MODÜLX-PAZARLAMA-ÖNCESI-YARAR-RISK-DEGERLENDIRMESI-EN

GuidelineonGood Pharmacovigilance Practices(GVP) ModuleX-Pre-Marketing Benefit/RiskEvaluation TURKISHMEDICINESANDMEDICALDEVICESAGENCY 20.06.2022

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2 SECTIONI IntroductionandScope 1.1.Introduction

Summarizethebackgroundandtreatmentsofdisease(e.g.;alifethreateningdiseasevs. adiseasetreatedwithaspecifictreatmentoraself-limitingdisease,availabilityofdifferent treatments).Ifindicationincludesdifferentconditionswithdifferentbenefit/riskcategories (multipleindications,populationsordosage)thismaycausecomplexity.

Brieflydefinetheissue.Makesurerequestedtherapeuticindicationisclearlystated.

Indicateothertherapeuticalternativesrelatedtothisbenefit/riskevaluationincluding othertreatmentmethods,theirobjectivesorintendedoutcomes(Newtreatmentis evaluatedaccordingtocurrenttreatmentoptionsandstandardtreatment).

Discusstreatmentobjectivesingeneraltermsandtrytoidentifyacceptabilitylimits, i.e.evaluationcriteriawhichamedicinemustmeet. 1.2.Objective

Thisguidelineisintendedtoidentifykeyobservationsanduncertaintiesthatsteer benefit/riskevaluation.Inparticular,withrespecttomethodsandresultsofvarioustestsand studies,itisimportanttoavoidneedlessrepetitionoftechnicaldetailsthatarealready explainedelsewhere.Onlykeyfindingsmustbedescribedherewithoutgivingany comprehensiveexplanation.

Firstly,itisadvisedthatmainevidenceanduncertaintiesthatareconsideredkeyto benefit/riskevaluationareidentified.Accordingly,alistofbenefitandriskcriteriais provided.Thelistisexhaustiveandthosetobeincludedmustbeevaluatedonacase bycasebasis.

Secondly,significantbenefitsandrisksarecomparedtoeachotherwithinspecific therapeuticcontextandaconclusionisdrawnaboutbenefit/riskbalance,asfaras possible,byexplainingtherelationsbetweenprinciples,dataandresults,and unresolvedissues.

Itisnecessarytobeimpartialandclearabouttheevidenceusedtosupportresults,and toavoidrepetitionandseparatelistingofqualitymatters,non-clinicalmatters,clinical efficacyandsafetyresultsunlessthereisclearlyspecifiedrelationshipwithresults.Instead, descriptionofsignificantfindingsanduncertaintiesmustbegivenwithrespecttotheireffects onevaluationofbenefitsandrisks. 1.3.Demonstratedbenefitsanduncertainties

Thissectionisintendedforidentifyingbenefitsanddiscussthemcritically.Only significantresultsandmattersthataffectbenefit/riskbalancemustbeexplained.In addition,unresolvedissuesoruncertaintiesmustbeidentifiedandtheireffectsonbalance evaluationmustbeclearlystated.

Thefirstrequirementissatisfactorilyprovenefficacy.Benefitsaretypicallydefinedas positiveresultsforanindividualorcommunityandthelikelihoodofachievingthoseresults.

Explainanyofthefollowingforthissection(Thisisnotalistofmandatorypointstobe explained.Whethereachpointneedstobediscussedornotmustbedeterminedonacaseby casebasis.)

Formainstudies, Definekeybenefits,e.g.intermsofprimaryendpointsandbasicsecondary endpoints,ascomparedtobenchmarkproduct(productusedasareferenceinclinical trialorplacebo).Discussthemagnitudeofeffectandstatisticalevidence(confidence

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intervalsandp-values).Considerdefiningbenefitsinrelevantsub-groups(e.g.;age,
3 gender,ethnicity,organfunction,diseaseseverityandgeneticpolymorphism)
Forotherbenefits,iftheyareofkeyimportanceforbenefit/riskevaluation,considerthe following:
Explainthebenefitsobservedinnon-pivotalstudiesandtheirextensions.
Defineotherexistingbenefitoutcomecriteria(includingresultsreportedbypatient,
preferenceofpatientetc.) Definepatientcomplianceobservedinclinicaltrials.
Definebenefitpotentialofnewtreatment.(e.g.;basedonanyknownbenefitfor pharmaceuticalclass)
Reviewresultsinacriticalmanner.Summarizethemostsignificantfindingsof
scientificevaluationofefficacy.Here,thepurposeistodefineuncertaintiesandthestrength
ofevidence.Consideranyofthefollowing:
Discussselectionofdose,benchmarkproductandendpoints(includingsurrogates, ifappropriate).
Definesignificantmethodologicaldefectsorshortcomings.Refertoguidelinesor
scientificliteratureandexplainhowdeviations,ifany,fromguidelinesorscientific advicesarejustified.
Describetheeffectofmethodologicalshortcomingsonestimatedbenefit,e.g.;
considerpointssuchasmultiplicity,discoverytechniques,posthocanalysesetc.
Weremeasurementsandscalesvalidated?Whataretheunresolvedissues?Are furtherstudiesneeded?
Definenegativestudiesandstudiesthatdonotvary. Explainthequalityofsupportingscientificliterature.
Explainotherpointsthatmayhaveaffectonestimatedbenefits.
Aretheresultsconsistentamongdifferentfactors?pivotalstudiesandsupporting
studies,allstudiesandliteratureprovided,differentpopulations,centers,dosesetc.?
1.4.Demonstratedrisksanduncertainties
Thissectionisintendedforprovidingahighlevelsummaryofthelikelihoodof
occurrenceofsignificantadverseevents.Referencemustbemadeonlytoriskthatarepartof
benefit/riskbalanceandpotentialrisks.Consideringtheimportanceofdifferentevents,itmay
beusefultorefertotheintensity(e.g.severity)ofadverseevent,thetimeofevent
(commencement,duration)andthetimeframewhenthelikelihoodisapplicable.Thismustnot
beadetailedexplanationofsafetyprofileexplainedelsewhere.
Inaddition,uncertaintiesregardingpotentialrisksorunresolvedissuesmustbedefined.
Providethemostimportantnon-clinicalsafetyfindingsthatarenotsufficiently
addressedbyclinicaldata.Ifany,lookintokeyfindingswithrespecttotoxicity
(includingrepeatdosetoxicity,reproductive/developmentaltoxicity,nephrotoxicity,
hepatotoxicity,genotoxicity,carcinogenicityetc.)anddruginteractions.
Relationshipoffindingswithhumanusemustbediscussed.
Regardingclinicalfindings,lookintothemostsignificanttoxicityandotherrisks
explainedinclinicalsafetysectionofreport,i.e.summarizewhatarethemost
importantadversedrugreactions(orevents).Indicatetowhatextentttheserisks contributetoriskprofile.
4 Onacasebycasebasis,forexample,considerdiscussingtheeffectoffollowing safetyissues:
oGeneralincidenceofadverseeffects. oThemostserious/significantidentifiedrisks.
oDurationandwhetherobservedreactionsarereversible.
oPossiblemechanisms(pre-clinicaldataontoxicityandgeneralpharmacology).
oKnownandpotentialinteractions.
oLimitationsofdataset(e.g.;missingdata,possibleriskfactors,patientsub-
groupssusceptibletounexaminedbutpotentiallynegativeeffects).Discussthe
effectofthiskindoflimitationonestimatingsafetyofdrug.
oEvaluationofdurationoftherealized/ongoingsafetystudiesandtheneedfor
resultsobtainedfromlong-termstudies.Discusswhethersafetyprofileis
quantifiedanddefinedforanappropriateperiodinconsistencywiththeintended use.
oDiscussclasseffects. Riskvs.standardtreatment
Riskvs.benchmarkdrugsfromthesamepharmacologicalclass
oDiscussoff-labelusepotentialandrisksassociatedwithsuchuse.
Considerdiscussingfactorssuchasdefinedandpotentialpharmacokineticsand

