SUMMARY OF PRODUCT CHARACTERISTICS

1. NAMEOFTHEFINISHEDPHARMACEUTICALPRODUCT

TRAMA50(TramadolcapsulesBP)

2. QUALITATIVEANDQUANTITATIVECOMPOSITION

Eachhardgelatincapsulecontains:

TramadolhydrochlorideBP…….50mgExcipient

s…….q.s.

Excipient(s) with known effect Each Capsule Contains Lactose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICALFORM

SolidDosageform(Capsules)

HardgelatinfilledCapsuleswithBluecapandBlueColourbodysize"2"containswhitepowder.

4. CLINICALPARTICULARS

4.1 Therapeuticindications

Treatmentofmoderatetoseverepain.

4.2 Posologyandmethodofadministration

Methodofadministration:Oral

Thedoseshouldbeadjustedtotheintensityofthepainandthesensitivityoftheindividualpatient.Unlesso therwiseprescribed,Tramashouldbeadministeredasfollows:

AdultsandChildrenaged12yearsandover

Oraladministration

AcutePain:Aninitialdoseof100mgisusuallynecessary.Thiscanbefollowedbydosesof

50or100mgnotmorefrequentlythan4hourly,anddurationoftherapyshouldbematchedtoclinicalneed.

PainAssociatedwithChronicConditions: Useaninitialdoseof50mgandthentitratedoseaccordingtopainseverity.Theneedforcontinuedtreatmentshouldbeassessedatregularintervalsaswithdrawalsymptomsanddependencehavebeenreported.
Thelowestanalgesicallyeffectivedoseshouldgenerallybeselected.Dailydosesof400mgactivesubstanceshouldnotbeexceeded,exceptinspecialclinicalcircumstances.

Thecapsulesaretobetakenwhole,notdividedorchewed,withsufficientliquid,independentofmeals.

Tramashouldundernocircumstancesbeadministeredforlongerthanabsolutelynecessary.Iflong-
termpaintreatmentwithTramaisnecessaryinviewofthenatureandseverityoftheillness,thencarefulandregularmonitoringshouldbecarriedout(ifnecessarywithbreaksintreatment)toestablishwhetherandtowhatextentfurthertreatmentisnecessary.

Children
Tramacapsulesarenotsuitableforchildrenbelowtheageof12years.

Geriatricpatients
Theusualdosagesmaybeusedalthoughitshouldbenotedthatinvolunteersagedover75yearstheeliminationhalf-lifeoftramadolwasincreasedby17%followingoraladministration.

RenalInsufficiency/DialysisandHepaticInsufficiency
Theeliminationoftramadolmaybeprolonged.Theusualinitialdosageshouldbeused.Forpatientswithcreatinineclearance<30ml/min,thedosageintervalshouldbeincreasedto12hours.Tramadolisnotrecommendedforpatientswithsevererenalimpairment(creatinineclearance<10ml/min).Astramadolisonlyremovedveryslowlybyhaemodialysisorhaemofiltration,post-dialysisadministrationtomaintainanalgesiaisnotusuallynecessary.

Hepaticimpairment

Theeliminationoftramadolmaybeprolonged.Theusualinitialdosageshouldbeusedbutinsevere hepaticimpairmentthedosageintervalshouldbeincreasedto12hours.

4.3 Contraindications

Tramaiscontraindicated

- inhypersensitivitytotramadoloranyoftheexcipients,
- inacuteintoxicationwithalcohol,hypnotics,analgesics,opioids,orpsychotropicmedicinalproducts,
- inpatientswhoarereceivingMAOinhibitorsorwhohavetakenthemwithinthelast14days,
- inpatientswithepilepsynotadequatelycontrolledbytreatment,
- foruseinnarcoticwithdrawaltreatment

4.4 Specialwarningsandspecialprecautionsforuse

Tramamayonlybeusedwithparticularcautioninopioid-dependentpatients,patientswithheadinjury,shock,areducedlevelofconsciousnessofuncertainorigin,disordersoftherespiratorycentreorfunction,increasedintracranialpressure.

Inpatientssensitivetoopiatestheproductshouldonlybeusedwithcaution.
Careshouldbetakenwhentreatingpatientswithrespiratorydepression,orifconcomitantCNSdepressantdrugsarebeingadministered,oriftherecommendeddosageissignificantlyexceededasthepossibilityofrespiratorydepressioncannotbeexcludedinthesesituations.

Convulsionshavebeenreportedinpatientsreceivingtramadolattherecommendeddoselevels. Theriskmaybeincreasedwhendosesoftramadolexceedtherecommendedupperdailydoselimit(400mg).

