prothrombin time. All were reversible on discontinuation of therapy.

Immune systemdisorders

- *Rare*

Laryngeal oedema, serum sickness, allergic vasculitis, anaphylaxis and anaphylactic shock.

Nervous systemdisorders

- *Rare*

CNSeffectsincludinghyperkinesia,dizzinessandconvulsions.Convulsionsmayoccurinpatients with impaired renal function, epilepsy, meningitis or in those receiving high doses.

Gastrointestinaldisorders:

- *Common*

  Gastriccomplaints,nausea,lossofappetite,vomiting,flatulence,softstools,diarrhoea,enanthem as(particularlyintheregionofthemouth),dry mouth, taste disturbances.These effects on the gastrointestinal system are mostly mild and frequently disappeareitherduringthetreatmentorverysoonaftercompletionoftherapy.Theoccurrenceofth ese side effects can generally be reduced by taking amoxicillin during meals.

- *Rare*

  Superficialdiscolorationoftheteeth(especiallywiththesuspension).Usuallythediscoloration can be removed by teethbrushing

- *Veryrare*

  Ifsevereandpersistentdiarrhoeaoccurs,theveryrarepossibilityofpseudomembranouscolitissho

uldbeconsidered.Theadministrationofanti-peristalticdrugiscontraindicated.Development of a blacktongue.

Hepato-biliarydisorders:

Uncommon

Moderate and transient increase of liverenzymes.

- *Rare*

  Hepatitis and

cholestaticjaundice.Skin and subcutaneous

tissue disorders:***Common***

Cutaneousreactionssuchasexanthema,pruritus,urticaria;thetypicalmorbilliformexanthemaoccurs5-11daysafterstartoftherapy.Immediateappearanceofurticariaindicates an allergic reaction to amoxicillin and therapy should therefore be discontinued.

- *Rare*

  Angioneuroticoedema(Quincke'soedema),Erythemamultiformeexsudativum,acutegeneralizedpustulosis,Lyell'ssyndrome,Stevens-Johnsonsyndrome,toxicepidermalnecrolysis, bullous and exfoliativedermatitis.

Renaldisorders

- *Rare*

  Acute interstitial nephritis.Crystalluria.

General disorders and administration siteconditions

- *Rare*

  Drugfever.

4.9 OVERDOSE

Symptoms ofoverdose:

- Amoxicillinisnotgenerallyassociatedwithacutetoxiceffects,evenwhenaccidentallyconsumed inhighdoses.Overdosagecanleadtosymptomssuchasgastrointestinalrenalandneuro-psychicdisturbancesandfluidandelectrolyteimbalance.Inpatientswithseverelyimpairedrenalfunction,largeoverdosescanresultinsignsofrenaltoxicity;crystalluria ispossible.

Management ofoverdose:

- There is no specific antidote for an overdose ofamoxicillin.
- Treatmentconsistsprimarilyofadministrationofactivatedcharcoal(agastriclavageisusuallynot necessary),orsymptomaticmeasures.Particularattentionshouldbepaidtothe water and electrolyte balance of thepatients.
- Amoxicillin can be eliminated viahaemodialysis.

5. PHARMACOLOGY:

5.1 PHARMACODYNAMIC PROPERTIES

ATC-Code:J01CA04

Pharmacotherapeutic group: Beta-lactam antibacterials, Penicillins with extended spectrum.

Mechanism ofresistance

Bacteriamayberesistanttoamoxicillinduetoproductionofbeta-lactamaseswhichhydrolyseaminopenicillins,duetoalterationinpenicillin-bindingproteins,duetoimpermeabilitytothedrug,orduetodrugeffluxpumps.Oneormoreofthesemechanismsmayco-existinthesameorganism,leadingtoavariableandunpredictablecross-resistancetootherbeta-lactamsandtoantibacterial drugs of otherclasses.

Mechanism ofAction

Amoxicillinissimilartopenicillininitsbactericidalactionagainstsusceptiblebacteriaduringthestageofactivemultiplication.Itactsthroughtheinhibitionofcellwallbiosynthesisthatleadsto the death of thebacteria.

Breakpoints(EUCAST)

Organism	**Susceptibility Breakpoints(µg/ml)**		
	Susceptible	**Intermediate**	**Resistant**
Haemophilusinfluenzae	≤1	-	>1
Moraxellacatharrhalis	≤1	-	>1
Enterococcus	≤4	8	>8
Streptococcus A, B, C,G[1]	≤0.25	-	>0.25
Streptococcuspneumoniae[2]	≤0.5	1-2	>2
Enterobacteriaceae'[3]	-	-	>8
Gram-negativeanaerobes	≤0.5	-	>2
Gram-positiveAnaerobes	≤4	8	>8
Non-species related	≤2	4-8	>8

[1] Breakpoint values in the table are based on Benzylpenicillinbreakpoints.

