MODÜL III PERIYODIK YARAR RISK DEĞERLENDIRME RAPORU_EN

GuidelinesonGood Pharmacovigilance Practices(GVP) ModuleIII-Periodic Benefit/RiskEvaluationReport (revised1stedition) Dateoffirstissue 26.09.2014 Dateofrevised1stedition 25.08.2022 TURKISHMEDICINESANDMEDICALDEVICESAGENCY 25.08.2022

1 Tableofcontents CHAPTERI Introduction

TABLE OF CONTENTS

1.1.Introduction

CHAPTERII StructuresandProcesses

2.1.ObjectiveofPBRER

2.2.Principlesfortheevaluationofthebenefit/riskbalancewithinPBRERsandscopeofthe **informationtobeincluded**

2.3.PrinciplesforthepreparationofPBRERs

2.4.Referenceinformation

2.5.FormatandcontentsofthePBRER

2.5.1.PBRERsection“Introduction”

2.5.2.PBRERsection“Worldwidemarketingauthorisationstatus"

2.5.3.PBRERsection“Actionstakenin thereportingintervalforsafetyreasons"

2.5.4.PBRERsection“Changestoreferencesafetyinformation"

2.5.5.PBRERsection“Estimatedexposureandusepatterns”

2.5.5.1.PBRERsub-section“Cumulativeexposureinclinicaltrials”

2.5.5.2.PBRERsub-section“Post-marketingcumulativeandreportingintervalpatient **exposure”**

2.5.6.PBRERsection“Datainsummarytabulations”

2.5.6.1.PBRERsub-section“Referenceinformation”

2.5.6.2.PBRERsub-section“Cumulativesummarytabulationsofseriousadverseevents **fromclinicaltrials”**

2.5.6.3.PBRERsub-section“Cumulativeandreportingintervalsummarytabulations **frompost-marketingdatasources”**

2.5.7.PBRERsection“Summariesofsignificantfindingsfromclinicaltrialsduringthe **reportinginterval”**

2.5.7.1.PBRERsub-section“Completedclinicaltrials”

2.5.7.2.PBRERsub-section“Ongoingclinicaltrials”

2.5.7.3.PBRERsub-section“Longtermfollow-up”

2.5.7.4.PBRERsub-section“Othertherapeuticuseofmedicinalproduct”

2.5.7.5.PBRERsub-section“Newsafetydatarelatedtofixedcombinationtherapies”

2.5.8.PBRERsection“Findingsfromnon-interventionalstudies”

2.5.9.PBRERsection“Informationfromotherclinicaltrialsandsources”

2.5.9.1PBRERsub-section“OtherClinicalTrials”

2.5.9.2PBRERsub-section“Medicationerrors”

2.5.10.PBRERsection“Non-clinicaldata”

2.5.11.PBRERsection“Literature”

2.5.12.PBRERsection“Otherperiodicreports”

2.5.13.PBRERsection“Lackofefficacyidentifiedincontrolledclinicaltrials”

2.5.14.PBRERsection“Late-breakinginformation”

2.5.15.PBRERsection“Overviewofnew,ongoingorclosedsignals”

2.5.16.PBRERsection“Signalandriskevaluation”

2.5.16.1.PBRERsub-section“Summaryofsafetyconcerns”

2.5.16.2.PBRERsub-section“Signalevaluation”

2.5.16.3.PBRERsub-section“Evaluationofrisksandnewinformation”

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

2.5.16.4.PBRERsub-section“Characterisationofrisks”
2.5.16.5.PBRERsub-section:“Effectivenessofriskminimisationmeasures(ifapplicable)”22
2.5.17.PBRERsection“Benefitevaluation”
2.5.17.1.PBRERsub-section“Importantbaselineefficacyinformationidentifiedduring **clinicaltrialsandinthepost-marketingperiod”**
2.5.17.2.PBRERsub-section“Importantbaselineefficacyinformationnewlyidentified **duringclinicaltrialsandinthepost-marketingperiod”**
2.5.17.3.PBRERsub-section“Characterisationofbenefits”
2.5.18.PBRERsection“Integratedbenefit-riskanalysisforauthorisedindications”
2.5.18.1.PBRERsub-section“Benefit-riskcontext(medicalneedandimportant **alternatives)”**
2.5.18.2.PBRERsub-section“Benefit/riskanalysisevaluation”
2.5.19.PBRERsection“Conclusionsandactions”
2.5.20.AppendicestothePBRER
2.5.21.MappingsignalsandriskstoPBRERsections/sub-sections
2.6.QualitysystemsforPBRERsatthelevelofmarketingauthorisationholders
2.7.TrainingofstaffmembersrelatedtothePBRERpreparationprocess
SECTIONIII Operationofbenefit/riskevaluationprocess
3.1.Generalprinciplesforthepreparationandsubmissionof PBRERs
3.2.PreparationandsubmissionscheduleofPBRERs
3.3.RelationshipbetweenPBRERandriskmanagementplan
3.3.1.PBRERandRMP–commonmodules
3.4.EU-specificrequirements
3.4.1.PBREREUregionalappendix,sub-section“Proposedproductinformation”
3.4.2.PBREREUregionalappendix,sub-section“Proposedadditionalpharmacovigilance **andriskminimisationactivities”**
3.4.3.PBREREUregionalappendix,sub-section“Summaryofongoingsafetyconcerns”
3.4.4.PBREREUregionalappendix,sub-section“Reportingoffindingsfrompost-**authorisationsafetystudies”**
3.4.5.PBREREUregionalappendix,sub-section“Effectivenessofriskminimisation”
3.5.Requirementsspecifictoourcountry
3.6.QualitysystemsandrecordmanagementsystemsforPBRERs
3.6.1.Preparationandsubmissionscheduleforqualitysystemsandrecordmanagement **systemsatthelevelofthemarketingauthorisationholder**
APPENDICES
Appendix1.Examplesoftabulationsforestimatedexposureandadverseevents/reactions **data**
Appendix2.Exampleoftabularsummaryofsafetysignalsthatwereongoingorclosed **duringthereportinginterval**
Appendix3.CoverletterforPBRERSubmission
3 CHAPTERI Introduction 1.1.Introduction
Periodicbenefit/riskevaluationreports(PBRERS)arepharmacovigilancedocuments thatareintendedtoprovideanevaluationoftherisk-benefitbalanceofamedicinalproduct andpreparedbymarketingauthorisationholdersatdefinedtimepointsduringthepost-authorisationphase. Basicguidanceontheformat,contentandsubmissionofPBRERsareprovidedin"the RegulationontheSafetyofMedicinalProducts"and"theRegulationamendingthe RegulationontheSafetyofMedicinalProducts".Thismodulehasbeenpreparedasa guidelineintendedforprovidingdetailedinformationonthepreparation,evaluationand submissiontotheAgencyofPBRERs.
ThereportwhichisdefinedasaPeriodicSafetyUpdateReport(PSUR)intheEUis calledaPBRERinourcountry.

