150225128022

Mobitil

Meloxicam 15 mg tablets & suppository

1- NAME OF THE MEDICINAL PRODUCT Mobitil 15 mg filmcoatedtablets&suppository
2- QUALITATIVE AND QUANTITATIVE COMPOSITION
Eachtabletcontains 15 mg of Meloxicam.Eachsuppository conteins 15 mg of Meloxicam.Forafullilstofexcipients,seesection6.1
3- PHARMACEUTICAL FORM Fiimcoatedtablet&suppository
4- CLINICAL PARTICULARS
4.1-Tharepeuticindications -Short-tennsymptomatictreatrnentofexacerbationsofosteoarthrosis
Long-termsymptomatictreatmentofrheumatoidarthritisorankylosingspondylitis
4.2-Posologyand methodofadministration
Oral use: The total daliy amount should be taken as a singledose, withwaterorantherliquid, during a meal. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4). The patient's need for symptomatic reliefand response to therapyshould be re-evaluated periodically, especially in patientswith osteoarthritis
-Rheumatoic arthritis,ankylosingspondylitis:15 mg/day(sseaIsosection'Specialpopulations'below)
DONOTEXCEEDTHEDOSEOF15mg/day.
Rectal: Onesuppository / day
<u>Special populations</u> *Elderly patientsand patientswithincreased risksfor adverse reaction(.seesection5.2)*
Therecommendeddoseforlongterm treatmentofrheumatoid arthritisandankylosingspondylitisIneIderlypatientsis7.5mgperday.Patientswith increasedrisksforadversereactionsshouldstarttreatment with7.5mg perday(seesection4.4)
Renal impairment (.see section 5.2): Indialysis patients with severerenalfailure,thedoseshouldnotexceed7.5mg per day. Nodosereductionis requiredinpatientswith mildtomoderaterenalimpairment(i.e.patientswithacreatinineciearanceofgreaterthan25ml/min).
(For patients with non-dialysedsevererenalfailure,seesection4.3)
Hepatic impairment (.see section 5.2): Nodosereductionisrequiredinpatientswith mild to moderatehepaticimpelrment.
(Forpatients withseverelyimpairedliver function,seesection4.3)
Childrenandadolescents: Mobitil7.5mgtabletsiscontraindicatedinchildrenand adolescentsagedunder16years(seesection4.3)
4.3- Contraindicetions This medicinal product is contra-indicated In the following situations'
thirdtrimester of pregnancy(seesection 4.6'Pregnancyendlactetion');
-childranandadolescents agedunder 16 years;
-hypersensitivitytomeloxicamortooneofthe excipientsorhypersensitivity tosubstanceswithasimilaraction,e.g. NSAIDs,aspirin.Meloxicam shouldnotbegivento patients whohavedevelopedsignsofasthma,nasai polyps,angioneuroticedemaorurticariafollowingtheadministrationof espirinorotherNSAIDs
historyofgastrointestinalbleedingorperforation, relatedtopreviousNSAIDstherapy;
-active,orhistoryofrecurrentpepticulcer/haemorrhage(twoormoredistincteplsodesofprovenulcerationorbleeding);
-severelyimpairedliver function -non-dialysedsevererenaifaiiure
gastrointestinalbleeding,historyofcerebrovascularbleedingorotherbieeding disorders; -severeheartfallure
4.4-Specialwarningsandprecautionsforuse
Undesirable effectsmaybeminimisedbyusingthalowesteffectivedoseforthe shortest durationnecessary tocontrolsymptoms(seesection4.2, andGIandcardiovascularrisksbelow).The recommendedmaximumdaliydoseshouid not be exceeded Incase of Insufficienttherapeuticeffect, norshouldanadditional NSAIDbeaddedtothetherapy becausethismay increasethetoxicitywhiletherapeutic advantage hasnotbeenprover.
Theuseofmeloxicamwlthconcomitant NSAIDs includingcyclooxygenase-2 selectiveinhibitorsshouldbe avoided.Meloxicamis notappropriate forthetreatmentofpatientsrequiring relief fromacutepain.Intheabsenceofimprovement afterseveraldays,theciinicalbenefitofthetreatment should be reassessed. Any history of oesophagitis, gastritis and/or peptic ulcer must be considered in order to ensure their total cure before startingtreatmentwithmeloxicam.Attention shouldroutinelybepaidtothepossibleonsetof arecurrence inpatientstreatedwithmeloxicamand withapasthistoryofthistype.