Inaddition,tramadolmayincreasetheseizureriskinpatientstakingothermedicinalproductsthatlowerstheseizurethreshold.Patientswithepilepsyorthosesusceptibletoseizuresshouldbeonlytreatedwithtramadoliftherearecompellingcircumstances.

Tramadolhasalowdependencepotential.Onlong-termusetolerance,psychicandphysicaldependencemaydevelop.Inpatientswithatendencytodrugabuseordependence,treatmentwithTrama-

50shouldonlybecarriedoutforshortperiodsunderstrictmedicalsupervision.

Tramadolisnotsuitableasasubstituteinopioid-dependentpatients.Althoughitisanopioidagonist,tramadolcannotsuppressmorphinewithdrawalsymptoms.

InteractionwithotherFPPsandotherformsofinteraction

TramashouldnotbecombinedwithMAOinhibitors.

InpatientstreatedwithMAOinhibitorsinthe14dayspriortotheuseoftheopioidpethidine,life-threateninginteractionsonthecentralnervoussystem,respiratoryandcardiovascularfunctionhavebeenobserved.ThesameinteractionswithMAOinhibitorscannotberuledoutduringtreatmentwithTrama.

ConcomitantadministrationofTramawithothercentrallydepressantmedicinalproductsincludingalcoholmaypotentiatetheCNSeffects.

Theresultsofpharmacokineticstudieshavesofarshownthatontheconcomitantorpreviousadministrationofcimetidine(enzymeinhibitor)clinicallyrelevantinteractionsareunlikelytooccur. Simultaneousorpreviousadministrationofcarbamazepine(enzymeinducer) mayreducetheanalgesiceffectandshortenthedurationofaction.

Thecombinationwithmixedagonist/antagonists(e.g.buprenorphine,nalbuphine,pentazocine)andtramadolisnotadvisable,becausetheanalgesiceffectofapureagonistmaybetheoreticallyreducedinsuchcircumstances.

Tramadolcaninduceconvulsionsandincreasethepotentialforselectiveserotoninre-uptakeinhibitors,tricyclicanti-depressants,anti-psychoticsandotherseizurethresholdloweringmedicinalproductstocauseconvulsions.

Inisolatedcasestherehavebeenreportsofserotoninsyndromeinatemporalconnectionwiththetherapeuticuseoftramadolincombinationwithotherserotoninergicmedicinalproductssuchasselectiveserotoninre-uptakeinhibitors(SSRIs)orwithMAOinhibitors.Signsofserotoninsyndromemaybeforexam

pleconfusion,agitation,fever,sweating,ataxia,hyperreflexia,myoclonusanddiarrhoea.With drawaloftheserotoninergicmedicinalproductsusuallybringsaboutarapidimprovement.Trea tmentdependsonthenatureandseverityofthesymptoms.

Cautionshouldbeexercisedduringconcomitanttreatmentwithtramadolandcoumarinderivati ves(e.g.warfarin)duetoreportsofincreasedINRwithmajorbleedingandecchymosesinsomep atients.

Otheractivesubstancesknowntoinhibit CYP3A4,suchasketoconazoleanderythromycin,mig htinhibitthemetabolismoftramadol(N-demethylation)probablyalsothemetabolismoftheactiveO-demethylatedmetabolite.Theclinicalimportanceofsuchaninteractionhasnotbeenstudied.

Inalimitednumberofstudiesthepre-orpostoperativeapplicationoftheantiemetic5-HT3antagonistondansetronincreasedtherequirementoftramadolinpatientswithpostoperativ epain.

4.5 Pregnancyandlactation

Animalstudieswithtramadolrevealedatveryhighdoseseffectsonorgandevelopment,ossificat ionandneonatalmortality.Teratogeniceffectswerenotobserved.Thereisinadequateevidence availableonthesafetyoftramadolinhumanpregnancy.ThereforeTramashouldnotbeusedinpr egnantwomen.

Tramadol-administeredbeforeorduringbirth-doesnotaffectuterinecontractility.Inneonatesitmayinducechangesintherespiratoryratewhic hareusuallynotclinicallyrelevant.Chronicuseduringpregnancymayleadtoneonatalwithdraw alsymptoms.

UsageinNursingMothers

Tramadolcrossestheplacenta.Duringlactationabout0.1%ofthematernaldoseissecretedintot hemilk.Tramaisnotrecommendedduringbreast-feeding.Afterasingleadministrationoftramadolitisnotusuallynecessarytointerruptbreast-

feeding.

4.6 Effectsonabilitytodriveandusemachines

Evenwhentakenaccordingtoinstructions,Tramamaycauseeffectssuchassomnolenceanddizzinessandthereforemayimpairthereactionsofdriversandmachineoperators.Thisappliesparticularlyinconjunctionwithalcoholandotherpsychotropicsubstances.