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

Theobjectives,scope,formatandcontentofthePBRERaredescribedinthe"Structures andProcesses"chapter.Detailsfortheoperationofbenefit/riskevaluationprocessaregiven inthethirdchapter.
Marketingauthorisationholdersshouldpreparetheir PBRERsinlinewiththefollowing timelines:
within70calendardaysofthedatalockpoint(day0)forPBRERscoveringintervalsup to12months(includingintervalsofexactly12months).
within90calendardaysofthedatalockpoint(day0)forPBRERscoveringintervalsin excessof12months.
IfthetimelineforthesubmissionofPBRERsrequestedbytheAgencyisnotspecified intherequest,within90calendardaysofthedatalockpoint.
Itshouldbenotedthatdetailedlistingsofindividualcasesshouldnotbeincluded systematically.ThePBRERshouldfocusonsummaryinformation,scientificsafety assessmentandintegratedbenefit/riskevaluation.
PBRERsareofcriticalimportanceastheyprovideinformationonwhethertherearеany newrisks,anychangehasoccurredintherisksorinthebenefit/riskbalanceofthemedicinal productandarethereforelinkedtotheriskmanagementplan. CHAPTERII StructuresandProcesses
2.1.ObjectiveofPBRER
ThemainobjectiveofaPBRERistoevaluatecumulativeinformationonrisksandbenefits, inthiscontext,topresentacomprehensive,conciseandcriticalanalysisoftherisk/benefit balancetakingintoaccountallinformationthatmakessensewiththeneworemerging information.Inthisway,thePBRERallowspost-authorisationevaluationatcertaintimepoints inthelife-cycleofamedicine.
Sincebenefit/riskmanagementisaprocessthatneedstobemaintainedthroughoutthe life-cycleofamedicine,itisnecessarytocontinueevaluatingtherisksandbenefitsofthe useofamedicineindailylifeanditslongtermuseinthepost-authorisationphase.Thismay includeevaluationofpopulationsandendpointsthatcouldnotbeinvestigatedduringthepre-authorisationclinicaltrials.Adifferentbenefit/riskbalancemayemergeaspharmacovigilance activitiesrevealfurthersafetyinformation.Therefore,themarketingauthorisationholder shouldre-evaluatethebenefit/riskbalanceofpopulationsusingitsmedicines.Thisevaluation shouldbeundertakeninthecontextof"ongoingpharmacovigilance"and"riskmanagement" modules(ModuleVI)aimedatoptimisationofthebenefit/riskbalancethrougheffectiverisk minimisation.
4 Urgentsafetyinformationshouldbereportedthroughtheappropriatemechanism.APBRER isnotintendedforreportingsignificantnewsafetyorefficacyinformationorprovidingthe meansbywhichnewsafetyissuesaredetected(seeModuleVII).Itisacknowledgedthatthe reviewofthedatainthePBRERmayleadtonewsafetyissuesbeingidentified.
2.2.Principlesfortheevaluationofthebenefit/riskbalancewithin PBRERsandscope oftheinformationtobeincluded
Benefit/riskevaluationshouldbecarriedoutthroughoutthelife-cycleofthemedicinal producttopromoteandprotectpublichealthandtoenhancepatientsafetythrougheffective riskminimisation. Afteramarketingauthorisationisgranted,itisnecessarytocontinueevaluatingthe benefitsandrisksofmedicinalproductsinactualuseand/orlongtermuse,toconfirmthatthe benefit/riskbalanceremainsfavourable.
Theanalysisofthebenefit/riskbalanceshouldincorporateanevaluationofthe informationonsafety,efficacyduringclinicaltrialsandeffectivenessinrealworldthat becomesavailablewithreasonableandappropriateeffort,duringthereportingintervalforthe medicinalproductinthecontextofwhatwasknownpreviously.
Theriskevaluationshouldbebasedonallusesofthemedicine.Theevaluationshould includeevaluationofsafetyinrealmedicalpracticeincludinguseinunauthorisedindications andusewhichisnotinlinewiththeproductinformation.Ifuseofthemedicinalproductis identifiedwheretherearecriticalgapsinknowledgeforimportantsafetyissuesorpopulations, suchuseshouldbereportedinthePBRER(e.g.useinpaediatricpopulationorinpregnant

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

women).Sourcesofinformationonuseoutsideauthorisationmayincludedrugutilisation data,spontaneousreportsandinformationfrompublicationsintheliterature.
Thescopeofthebenefitinformationshouldincludebothclinicaltrialandrealworld dataforauthorisedindications.
Theintegratedbenefit/riskevaluationshouldbebasedonallauthorisedindicationsand shouldcovertheevaluationofrisksinallusesofthemedicinalproductincludingusein unauthorisedindications. Thisevaluationshouldincludethefollowing:
1.Adelicate,seriousandcriticalexaminationoftheinformationwhichhasbeen obtainedduringthereportingintervaltodeterminewhetherithasgeneratednew signals,ledtotheidentificationofnewpotentialoridentifiedrisksorcontributedto knowledgeofpreviouslyidentifiedrisks.
2.Acriticalsummaryoftherelevantnewinformationonsafety,efficacyduringclinical trialsandcurrenteffectivenessthatcouldhaveanimpactonthebenefit/riskbalanceof themedicinalproduct. 3.Anintegratedbenefit-riskanalysisforallauthorisedindicationsbasedonthe cumulativeinformationavailablesincetheDevelopmentInternationalBirthDate (DIBD),thedateoffirstauthorisationfortheconductofaninterventionalclinicaltrial inanycountry.(IncaseswheretheDIBDisunknownorthemarketingauthorisation holderdoesnothaveaccesstodatafromtheclinicaldevelopmentperiod,theearliest possibleapplicabledateshouldbeconsideredstartingpointfortheinclusionand evaluationofthecumulativeinformation.)
4.Summaryofanyriskminimisationactionsaddressedorimplementedduringthe reportinginterval,aswellasriskminimisationactionsthatareplannedtobe implemented.
5.Outlineofsignalandriskevaluationplansincludingtimelinesand/orproposalsfor additionalpharmacovigilanceactivities.

2.3.PrinciplesforthepreparationofPBRERs
UnlessotherwisespecifiedbytheAgency,asinglePBRERshallbepreparedforall medicinalproductscontainingthesameactivesubstanceandauthorisedunderthenameofa singlemarketingauthorisationholder.PBRERcoversallindications,routeofadministration, dosageformsanddosingregimens,irrespectiveofwhetherauthorisedunderdifferentnames andthroughseparateprocedures.Whererelevant,datarelatingtoaparticularindication, dosageform,routeofadministrationordosingregimen,shallbepresentedinaseparate sectionofthePBRERandanysafetyconcernsshallbeaddressedaccordingly.Theremightbe scenarioswhereseparatePBRERsareprepared,e.g.intheeventofdifferentformulationsfor entirelydifferentindications.Inthiscase,approvalshouldbeobtainedfromtheAgency, preferablyatthestageofauthorisation.
Casenarrativesshouldbeprovidedintherelevantriskevaluationsectionofthe PBRER whereintegraltothescientificanalysisofasignalorsafetyconcern.Inthiscontext,theterm “casenarratives”referstoclinicalevaluationsofindividualcasesratherthantheCIOMS narratives.Itisnotnecessarytoprovidetheactual CIOMSnarrativetextincludedinthe individualcasesafetyreport(ICSR)butinsteadaclinicalevaluationofimportantor illustrativecasesinthecontextoftheevaluationofthesafetyconcern/signalshouldbe undertaken.
Whenthemarketingauthorisationholderreceivesfrombusinesspartnersdatawhich mightcontributemeaningfullytothesafety,benefitand/orbenefit/riskanalysesandinfluence productinformation,thesedatashouldbeincludedanddiscussedinthePBRER.
AsaPBRERisasinglestand–alonedocumentthatcontainscumulativedatafora specifictimeinterval,summarybridgingreportsandaddendumreportswillnotbeaccepted.
2.4.Referenceinformation
RiskminimisationactivitiesevaluatedinthePBRERalsoincludeupdatestotheproduct information.
Thereferenceproductinformationforthe PBRERshouldinclude“coresafety”and “authorisedindications”components.Inordertofacilitatetheassessmentofbenefitand benefit/riskbalancebyindicationintheevaluationsectionsofthePBRER,thereference

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

productinformationshouldlistallauthorisedindicationsinICH(TheInternational ConferenceonHarmonisationofTechnicalRequirementsforRegistrationofPharmaceuticals forHumanUse)countriesorregions(http://www.ich.org/).WhenthePBRERisalso submittedtoothercountriesinwhichthereareadditionallocalindications,theseindications maybeeitheraddedtothereferenceproductinformationorhandledasaregionalappendixas consideredappropriatebythemarketingauthorisationholder.Thebasisforthebenefit evaluationshouldbethePBRERsub-section17.1("Importantbaselineefficacyinformation identifiedduringclinicaltrialsandinthepost-marketingperiod")underwhichimportant efficacyinformationduringclinicaltrialsandinthepost-marketingperiodissummarised. Thefollowingpossibleoptionscanbeconsideredbythemarketingauthorisation holderswhenselectingthemostappropriatereferenceproductinformationforaPBRER:

CompanyCoreDataSheet(CCDS)

- oItiscommonpracticethatmarketingauthorisationholdersprepareCCDSs whichcoverdatarelatingtosafety,indications,dosing,pharmacology,and otherinformationconcerningthemedicinalproduct.Thecoresafety informationcontainedintheCCDSshallbereferredtoasthecompanycore safetyinformation(CCSI).Itisapracticaloptionthatamarketing authorisationholderusestheCCDSineffectattheendofthereporting interval,asreferenceforthebenefitsectionscontainingtheriskandmain authorisedindications.
- oWhentheCCDSdoesnotcontaintheauthorisedindication,themarketing authorisationholdershouldclearlyspecifywhichdocumentisusedas reference.

Otheroptionsforthereferenceproductinformation

6

- oWhennoCCDSorCCSIexistsforamedicinalproduct(e.g.wherethe medicinalproductisauthorisedinonlyonecountryorregion,orfor established/genericproductsthatareonthemarketformanyyears),the marketingauthorisationholdershouldclearlyspecifythereference informationbeingused.
- oIfthereferenceinformationfortheauthorisedindicationisaseparate documentotherthanthereferencesafetyinformation(thecoresafety informationcontainedwithinthereferenceproductinformation),theversion ineffectattheendofthereportingintervalshouldbeincludedasanappendix tothePBRER(see2.5.20).