Gastrointestinal effects GIbleeding,ulcerationorperforation,which canbefatal, hasbeenreportedwithaIlNSAIDsatanytimeduringtreatment, withorwithoutwarning symptoms or a previous history of serious GI events. TheriskofGI bleeding,ulceration orperforation is higherwith increasing NSAID doses, in patients with a historyofulcer, particularly if complicatedwith haemorrhage or perforation (see section4.3),andinthe elderly Thseepatientsshouldcommencetreatmentonthe lowestdoseavailable.Combinationtherapywith protective agents (e.g.misoprostolor protonpumpInhibitors)shouldbeconsideredforthesepatients,and alsoforpatientsrequiring concomitantlowdoseaspirin,orotherdrugslikelyto increase gastrointestinal risk (seebelow and 4.5). Patientswith a history of GI toxcity, particularlywhen elderly, should reportanyunusual abdominalsymptoms(especiallyGI bleeding)particularlyinthe initialstegesoftreatment. Caution isadvisedin patientsreceivingconcomitant medicationswhichcouid increasetheriskofulcerationorbleeding,suchasheparinascurativetreatmentorgivenIngeriatrics,anticoagulantssuch aswarfarin,orothernonsteroidalanti-inflammatorydrugs,includingacetylsalicylicacidgivenatanti-inflammatorydoses (≥1gassingleintakeor ≥3g as toteldallyamount)(seesection 4.5). When GI bleeding orulceration occursin patients receivingmeloxicam, thetreatmentshould be withdrawn.NSAIDsshouldbegivenwith care to patients with a historyofgastrointestinal disease(ulcerativecolitis,Crohn'sdisesee)asthese conditions may be exacerbated (see section 4.8 -undesirableeffects)
Cardiovascular and cerebrovascular effects
Appropriatemonitoringandadvicearerequiredforpatients withahistoryof hypertensionand/or mild to moderate congestiveheartfailureasfluid retentionandoedema have been reported in association with NSAIDtherapy Clinical monitoring of bioodpressureforpatientsatriskis recommendedatbaselineand especiallyduringtreatmentinitiationwithmeloxicam. Theuseof some NSAIDsincludingmeloxicam(particularlyat highdosesandIn long term treatment) may be associatedwith asmallincreasedriskofarterial thromboticevents(forexamplemyocardlal infarction or stroke). Thereare insufficient datatoexcludesuch ariskformeloxicam.Patientswith uncontrolled hypertension, congestiveheart failure,establishedischaemicheartdisease,peripheralarterial disease,and/orcerebrovasculardisease shouldonlybe treated with meloxicam aftercareful consideration. Similar consideration should be made before initiating longer-termtreatment of patientswith risk factors for cardiovasculardiseese (e.g.hypertension,hyperlipidaemia,diabetesmellitus,smoking)
Skin reactions Serious skinreactions, someofthemfatal,Includingexfoliativedermatitis, Stevens-Johnsonsyndrome,and toxicepidermal necrolysis,havebeenreportedveryrarely inassociationwith theuseofNSAIDs(see4.8).Patientsappeartobe athighestriskofthesereactions earlyInthecourseoftherapy theonsetofthereaction occurringIn the majority of caseswithinthefirstmonthoftreatment.Meloxicamshouldbe discontinuedatthefirstappearanceofskinrash,mucosal lesions,oranyothersignofhypersensitivity
Parameters of liver and renal function as with most NSAIDs,occasionalincreasesinserum transaminase ieveis, increseesinserumbilirubinor otherliverfunction parameters, as wellasincreases In serum creatinine and blood urea nitrogen and other laboratory disturbances, have been reported.Themajorityoftheselnstanceseratemporaryandmild.Shouldanysuchabnormalityprovesignificantorpersistent,theadministrationof Meloxicamshould be stopped and appropriate investigations undertaken