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pharmacodynamicsinteractions,overdosepotential,abuseandmisusepotential,
transmissionpotentialoftransmissibleagents,abusepotentialforillegalpurposes,
off-labelusepotentialetc.providedthatthesefactorssignificantlyaffectbenefit/risk balance.
1.5.Benefit/riskbalance
Thissectionisintendedforcomparingthebenefitsandrisksdescribedabovebyputting
alternativetreatmentsorinterventions(asapplicableandrelevant)intoperspectiveand
concludingaboutwhetherbenefit/riskbalanceispositiveinthetargetpopulation(s)specified.
Inevaluatingthebalance,observedbenefitsandharmsanduncertaintiesandrisksmust
betakenintoconsideration.
Duringevaluationmadewhentakingregistrationdecisions,suchdecisionsmustbe
takenonthebasisofobjectivescientificcriteriaregardingthequality,safetyandefficacyof
relatedmedicinalproduct,factorssuchascost-effectivenessmustbeexcluded.
Evaluationofbenefit/riskbalancemustbebasedoncurrenttestsandresearchdesigned
toidentifytheefficacyandsafetyofproductundernormalusageconditionsandgenerally
performedunderidealconditions.
Itisofimportancetobeclearaboutviewpointsofvariousstakeholderstakeninto
accountinevaluationofbenefit/riskbalance,inparticular,viewpointsofpatientsandtreating
physicians.
Therearenostandardquantitativemethodstoberecommendedforevaluationofbenefitand
riskbalance.Ingeneral,evaluationofbalancedependsonbalancingasimpartialaspossible
thebenefitsandharmswhichcompriseafeweventsdifferentfromeachotherandare
estimatedatavaryingcertainty.
5 Estimationofbalanceisusuallynotcertainandgenerallyextensiveestimatesareused.
Whenbenefitsareapparentlymuchgreaterthanrisks(orviceversa),thisisgenerallynota
problem.Ifbenefitsandrisksarestatedintermsofthesameevent(forexampledeaths),the
balancecanalsobeeasilystatedquantitatively.Likewise,ifdifferenttreatmentsvaryonlyin
termsofoneeventtype(e.g.magnitudeofaneffectorfrequencyofanadverseevent),the
balancecaneasilybemeasuredwhencomparedwithothertreatments.
Inaddition,whenthedifferenceislessapparentandbenefitsandriskscomprise
differenteventtypes,itisimportanttoidentifyandestimateallcontributingfactorsasprecise
aspossibleanddescribetheimportanceattachedtovariousfactorsinasmanydetailsas
possible.Moreover,itisalsoimportanttoevaluatetheeffectofanysignificantestimationon theresults.
Itisalsoimportanttotakedifferentregulatoryoptionsforregistration(standard
marketingauthorization,conditionalmarketingauthorization,registrationinexceptional
cases).Ifany,discusscomplianceandrequirementsforthesedifferentregulatoryoptions.
Ingeneral,itwouldbeimportanttoexplainthefollowing(detaillevelmustbe
evaluatedonacasebycasebasis):
Amountofavailableevidenceforcharacterizingbenefit-riskassessment.
Availabilityofcomparativedata,limitationsandpotentialtrapsofcomparative analyses.
Interpretthemagnitudeofkeybenefitsandrisksfromtheviewpointofdifferent
stakeholders,especiallypatientsandtreatingphysicians.
Discusstheacceptabilitylevelofriskscorrespondingtoclinicalbenefitperceivedin aspecificcontext.
Whereverpossible,specifytherelevantbenefitsinawaytobecomparablewith
risks(e.g.;possiblelivessavedasaresultoftreatmentvs.possibleliveslostasa resultofadversereaction)
Describehowbenefit/riskbalancemayvarybetweendifferentfactors,e.g.between
differentpatientordiseasecharacteristics.Becautiousabouttheuseofgeneralrisk
orbenefitexpressioninanoncriticalmanner.
Discusssensitivityofbenefit/riskbalanceevaluationtodifferentassumptions.For
example,ifassumptionsareviolated,define“theworstcasescenario”.
Thefollowingpotentialpointsmustbedulytakenintoconsideration.Thisisnota
listofmandatorypointsthatmustbeexplained.Whetherornottodiscusseachpoint

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mustbeevaluatedonacasebycasebasis.
oWhenproposedtreatmentislesseffectivecomparedtocurrenttreatment options,discusstheeffectoflossofefficacy.
oIfbalanceisconsideredasnegative,definetheharmwhichmaybecaused bythemedicineifusedforclaimedindication(forexample,lackofefficacy, intermsoftoxicity)(seetheimportanceofsensitivityanalysesasdescribed below).
oExplainhowbenefit/riskbalanceisexpectedtoprogressintime(for example,whenlatesideeffectsoccurorefficacydeclinesinthelongterm).
oDefinependingissues,additionalreportsthatmustbesubmittedbythe companytorespondtothoseissues.

6 oRefertoevaluationofpharmacovigilanceplanand(ifany)riskminimization plan.Definethestepstobetakenforannouncingimportantinformationto healthcareprofessionals,patientsorpublic.Explainlimitationsforproduct availabilityorusage.
oDescribetheneedforfurtherstudies(forexample,theneedforstudiestobe carriedouttoimprovebenefit/riskbalance,theneedforintensiveadditional follow-upmeasuresorspecialobligationsandtheneedforfurther developmentincludinganypediatricdevelopmentplan).
oDescribeinvolvementofscientificexperts,patients,consumersandother stakeholdersinbenefit-riskevaluation.
Provideanetconclusionregardingwhetherbenefit/riskbalanceispositiveforeach indicationclaimed.

7 BENEFIT/RISKEVALUATIONTEMPLATE <DrugName> <Activesubstance> Applicant:<xxx> Drugname INNofactivesubstance Applicant Indicationappliedfor Pharmacotherapeuticgroup(ATCcode) 1.TherapeuticContext 1.1.Diseaseorcondition Statetheindicationrequestedbytheapplicant.Ifappropriate,brieflydescribekey aspects(ifany)ofdiseaseorconditionstudiedonwhichareimportantforbenefit/risk evaluation(e.g.definitions).
Definetheobjectives(e.g.toextendsurvivalperiod)andkeyefficacyendpointsof treatment.
1.2.Currenttreatmentsandunmetmedicalneed
Summarizeexistingprimarytreatmentoptionsandifany,unmetmedicalneed(e.g. severityofdisease,whetheritislifethreateningornot,affectedpopulation). 1.3.Keyclinicaltrials
Brieflydescribedesignofkeystudiesandselectedpopulation(s). Comments
Describetheaspectsofconditionthataremostrelevantforthetargetgroupand medicineandthereforethatcanbeconsideredrelevantkeyeffectstobeevaluatedin thestudies.(Forexample,describemortalityforaproductthatisintendedfor extendingsurvivalperiod.)
Unmetmedicalneedmustbedefinedwithepidemiologicaltermsthatareasaccurate aspossible(e.g.;incidence,mortality).Effectsofconditiononcommunityorpublic health(e.g.;theeffectoflackofsufficientcontagiousdiseasecontrolandof insufficientpreventivemeasures)mustalsobeaddressedwhererelevant.
Keyclinicaltrialsmustbedefinedaccordingtorandomization,blinding,control, dosageandstudysize.
Onlydescribethesekeymattersinbrief. Hypotheticalexample[mustbedeletedfromthefinalreport]