Themarketingauthorisationholdershouldcontinuouslydiscusswhetheranyrevisionof thereferenceproductinformation/referencesafetyinformationisneededduringthereporting intervalandwhenevernewsafetyinformationisobtainedduringthisinterval,itshouldensure thatallchangesmadearedescribedintheappropriatepartsofPBRERsection4("Changesto thereferencesafetyinformation")andsection16("Signalandriskevaluation").Thesechanges mayincludethefollowing:

Changestocontraindications,warnings/precautionssections.

Additiontoadversereactionsandinteractions.

Additionofimportantnewinformationonuseinoverdose.

Removalofanindicationorotherrestrictionsduetosafetyorlackofefficacy

Themarketingauthorisationholdershouldprovideacleancopyofallversionsofthe referenceproductinformationineffectattheendofthereportinginterval(e.g.different formulationsincludedinthesamePBRER)asanappendixtothePBRER(see2.5.20.).The referenceproductinformationshouldbedatedandversioncontrolled.

Iffeasible,wherenewinformationonsafetythatcauseschangestotheauthorised productinformation(e.g.newadversemedicinereaction,warningorcontraindication)has beenaddedtothereferencesafetyinformation(coresafetyinformationisincludedin referenceinformation)duringtheperiodfromthedatalockpointtothesubmissionofthe PBRER,thisinformationshouldbeincludedinthePBRERsection14("Late-breaking information").

Themarketingauthorisationholdermayprovide,intheregionalappendix,theauthorised productinformationandproposedsummaryofproductcharacteristics(SmPC)inourcountry.

2.5.FormatandcontentsofthePBRER

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

ThePBRERshallbebasedonallavailabledatarelatingtothebenefitsandrisksofthe medicinalproductincludingdataassociatedwithoff-labeluseanddataobtainedfromthe clinicaltrials,andincludeacumulativescientificevaluationofbenefit/riskbalanceby focusingonnewinformationwhichhasemergedsincethedatalockpointofthelastPBRER. Becauseclinicaldevelopmentofamedicinalproductoftencontinuesfollowing marketingauthorisation,relevantdatafrompost-authorisationstudiesorclinicaltrialson unauthorisedindicationsorpopulationsshouldalsobeincludedinthePBRER.Similarly,as safetyinformationofamedicinalproductmaybederivedfromevaluationofotherdata associatedwithoff-labeluse,suchinformationshouldbeincludedintheriskevaluation whererelevantandappropriate.
ThePBRERshouldprovidesummariesofdatarelevanttothebenefitsandrisksofthe medicinalproduct,includingresultsofallstudieswithaconsiderationoftheirpotential impactonthemarketingauthorisation.
Examplesofsourcesofefficacyandsafetyinformationthatmaybeusedinthe preparationofPBRERsincludethefollowing: Non-clinicalstudies. Spontaneousreports(e.g.reportsavailableonthemarketingauthorisationholder'ssafety database). Activesurveillancesystems. İnvestigationsofmedicinalproductquality. Medicinalproductusagedata.
7 Clinicaltrials,includingthoseinunauthorisedindicationsorpopulations. Observationalstudies,includingregistries. Patientsupportprograms. Systematicreviewsandmeta-analysis. Websitessponsoredbymarketingauthorisationholders. Publishedscientificliteratureorreportsfromabstracts,includinginformationpresented atscientificmeetings. Unpublishedmanuscripts. Academicinstitutionsandresearchnetworks. Competentauthorities(worldwide).
Theabovelistisdoesnotincludeallsources.Themarketingauthorisationholdermay useadditionaldatasourcestopresentsafetyandefficacyinthePBRERandtoevaluatethe benefit/riskbalancespecifictomedicinalproduct.Themarketingauthorisationholder,atits option,mayprovidealistofthesourcesofinformationused,asanappendixtothePBRER.
APBRERshouldbepreparedfollowingthefullmodularstructuresetoutinthe Appendix1totheRegulationontheSafetyofMedicinalProducts.
Forthepurposesofthismodule,sourcesofinformationincludedataregardingtheactive substance(s)includedinthemedicinalproduct,andregardingtheevaluationoftherelevant safety,and/orbenefit/riskbalance.Whilethesameformatshallbefollowedforallproducts,it isacknowledgedthattheextentoftheinformationprovidedmayvarywherejustified accordingtowhatisaccessibletothemarketingauthorisationholder.Forexample,fora marketingauthorisationholdersponsoredclinicaltrial,thereshouldbeaccesstopatientlevel datawhileforaclinicaltrialnotsponsoredbythemarketingauthorisationholder,onlythe publishedreportmaybeaccessible.
Thelevelofdetailprovidedincertainsectionsofthe PBRERshoulddependonknownor emergingimportantinformationonthebenefitsandrisksofthemedicinalproduct.This approachisapplicabletothosesectionsofthePBRERinwhichinformationaboutsafety, efficacy(clinicalstudies+realworld),safetysignalsandbenefit/riskbalanceisevaluated.
Thetitles,orderandcontentofthePBRERsectionsareprovidedbelow.Whenthereisno relevantinformationforanyofthesections,thisshouldbestated. PartI:Titlepagewithsignature PartII:ExecutiveSummary PartIII:Tableofcontents 1.Introduction 2.Worldwidemarketingauthorisationstatus 3.Actionstakeninthereportingintervalforsafetyreasons 4.Changestoreferencesafetyinformation 5.Estimatedexposureandusepatterns 5.1.Cumulativeexposureinclinicaltrials
5.2.Post-marketingcumulativeandreportingintervalpatientexposure 6.Datainsummarytabulations 6.1.Referenceinformation
6.2.Cumulativesummarytabulationsofseriousadverseeventsfromclinicaltrials 6.3. Cumulativeandreportingintervalsummarytabulationsfrompost- marketingdatasources

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

7.Summariesofsignificantfindingsfromclinicaltrialsduringthereportinginterval
7.1.Completedclinicaltrials 7.2.Ongoingclinicaltrials 7.3.Long-termfollow-up
7.4.Othertherapeuticuseofmedicinalproduct
8 7.5.Newsafetydatarelatedtofixedcombinationtherapies
8.Findingsfromnon-interventionalstudies 9.Informationfromotherclinicaltrialsandsources
9.1Otherclinicaltrials 9.2Medicationerrors 10.Non-clinicaldata 11.Literature
12.Otherperiodicreports 13.Lackofefficacyidentifiedincontrolledclinicaltrials
14.Late-breakinginformation 15.Overviewonsignals:new,ongoingorclosed
16.Signalandriskevaluation 16.1.Summaryofthesafetyconcerns. 16.2.Signalevaluation
16.3.Evaluationofrisksandnewinformation 16.4.Characterisationofrisks
16.5.Effectivenessofriskminimisationmeasures(whererelevant) 17.Benefitevaluation
17.1.Importantbaselineefficacyinformationidentifiedduringclinicaltrialsandin
thepost-marketingperiod
17.2.Importantbaselineefficacyinformationnewlyidentifiedduringclinicaltrials
andinthepost-marketingperiod 17.3.Characterisationofbenefits
18.Integratedbenefit/riskanalysisforauthorisedindications
18.1.Benefit/riskcontext(medicalneedandimportantalternatives)
18.2.Benefit/riskanalysisevaluation 19.Conclusionsandactions
20.AppendicestothePeriodicBenefit/RiskEvaluationReport PBRER'sTitlePagewithSignature
Thetitlepageshouldincludethenameofthemedicinalproduct(s)andactivesubstance,
internationalbirthdate,reportinginterval,dateofthereport,detailedinformationabout
marketingauthorisationholderandstatementofconfidentialityoftheinformationincludedin
thePBRER.Thetitlepageshouldalsocontainsignature. Executivesummary
Anexecutivesummaryshouldbeprovidedimmediatelyafterthetitlepageandbefore
thetableofcontents.Thepurposeoftheexecutivesummaryistoprovideaconcisesummary
ofthecontentandthemostimportantinformationinthePBRERandshouldcontainthe
followinginformation: Introductionandreportinginterval.
Medicinalproduct(s),therapeuticclass(es),mechanism(s)ofaction,indication(s),
pharmaceuticalformulation(s),dose(s)androute(s)ofadministration.
Estimatedcumulativeclinicaltrialsexposure.
Estimatedperiodicalandcumulativeexposurefrommarketingexperience.
Numberofcountriesinwhichthemedicinalproductisauthorised.
Summaryoftheoverallbenefit/riskanalysisevaluation(basedonPBRERsub-
section18.2“benefit/riskanalysisevaluation”).
Actionstakenandproposedforsafetyreasons,(e.g.significantchangestothe
referenceproductinformation,orotherriskminimisationactivities). Conclusions.
9 Tableofcontents Theexecutivesummaryshouldbefollowedbythetableofcontents.
2.5.1.PBRERsection“Introduction”
Themarketingauthorisationholdershouldbrieflyintroducethemedicinalproduct(s)so
thatthePBRER“standsalone”anditalsoprovidesperspectiverelativetopreviousPBRERs
andcircumstances.Theintroductionshouldcontainthefollowinginformation:
Internationaldateofbirthandreportinginterval.
Medicinalproduct(s),therapeuticclass(es),mechanism(s)ofaction,authorised
indication(s),pharmaceuticalform(s),dose(s)androute(s)ofadministration.
Abriefdescriptionofthepopulation(s)beingstudiedandtreated.
2.5.2.PBRERsection“Worldwidemarketingauthorisationstatus"
ThissectionofthePBRERshouldcontainabriefoverviewofthemedicinalproduct
includingthedateofthefirstauthorisationworldwide,indications(s),authoriseddose(s),and
whereauthorised. 2.5.3.PBRERsection“Actionstakenin thereportingintervalforsafetyreasons”
ThissectionofthePBRERshouldincludeadescriptionofsignificantactionsrelatedto
safetytakenworldwideduringthereportinginterval,relatedtoinvestigationalusesor