Functional renal failure NSAIDs,byinhibitingthevasodilating effectofrenalprostaglandins,mayInducea functional renalfailurebyreductionof glomerularfiltration.Thisadverseevent isdose-dependant.Atthebeginningofthetreatment, orafterdoseincrease,carefulmonitoringofdiuresis andrenalfunctionisrecommendedinpatientswiththefollowingriskfactors
•Elderly •Concomitant treatments such as ACE Inhibitors, angiotensin-II antagonists, sartans,diuretics (Seesection 4.5.Interactionwithothermedicinalproductsandother formsofinteraction)
•Hypovolemia(whateverthecause) •Congestiveheartfailure
•Renalfailure •Nephroticsyndrome
•Lupusnephropathy •Severehepaticdysfunction(serumalbumin<25g/lorChild-Pughscore≥10)
In rare instance NSAIDs may be the cause ofinterstitial nephritis, glomerulonephritis, renal medullary necrosisornephrotic syndrome. The dose of meloxicaminpatientswithend-stagerenalfailureonhaemodlalysisshouid notbehigherthan7.5mg.Nodosereduction isrequiredInpatientswith mildormoderaterenalimpairment (i.e.in patientswithacreatinineclearanceof greaterthan25ml/min)
Sodium, potassium and water retention Induction of sodium, potassium andwaterretention and Interference with the natriuretic effects of diuretics mayoccurwith NSAIDs. Furthermore, a decrease of theantihypertensiveeffectof antihypertensive drugs can occur (seesection 4.5). Consequently, oedema,cardiacfailureorhypertensionmaybe precipitatedorexacerbatedinsuscaptible patientsasaresult.Clinicalmonitoringis thereforenecessary forpatientsatrisk(Seesections4.2and4.3)
Hyperkalaemia Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase potassium (seesection4.5). Regular monitoring of potassium values should beperformedInsuchcases
Other warnings and precautions Adverse reactions are often lesswelltolerated ineIderly fragileorweakened individuais, whotherefore require carefulmonitoring. As withotherNSAIDs,particular caution Isrequiredinthe elderly, in whom renal,hepaticandcardiacfunctionsarefrequently Impaired.Theelderlyhaveanincreasedfrequencyofadversereactionsto NSAIDsespeciallygastrolntestinal bleedingandperforationwhichmay befatal(see section4.2).
Meloxicam,esanyotherNSAIDmaymasksymptomsofanunderlyinginfectiousdisease.Theuse of meloxicam,aswithany drugknowntoInhibit cyclooxygenase/prostaglandin synthesis, may impair fertilityand isnotrecommended inwomenattemptingtoconceive. In women whohave difficultiesforconceiving,orwhoareundergoinginvestigationofinfertility,withdrawalofmeloxicamshouldbaconsidered
•<u>Cardiovascular Risk</u>
NSAIDsmaycauseanincreasedriskof seriouscardiovescular thromboticevents,myocardial infarction,andstroke,whichcanbefatel.Thisrisk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be atgrealer risk (sse SPECIAL WARNINGSANDPRECAUTIONS FORUSE).
•Meloxicam is contraindicated forthe treatment ofperi-operative pain in thesetting of coronary artery bypass graft (CABG) surgery(see WARNINGS)
•<u>Gastrointestinal Risk</u>
•NSAIDs cause an increased riskof seriousgastrointestinal adverse events includingbleeding, ulceration,and perforation of the stomach or inteatines, whichcanbefatal
•These eventscanoccurat anytimeduringuseand withoutwarningsymptoms.Elderly patients areatgreaterriskfor seriousgastrointestinal events.
4.5- Interactionwithothermedicinal productsandotherforms ofinteraction Interactionstudiashaveonlybeenperformedinadults.