[2] Breakpoint values in the table are based on ampicillinbreakpoints.

[3]TheresistantbreakpointofR>8mg/Lensuresthatallisolateswithresistancemechanismsare reportedresistant.

Susceptibility:

Theprevalenceofresistancemayvarygeographicallyandwithtimeforselectedspeciesandlocal information onresistanceis desirable,particularlywhentreatingsevere infections. Asnecessary,expertadviceshouldbesoughtwhenthelocalprevalenceofresistanceissuchthattheutility of the agent in at least some types of infections is questionable.

Commonly susceptiblespecies
Aerobic Gram-positive*Corynebactierumdiphteriae**Enterococcus faecalis*[$] *Listeria monocytogenes**Streptococcus agalactiae**Streptococcus bovis**Streptococcus pyogenes** **Aerobic Gram-negative***Helicobacter pylori***Anaerobes***Peptostreptococci***Others***Borrelia*
Species for which acquired resistance may be a problem
Aerobic Gram-positive*Corynebacteriumspp**Enterococcus* *[$]*
*Streptococcus pneumoniae ** [+]*Streptococcus viridans***Aerobic Gram-negative***Escherichia coli**+Haemophilusinfluenzae***Haemophiluspara-influenzae**Moraxella catarrhalis +Proteusmirabilis***Anaerobes***Prevotella**Fusobacteriumspp*
Inherently resistantorganisms

Aerobic Gram-positive*Staphylococcusaureus***Aerobic Gram-negative***Acinetobacterspp Citrobacterspp Enterobacterspp Klebsiellaspp Legionella Morganellamorganii Proteus vulgaris Providenciaspp Pseudomonasspp Serratiaspp***Anaerobes***Bacteroidesfragilis*
Others*Chlamydia**Mycoplasma**Rickettsia*

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

+ pathogens resistance prevalence is >50%

$ Naturally intermediatespecies

Clinical efficacy andsafety:

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Randomized,double-blindclinicalstudiesperformedintheUnitedStatesinpatientswithH.pyloriandduodenalulcerdisease(definedasanactiveulcerorhistoryofanulcerwithin1year)evaluated the efficacy of lansoprazole in combination with Amoxicillin capsulesandclarithromycintabletsastriple14daytherapy,orincombinationwithAmoxicillincapsulesasdual14daytherapy,fortheeradicationofH.pylori.Basedontheresultsofthesestudies,thesafety and efficacy of 2 different eradication regimens were established:TripleTherapy:Amoxicillin1gramtwicedaily/clarithromycin500mgtwicedaily/lansoprazole30mgtwicedaily(seeTable6).DualTherapy:Amoxicillin1gramthreetimesdaily/lansoprazole30mgthreetimesdaily(seeTable7).Alltreatmentswerefor14days.H.pylorieradicationwasdefinedas2negative tests(cultureandhistology)at4to6weeksfollowingtheendoftreatment.Tripletherapywasshowntobemoreeffectivethanallpossibledualtherapycombinations.Dualtherapywasshowntobemoreeffectivethanbothmonotherapies.EradicationofH.pylorihasbeen shown to reduce the risk of duodenal ulcerrecurrence.

PediatricpopulationBecauseofincompletelydevelopedrenalfunctioninneonatesandyounginfants,theeliminationofAmoxicillinmaybedelayed.DosingofAmoxicillinshouldbemodified in pediatric patients 12 weeks or younger (≤ 3months)

5.2 PHARMACOKINETICPROPERTIES

Absorption:

Theabsolutebioavailabilityofamoxicillindependsonthedoseandrangesbetween75and90%.Inthedoserangebetween250mgand1000mgthebioavailability(parameters:AUCandCmax)islinearlyproportionaltothedose.Athigherdosestheextentofabsorptiondecreases.Theabsorptionisnotaffectedbyconcomitantfoodintake.Oraladministrationofasingledoseof500mgamoxicillinresultsinplasmaconcentrationsof6-11mg/l.Afteradministrationofasingledoseof3gamoxicillin,theplasmaconcentrationsreach27mg/l.Peakplasmaconcentrationsarepresent about 1-2 hours afteradministration.

Distribution:

Proteinbindingforamoxicillinisapproximately17%.Therapeuticdruglevelsarerapidlyachievedinserum,lungtissue,bronchialsecretions,middleearfluid,bileandurine.Inhealthymeningesamoxicillindiffusesbadlyinliquorcerebrospinalis.Amoxicillincrossestheplacentaand a small percentage is excreted into the breast milk.