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

marketingexperiencegainedbythemarketingauthorisationholder,sponsorsofclinical trial(s),datamonitoringcommittees,ethicscommitteesorcompetentauthoritiesthathad either: asignificantinfluenceonthebenefit/riskbalanceoftheauthorisedmedicinalproductand/or animpactontheconductofspecificclinicaltrial(s)orontheoverallclinical developmentprogramme. Ifknown,thereasonforeachactionshouldbeprovidedandanyadditionalrelevant informationshouldbeincludedasappropriate.Relevantupdatestopreviousactionsshould alsobesummarisedinthissection. Examplesofsignificantactionstakenforsafetyreasonsinclude: Actionsrelatedtoinvestigationaluses: Refusaltoapproveaclinicaltrialforethicalorsafetyreasons. Earlyterminationofanongoingclinicaltrialorpartialorcompletesuspensionof clinicaltrialbecauseofsafetyfindingsorlackofefficacy. recallofinvestigationaldrugorcomparator. Failuretoobtainmarketingauthorisationforaninvestigatedindicationincluding voluntarywithdrawalofamarketingauthorisationapplication. Riskmanagementactivitiesincluding: oProtocolchangesduetosafetyorefficacyconcerns(e.g.dosagechanges, changesinstudyinclusion/exclusioncriteria,intensificationofsubject monitoring,limitationsintrialduration). oRestrictionsinstudypopulationorindications. oChangestotheinformedconsentformrelatingtosafetyconcerns. oFormulationchanges. oAdditionbythecompetentauthorityofaspecialsafety-relatedreporting requirement. oCommunicationwithinvestigatorsorhealthcareprofessionals.

oPlanningnewstudiestoclearsafetyconcerns. Actionsrelatedtomarketingexperience: Failuretoobtainorapplyforamarketingauthorisationextension suspensionorcancellationofamarketingauthorisation. Actionstakenduetomedicinalproductdefectsandqualityissues. Suspensionofsupplybythemarketingauthorisationholder Riskmanagementactivitiesincluding: oSignificantrestrictionsondistributionorimplementationofotherrisk minimisationmeasures. oSignificantsafety-relatedchangesininnerandouterpackagingdocuments includingrestrictionsonuseorpopulationtreated. oHealthcareprofessionalcommunication. oNewpost-marketingstudyrequirement(s)stipulatedbycompetentauthorities.

2.5.4.PBRERsection“Changestoreferencesafetyinformation”

ThisPBRERsectionshouldlistanysignificantchangesmadetothereferencesafety informationwithinthereportinginterval.Suchchangesmayincludeinformationrelatingto contraindications,warnings,precautions,seriousadversedrugreactions,interactions, importantfindingsfromongoingorcompletedclinicaltrialsandsignificantnon-clinicalstudy findings(e.g.carcinogenicitystudies).Specificinformationrelevanttothesechangesshould beprovidedintheappropriatesectionsofthePBRER.

2.5.5.PBRERsection“Estimatedexposureandusepatterns”

PBRERsshallcontainanaccurateestimateofthepopulationexposedtothemedicinal product,includingalldatarelatingtothevolumeofsalesandvolumeofprescriptions.This estimateofexposureshallbeaccompaniedbyaqualitativeandquantitativeanalysisofactual use,whichshallindicate,whereappropriate,howindicatedusediffersfromtheactualuse basedonalldataavailabletothemarketingauthorisationholder,includingtheresultsof observationalordrugutilisationstudies.

ThisPBRERsectionshallprovideestimatesofthesizeandnatureofthepopulation exposedtothemedicinalproducttogetherwithabriefdescriptionofthemethod(s)usedto calculatethesubjectexposureandthelimitationsofthemethod.

Whencalculatingsubject/patientexposure,consistentmethodsshouldbeusedacross PBRERSforthesamemedicinalproduct.Ifachangeinthemethodisappropriate,both methodsandcalculationsshallbeprovidedinthePBRERexplainingthechangeandany importantdifferencebetweentheresultsobtainedusingthetwomethodsshallbehighlighted.

2.5.5.1.PBRERsub-section“Cumulativeexposureinclinicaltrials”

ThissectionofthePBRERshouldcontainthefollowinginformationonthepatients studiedinclinicaltrialssponsoredbythemarketingauthorisationholder,ifapplicable

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

presentedintabularformat:
Totalnumberofsubjectsinongoingandcompletedclinicaltrialsexposedtothe investigationalmedicinalproduct,placebo,and/oractivecomparator(s)sincethe DIBD(For“oldproducts”,detaileddatamightnotbeavailable).
Ifavailable,cumulativesubjectexposureinclinicaltrialsshouldbepresentedin moredetail(e.g.sub-groupscategorizedbyage,sexandracial/ethnicgroupforthe entiredevelopmentprogramme).
Importantdifferencesamongtrialsintermsofdose,routesofadministrationor patientpopulationscanbenotedinthetables,ifappropriate,orseparatetablescanbe prepared.
11 Ifclinicaltrialshavebeenorarebeingperformedinspecialpopulations(e.g. pregnantwomen;patientswithrenal,hepatic,orcardiacimpairment;orpatientswith geneticpolymorphisms),exposuredatashouldbeprovidedasappropriate.
Whentherearesignificantdifferencesintimeofexposurebetweenrandomised subjectstotheinvestigationalmedicinalproductorcomparator(s),ordisparitiesin lengthofexposurebetweenclinicaltrials,itcanbeusefultoexpressexposurein subject-time(subject-days,-months,or-years).
Investigationaldrugexposureinhealthyvolunteersmightbelessrelevanttothe overallsafetyprofile,dependingonthetypeofadversereaction,particularlywhen subjectsareexposedtoasingledose.Suchdatacanbepresentedseparatelywithan explanationasappropriate.
Iftheseriousadverseeventsfromclinicaltrialsarepresentedbyindicationinthe summarytabulations,thepatientexposureshouldalsobepresentedbyindication, whereapplicable.
Forindividualtrialsofparticularimportance,demographiccharacteristicsshouldbe providedseparately.
Examplesoftabularformatfortheestimatedexposureinclinicaltrialsarepresentedin Appendix1,Tables2,3and4.
2.5.5.2.PBRERsub-section“Post-marketingcumulativeandreportinginterval patientexposure”
Separateestimatesshouldbeprovidedforcumulativeexposure(sincetheinternational birthdate),wherepossible,andperiodicalexposure(sincethedatalockpointoftheprevious PBRER).Althoughitisrecognisedthatitisoftendifficulttoobtainandvalidateexposure data,thenumberofpatientsexposedshouldbeprovidedwheneverpossible,alongwiththe method(s)usedtodeterminetheestimate.Justificationshouldbeprovidedifitisnotpossible topredictthenumberofpatientsexposed.Inthiscase,alternativeestimatesofexposure,if available,shouldbepresentedalongwiththemethod(s)usedtoderivethem.Examplesof alternativemeasuresofexposureincludepatient-daysofexposureandnumberof prescriptions.Onlyifsuchmeasuresarenotavailable,measuresofmedicinesales,suchas tonnageordosageunits,maybeused.Theconceptofa"defineddailydose"mayalsobeused toobtainpatientexposureestimates.
Thedatashouldbepresentedaccordingtothefollowingcategories:
1.Post-authorisation(non-clinicaltrial)exposure:
Anoverallestimationofpatientexposureshouldbeprovided.Inaddition,thedata shouldberoutinelypresentedbysex,age,indication,dose,formulationandregion, whereapplicable.Dependingonthemedicinalproduct,useofothervariablesmayalso beappropriate,suchasvaccinationcourses,route(s)ofadministration,anddurationof treatment.
Whentherearepatternsofreportsindicatingasafetysignal,exposuredatarelatingto relevantsubgroupsshouldbepresented,ifpossible. 2.Post-authorisationuseinspecialpopulations:
Wherepost-authorisationusehasoccurredinspecialpopulations,available informationsuchascumulativepatientnumbersexposedandthemethodof calculationshouldbeprovided.Sourcesofsuchdatawouldalsoincludenon-interventionalstudiesdesignedtoobtainthisinformation,includingregistries.
Populationstobeconsideredfordiscussionincludebutarenotlimitedto: Paediatricpopulation.