<u>Pharmacodynamic nteractions</u>
~~Other nonsteroidal anti-inflammatory~~ drugs(NSAIDs)andacetylsalicylicacid≥3g/d: combination(seesection4.4)withothernonsteroidalanti-inflammatory drugs, includingacetylsalicylic acidgivenat anti-inflammatory doses (≥1gas singleintake or ≥ 3gas toteldallyamount)Is not recommended
Corticosteroids (e.g.Glucocorticoids): Theconcomitantusewithcorticosteroids requests cautionbecause ofanincreasedriskof bleedingor gastrointestinalulceration.
anticoagulantorheparin administered ingeriatricsoratcurative doses: Considerablyincreased riskofbleeding,viainhibitionof platelatfunction and damage to thegastroduodenalmucosa. NSAIDs may enhance the effects of anti-coagulants, such es warfarin (see section4.4).The concomitantuse of NSAIDsandanticoagulantsorheparinadministeredIngeriatrics oratcurativedoseisnotrecommended(seesection4.4).In remaining casesofheparinusecautionisnecessarydue toan increased bleedingrisk. Carefui monitoring of theINRis required if it proves impossibletoavoidsuchcombination
Thrombolyticsand antiplatelet drugs: Increased riskof bleeding,viaInhibitionofplatelet functionanddamagetothegastroduodenalmucosa.
SelectiveSerotonin Reuptake Inhibitors (SSRIs). Increasedriskofgastrointestinalbleeding
Diuretics,ACE inhibitors and Angiotensin-II Antagonists: NSAIDs may reduce the effect of diureticsand otherantihypertensivedrugs. In some patientswithcompromisedrenalfunction(e.g.dehydratedpatientsorelderlypatientswithcompromisedrenalfunction)theco-administrationofan ACEInhibitororAngiotensin-IIantagonistsand agentsthat inhibit cyclo-oxygenase may result In furtherdeterioration of renal function, including possibleacuterenalfailure, which is usuailyreversible.Therefore,thecombinationshouldbeadministeredwithcaution,especiallyIn theelderly. Patientsshouldbeadequatelyhydratedand consideration shouldbegivento monitoringofrenalfunctionafterinitiationofconcomitanttherapy, andperiodicallythereafter(seealsosection4.4)
Other antihypertensive drugs (e.g. Beta-blockers): Asforthelatler, adecrease of the antihypertensive effect of beta-blockers (duetoInhibition of prostaglandinswithvasodilatoryeffect)canoccur.
Calcineurin inhibitors (e.g cyclosporin, tacrolimus): Nephrotoxicityofcalcineurininhibitorsmaybeenhancedby NSAIDsviarenalprostaglandin mediated effects.During combined treatment renal function is to be measured. Acarefuimonitoringof therenal functionis recommended, especiallyintheelderly..
Intrauterine devices: NSAIDshavebeen reported to decrease the efficacy of intrauterine devices. Adecrease of the efficacy of Intrauterine devices byNSAIDshasbeenpreviouslyreportedbutneedsfurtherconfirmation

<u>Pharmacokinetic Interactions·Effect of meloxicam on thepharmacokineticsof otherdrugs</u>
Lithium: NSAIDshavebeenreportedtoincrease bloodlithium levels(viadecreasedrenalexcretionoflithium),whichmayreachtoxicvalues.The concomitant use of lithium and NSAIDs is not recommended (see section 4.4). If this combination appears necessary lithium plasma concentrations shouldbemonitoredcarefullyduringtheinitiation, adjustmentandwithdrawal ofmeloxicamtreatment.*Methotrexate.* NSAIDscan reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosagesofmethotrexate(more than 15 mg/week)theconcomitant useofNSAIDsisnotrecommended(see section4.4).Theriskofaninteraction betweenNSAID preparationsandmethotrexate, shouldbeconsideredalsoinpatientsonlowdosageof methotrexate,especiallyinpatientswith impairedrenalfunction.Incasecombinationtreatmentisnecessarybloodcellcountandtherenalfunction shouldbemonitored.Cautionshouldbe taken in case bothNSAIDand methotrexate aregivenwithin 3 days,inwhich case theplasma level of methotrexatemayincrease andcause increasedtoxicity Althoughthepharmacokineticsofmethotrexate(15mg/week)werenotrelevantlyaffectedbyconcomitantmeloxicamtreatment, itshouldbeconsideredthatthehaematologicaltoxicityofmethotrexatecanbeamplifiedbytreatmentwithNSAIDdrugs(seeabove).(Seesection 4.6)
<u>Pharmacokinetic Interactions· Effectof other drugsonthepharmacokinetics of meloxicam</u>