8 1.TherapeuticContext 1.1.Diseaseorcondition Targetindicationappliedforbytheapplicantisfortreatmentofadultpatientswith relapsed/resistantmultiplemyeloma(MM).Definitionsofrelapseandrefractoryarethe definitionsofInternationalMyelomaWorkingGroup(IMWG).
Theobjectiveofnewtreatmentsistominimizetoxicitywhileextendingprogression-free survivalandoverallsurvivalortoimprovesymptoms. 1.2.Currenttreatmentsandunmetmedicalneed
Fortreatmentofrelapse/refractoryMM,traditionaldosechemotherapyandhigh-dose chemotherapysupportedbystemcellcontinuetobecurrentcarestandardbesides supportivecareincludingbisphosphonates(Palumbo,2008b).Despiteenhancementin currenttreatmentanditsmanagement,MMisirremediable.Treatmentoptionsofpatients withrelapsed/resistantdiseaseaftertreatmentwithconventionalagentsarelimitedand

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averagelifetimeisaround9months(Kumar,2012). 1.3.Keyclinicaltrials Primaryevidenceofefficacypresented,inadultpatientswithrelapse/refractoryMMwho haspreviouslyreceivedatleasttwotreatmentregimesincludinglenalidomideand bortezomibandinwhomdiseasehasprogressedaftertreatment,efficacydataobtained fromsingle,phaseIII,multicenter,randomized,open-labelstudywherebypomalidomide+ low-dosedexamethasone(n=302)iscomparedtohigh-dosedexamethasone(n=153) Hypotheticalexample-Biosimilar[mustbedeletedfromthefinalreport] 1.TherapeuticContext 1.1.Diseaseorcondition [X]isdevelopedasabiosimilarinfliximabbyusingRemicadeascomparatorandintended foruseinthesameindicationsasthecomparatorproduct. 1.2Keystudies Qualitycomparabilitystudyincludedcomprehensiveandcutting-edgetechnologyproduct characterizationcoveringallrelevantstructural,physicochemicalandbiological characteristicsofinfliximab.Non-clinicalstudyincludedaseriesofin-vitrostudy,onein-vivoefficacystudy,singleandrepeat-dosepharmacokineticsstudiesinratsandoneTg197 mousemodelofarthritis. ClinicaldevelopmentcomprisedasingledosePKstudycomparingthreeinfliximab formulations(X,EuropeanUnion(EU)originRemicadeandUnitedStatesorigin Remicade)inhealthysubjectsandakeyclinicaltrialinpatientswithmediumtosevere rheumatoidarthritis(N=450)despitemethotrexatetreatment.Keystudywasarandomized, double-blind,parallelgroup,multicenterclinicalstudyforevaluatingefficacy,safety, pharmacokineticsandimmunogenicityofXwhencomparedtoEURemicade. 2.Positiveeffects Indicatesignificantpositiveeffects(i.e.primaryendpointandsecondaryendpoints) andbrieflydescribethem(e.g.pointestimates,confidenceintervals). Considerdefiningkeyeffectsinimportantsub-groups(e.g.;age,gender,ethnicity, organfunction,diseaseseverityandgeneticpolymorphism). 9 Consideralsoexplainingconsistencyoffindingsbetweenstudiesandprevious information(ifinconsistent,thismustbeindicatedinSection1.3asanuncertainty) andstrengthofdata. Comments Beclearandunderstandable.Forexample,a6.8-monthdifferencewasobservedin medianoverallsurvivalforXtreatmentcomparedtoYtreatment,HR=0.8(95%CI: 0.6,0.9;logrankP=.001). Avoidmakingcommentsandjudgments(Forexample,itwasconvincingly demonstratedthatoverallsurvivalforXtreatmentwassubstantiallyimproved). Thissectionmustbeincompliancewithpositiveeffectsexplainedin1.6.,Effects Tableandsection5.1.ofSmPC.Nonewresultwhichisnotexplainedindetailin previoussectionsmustbeprovidedhere. Unlessnewkeyresultsareprovided,thereisnoneedtoupdatethissectionduringthe procedure. Whatarepositiveeffects? Thissectionisintendedtoexplainkeyusefuleffects(typicallyreferredtoas “benefit(s)”or“clinicalbenefit(s)”)fortargetpopulationassociatedwithdrugwithrealterms. Positiveeffectsarenotlimitedtoefficacy(e.g.decreaseintoxicitymayalsobepositive effect).Insomecasesthesameeffect(e.g.toxicity)canbedefinedasapositiveeffect(when suchtoxicityislowandthisistheobjectiveofnewtreatment)oranegativeeffect(when toxicityishigh).Inpractice,classificationofaneffecteitheraspositiveornegativeisnot importantunlessthateffectisdefinedtwice. Whatare“Key”PositiveEffects? Theimportantpointtotakeintoconsiderationwhendecidingwhichcurrentstudy resultstoexplaininbenefit/riskevaluationistodothatwithoutelaboratingtoomuch.In practice,thiscanusuallybeachievedbyincludingprimaryefficacyendpointsand additionallysecondaryendpointswhicharethoughttobethemostimportantinclinicalterms (i.e.keysecondaryendpoints).Eventhoughthisstrategywouldworkinmostcases,therewill becircumstanceswhereselectionofkeyeffectswouldrequiremorereflection.Insuchcases, primaryendpointofkeystudymaynotbethemostimportanteffectandinthiscasesecondary endpoints(orifthestudyisnotdesignedaccuratelyenough,endpointsarenotmeasuredinthe study)maybeofpriority. Aboutmultiplicity(“Double-Counting”)

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Multiplicitymayoccurinaseriesofcircumstancessuchaswhendefiningassociated endpoints(e.g.whenbothofsurrogateendpointandrealendpointareincluded),whenusing differentresponsevariablesbasedonslightlydifferentcut-offpointsorwhendefiningthe effectwithinawidergroupandasubgroupcontainedtherein.Inprinciple,thiskindof redundancymustbeavoidedasitmayoveremphasizecertaineffects.
3.Uncertaintiesandlimitationsregardingpositiveeffects
Definesignificantuncertaintiesandlimitationsaboutpositiveeffectsthatare importantforbenefit/riskbalanceincludingmattersrelatingtoreliabilityofresults. Iftherearenouncertaintiesandlimitationsthathaveaneffectonbenefit/riskbalance, thissectionmustbecompletedasfollows:“Thereisnouncertaintyandlimitationthat hasaneffectonbenefit/riskbalance(seesection1.7.Benefit-riskevaluationand discussion)”.