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

Elderlypopulation.
12 Pregnantorbreastfeedingwomen. Patientswithhepaticand/orrenalimpairment. Patientswithotherrelevantco-morbidity.
Patientswithdiseaseseveritydifferentfromthatstudiedinclinicaltrials.
Sub-populationscarryingrelevantgeneticpolymorphism(s).
Populationswithspecificracialand/orethnicorigins. 3.Otherpost-authorisationuse:
Ifthemarketingauthorisationholderbecomesawareofapatternofuseofthe medicinalproduct,whichmayberegional,consideredimportantfortheinterpretation ofsafetydata,themarketingauthorisationholdershouldprovideabriefdescription thereof.Examplesofsuchpatternsofusemayincludeoverdose,abuse,misuseanduse beyondtherecommendation(s)providedinthereferenceproductinformation(e.g.an anti-epilepticdrugusedforneuropathicpainand/orprophylaxisofmigraine headaches).Ifknown,themarketingauthorisationholdershouldbrieflycommenton whetherotherusebeyondtherecommendation(s)inthereferenceproductinformation issupportedbyclinicalguidelines,clinicaltrialevidence,orabsenceofauthorised alternativetreatment.Ifquantitativeinformationonuseisavailable,itshouldbe provided.
Ifknown,themarketingauthorisationholdermaybrieflycommentonwhetherotheruse beyondtherecommendation(s)inthereferenceproductinformationislinkedtoclinical guidelines,clinicaltrialevidenceorabsenceofauthorisedalternativetreatments.Forpurposes ofidentifyingpatternsofuseoutsidethereferenceproductinformation,themarketing authorisationholdershouldusetheappropriatesectionsofthereferenceproductinformation thatwasineffectattheendofthereportingintervalofthePBRER(e.g.authorisedindication, routeofadministration,contraindications).
Signalsorrisksidentifiedfromanydataorinformationsourceshouldbepresentedand evaluatedintherelevantsectionsofthePBRER.
Examplesoftabularformatfortheestimatedexposurefrommarketingexperienceare presentedinAppendix1,Tables5and6. 2.5.6.PBRERsection“Datainsummarytabulations”
TheobjectiveofthisPBRERsectionistopresentsafetydatathroughsummary tabulationsofseriousadverseeventsfromclinicaltrials,spontaneousseriousandnon-serious reactionsfrommarketingexperience(includingreportsfromhealthcareprofessionals, consumers,scientificliterature,competentauthorities(worldwide))andseriousreactionsfrom non-interventionalstudiesandothernon-interventionalbutsolicitedsources.Ontheinitiative ofthemarketingauthorisationholder,graphicscanbeusedtoillustratespecificcharacteristics ofthedatatofacilitateunderstandingthem.
Whentheadverseevent/reactiontermsarecodedusingMedDRAterminology,the preferredterm(PT)levelandsystemorganclass(SOC)shouldbepresentedinthesummary tabulations.
Theseriousnessoftheadverseevents/reactionsinthesummarytabulationsshould correspondtothedescriptionsofadverseevents/reactionsincludedintherelevantregulations.
Theseriousnessoftheadverseevents/reactionsinthesummarytabulationsshould correspondtotheseriousnessassignedtoevents/reactionsincludedintheICSRsusingthe criteriaestablishedinICHE2A9(seeAppendixIV).Whenseriousandnon-serious events/reactionsareincludedinthesameICSR,theindividualseriousnessperreactionshould bereflectedinthesummarytabulations.Seriousnessshouldnotbechangedspecificallyfor thepreparationofthePBRERs. 2.5.6.1.PBRERsub-section“Referenceinformation”
Thissub-sectionofthePBRERshouldspecifytheversion(s)ofthecodingdictionary usedforpresentationofadverseevents/reactions.
13 2.5.6.2.PBRERsub-section“Cumulativesummarytabulationsofseriousadverse eventsfromclinicaltrials”
ThisPBRERsub-sectionshouldprovidebackgroundinformationfortheappendixthat providesacumulativesummarytabulationsofseriousadverseeventsreportedinthe marketingauthorisationholder’sclinicaltrials,fromtheDIBDtothedatalockpointofthe

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

currentPBRER.Themarketingauthorisationholdershouldexplainthereasonforany omissionofdata(e.g.clinicaltrialdatamightnotbeavailableforproductsthathavebeen marketedformanyyears).Thetabulation(s)shouldbeorganisedusingMedDRASOC(listed intheinternationallyagreedorder),fortheinvestigationaldrug,aswellasforthecomparator arm(s)(activecomparator,placebo)usedintheclinicaldevelopmentprogramme.Datacanbe integratedacrosstheprogramme.Alternatively,whenusefulandfeasible,datacanalsobe presentedbytrial,indication,routeofadministrationorothervariables.
Thissub-sectionisnotintendedtopresentanalysesorconclusionsbasedontheserious adverseevents. Thefollowingpointsshouldbeconsidered:
Causalityassessmentisusefulfortheanalysisofindividualrareadversedrug reactions.Individualcasecausalityassessmenthaslessimportanceintheanalysisof aggregatedata,asgroupcomparisonsofratesarepossible.Therefore,thesummary tabulationsshouldincludeallseriousadverseeventsandnotjustseriousadverse reactionsfortheinvestigationaldrug,comparatorsandplacebo.Itmaybeusefulto presentratesbydose.
Ingeneral,thetabulation(s)ofseriousadverseeventsfromclinicaltrialsshould includethetermsthatwereusedindefiningthecaseas"serious"and"non-serious" inthestudyreports.
Thetabulationsshouldincludeblindedandunblindedclinicaltrialdata.Unblinded (unmasked)seriousadverseeventsmightoriginatefromcompletedtrialsor individualcasesthathavebeenunblindedforsafety(e.g.expeditedreporting).
Sponsorsofclinicaltrialsandmarketingauthorisationholdersshouldnotspecifically unblinddataforpreparingthePBRER.
Certainadverseeventscanbeexcludedfromtheclinicaltrialssummarytabulations, butsucheventsshouldbeexplainedinthereport.Forexample,adverseeventsthat havebeendefinedintheprotocolas“exempt”fromspecialcollectionandentryinto thesafetydatabasebecausetheyareanticipatedinthepatientpopulation,andthose thatrepresentstudyendpointscanbeexcluded(e.g.deathsreportedinatrialofa drugforcongestiveheartfailurewhereall-causemortalityistheprimaryefficacy endpoint,diseaseprogressionincancertrials).
Anexampleofsummarytabulationofseriousadverseeventsfromclinicaltrialsis presentedinAppendix1,Table7.
2.5.6.3.PBRERsub-section“Cumulativeandreportingintervalsummary tabulationsfrompost-marketingdatasources”
Thissub-sectionofthePBRERshouldprovidebackgroundinformationforthe appendixthatprovidescumulativeandinterimsummarytabulationsofadversereactions, fromtheinternationalbirthdatetothedatalockpointofthecurrentPBRER.Theadverse reactionsinthissectionarederivedfromspontaneousICSRs(fromhealthcareprofessionals, consumers,scientificliteratureandcompetentauthorities(worldwide))andfromsolicited non-interventionalICSRsincludingthosefromnon-interventionalstudies.Seriousandnon-seriousreactionsfromspontaneoussources,aswellasseriousadversereactionsfromnon-interventionalstudiesandothernon-interventionalsolicitedsourcesshouldbepresentedina singletabulation,withperiodicalandcumulativedatapresentedside-by-side.Thetabulation shouldbeorganisedaccordingtoMedDRASOC(shouldbelistedintheinternationally agreedorder).Forspecialissuesorconcerns,additionaltabulationsofadversereactionscan bepresentedbyindication,routeofadministrationorothervariables.

14 Formarketedmedicinalproducts,spontaneouslyreportedadverseeventsusually indicateatleastasuspicionofcausalitybythereporterandshouldbeconsideredtobe suspectedadversereactions.

Analysisorconclusionsbasedonthesummarytabulationsshouldnotbeprovidedin thisPBRERsub-section.
Anexampleofsummarytabulationsofadversedrugreactionsfrompost-marketingdata sourcesaregiveninAppendix1Table8.