4.7 Adversereaction

Themostcommonlyreportedadversereactionsarenauseaanddizziness,bothoccurringinmorethan10%ofpatients.

Cardiovasculardisorders:
*Uncommon:*cardiovascularregulation(palpitation,tachycardia,posturalhypotensionorcardiovascularcollapse).Theseadversereactionsmayoccurespeciallyonintravenousadministrationandinpatientswhoarephysicallystressed.
*Rare:*bradycardia,increaseinbloodpressure

Nervoussystem
*disorders:Verycommon:*d
izziness
*Common:*headache,somnolence
*Rare:*changesin
appetite,paraesthesia,tremor,respiratorydepression,epileptiformconvulsions,involuntarymusclecontractions,abnormalcoordination,syncope.

Iftherecommendeddosesareconsiderablyexceededandothercentrallydepressantsubstancesareadministeredconcomitantly,respiratorydepressionmayoccur.

Epileptiformconvulsionsoccurredmainlyafteradministrationofhighdosesoftramadolorafterconcomitanttreatmentwithmedicinalproductswhichcanlowertheseizurethreshold.

Psychiatricdisorders:
*Rare:*hallucinations,confusion,sleepdisturbance,anxietyandnightmares.Psychicadverserea

ctionsmayoccurfollowingadministrationofTramawhichvaryindividuallyinintensityandnature(dependingonpersonalityanddurationoftreatment).Theseincludechangesinmood(usuallyelation,occasionallydysphoria),changesinactivity(usuallysuppression,occasionallyincrease)andchangesincognitiveandsensorialcapacity(e.g.decisionbehaviour,perceptiondisorders).Dependencemayoccur.

Eyedisorders:Rare
*:*blurredvision

Respiratorydisorders:Rar
*e:*dyspnoea
Worsening ofasthmahasbeen reported,thougha causal relationshiphasnotbeenestablished.

Gastrointestinaldisorders
*:Verycommon:*nausea

*Common:*vomiting,constipation,drymouth
*Uncommon:*retching;gastrointestinalirritation(afeelingofpressureinthe stomach,bloating),diarrhoea

Skinandsubcutaneousdisorders:commo
*n:*sweating
*Uncommon:*dermalreactions(e.g.pruritus,rash,urticaria)

Musculoskeletaldisorders:
*Rare:*motorialweakness

Hepatobiliarydisorders:
Inafewisolatedcasesanincreaseinliverenzymevalueshasbeenreportedinatemporalconnection withthetherapeuticuseoftramadol.

Renalandurinarydisorders:
Rare:micturitiondisorders(difficultyinpassingurine,dysuriaandurinaryretention)

Generaldisorders:Commo

*n:*fatigue

*Rare:*allergicreactions(e.g.dyspnoea,bronchospasm,wheezing,angioneuroticoedema)and anaphylaxis;Symptomsofwithdrawalreactions,similartothoseoccurringduringopiatewithdrawal,mayoccurasfollows:agitation,anxiety,nervousness,insomnia,hyperkinesia,tremorandgastrointestinalsymptoms.Othersymptomsthathaveveryrarelybeenseenwithtramadoldiscontinuationinclude:panicattacks,severeanxiety,hallucinations,paraesthesias,tinnitusandunusualCNSsymptoms.

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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.8 Overdose

Symptoms

Inprinciple,onintoxicationwithtramadolsymptomssimilartothoseofothercentrallyactinganalgesics(opioids)aretobeexpected.Theseincludeinparticularmiosis,vomiting,cardiovascularcollapse,consciousnessdisordersuptocoma,convulsionsandrespiratorydepressionuptorespiratoryarrest.

Treatment

Thegeneralemergencymeasuresapply.Keepopentherespiratorytract(aspiration!),maintainrespirationandcirculationdependingonthesymptoms.Thestomachistobeemptiedby vomiting(consciouspatient)orgastricirrigation.Theantidoteforrespiratorydepressionisnaloxone.Inanimalexperimentsnaloxonehadnoeffectonconvulsions.Insuchcasesdiazepamshouldbegivenintravenously.

Tramadolisminimallyeliminatedfromtheserumbyhaemodialysisorhaemo-filtration.ThereforetreatmentofacuteintoxicationwithTramawithhaemodialysisorhaemofiltrationaloneisnotsuitablefordetoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamicproperties

Pharmacotherapeutic group: Analgesic

ATC code: N02AX02

Mode of action

Tramadolisacentrallyactingopioidanalgesic.Itisanon-selectivepureagonistatμ,δandκopioidreceptorswithahigheraffinityfortheμreceptor.Otherm echanismswhichcontributetoitsanalgesiceffectareinhibitionofneuronalreuptakeofnoradren alineandenhancementofserotoninrelease.