10 Comments Focusonsignificantuncertaintiesthathaveaneffectonbenefit/riskevaluation. Explanationmustbetrueandavoidmakingajudgement.
Relianceonthedecision,theeffectofuncertaintiesonbenefit/riskbalanceand judgmentsontakinganyaction(e.g.indicationrestriction)mustbeexplainedin Section7.1Importanceofpositiveandnegativeeffectsand7.2.
Thereisnoneedtorepeatthereminoruncertaintiesregardingpositiveeffectsthat donothaveaneffectonbenefit/riskevaluationandthatcanbemanagedeasily (e.g.productinformation).Ifstillconsideredworthmentioning,brieflymention uncertaintyandhowitwillbemanaged. Examplesofuncertaintyandlimitation; oUncertainestimates,forexample;toosmallsamplesize,toolarge confidenceintervals,insufficientstatisticalsignificance,withdrawal modelsthatmayaffectinterpretationofresults
oStatisticalaspects,forexample;suitabilityofstatisticalmodel,validityof hypotheses,evaluation,conjointanalyses,missingdata,causality evaluationmethods,multiplicity oAnalysissensitivityissues(non-inferioritystudies/equivalencestudies, adherencetotreatment) oRepresentabilityofpatientpopulationwhichisexpectedtobetreated withtheproduct(externalvalidity) oSelectionofbenchmarkproduct oSelected“key”effectsbeingdifferentfromtheobjectivesoftreatment explainedin1.1TherapeuticContext
oPositivefindingsregardingprimaryefficacyendpointsnotsupportedin specifiedsecondaryefficacycriteriaatleastbypositivetrends,asingle pivotalstudy oGoodclinicalpractices(GCP)complianceissues
oDrugusedinclinicaltrialsdoesnotrepresentdulythedrugwhose registrationisrequested oFormulationoftheproduct(compositionordevelopment)hasany specificaspectthataffectssafeandeffectiveuseofit
oInconsistencyoffindingsbetweenstudiesandpreviousinformation
oInconsistentfindingsinimportantsubgroups(e.g.age,gender,disease characteristicsandaccompanyingtreatment),differencesbetween geographicalregions Ifrelevant,indicatewhetherthereare(in-process)controlswhichmay compromisebatch-to-batchconsistencyandafixedefficacyprofile(especially mustbeconsideredfornegativeopinions)orsourcesofuncertaintyregarding stability,characterization,manufacturingmethod.
Hypotheticalexample[mustbedeletedfromthefinalreport] 2.Positiveeffects HRforOS(secondaryendpoint)was0,53infavorofPOM+LoDEXv.HiDEX(95%GA: 0,37–0,74;logrankPvalue<0,001).Medianprogression-freesurvival(primaryendpoint) was8.0weeksagainst15.7weeksforPOM+LoDEXandHiDEX(HR=0.45;95% CI=0.35–0.59;logrankP<0.001). 3.Uncertaintiesandlimitationsregardingpositiveeffects

11 MedianOScannotbeevaluatedyetandforahighportionofpatientssurvivalperiodwas notknownduringanalysis(75%and62%ofrandomizedpatients,respectively),therefore therearelimitationsformaturityofdata. 4.Negativeeffects “NegativeEffect”Definition

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Thissectionisintendedtoexplainkeynegativeeffects(generallyreferredtoasboth knownandunknown“risks”,“harms”,“hazards”)causingconcernduetoitsundesirable effectsattributabletoproductoronpatienthealthorpublichealthwithfactualterms. Negativeeffectsarenotonlylimitedtoclinicalsafetyendpoints.Forexample,negative effectsmayalsobeefficacylossatsomesignificantefficacyendpointsorotherundesirable effects.Inaddition,considerpharmacokineticandpharmacodynamicinteractions,specific non-clinicalandqualityaspects,especiallysignificantnegativeeffectsofGenetically ModifiedOrganisms(GDOs)intermsofpublichealthandenvironment,abuseandmisuse potentialwhichcanbedescribedasnegativeeffects. Whatare“Key”NegativeEffects? Oneimportantpointtotakeintoconsiderationwhendecidingwhichoftheeffectswill beexplainedistoavoidexcessivedetails.Inpractice,thiscanusuallybeachievedby includingmajornegativeeffectsthatareconsistentwithsignificant(andinsomecases potential)identifiedrisksinRiskManagementPlan. Trytoavoidlonglistsofindividualsideeffects.Ifpossible,trytogroupthemaccording toresults,forexample,groupallsideeffectsbasedontheirseverityusingagreeduponcriteria. Rememberthatthemostsignificanteffectsarenotnecessarilythemostcommonones. Usesubtitles(orboldfont)toenhanceunderstandabilitywherenecessary.Donotrepeatthe resultscomprehensively,theyareexplainedindetailelsewhereinthereport. Howarenegativeeffectsdescribed? Oncekeynegativeeffectsareidentified,theymustbeexplainedusingfreetext.Below isalistofitemsthatneedtobeconsideredonacasebycasebasisinordertoexplainkey negativeeffectswithquantitativeandqualitativeterms.Allaspectsneednotbeexplainedfor eachnegativeeffect,onlythemostrelevantonesmustbeexplained. Quantitatively Summarizethe mostsignificant negativeeffect accordingtothe nextcriteria Duration,severity,frequencyandreversibility (associatedabsoluteoutcomevs.benchmarkdrug,associatedabsolute outcomevs.thosereceivingstandardtreatmentotherthanthose receivingthedrug) Relativesafetycomparedtostandardcare,drugsfromthesame pharmacologicalclass Treatmentdiscontinuation Importantsubgroups(suchasage,gender,ethnicity,organfunction, diseaseseverity) Qualitatively Mechanismofaction

12 Describethe negativeeffect accordingtothe nextcriteria: Relativesafetycomparedtotoxicityprofileofstandardcareordrugs fromthesamepharmacologicalclass Typeofeffect(subjective,idiosyncratic,laboratory...) Dose-responserelationship Severityoftreateddisease Isthisadversereactionanatypicaladversereactionfordrugsofsame class? Abilitytoestimate,monitor,treatandpreventrisk Publichealthassociatedwithnegativeeffectandenvironmentalrisk Indicatekeynegativeeffectsandbrieflydescribethem(e.g.incidence,severity, duration,reversibility,dose-responserelationship;incidenceofadverseeventsthat leadtodiscontinuationofmedicationand/orhospitalization). Considerdefiningkeynegativeeffectsinimportantsub-groups(e.g.;age,gender, ethnicity,organfunction,diseaseseverityandgeneticpolymorphism). Comments Trytobeclearandunderstandable(forexample,Xtreatmentwasassociatedwith toxicityclass1-2in95%ofpatients). Avoidmakingcommentorjudgment(e.g.lowdegreetoxicitywasimportantforX treatment). Thissectionmustbeconsistentwith1.6EffectsTable,Section1.4Significant IdentifiedRisks,riskmanagementplanandnegativeeffectsdescribedinSmPC Section4.8.Nonewresultwhichisnotexplainedindetailinprevioussections (usuallyundertheheadingClinicalAspects)mustbeprovidedhere. Unlessnewsignificantresultsaresent,thissectionneednotbeupdatedduring procedure. 5.Uncertaintiesandlimitationsregardingnegativeeffects Describesignificantuncertaintiesandlimitationsaboutnegativeeffectsthatare

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importantforbenefit/riskbalance.
Thissectionmustbeupdatedduringprocess.Ifthereisnouncertaintyandlimitation leftthathasaneffectonbenefit/riskbalance,thefollowingexpressionmustbewritten inthissection:“Thereisnouncertaintyandlimitationthathasaneffectonbenefit/risk balance(seeSection1.7.Benefit-riskevaluationanddiscussion)”. Comments Focusonsignificantuncertaintiesthathaveaneffectintermsofbenefit/risk evaluation.Explanationmustbetruthful.
Relianceonthedecision,theeffectofuncertaintiesonbenefit/riskbalanceand judgmentonanyaction(e.g.indicationrestriction)mustbeexplainedinSection 1.7.1ImportanceofpositiveandnegativeeffectsandSection1.7.2.Benefitand RiskBalance.
Minoruncertaintiesthathavenoeffectonbenefit/riskevaluationandthatcanbe easilymanaged(e.g.productinformation)shallbeexplainedindetailinprevious sections.
Thereisnoneedtorepeatherethediscussionsonclinicalefficacyandclinical safety.Ifstillconsideredworthmentioning,brieflymentionuncertaintyandhowit willbemanaged.