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

2.5.7.PBRERsection“Summariesofsignificantfindingsfromclinicaltrialsduring thereportinginterval”
ThisPBRERsectionshouldincludeasummaryoftheclinicallysignificantlyemerging efficacyandsafetyfindingsobtainedfromclinicaltrialssponsoredbythemarketing authorisationholderduringthereportinginterval,fromthesourcesspecifiedinthesub-sectionslistedbelow.Wherepossibleandrelevant,datacategorisedbysexandage (particularlypaediatrics-adults),indication,doseandregionshouldbepresented.
Signalsarisingfromclinicaltrialsourcesshouldbepresentedintabulationsin PBRER section15(“Overviewonsignals:new,ongoingorclosed”).Evaluationofthesignals, whetherornotcategorisedasrefutedsignalsoreitherpotentialoridentifiedrisk,thatwere closedduringthereportingintervalshouldbepresentedinPBRERsection16.2(“Signal evaluation”).Newinformationinrelationtoanypreviouslyknownpotentialoridentifiedrisk andnotconsideredtoconstituteanewlyidentifiedsignalshouldbeevaluatedanddescribedin PBRERsections16.3(“Evaluationofrisksandnewinformation”)and16.4 (“Characterisationofrisks”)respectively.
Findingsfromclinicaltrialsnotsponsoredbythemarketingauthorisationholdershould bedescribedintherelevantsectionsofthePBRER.
Whenrelevanttothebenefit/riskevaluation,informationonlackofefficacyfrom clinicaltrialsfortreatmentsofnon-life-threateningdiseasesinauthorisedindicationsshould besummarisedinthissection.Informationonlackofefficacyfromclinicaltrialswith medicinalproductsintendedtopreventortreatseriousorlife-threateningdiseasesshouldbe summarisedinSection13(“Lackofefficacyidentifiedincontrolledclinicaltrials”).
Inaddition,themarketingauthorisationholdershouldprovideanappendixlistingthe sponsoredpost-authorisationinterventionaltrialswiththeprimaryaimofidentifying, characterising,orquantifyingasafetyhazardorconfirmingthesafetyprofileofatrialthat wascompletedorongoingduringthereportinginterval.Thelistingshouldincludethe followinginformationforeachtrial:
Studyinformation(identification)(e.g.protocolnumberorotheridentifiers).
Studytitle(abbreviatedstudytitle,ifpossible).
Studytype(e.g.randomisedclinicaltrial,cohortstudy,case-controlstudy).
Populationstudied,includingthecountrystudiedandotherrelevantpopulation identifiers(e.g.paediatricpopulationortrialsubjectswithimpairedrenalfunction).
Studystart(asdefinedbythemarketingauthorisationholder)andtargeted completiondates.
Status:ongoing(clinicaltrialhasbegun)orcompleted(clinicalstudyreportis finalised).

2.5.7.1.PBRERsub-section“Completedclinicaltrials”
Thissub-sectionofthePBRERshouldprovideasummaryofclinicallyimportant efficacyandsafetyfindingsobtainedfromclinicaltrialscompletedduringthereporting interval.Thisinformationcanbepresentedinnarrativeformatorasasynopsis.Itmayinclude informationthatsupportsorrefutespreviouslyidentifiedsafetyconcernsaswellasfindings ofnewsafetysignals.
2.5.7.2.PBRERsub-section“Ongoingclinicaltrials”
Ifthemarketingauthorisationholderisawareofclinicallyimportantinformation obtainedfromongoingclinicaltrials(e.g.learnedthroughinterimsafetyanalysisorasaresult ofunblindingofsubjectswithadverseevents),thissub-sectionshouldsummarisetherelevant concerns.Itmayincludeinformationthatsupportsorrefutespreviouslyidentifiedsafety concernsaswellasfindingsofnewsafetysignals.
2.5.7.3.PBRERsub-section“Longtermfollow-up”
Whereapplicable,thissub-sectionshouldprovideinformationobtainedfromlong-term follow-upofsubjectsinclinicaltrialsofinvestigationaldrugs,particularlyadvancedtherapy products(e.g.genetherapy,celltherapyproductsandtissueengineeringproducts).
2.5.7.4.PBRERsub-section“Othertherapeuticuseofmedicinalproduct”
Thissub-sectionofthePBRERshouldincludeclinicallyimportantsafetyinformation fromotherprogrammesconductedbythemarketingauthorisationholderthatfollowa specificprotocol,withsolicitedreporting,(e.g.expandedaccessprogrammes,compassionate

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

useprogrammes,particularpatientuse,andotherorganiseddatacollection).
2.5.7.5.PBRERsub-section“Newsafetydatarelatedtofixedcombination therapies”
Thefollowingoptionscanbeusedtopresentdataoncombinationtherapies:
Iftheactivesubstancethatisthesubjectofthe PBRERisalsoauthorisedorunder developmentasacomponentofafixedcombinationproductoramulti-drugregimen, thissub-sectionshouldsummariseimportantsafetyfindingsfromuseofthe combinationtherapy.
Ifthemedicinalproductitselfisafixedcombinationproduct,thisPBRERsub-sectionshouldsummariseimportantsafetyinformationobtainedfromeach componentwhetherauthorisedorunderdevelopment.
Theinformationspecifictothecombinationcanbeincorporatedintoaseparate section(s)ofthePBRERforoneoralloftheindividualcomponentsofthecombination.
2.5.8.PBRERsection“Findingsfromnon-interventionalstudies”
Thissectionshouldsummariseimportantsafetyinformationorinformationlikelyto haveimpactonthebenefit/riskassessmentobtainedfrommarketingauthorisationholder-sponsorednon-interventionalstudiesthatbecameavailableduringthereportinginterval(e.g. observationalstudies,epidemiologicalstudies,registriesandactivesurveillanceprogrammes).
Whenrelevanttomultipleregions,thisshouldalsoincluderelevantinformationfromdrug utilisationstudies(see2.5.7forinformationthatshouldbeincludedinthelist).
Themarketingauthorisationholdershouldincludeanappendixlistingnon-interventional studiessponsoredbyitwiththeprimaryaimofidentifying,characterisingorquantifyinga safetyhazard,confirmingthesafetyprofileofamedicinalproduct,orofmeasuringthe effectivenessofriskmanagementmeasureswhicharecompletedorongoingduringthe reportinginterval.Finalstudyreportscompleteddurингthereportingintervalforthestudies describedintheparagraphaboveshouldalsobeincludedintheregionalappendixofthe PBRER(see2.5.20and3.4.4).
16 Summaryinformationbasedonaggregateevaluationofdatageneratedfrompatient supportprogramsmaybeincludedinthissectionwhennotpresentedelsewhereinthe PBRER.Asforotherinformationsources,themarketingauthorisationholdershouldpresent signalsorrisksidentifiedfromsuchinformationintherelevantsectionsofthePBRER.
2.5.9.PBRERsection“Informationfromotherclinicaltrialsandsources”
2.5.9.1PBRERsub-section“Otherclinicaltrials”
Thissub-sectionshouldsummariseinformationrelevanttothebenefit/riskassessment ofthemedicinalproductfromotherclinicaltrialsourcesincludingpatientsupportprograms whichareaccessiblebythemarketingauthorisationholderduringthereportinginterval(e.g. resultsfromcombinedanalysisormeta-analysisofrandomisedclinicaltrials,safety informationfromco-developmentpartnersduringdrugdevelopmentorfrominvestigator-initiatedtrials). 2.5.9.2PBRERsub-section“MedicationErrors”
Thissub-sectionshouldsummariseinformationonpatternsofmedicationerrorsand potentialmedicationerrors,evenwhennotassociatedwithadverseoutcomes.Apotential medicationerroristherecognitionofcircumstancesthatcouldleadtoamedicationerror, whichmayormaynotinvolveapatient.Suchinformationmayberelevanttothe interpretationoftheoverallbenefit/riskevaluationofthemedicinalproductorsafetydata.A medicationerrormayariseatanystageinthemedicationprocessandmayinvolvepatients, consumersorhealthcareprofessionals. 2.5.10.PBRERsection“Non-clinicaldata”
ThisPBRERsectionshouldsummariseimportantsafetyfindingsfromnon-clinicalin vivoandinvitrostudies(e.g.carcinogenicity,reproductionorimmunotoxicitystudies) ongoingorcompleteddurингthereportinginterval.Regardlessoftheoutcome,resultsfrom studiesdesignatedtoaddressspecificsafetyconcernsshouldbeincludedinthePBRER.
2.5.11.PBRERsection“Literature”
ThisPBRERsectionshouldincludeasummaryofnewandsignificantsafetyfindings publishedinthepeer-reviewedscientificjournalsormadeavailableasunpublished

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

manuscriptsthatthemarketingauthorisationholderbecameawareofduringthereporting interval.
LiteratureresearchforPBRERSshouldhaveawiderscopethanthatofindividualadverse reactioncasesastheyshouldalsoincludestudiesreportingsafetyoutcomesingroupsof subjectsandothermedicinalproductscontainingthesameactivesubstance.
Thespecialtypesofsafetyinformationthatshouldbeincludedbutwhichmaynotbe foundthroughasearchconstructedtoidentifyindividualcasesshouldincludethefollowing:
Pregnancyoutcomes(includingcurettage)withnoadverseoutcomes. Useinpaediatricpopulation.
Compassionatesupply,off-labeldruguse. Lackofefficacy.
Asymptomaticoverdose,abuseormisuseofdrug. Medicationerrorwherenoadverseeventsoccurred.
Importantnon-clinicalsafetyresults.
Ifrelevantandapplicable,informationonotheractivesubstancesofthesameclass shouldalsobeconsidered.
Thepublicationreferenceshouldbeprovidedinthestyleofthe VancouverConvention.