Cholestyramine: Cholestyramineacceleratesthe elimination of meloxicam by interruptingtheenterohepatic circulationsothatclearance for meloxicam increases by 50% and the half-life decreasesto 13±3 hrs. This interaction is of clinical sgnificance. No ciinically relevant pharmacokineticdrug-druginteractions weredetected withrespect to the concomitantadministrationofantacids,cimetidineanddigoxin
4.6-Pregnancyandlactation
Pregnancy inhibition of prostaglandin synthesismay adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studiessuggest an increased riskof miscarriageandofcardiacmalformationand gastroschisis after use of a prostaglandin synthesisinhibitorinearlypregnancy The absoiute riskforcardiovascularmalformationwasincreasedfrom less than1%,up to approximately1.5 %. The risk is believed to increasewithdoseand duration of therapy. Inanimals,administration of a prostagiandinsynthesisinhibitorhas been showntoresultinincreasedpre-and post-Implantationlossandembryo-foetel lethality Inaddition,increased incidencesofvariousmaiformations, includingcardiovascular, havebeenreported inanimalsgivena prostaglandinsynthesisinhibitor during the organogeneticperiod.During the first and second trimesterofpregnancy, meloxicam shouid notbe given unless ciearlynecessary If meloxicam is used by a women attempting to conceive, or during the first and second trimester of pregnancy,, the dose should be keptas lowand duration of treatment as short as possibla
During the third trimesterofpregnancy,, all prostaglandin synthesis inhibltors may expose the foetus to
•Cardiopulmonarytoxicity(withprematureclosureoftheductusarteriosusandpulmonaryhypertension)
•renaldysfunction,whichmayprogresstorenalfailurewithofigo-hydroamniosis
*themotherandtheneonate,at the endofpregnancy to:
•possibleprolongationofbleedingtime,ananti-aggregating effect whichmayoccurevenatverylowdoses.
•Inhibitionofuterinecontractionsresultingindelayedorprolongedlabour
Consequently, meloxicamiscontraindicatedduring the thirdtrimesterofpregnancy
Lactation While no specific experience exists for meloxicam, NSAIDs are known to passinto mother's miik. Administration therefore is not recommended Inwomenwhoarebreastfeeding.
4.7- Effects on ability to drive and use machines There are no specificstudies of the ability to drive and use machinery. However, on the basis of thepharmacodynamic profile and reported adversedrug reactions, meloxicamis likelylo have noornegligibleinfluenceon thseeabilities However.,whenvisualdisturbancesordrowsiness,vertigoorothercentralnervous systemdisturbences occur,itisadvisabletorefrainfromdriving andoperatingmachinery.
4.8-Undesirable effects
a) General Description Oedema, hypertension, andcardiac failure, have been reported in association with NSAID treatment. The most commonly-observedadverse events are gastrointestinal in nature. Pepticulcers, perforation or GIbleeding, sometimes fatal,particularlyinthe elderly,, mayoccur (seesection 4 4). Nausea, vomiting,diarrhoea,flatulence,constipation,dyspepsia,abdominal pain,melaena,hsematemesis, ulcerativestomatitis,exacerbationofcolitisandCrohn'sdiseese(seesection 4.4 - Specialwarningsandprecautionsforuse)havebeenreported followingadministration.Lessfrequently gastritishasbeenobserved.Adversereactionshavebeenrankedunderheadingoffreguenryusingthe following convention verycommon (≥1/10),common(1/10-1/100),uncommon(1/100 - 1/1000),rare(1/1000-1/10 000),veryrare(<1/10.000) Unknown(can'tbeestimatedfromavailebledata)
b) Table of adversereact <u>Blood andlymphaticsystem disorders</u>
Uncommon: Anaemia **Rare:** Bloodcountabnormal(includingdifferentialwhitecellcount), leukopenia thrombocytopenia
Veryrare: casesofagranuiocytosishavebeen reported (see section c)
<u>Immune system disorders</u>
Uncommon: Allergicreactionsotherthananaphylacticoranaphylactoidreactions
Notknown: Anaphylacticreaction,anaphylactoidreaction
<u>Psychiatric disorders</u>
Rare: Moodaltered,nightmaras
<u>Nervous system disorders</u>
Common: Headache.