13 Belowisanon-exhaustivelistofcommonuncertaintysourcesrelatedtonegativeeffects. Definesufficiency/limitsofdatabase accordingtothenextcriteria. Samplesize StudyDesign Follow-upperiod Sizeofkey(sub)populations Importantqualityissues Non-clinicalsafetyresults Dosing Typeofcontrolgroup Likelihoodofgeneralizationtoclinicalpractice Missingdata Treatmentdiscontinuation Adequacyoffollow-up 6.EffectTable
EffectTablemustbeusedforthefirst-timeadministrationofnewactivesubstances (exceptforbiosimilars)andextensionofindications.
EffectsTablemustbekeptup-to-datethroughouttheevaluation.Intheend,itmustbe incorporatedinGeneralEvaluationReport.Iftherearechangesintherequestedindication duringevaluation,EffectTablemustreflectthosechanges.FinalEffectTablemustreflect finalindicationandonlymentiondataanduncertaintiesrelatingtoapprovedtargetpopulation.
Effectcolumn:Theabbreviationorveryshortidentifieroftheeffectisgivenplace (e.g.RRforresponserate;ReportingRate).Theobjectiveistoprovideanidentifier whichreaderswhoareexpertsintheirfieldswouldbefamiliarwith.SinceEffect Tableservescompletionofnarrationinbenefit/riskbalancesectionofevaluation report,itmustincludepositiveandnegativekeyeffectsmentionedinthissectionof evaluationreport,includinguncertainties.Wherepossible,degreeofstatistical uncertaintymustbemeasuredbyprovidingstandarderrorsorconfidenceintervals.
Explanationcolumn:Averyshortdescriptionofeffectisgiven[forexample;ifthe effectisoverallsurvival(OS),thismaybe“survivalperiodfromrandomizationto deathirrespectiveofreason”].Makesurethatcomplexabbreviationsorspecifictools areexplained(theobjectiveistoenablereaderwhoisnotfullyfamiliarwith therapeuticareatounderstandwhattheeffectisswiftly).Ifrequired,further explanationisincludedinfootnotes(e.g.withreferencetoliterature).
Unitcolumn:Unitofmeasureforeacheffectisindicated(e.g.mmHg,months,%).
Theobjectiveistoprovideaclearexplanationofestimatesinthenextcolumns.
Treatmentgroupcolumns:Summarizebasiceffectsofindexdrugthatsteers benefit/riskdiscussion.Theobjectiveistoprovideaclearandconcisecomparative presentation.Separatecolumnsareincludedforeachtreatmentgroupforwhich adequateclinicaldataareavailable(forexample,placebo,differentdosesofnew substance,activecontrols).Ifrequired,reference(s)tospecificstudieswhichexplain theeffectcanbeincludedinfootnotes.Columntitles(“Treatment”,“Control”)canbe replacedwiththenamesorabbreviationsofdifferentdrugs(andcolumnscanbeadded asappropriate).Ifexternal(datecontrols)areused,theymustbeenteredinthe appropriatecolumn.

14 StrengthofEvidence/Uncertaintiescolumn:Inthissection,strengthofevidenceand anysignificantuncertaintyorlimitationforeacheffectisbrieflyexplained.The objectiveistomentionthestrengthsandweaknessesdescribedaboveatleastinbrief

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inordertoavoidmisunderstandingoftreatmentestimates.
Referencescolumn(optional):Thiscolumnhasmorethanoneobjective.Especially foreffectsforwhichcomplexissuesarise,thiscolumnprovidesreferencetothe relatedpartofthetext,forexample;thenumberofbasicobjectionsorotherconcerns, riskminimizationmeasure,relatedpartofSmPC.Thisisimportantforavoidanceof oversimplificationifthetableisreadoutsidethecontextofevaluationreport.This columnmayalsobeusedtorefertocertaindatasources(forexample,abbreviationof astudyincaseofpresenceofevidenceobtainedfrommultiplestudiesorpublications).
Table1.EffectTable[pleaseinsertthenameandindicationofdrug]<(datacut-offdate.....)> Effect BriefdescriptionUnit Treatmen t ControlUncertainties/Strength ofEvidence References PositiveEffects NegativeEffects Comments
EffectTableisbasedcompletelyonevaluationofkeypositiveandnegativeeffects explainedinprevioussections,strengthofevidence,limitationsanduncertainties. Therefore,thereisnonewelementthatisnotexplainedelsewhereinthetable. EnsureconsistencybetweentheTableandpositive,negativeeffectsdescribed aboveandthestrengthofevidence,uncertaintiesandlimitations. Eventhoughcertainnumericaldetailscanonlybeseeninthetable,EffectsTable mustnotreplacetextualexplanationofeffectsintherelatedsections.
HowAreMultipleStudiesDescribed?
EffectsTablemustprovidedatathatareasintegrated(“combined”)aspossible wherevermeaningfultofacilitatecommunication.Repeatofdataobtainedfromindividual studiesthataddresscompletelythesamequestionsisusuallylessinformational. Incaseofmorethanonestudy,keystudiesthatsteertheevidenceofbenefit/risk discussionmustbefocusedon.Ifrequired,reference(s)tospecificstudieswhichexplainthe effectscanbeincludedinReferencecolumnorthefootnotes.Effectsobtainedfrom supportingstudiescanbesimilarlydefinedunderstrengthofevidenceandtheyneednotbe indicatedasseparatepointestimates.
Whenstudiesarecomparablewithrespecttodesignandsignificance,ifitisnotpossible toprovidesomecollectivestatistics(forexample,combineddataormeta-analysis) informationobtainedfrommultiplestudiesmustbeshownaseffectpredictionintervals(for example,ifaveragevariationofthreeclinicalstudiescomparedtobeginningis1.1,1.3and 1.4,itcanbeshownasanintervalbetween1.1and1.4).
15 Hypotheticalexample[mustbedeletedfromthefinalreport]
BelowisanexampleofhypotheticalEffectTablebasedonselectionofpositiveandnegativeeffects presentedinthenarrationofbenefit/risksectioninEPAREMEA/H/C/002445publishedon28 November2012.
Table1.HypotheticalETforlixisenatidefortreatmentofadultswithtype2diabetesinordertoensure glycemiccontrolinpatientswhoarenotsufficientlycontrolledbyoralantidiabetics(datacutoffpoint 2-10April2011). Effect DescriptionU LIX PBO EXE Uncertainties/Stren gthofEvidence Reference PositiveEffects HbA1c Average deviationof HbA1cfrom thebasic level % -0.79 (-0.95,-0.63) -0.19 (-0.43,0.05) Effect of Lixisenatidewas moreapparentin Asianpatients compared to Caucasian patients.Lower effect in Caucasians is partlyexplained byagreatplacebo effectespecially in some geographical regions. (1) -0.83 (-0.91,-0.75) -0.39 (-0.51,0.28) (2) -0.79 (-0.89,-0.68) -0.96 (-1.06,-0.86) (3) -0.82 (-0.91,-0.73) -0.10 (-0.24,0.04) (4) BodyweightAverage deviationof bodyweight fromthe basiclevel kg -1.94 (-2.40,-1.48) -1.98 (-2.65,-1.31) (1) -2.12 (-2.42,-1.82) -1.64 (-2.07,-1.20) (2),(3) -2.19 (-2.47,-1.91) -3.98 (-4.43,- 3.53) (3) -2.87 (-3.26,-2.48) -0.93 (-1.39,-0.47) NegativeEffects Nausea Nausea incidence % 26.9 7.3 Around70-80% of patients sufferingfrom nausea or vomitinghave completed treatment. (5) Vomiting Vomiting incidence % 11.4 2.7 (5) Diarrhea Diarrhea incidence % 11.1 8.0 (5) HypoglycemiaHypoglycemi aincidence % 1.7 1.6 Hypoglycemia basicallyoccurs whenlixisenatide treatment is combinedwith sulphonylurea. (1) 7.0 4.8 (2) 2.5 7.9 (3) 22.7 15.2 (4) ISRs ISRs incidence % 5.3 1.9 (5) Allergic reactions Incidenceof