2.5.12.PBRERsection“Otherperiodicreports”
ThisPBRERsectionwillonlyapplyincertaincircumstancesconcerningfixed combinationmedicinalproductsormedicinalproductswithmultipleindicationsand/or formulationswheremultiplePBRERsarepreparedinagreementwiththeAgency.Ingeneral, themarketingauthorisationholdershouldprepareonePBRERforasingleactivesubstance unlessotherwisespecifiedbytheAgency;howeverifmultiplePBRERSarepreparedfora singlemedicinalproduct,thissectionshouldalsosummariseimportantfindingsforother PBRERSiftheyarenotpresentedelsewherewithinthereport.
Whenavailable,basedonthewrittenagreements,themarketingauthorisationholder shouldsummarisesignificantfindingsfromperiodicreportsprovidedduringthereporting intervalbyotherparties(e.g.sponsors,othermarketingauthorisationholders).
2.5.13.PBRERsection“Lackofefficacyidentifiedincontrolledclinicaltrials”
Thissectionshouldsummarisedatafromclinicaltrialsindicatinglackofefficacy,or lackofefficacycomparedtoestablishedtreatment(s),formedicinalproductsintendedtotreat orpreventseriousorlife-threateningdiseases(e.g.excesscardiovascularadverseeventsina trialofanewanti-plateletmedicineforacutecoronarysyndrome)assuchdatacouldreflecta significantrisktothetreatedpopulation. 2.5.14.PBRERsection“Late-breakinginformation”
Themarketingauthorisationholdershouldsummariseinthis PBRERsectionthe potentiallyimportantsafetyandefficacyfindingsthatareobtainedafterthedatalockpoint butduringtheperiodofpreparationofthePBRER.Examplesincludeclinicallysignificant newpublications,importantfollow-updata,clinicallysignificanttoxicologicalfindingsand anyactionthatthemarketingauthorisationholder,adatamonitoringcommitteeora competentauthority(worldwide)hastakenforsafetyreason.Newindividualcasereports shouldnotberoutinelyincludedunlesstheyareconsideredtoconstituteanimportantindex case(i.e.thefirstinstanceofanimportantevent)oranimportantsafetysignalorwherethey mayprovideadditionalinformationtotheevaluationofsafetyconcernsalreadypresentedin thePBRER(e.g.awelldocumentedcaseofaplasticanaemiainamedicinalproductknownto beassociatedwithadverseeffectsonthebonemarrowintheabsenceofpossiblealternative causes).
ThissectionofthePBRER,wherepossible,shouldalsoincludeanysignificantchange proposedtothereferenceproductinformation(e.g.newadversereaction,warningor contraindication)whichhasoccurredduringthisreportinginterval(see2.4).
Thedatapresentedinthissectionshouldalsobetakenintoaccountintheevaluationof risksandnewinformation(see2.5.16.3).
2.5.15.PBRERsection“Overviewofnew,ongoing,orclosedsignals”
Thelocationforpresentationofinformationonsignalsandriskswithin thePBRERis showninFigure1.Thepurposeofthissectionistoprovideahighleveloverviewofsignals thatwereclosed(i.e.completedevaluation)duringthereportingintervalaswellasongoing signalsthatwereundergoingevaluationattheendofthereportinginterval.Asignalshouldbe

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

includedinthePBRERoncetheinitialscreeningisperformedortheclarificationstepis entered,andadeterminationshouldbeshownbythemarketingauthorisationholderto conductfurtherevaluation.(Thesignalmentionedhereisavalidatedsignal).Itshouldbe notedthatasafetysignalisnotequivalenttoastatisticofdisproportionatereportingfora specificmedicine/eventcombinationasavalidationstepisrequired.Signalsmaybe qualitative(apivotalindividualcasesafetyreport,caseseries)orquantitative(a disproportionalityscore,findingsofanepidemiologicalstudyoraclinicaltrial).Signalsmay ariseintheformofaninformationrequestorinquiryonasafetyissuefromacompetent authority(worldwide)(seeModuleVII).

18 Decisionsregardingthesubsequentclassificationofthesesignalsandtheconclusionsof theevaluationarepresentedinPBRERsection16("Signalandriskevaluation")soasto includescientificinterpretationandmedicaljudgementofavailabledata. Anewsignalrepresentsasignalthatisidentifiedduringthereportinginterval.Where newclinicallysignificantinformationonapreviouslyclosedsignalbecomesavailableduring thereportingintervalofthePBRER,thiscouldalsobeconsideredanewsignalbecauseanew aspectofapreviouslyrefutedsignaloridentifiedriskrequiresfurtheractiontobeverified. Newsignalsmaybeclassifiedasclosedorongoing,dependingonthestatusofsignal evaluationattheendofthereportingintervalofthePBRER. Examplesofnewsignalswouldthereforeincludenewinformationonapreviously: Closeorrefutedsignal,whichisre-opened. Identifiedriskwherethenewinformationsuggestsaclinicallysignificantdifference intheseverityorfrequencyoftherisk(e.g.transientliverenzymeincreasesare identifiedrisksandnewinformationindicativeofamoresevereoutcomesuchas hepaticfailureisreceived,orneutropeniaisanidentifiedriskandawelldocumented casereportofagranulocytosiswithnopresenceofpossiblealternativecausesis received). Identifiedriskforwhichahigherfrequencyorseverityisnewlyfound(e.g.inan indicatedsubpopulation). Potentialriskwhich,ifconfirmed,wouldrequireanewwarning,precaution,anew contraindicationorrestrictioninindication(s)orpopulationorotherrisk minimisationactivities. Themarketingauthorisationholdershouldlistinatableallsignalsongoingorclosed attheendofthereportinginterval,withinthissectionorasanappendix.Thistableshould includethefollowinginformation: Abriefdescriptionofthesignal. Datewhenthemarketingauthorisationholderbecameawareofthesignal. Statusofthesignalattheendofthereportinginterval(closedorongoing). Ifapplicable,datewhenthesignalwasclosed. Sourceofthesignal. Abriefsummaryofthekeydata. Plansforfurtherresearch. Actionsplannedortaken. AnexampleoftabulationofsignalscanbefoundinAppendix2. Detailsofsignalassessmentsforclosedsignalsshouldbepresentedinsub-title("Signalevaluation") ofthePBRERinsteadofthissection. Newinformationinrelationtoanypreviouslyknownidentifiedandpotentialrisksand notconsideredtoconstituteanewsignalshouldbeprovidedinPBRERsub-section16.3 ("Evaluationofrisksandnewinformation"). Ifacompetentauthority(worldwide)requeststhataspecifictopic(notconsidereda signal)bereportedinaPBRERandfollowedup,themarketingauthorisationholdershould summarisetheresultsoftheanalysisinthissectioniftheyarenegative.Ifthespecifictopic becomesasignal,itshouldbeincludedinthesignaltabulationanddiscussedinsub-section 16.2("Signalevaluation"). 2.5.16.PBRERsection"Signalandriskevaluation" ThepurposeofthissectionofthePBRERistoprovidethefollowing: Asuccinctsummaryofwhatisknownaboutimportantidentifiedandpotentialrisks andimportantmissinginformationatthebeginningofthereportinginterval (2.5.16.1). Evaluationofallsignalsclosedduringthereportinginterval(2.5.16.2).