<u>Eye disorders</u>
Rare: Visualdisturbanceincludingvisionblurred;conjunctivitis
<u>Ear and labyrinth disorders</u>
Uncommon: Vertigo
<u>Cardiac disorders</u>
Rare: Palpitations. CardiacfailurehasbeenreportedinassociationwithNSAIDtreatment
<u>Vascular disorders</u>
Uncommon: Bloodpressureincreased(see section 4.4), flushing
<u>Respiratory, thoracic and mediastinal disorders</u>
Rare: AsthmaInindividualsallergictoaspirinorotherNSAIDs.
<u>Gastrointestinal disorders</u>
Verycommon: Dyspepsia,nausea,vomiting,abdominalpain,constipetion, flatulence,diarrhoea
Uncommon: Occultormacroscopicgastrointestinalhaemorrhage,stomatitis,gastritis,eructation.
Rare: Colitis,gestroduodenalulcer,oesophagitis **Veryrare:** Gastrointestinalperforation
Gastrointestinalhaemorrhage, ulcerationorperforationmaysometimesbesevereand potentiallyfatal,especiallyinelderly(seesection4.4)
<u>Hepatobiliary disorders</u>
Uncommon: Liver functiondisorder (e.g.raisedtransaminasesorbilirubin) **Veryrare:** Hepatitis.
<u>Skin and subcutaneous tissue disorders</u>
Uncommon: Angioedema,pruritus,rash **Rare:** Stevens-Johnsonsyndrome,toxicepidermal necrolysis,urticaria.
Veryrare: Dermatitsbullous,erythemamultiforme **Notknown:** Photosensitivityreaction.
<u>Renal and urinary disorders</u>
Uncommon: Sodiumandwater retention,hyperkalaemia(seesection4.4.Special warningsandspecialprecautionsforuse andsection4.5.) renalfunctiontestabnormal(increasedserum creatinineand/orserum urea).
Veryrare: Acuterenalfailureinparticularinpatientswith riskfaciors(seesection4.4.).
<u>General disorders and administration site conditions</u>
Uncommon: Oedemaincludingoedemaofthelowerlimbs.
c) InformationCharecterisingIndividual Serious and/or Frequently Occurring AdverseReactions
Veryrarecasesofagranulocytosishavebeenreportedinpatients treatedwithmeloxicamandotherpotentiallymyelotoxicdrugs(seesection4.5)
d) Adversereactionswhichhavenotbeenobservedyetin relation totheproduct, but which are generally accepted as being attributable toothercompounds Intheclass
Organicrenalinjuryprobablyresultinginacuterenalfailure:veryrarecaseaofinterstitialnephritis,acutetubularnecrosis,nephroticsyndrome,and papiliary necrosishave been reported (see section 4.4)
4.9-Overdose SymptomsfollowingacuteNSAIDoverdoseare usuallylimitedtolethargy, drowsiness,nausea, vomitingand epigastricpain,which aregenerallyreversiblewithsupportive care.Gastrointestinalbleedingcanoccur. Severepoisoningmayresultinhypertension,acuterenalfailure, hepaticdysfunction,respiratory depression,coma,convulsions,cardiovascularcollapseand cardiacarrest.Anaphylactoidreactionshavebeen reportedwiththerapeuticingestionofNSAIDsandmay occur followinganoverdose.Patientsshouldbe managedwithsymptomaticandsupportive care following an NSAID overdose. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.
5-PHARMACOLOGICAL PROPERTIES
5.1-Pharmacodynamicproperties Pharmacotherapeutic group:Non SteroidalAnti-Inflammatory agent,Oxicams:Meloxicamisanon-steroidal anti-inflammatorydrug(NSAID) of theoxicamfamily withanti-inflammatory analgesic andantipyreticproperties.Theanti-inflammatoryactivityof meloxicamhasbeen proven in classical models of inflammation. As with other NSAIDs, its precisemechanism of actionremainsunknown However, there is at least onecommonmodeofactionsharedbyall NSAIDs(includingMeloxicam) inhibitionofthebiosynthesisofprostaglandins, known inflammation mediators.