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allergic reactions % 0.4 <0.1 (5) Palpitation Palpitation incidence % 1.5 0.7 (5) Tachycardia Tachycardia incidence % 0.7 <0.1 (5)

16 , Comparedtoplacebo, slightly increasing palpitation and tachycardiaincidence indicatesthetendencyof lixisenatidetoincrease heartrate.However,total numberofCVevents,did notdiffersignificantly betweenlixisenatideand placebo(HR1.25,95% confidenceinterval0.67- 2.35). Abbreviations:U:Unit,LIX:lixisenatide,PBO:placebo,EXE:exenatide,kg:kilogram,ISRs:injection-siterea ctions, Hypo:Hypoglycemia. 7.Benefit/riskevaluationanddiscussion 7.1.Significanceofpositiveandnegativeeffects

Discussthesignificance(typicallyintermsofclinicalcompliance)ofpositiveeffects (asdescribedabove)observedinrelationtotargetdiseaseandtargetpopulationand unmetmedicalneed.Whatarethemostsignificanteffectsinthisdiseasegivenas objectivesoftreatment?Whichmagnitudeofeffectcanbeacceptedsignificantand howareobservedeffectscomparedwiththis?

Ifeffectsaremeasuredwithrespecttosurrogateendpoint(s),discusswhatthe expectedresultcouldbeanditsimportancewithrespecttorealclinicalendpoint(s).

Discusstheeffectofuncertaintiesandlimitationsofdata(asdescribedabove)onthe significanceofpositiveeffects.Forexample,ifrealmagnitudeoftreatmenteffectis potentiallysmallerthanpredictedduetodefineduncertainties,howdoesthisaffectthe clinicalcomplianceoftheeffect?

Discusswhethernegativeeffectscausediscontinuationoftreatmentwithrespectto theirseverity,reversibility.Howdonegativeeffectsaffectthelifequalityofpatient?

Discusstheeffectofuncertaintiesandlimitationsofdata(asdescribedabove)onthe significanceofnegativeeffects.

Ifappropriate,discusswhethersignificanceofpositiveandnegativeeffectsdiffer betweensubgroupsofproposedtargetpopulation. Comments

Whilepreviussectionsprimarilyfocusedondefinitionofdata,thissection generallyfocusesoninterpretationofdatabymakingjudgmentaboutthe significanceofobserveddataanduncertaintiesandlimitationsofdata.

Explanationsrelatingtoquantitativedataandstudiesneednotberepeatedinthis section.Instead,makejudgmenttointerprettheeffectsofuncertaintiesand limitationsofdataexplainedinpreviussectionsandthesignificanceofthose effects.

Thissectionisintendedforexplainingtheeffectsofuncertaintiesdescribedaboveand thesignificanceoftheseeffectsbymakingjudgment.Whenbenefit/riskbalanceisnotclear, thissectionwillbeatthecenteroftheentirebenefit/riskevaluation.Therefore,thissection mustbewrittencarefullyintendingtoexplainandjustifyjudgmentsasfaraspossible.

17 Ageneralapproachfordefiningjudgmentsistocomparesignificanceofdifferent effectswitheachother.Forexample,whereincreasingoverallsurvivalisthemostimportant outcome,extensionofoverallsurvivalfor1monthoralongerperiodisclinicallysignificant whileextensionofthesamefor2to4monthsisclinicallyverysignificant.

Ifapplicable,discussthesignificanceofeffectsincertainsubgroups(forexample, significanceofsurvivalperiodinasymptomaticcasemaybelowerinayoungerpopulation comparedtoelderlyindividuals). Descriptionoftheeffectofuncertaintiesandlimitations

Inthissection,itisimportanttoexplaintheeffectofuncertaintiesandlimitationson judgments.Forexample,ahighuncertaintywithrespecttosignificantpositiveeffectsay usuallydecreasetheirvalue.Uncertaintyabouttheharmlessnessofdrugmayaffectthe importanceattachedtosafetymattersaswell.Inordertoeliminatepresenceofsignificant uncertainty,forexample,itmaybeimportanttoemphasize“strengthofevidence”alsoby explainingthatthestudyismethodologicallystrongandthatresultsareconsistentamong statisticalanalyses,importantsubgroups,studies,preciseandimpartialestimatesorvery importantp-values.

Inpreviousevaluations,becauseofmanyunresolvedissue,itmightbedifficulttoassess

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thestrengthofevidence,therefore,thefocuswouldbeonshortcomingsandtheemerging uncertainty.Astheevaluationmatures,keyresults,strengthofevidenceandunresolved uncertaintieswillhavebeendefinedandconstitutethebasisfortheconclusionson benefit/riskbalance.

7.2.Balanceofbenefitsandrisks

Definetradeoffs.Consideringthecurrentinformationstatus,uncertaintiesand limitations,dopositiveeffectsoutweighnegativeeffects?Explain.Ifpossible,discuss necessaryactionstohandleimportantlimitationsoruncertaintiessuchaswarningsin productinformation,indicationrestriction,contraindication,needforfuturestudies(if notpreviouslydescribedabove). Comments

Unlessrequiredtoexplaintheeffectofremaininguncertaintiesthathaveaneffect ontheconfidenceinbenefit/riskbalanceand,anylimitationindetail,thissection mayberelativelyshort.Inthefirststagesofevaluationprocess,expressionssuchas "benefit/riskbalanceiscurrentlynegative"or"benefit/riskbalanceiscurrentlynot identified"maythemostappropriateoptions.

Explainthereasonforproposedindication(restrictionorgeneralizationbasedon studydata;greatdeviationsfrompreviousexpressionsofindicationswithinthe sametherapeuticarea).Placeanddurationoftreatmentmayalsorequirefurther discussion.

Essentially,thedutyofcompletingtrade-offsconsistsofstatingtheintentionforgiving upachievingatargetinexchangeforreachinganother(forexample,iftheobjectivesof treatmentaretominimizetoxicityandincreaseefficacy,thenthequestioncanbeasfollows: isachievementofminimizationoftoxicityworthgivingupincreasingefficacy?).