Biotransformation andelimination:

Themainrouteofexcretionofamoxicillinisthekidney.About60-80%ofanoraldoseofamoxicillinisexcretedinunchangedactiveformintheurinewithin6hoursofadministration,andasmallfractionisexcretedinthebile.Approximately7-25%oftheadministereddoseismetabolizedtoinactivepenicilloicacid.Theserumhalf-lifeinpatientswithnormalrenalfunctionisapproximately1–1,5hour.Inpatientswithend-stagerenalfailurethehalf-liferanges between 5 to 20 hours. The substance is haemodialysable.

Pediatricpopulation

Inpreterminfantswithgestationalage26-33weeks,thetotalbodyclearanceafterintravenousdosingofamoxicillin,day3oflife,rangedbetween0.75–2ml/min,verysimilartotheinulinclearance (GFR) in this population. Following oral administration, the absorption pattern and thebioavailabilityofamoxicillininsmallchildrenmaybedifferenttothatofadults.Consequently,duetothedecreasedCL,theexposureisexpectedtobeelevatedinthisgroupofpatients,althoughthisincreaseinexposuremayinpartbediminishedbydecreasedbioavailabilitywhengivenorally.

5.3 PRECLINICAL SAFETYDATA

Preclinicaldatarevealnospecialhazardforhumansbasedonconventionalstudiesofsafetypharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction

TOXICOLOGY

An Unusual Case of Amoxicillin/Clavulanic Acid-Related Hepatotoxicity

M.G. Nathani, M.D.a, M.G. Mutchnick, M.D., F.A.C.G.a, D.J. Tynes, M.D.a, andM.N.Ehrinpreis, M.D.,F.A.C.G.a

Amoxicillin/clavulanicacidisawidelyusedantibiotic.Hepaticdysfunctionisarareadversereactionassociatedwiththiscombinationantibiotic.Wereportthecaseofa40-yr-oldwomanwith a somewhat unusual presentation of amoxicillin/clavulanate-related cholestatichepatotoxicityandmultipleduodenalerosionswhosediagnosiswasdelayeduntilinadvertentrechallengewiththeantibioticcombination.Therelevantliteratureisalsoreviewedanddiscussed.Thediagnosismaybemissedbecausetheonsetofsigns/symptomsmayoccurseveralweeksafterthecessationoftherapy.Thehepaticdysfunction,whichmaybesevereandismoreprevalentinelderlypatients,isusuallyreversible,althoughchronicliverdiseaseanddeathshavebeenreported.Immunologicalhypersensitivityisconsideredtobethemostlikelymechanismresultinginliverinjury.Amoxicillin/clavulanateshouldbeusedwithcautioninpatientswithunderlying liver disease and in theelderly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-termstudiesinanimalshavenotbeenperformedtoevaluatecarcinogenicpotential.Themutagenic potential of Coamoxiclav was investigated in vitro with an Ames test, ahumanlymphocytecytogeneticassay,ayeasttest,andamouselymphomaforwardmutationassay,andin vivowithmousemicronucleustestsandadominantlethaltest.Allwerenegativeapartfromtheinvitromouselymphomaassay,whereweakactivitywasfoundatveryhigh,cytotoxicconcentrations.

6. PHARMACEUTICALPROPERTIES

6.1 List of Excipients

- Microcrystalline Cellulose (PH 112)BP
- Colloidal anhydrous silicaBP
- Maize starchBP
- Sodium saccharineBP
- Flavour orange dry powder INH
- Magnesium stearateBP
- Crosspovidone NF
- Purified waterBP

6.2 Incompatibilities

Weevaluatedthecompatibilityoftheseexcipientswiththeactiveandfoundnoevidenceofincompatibility.

6.3 Shelf Life

36months from the date ofmanufacture

6.4 Special Precautions forstorage

Store in a dry place at a temperature of less than 25°C. Protect from light.

6.5 Nature and Contents ofContainer

Presentation: MEDOMOX 250 DT are available as 2 x 10's, 3x10's &10x10's PVDC blister pack.

Primary Container (s):

MEDOMOX 250 DT are available as strip pack. Each strip of 2 x 10's 3x10's & 10x10's PVDC blister pack contains10 tablets respectively.

Secondary Container:

Such strip packs are packed in a printed carton. Printed Cartons are printed with relevant batch details.

Outer Container:

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. Shippers are then strapped with Polypropylene tapes.

6.6 Special precautions for disposal and other handling

Dispersible tablets should be stirred into a little water before taking. No special requirements.

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/011 Certificate No.:N354/08

Renewal registration - 05262/07406/REN/2020

9. Date of first authorization/renewal of theauthorization

First authorization – 15/06/2016

Renewal authorization – 10/08/2020

10. Date of revision of thetext

12.07.2023