5.2- Pharmacokinetic properties <u>Absorption</u> Meloxicam iswell absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89% followingoral administration (capsule).Tableis,oralsuspensionandcapsules were shown to be bioequivalent.Following singledoseadministrationofmeloxicam, meanmaximumplasmaconcentrationsare achieved within 2 hoursforthe suspension and within 5-6 hours withsolidoraldosageforms (capsulesandtablats).With multipledosing, steadystateconditions werereachedwithin3to5days. Oncedaily dosingleadstodrug plasmaconcentrationswitharelativelysmallpeak-troughfluctuation intherangeof 0.4-1.0 µg/mL for7.5mgdosesand0.8-2.0 µg/mL for15mg doses, respectively (Cmin and Cmax at steady state, respectively). Maximum plasma concentrations of meloxicam atsteady statearea chievedwithinfivetosixhoursforthetablet,capsuleandtheoralsuspension,respectvely.Extentofabsorptionformeloxicamfollowing oraladministrationisnotalteredbyconcomitant food Intake.
<u>Distribution</u> Meloxicam is verystronglybound to plasmaproteins, essentiallyalbumin (99%). Meloxicam penetrates into synovial fluid to give concentrations approximately halfofthoseInplasma. Volumeofdistributionislow,onaverage 11L. Inter-individualvariationistheorderof30-40%
<u>Biotransformation</u> Meloxicam undergoesextensivehepatic biotransformation.Four differentmetabolites ofmeloxicamwere identified In urine, whichereall pharmacodynamicallyinactive.The majormetabolite,5'-carboxymeloxicam(60% of dose),is formedby oxidationofan intermediate metabolite5'-hydroxymethylmeloxicam, whichisalso excreted to a lesser extent (9%ofdose) In vitrostudiessuggestthatCYP2C9playsan importantrole Inthis metebolicpathway, with a minor contribution fromthe CYP3A4 isoenzyme. Thepatient's peroxidaseactivityIs probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose respectively.
<u>Elimination</u> Meloxicam is excreted predominantly Intheformofmetabolitesand occurs toequalextentsInurineandfaeces.Lessthan5%of the dailydoseIsexcretedunchangedInfaeces,whileonlytracesoftheparentcompoundareexcretedInurine.Themean eliminationhalf-lifeisabout 20hours.Totalplasmaclearanceamountson everage8mL/min
<u>Linearity/non-linearity</u>
Meloxicamdemonstrateslinearpharmacokineticsinthetherapeuticdose rangeof7.5mg15mgfollowingperoralorintramuscularadministration.
<u>Special populations</u> *Hepatic/ renal Insufficiency:* Neither hepatic,normildtomoderaterenal insufficiencieshaveasubstantialeffectonmeloxicam pharmacokinetics. Interminalrenalfailure,theincrease Inthevolumeof distribution mayresultInhigher freemeloxicamconcentrations,andadaily doseof7.5mgmustnotbeexceeded(seesection4.2).
Elderly: Meanplasma clearance at steady stateinelderlysubjectswasslightlylowerthanthatreportedforyoungersubjects
6- PHARMACEUTICAL PARTICULARS
6.1-Listofexcipients
- <u>Tablets:</u> βcyclodextrin,polysorbate80,microcrystallinecellulose(Avicel PH-101),hydroxypropyl methyicellulose,magnesiumstearate crosscamellosesodium(AC-Di-Sol),colloidalsilicondioxide (Aerosil-200),titaniumdioxide,talc,polyethylene glycol6000,aluminiumyellowlake (D&CyeliowNo.10).
- <u>Suppositories:</u> βcyclodextrin, hardfat(WitepsolE75), hardfat(Witepsol H15),propyl gallate, polysorbate 80, propylene glycol,cetamacrogol emulsifyingwax
6.2-Incompatibilities Nonapplicable
6.3-Shelf life and Storage conditions: Donotusethetabletsorsuppositoryafter theexpirydateprintedonthepackage.
Tablets:Storeatatemperaturenotexceeding30°C,Inadryplace.
Suppository: store at a temperature from 2°- 8°C.
6.4- Nature and contents of container A box conteining 10 tablets(6suppositories).
Manufactured by: Medical Union Pharmaceuticals,
Abu-Sultan, Ismailia, Egypt.
Issuedate: 10 / 6 / 2012,Rerevision Date: 14 / 5 /2013