Thisevaluationwouldrequiresubjectivejudgments,however,feedbackfromexperts (fromtheliteratureorexpertmeetings)andpatientsaswellaspreviousdecisions,ifany, takenforotherproductsintheareamustbetakenintoconsiderationandexplained.

18 Thereareafewapproachestohowtheweightoftrade-offsforthesakeofbenefit/risk evaluationwillbedefined.A"descriptive"approachincludingopenideasaboutsignificance ofdifferenteffectsandhowtrade-offsareweightedwouldgenerallybeappropriate.

"Descriptive"approach

Thisapproachusuallystartswithdescribingsignificanceofdifferenteffectsobserved. Whendifferenteffectsarelistedbasedontheirsignificance,valuetradeoffscanbedescribed acrosseffectshierarchybyindicatingwhatwouldbetheacceptablemaximumlosswith respecttoaparticulareffectinordertoincreasethelikelihoodofmakingagainonthenext mostsignificanteffect.Thesetradeoffsarethenevaluatedaltogetherinordertoidentify balanceofpositiveandnegativeeffects.Thesetradeoffsarethenevaluatedaltogetherinorder toidentifybalanceofpositiveandnegativeeffects. "Basic"approach

Amoreessentialapproachwhichcanbeareasonableoptionwherehighprecisionisnot requiredfordefiningtheweightoftradeoffsortradeoffisapparentistodefinetheweight giventoeacheffectusingasharedlanguage(Forexample;irrelevant,reasonable,slightly relevant,quiterelevantforclinicalcompliance).Inthesecases,benefitsandriskscanbe weightedintuitivelyandonlygeneralexpressionsmustbeprovided(e.g."benefit/riskbalance isclearlypositive"). "Quantitative"approaches

Thesemethodsuseaclearrelativeweightoftradeoffswhicharecombinedlateron usingdifferenttypesofanalysis(asin"descriptive"approachdescribedabove).Currentlyan optimalsinglemethodhasnotemergedyetandfurtherexperienceisneededtoseewhich methodsworkbestandinwhichcircumstancestheywork.Ifanyquantitativemethodis consideredtobeusefulforbenefit/riskevaluation,methodsmustbeexplainedandresults mustbesummarizedanddiscussedinthissection. Specialcircumstances

Therearecircumstancesinbenefit/riskevaluationwheretradeoffsneednotbecertainly weighted.Forexample,whentherearecomparativestudiesagainstawell-designedand acceptedgoldstandard,ifbothefficacyandsafetyaresimilarorsuperiortogoldstandardin termsofallsignificantresults,thereisnoneedforanytradeoff(benefit/riskbalancewillbe

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positivebydefinition). Verificationoftherapeuticindication
Carefuljustificationofevidenceandhypothesesisofcriticalimportanceespeciallyif
therapeuticindicationisrestrictedorgeneralizedwithrespecttopatient(e.g.benefit/riskwith
apopulationlimitedtoasubgrouporunlimitedpopulationbasedonkeyclinicaltrials),
disease(e.g.benefit/risklimitedtoahighrisksubgrouporunlimitedbenefit/riskbasedonkey
clinicaltrials)ortreatmentcharacteristics(e.g.primarycare-secondarycare;monotherapy-
combinationbasedonkeyclinicaltrials).
Hypotheticalexample(withexplanation)[mustbedeletedfromthefinalreport]
7.1.Significanceofpositiveandnegativeeffects
[Explainitsimportance:]Themostimporanteffectsobserved(byorderofsignificance)are
a4-monthextensioninoverallsurvival,10%increaseintoxicityclass3-4and10%increase
inchronictoxicityclass3-4.
[Justifywhythesareimportant]2-monthimprovementinoverallsurvivalisconsidered
clinicallysignificantminimaleffectworthdetection.Itisacceptedthatdifferenceswithin
therangeof3to5monthsisofgreatimportanceforpatients.Anythingover6monthswill
beacceptedadramaticaleffect.
19 [Strengthofevidence:]Efficacyevidencewasconsideredstatisticallyconvincingandthereis
agoodfitbetweenefficacyendpoints.
[Effectofuncertainty:]Evenifpopulationislesssuitableandthebenefitisabitlowerin
clinicalpractice,bigdifferencesarenotexpected.
Traditionally20%toxicityclass3-4isconsideredacceptablefortreatmentofprogressive
cancerwith6-monthmediansurvivalandwithoutanyavailableestablishedtreatment,
providedthatanextensionof2monthsormoreisavailableinoverallsurvival.Inprinciple,
worseningoftoxicityclass3-4over40-50%isconsideredaverypooroutcomeand
anythingaboveitispracticallyunacceptable.
[Effectofuncertainty:]Eventhoughtoxicityisabithigherinclinicalpractice,thisisnot
expectedtochangetheresults.Trainingmaterialandpost-marketingsurveillanceisapplied
tominimizethispotentialrisk(seeRMP).
Inthisdiseasetoxicityclass1-2incidenceisgenerally40%forsimilaragents.Higher
incidenceshavebeenobservedandareimportantforsomepatientsinclinicalterms.Ifthis
occursinagreatmajorityofpatients(75%orabove),this,evenifnotconsidered
unacceptablepreviously,wouldbeconsideredapoorresultthatrequiresacareful evaluation.
7.2.Balanceofpositiveandnegativeeffects Using“Descriptive”approach
[Increasetradeoffsbetweentoxicityclass3-4andsurvival:]Consideringpoorprognosis
andlackofcurrenttreatments,thistoxicitymaybepossiblyaccepted,however,atleast
three-montheffectonoverallsurvivalmustbeobserved.Itseffectonoverallsurvival
observedinpivotalstudieswasa4-monthextension.Consideringpoorlong-termprognosis,
4-monthimprovementoveractivecontrolisconsideredmoreimportantthan10%increase
intoxicityandtoxicitywouldbepossiblypositiveevenincaseofanincreaseupto20%.
Therefore,increaseintoxicityclearlyoutweighssignificantincreaseinoverallsurvival.
[Increasetradeoffsbetweentoxicityclass1-2andtoxicityclass3-4:]Observedchronic
toxicityclass1-2washigherandaround50%comparedto40%toxicityforstandard
treatment.Whencomparedwitha10%increaseintoxicityclass3-4,itissupposedthat
10%increaseintoxicityclass1-2islessconcerning.Thesewouldcauseasimilarconcern
onlyiftheyaffectagreatmajorityofpatients(e.g.75%orabove)andaresubstantially irreversible.
[Sumuptheweightsintuitivelyandconcludethat:]4-monthextensioninoverallsurvival
outweighs10%increaseintoxicityclass3-4andchronictoxicityclass3-4.Withtheeffecton
overallsurvival,muchhighertoxicitysuchasaworseningaround20%inclass3-4ora
worseningaround75%intoxicityclass3-4canevenbeconsideredacceptable.Whenall
positiveandnegativeeffectsareconsidered,benefit/riskbalanceisconsideredpositive.
•Using“Basic”approach

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[Sumuptheweightsintuitivelyandconcludethat:]4-monthextensioninobservedmedian overallsurvivalwasconsideredtobeclinicallyverysignificant,10%increaseintoxicityclass 3-4wasconsideredtohavelimitedclinicalsignificanceand10%increaseintoxicityclass1-2 wasconsideredtobeclinicallyinsignificant.Whenallpositiveandnegativeeffectsare considered,benefit/riskbalanceisconsideredpositive.