Tramadolhasanantitussiveeffect.Incontrasttomorphine,analgesicdosesoftramadoloverawi derangehavenorespiratorydepressanteffect.Alsogastrointestinalmotilityislessaffected.Effe ctsonthecardiovascularsystemtendtobeslight.Thepotencyoftramadolisreportedtobe1/10(o netenth)to1/6(onesixth)thatofmorphine.

5.2 Pharmacokineticproperties

Morethan90%ofTramaisabsorbedafteroraladministration.Themeanabsolutebioavailability isapproximately70%,irrespectiveoftheconcomitantintakeoffood.Thedifferencebetweenab sorbedandnon-metabolizedavailabletramadolisprobablyduetothelowfirst-passeffect.Thefirst-passeffectafteroraladministrationisamaximumof30%.

Tramadolhasahightissueaffinity(Vd,ß=203±40l).Ithasaplasmaproteinbindingofabout20% .

Followingasingleoraldoseadministrationoftramadol100mgascapsulesortabletstoyounghea lthyvolunteers,plasmaconcentrationsweredetectablewithinapproximately15to 45minuteswithinameanC of280to208mcg/LandT of1.6to2h.
max max

Tramadolpassestheblood-brainandplacentalbarriers.VerysmallamountsofthesubstanceanditsO-desmethylderivativearefoundinthebreast-milk(0.1%and0.02%respectivelyoftheapplieddose).

Eliminationhalf-lifet1/2,ßisapproximately6h,irrespectiveofthemodeofadministration.Inpatientsabove75yearsofageitmaybeprolongedbyafactorofapproximately1.4.
InhumanstramadolismainlymetabolizedbymeansofN-andO-demethylationandconjugationoftheO-demethylationproductswithglucuronicacid.OnlyO-desmethyltramadolispharmacologicallyactive.Thereareconsiderableinterindividualquantitativedifferencesbetweentheothermetabolites.Sofar,elevenmetaboliteshavebeenfoundintheurine.AnimalexperimentshaveshownthatO-desmethyltramadolismorepotentthantheparentsubstancebythefactor2-4.Itshalf-lifet1/2,ß(6healthyvolunteers)is7.9h(range5.4-9.6h)andisapproximatelythatoftramadol.

Theinhibitionofoneorbothtypesoftheisoenzymes CYP3A4andCYP2D6involvedinthebiotransformationoftramadolmayaffecttheplasmaconcentrationoftramadoloritsactivemetabolite.Uptonow,clinicallyrelevantinteractionshavenotbeenreported.

Tramadolanditsmetabolitesarealmostcompletelyexcretedviathekidneys.Cumulativeurinaryexcretionis90%ofthetotalradioactivityoftheadministereddose.Incasesofimpairedhepaticandrenalfunctionthehalf-lifemaybeslightlyprolonged.Inpatientswithcirrhosisoftheliver,eliminationhalf-livesof13.3±4.9h(tramadol)and18.5±9.4h(O-desmethyltramadol),inanextremecase22.3hand36hrespectively,havebeendetermined.Inpatientswithrenalinsufficiency(creatinineclearance<5ml/min)thevalueswere11±3.2hand16.9±3h,inanextremecase19.5hand43.2hrespectively.

Tramadolhasalinearpharmacokineticprofilewithinthetherapeuticdosagerange.
Therelationshipbetweenserumconcentrationsandtheanalgesiceffectisdose-

dependent,butvariesconsiderablyinisolatedcases.Aserumconcentrationof100-300ng/mlisusuallyeffective.

5.3 Preclinicalsafetydata

None

6. PHARMACEUTICALPARTICULARS

6.1 Listofexcipients

Lactose
Magnesiumstearate
Purifiedtalc
Aerosil-200
Sodiumstarchglycolate
E.H.G.CapsulesBlue/BlueSize
"2"Plain

6.2 Incompatibilities

Notapplicable.

6.3 Shelflife

36months

6.4 Specialprecautionsforstorage

Storeinadryplace,below25°C.Protectfromlight.Keep outofreachofchildren.

6.5 Natureandcontentsofcontainer

10capsulesarepackedinAlu-PVDCblister.Such10BlisterpackincartonwithPackinsert.

6.6 Instructionsforuseandhandlinganddisposal

Nospecialrequirements.

7. MarketingAuthorizationHolde

rCachetPharmaceuticalsPvt.Ltd

415,ShahNaharIndustrialEstate,

Dr.E.MosesRoad,Worli,Mumbai-

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Manufacturer'sNameandAddress:C

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8. MarketingAuthorizationNumbers

2981/2855REN/2016

9. DateofRenewaloftheAuthorization

Date of first authorisation: 15/02/2013

Date of latest renewal: 26/04/2021

10. DateofRevisionoftheText

05/07/2023