20 7.3.Additionalissuesregardingbenefit/riskbalance Discussregulatoryoptionsforapproval(standardregistration,conditionalregistration, registrationinexceptionalcases).Ifany,explaindetailedreasons(scope,requirements) forconditionalapprovalorapprovalinexceptionalcases.Withintheframeworkofthis discussion,eachofthefollowingcriteriamustbetakenintoconsiderationanddiscussed whenevaluatingwhetherclinicaldatasubmittedformarketingauthorizationapplication willbeconsideredexhaustive: 1.Qualityofevidence(includingfeasibilityassessments) a.Strengthsandweaknessesinmethodologicaltermsofclinicalprogramfocusing onpivotalstudy b.Reliability/referentialityofeffectandsafetyfindings(bothefficacyandsafety) c.ConductofstudyandGCP(GCPfindingsleadingtoprohibitoryresults?) d.Inclusionby“evidencequality”decisionoffeasibilitymatters e.Basedonepidemiologicalissues,whichdata/studydesigns(e.g.randomized controlledclinicaltrial)canbeconsideredreasonable? f.Aretherelimitationsduetorarenessofdisease? g.Israndomizationapplicable? 2.Efficacy:Precisionofeffectmagnitude a.Quantitativemeasurementofeffectmagnitude/efficacysensitively b.Biostatisticalissues 3.Efficacy:clinicalsignificanceofendpoint a.clinicalendpointvs.biomarker b.Clinicalendpointvs.endpointcontainingmechanicalconnectionopento clinicaloutcomemeasurement Biomarkermayalsoreflectpharmacologicalactivity,however,itmaynotindicatea clinicallyrelevantoutcome. 4.Efficacy:efficacyperiod a.Diseaseformationandmaturityofefficacyfollow-upwithinthecontextof treatmentobjective 5.Safety:Exposure a.Forexample;about,forexample,mechanismofactionoftheproductand specificcharacteristicsofdiseasewithinthecontextofnumberofpatients, thoseexpected,tounderstandsafetyprofile. b.Wereanyadverseeventsidentifiedthatfallinspecialareaofinterest? 6.Safety:Follow-upperiod a.Identificationofacute,medium,longtermtoxicities b.Maturityanddetaillevelofffollow-upofadverseevent/adversedrugreaction 7.Targetpopulationvs.studypopulation a.Hasstudypopulationcoveredtargetpopulation(e.g.age,thestageof indication)? b.Ifextrapolationisused,isconfirmationofdatarequired(afterregistration)?

21 c.Isefficacysteeredbyasub-populationthatdoesnotrepresenttargetpopulation? 8.Pharmacologicaljustification a.Strongpharmacologicaljustification,forexample;monogenicdiseasetreated bygenetherapyofdefectivegeneorgeneproductorenzymereplacement therapy 9.Usualcourseofdisease a.Wasadditionalinformationthathelpsinterpretationofdataadded/incorporated? Basedontheforegoing,clinicaldataareconsidered<not>exhaustive. Discusswhatisrecommendedtoincreaseinformation(forexample,ifnotexplained inprevioussections,proposedfurtherstudies). Iftherearenoadditionalmattersapplicabletothisbenefit/riskevaluation,thissection canbecompletedwith“NotApplicable”. Comments Donotrepeatprevioussections.Inparticular,donotusethissectiontore-express significantbenefits,risks,uncertaintiesandtheireffectsondecisions;theymust havebeenexplainedinprevioussections. Considerdiscussingconsistencyofthisbenefit/riskevaluationwithsimilar evaluationsinthepastandexplaindifferences.

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Isbenefit/riskbalanceisexpectedtobethesamethroughouttreatmentperiod?

22 1.<BiosimilarityAssessment> 1.1.Comparabilitystudyandclaimedindications Staterequestedindicationsandwhethertheapplicantrequestsallorpartofthe approvedindicationsofthecomparatorproduct.
Summarize(inafewsentences)mainaspectsofcomparabilitystudyconducted (includinganalytical,functional(e.g.biologicalactivity),non-clinicalandclinicaldata)and whetherdevelopmentplancomplieswithrelevantregulationsandguidelines.
1.2.Resultssupportingbiosimilarity
Describetheresultsofcomparabilitystudywithrespecttoquality,non-clinicaland clinicalPK/PD,efficacy,safetyandimmunogenicitydatasupportingbiosimilarityclaim.
1.3.Uncertaintiesandlimitationsregardingbiosimilarity
Describeconcerns/uncertaintiesregardingbiosimilarityduetodifferencesobservedin analytical,functional,non-clinicaland/orclinicalaspects(e.g.comparabilitymargins notmet,differencesinreactionsrelatedtoimmunogenicityorinfusion;newdrug reactionsorsignalswhencomparedwiththecomparatorproduct)orduetomissing relevantdata. Thissectionmustbeupdatedduringprocess.Iftherearenouncertaintiesand limitationsleftthathaveeffectonbiosimilarityconclusion,writeinthissection: “Thereisnouncertaintyandlimitationthathasaneffectonbiosimilarityconclusion.”
1.4.Discussiononbiosimilarity
Explaintheimportanceofdatathatsupportorquestionsimilarityintermsofefficacy andsafety. Discusstheeffectofanyuncertaintyorissuewiththecomparabilitystudywithrespect toefficacyandsafety,e.g.Areobserveddifferencesappropriateandexpectedtohavean effectonefficacyand/orsafety/immunogenicityofbiosimilarcandidateversuscomparator?
Explainwhethercomparabilitystudywassuccessfulandprovidedsimilarityto referencemedicinalproductintermsofqualitycharacteristics,biologicalactivity,safetyand efficacy.Discussthestrengthofevidence.
Successfulcomparabilitystudies(forexample,forbiosimilarapplications)donot requiretradeoffs(seegeneralguideline),however,comparabilitystudyneedstobeconfirmed withrespecttowhetheritwassuccessfulaccordingtotraditionalscientificstandardsfor reaching“similarity”conclusionintermsofefficacyandsafety.
Ifapplicable,discussactionstoaddressimportantlimitationsoruncertainties(e.g.post-marketingstudytoensureamoreprecisepredictionofanidentifiedrisk).
1.5.Safetyandefficacyextrapolation
Whenclinicalcomparabilityisdemonstratedforanindicationandiftheapplicantis applyingformorethanoneindicationsofthecomparatorproduct,likelihoodofextrapolation ofsimilarsafetyandefficacyconclusiontootherindicationsmustbediscussedinthissection consideringthefollowing: Sumofdataobtainedfromcomparabilitystudy.

23 Discusswhetherappropriatequality,non-clinical,clinicaldata,mechanismofaction, andreceptorsmediatingtheeffectsupportextrapolationandwhethercomparability conclusioncanbereachedbetweenbiosimilarcandidateandthecomparatorforall claimedindicationsofthecomparatorproduct. 1.6.Additionalissues
Discusswhatisrecommendedtoincreaseinformation(forexample,ifnotexplained inprevioussections,proposedfurtherstudies).
Iftherearenoadditionalissuesapplied,thissectioncanbecompletedwith“Not Applicable”.
Discussmisuseandoff-labelusepotential(forexample,intheeventthatall indicationsoradministrationwaysofthecomparatorproductarenotapprovedfor biosimilar).
1.7.Conclusionsaboutbiosimilarityandbenefit/riskbalance
Basedonreviewofthedatasent,<productname>isconsidered<not>biosimilarto <referenceproduct>.Therefore,there<is><not>acomparablebenefit/riskbalancewith thecomparatorproduct.

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