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

19 Evaluationofnewinformationwithrespecttopreviouslyknownidentifiedand potentialrisks(2.5.16.3).
Whereappropriate,anupdatedcharacterisationofimportantpotentialandidentified risks(2.5.16.4).
Asummaryoftheeffectivenessofriskminimisationactivitiesinanycountryor regionwhichmayprovideutilityinothercountriesorregions(2.5.16.5.).
Aflowchartmappingthesignalsandriskstospecificsections/sub-sectionsofthe PBRERcanbefoundin2.5.21.
Theseevaluationsub-sectionsshouldprovideinterpretationandcriticalappraisalofthe information,withaviewtowardscharacterisingtheprofileofthoserisksassessedas importantratherthanrepeatingorsummarisingtheinformationpresentedinprevioussections ofthePBRER.Inaddition,asageneralrule,itisnotnecessarytoincludeindividualcase narrativesintheevaluationsectionsofthePBRER,however,whereitispartofthescientific analysisofasignalorrisk,aclinicalevaluationofpivotalorillustrativecases(e.g.thefirst caseofsuspectedagranulocytosiswithanactivesubstancebelongingtoaclassknowntohave thepotentialtocauseagranulocytosis)shouldbeprovided(see2.3.).
2.5.16.1.PBRERsub-section“Summaryofsafetyissues”
Thepurposeofthissub-sectionistoprovideasummaryofimportantsafetyconcernsat thebeginningofthereportinginterval,againstwhichnewinformationandevaluationscanbe made.Formedicinalproductswithanexistingsafetyspecification,thissectioncanbeeither thesameasorderivedfromthesafetyspecificationsummarythatiscurrentatthebeginning ofthereportingintervalofthePBRER. Thefollowingsafetyinformationshouldbeprovided: Importantidentifiedrisks. Importantpotentialrisks. Missinginformation.
Thefollowingfactorsshouldbeconsideredwhendeterminingtheimportanceofeachrisk:
Medicalseriousnessoftherisk,includingtheimpactoneachpatient.
Itsfrequency,predictability,preventabilityandreversibility.
Itspotentialimpactonpublichealth(frequency;sizeoftreatedpopulation).
Potentialforavoidanceoftheuseofamedicinalproductwithapreventivebenefit duetoadisproportionatepublicperceptionofrisk(e.g.vaccines).
Formedicinalproductswithoutanexistingsafetyspecification,thissectionshould provideinformationontheimportantidentifiedandpotentialrisksaswellasmissing informationassociatedwithuseoftheproduct,basedonpre-andpost-authorisation experience. Importantidentifiedandpotentialrisksmayincludethefollowing: Importantadversereactions. Interactionswithothermedicinalproducts. Interactionswithfoodsandothersubstances. Medicationerrors. Effectsofoccupationalexposure. Pharmacologicalclasseffects.
Whensummarisingimportantmissinginformation,itshouldbetakenintoaccount whethertherearecriticalgapsinknowledgeforspecificsafetyissuesorpopulationsthatuse themedicinalproduct.
20 2.5.16.2.PBRERsub-section“Signalevaluation”
Thissub-sectionofthePBRERshouldsummarisetheresultsofevaluationsofallsafety signals(whetherornotclassifiedasimportant)thatwereclosedduringthereportinginterval.
Followingevaluation,asafetysignalcanbeclosedeitherbecauseitisrefutedorbecauseitis determinedtobeapotentialoridentifiedrisk.Therearetwomaincategoriestobeincludedin thissub-section: 1.Signalswhich,followingevaluation,arerefutedbecausetheywerefoundtobe falsesignalsbasedonmedicaljudgementandscientificevaluationofthecurrently availableinformation. 2.Signalswhich,followingevaluation,arecategorisedaseitherapotentialor identifiedrisk,includinglackofefficacy.
Forbothcategoriesofclosedsignals,conciseandbriefdescriptionofeachsignal evaluationshouldbeprovidedinordertoclearlydescribethebasisuponwhichthesignalwas refutedorconsideredtobeapotentialoridentifiedriskbythemarketingauthorisationholder.
Thelevelofdetailprovidedinthedescriptionofthesignalevaluationshouldreflectthe medicalsignificanceofthesignal(e.g.severe,irreversible,leadingtoincreasedmorbidityor

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

mortality),itsimpactonpublichealth(e.g.wideusage,frequency,significantuseoutsidethe recommendationsoftheproductinformation)andtheextentoftheavailableevidence.Where multipleevaluationswillbeincludedunderbothcategoriesofclosedsignals,theycanbe presentedinthefollowingorder: Closedandrefutedsignals Closedsignalsthatarecategorisedasimportantpotentialrisks.
Closedsignalsthatarecategorisedasimportantidentifiedrisks.
Closedsignalsarisingfrompotentialrisksnotcategorisedasimportant.
Closedsignalsarisingfromidentifiedrisksnotcategorisedasimportant.
Ifapplicable,theevaluationsofclosedsignalscanbepresentedbyindicationor population.
Thedescriptionsofthesignalevaluationscanbeincludedinthissub-sectionofthe PBRERorasanappendix.Eachevaluationshouldincludethefollowinginformationas appropriate: Sourceortriggerofthesignal. Pastinformationrelevanttotheevaluation.
Method(s)ofevaluation,includingdatasources,searchcriteria(whereapplicable,the specificMedDRAterms(e.g.PTs,HLTs,SOCs,etc.)orStandardisedMedDRA Queries(SMQs)thatwerereviewed),andanalyticalapproaches.
Results-asummaryandcriticalanalysisofthedataconsideredinthesignal evaluation;whereintegraltotheevaluation,thismayincludeacaseseriesoran individualcase(e.g.asamplecaseofwelldocumentedagranulocytosisorStevens JohnsonSyndrome).
Discussion. Conclusion.
Marketingauthorisationholders'evaluationsandconclusionsforrefutedsignalsshouldbesupported bydataandclearlypresented. 2.5.16.3.PBRERsub-section“Evaluationofrisksandnewinformation” Thissub-sectionshouldprovideacriticalevaluationofnewinformationrelevantto previouslyrecognisedrisksthatisnotalreadyincludedinsub-section16.2(“Signal evaluation”).Newinformationthatconstitutesasignalwithrespecttoapreviouslyrecognised riskorpreviouslyrefutedsignalshouldbeevaluatedinsub-section16.2(“Signalevaluation”) andpresentedinthesignaltabulations(ifsuchsignalhasalsobeenclosedduringthe reportingintervalofthePBRER)(see2.5.15).

21 Updatedinformationonapreviouslyrecognisedriskthatdoesnotconstituteasignal shouldbeincludedinthissub-section.Examplesincludeinformationthatconfirmsapotential riskasanidentifiedrisk,orinformationthatallowsfurthercharacterisationofapreviously recognisedrisk.
Newinformationcanbeorganisedasfollows: 1.Newinformationonimportantpotentialrisks.
2.Newinformationonimportantidentifiedrisks.
3.Newinformationonotherpotentialrisksnotcategorisedasimportant.
4.Newinformationonotheridentifiedrisksnotcategorisedasimportant.
5.Updatesonmissinginformation.
Thefocusoftheevaluation(s)shouldbeonnewinformationthathasbeenobtained duringthereportingintervalofthePBRER.Theevaluationshouldbeshortandconcise,and interprettheimpact,ifany,ontheunderstandingandcharacterisationoftherisk.The evaluationwillformthebasisforanupdatedcharacterisationofimportantpotentialand identifiedrisksinsection16.4(“Characterisationofrisks”)ofthereport.Itisrecommended thatthelevelofdetailoftheevaluationincludedinthissub-sectionshouldbeproportionalto theavailableevidenceontheriskandthemedicalsignificanceoftheriskanditspublichealth relevance.
Theevaluationofthenewinformationandmissinginformationupdatecanbeincluded inthissub-sectionofthePBRER,orprovidedasanappendix.
Eachevaluationshouldincludethefollowinginformationasappropriate: Sourceofthenewinformation.
Pastinformationrelevanttotheevaluation.
Method(s)ofevaluation,includingdatasources,searchcriteriaandanalytical approaches.
Findings(asummaryandcriticalanalysisofthedataconsideredintheriskevaluation). Discussion.
Conclusion,includingwhetherornottheevaluationsupportsthecharacterisationof anyoftheimportantpotentialandidentifiedrisksinsub-section16.4 (“Characterisationofrisks”).
Anynewinformationonpopulationsexposedordataobtainedtocompensate

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

previouslymissinginformationshouldbecriticallyassessedinthissub-section.Unresolved concernsanduncertaintiesshouldbeexplained. 2.5.16.4.PBRERsub-section“Characterisationofrisks” Thissub-sectionshouldcharacteriseimportantidentifiedandpotentialrisksbasedon cumulativedata(notrestrictedtothereportinginterval),anddescribeimportantmissing information. Dependingonthenatureofthedatasource,thecharacterisationofriskmayinclude, whereapplicable,thefollowing: Frequency. Numberofcases(numerator)andprecisionofestimate,takingintoaccountthe sourceofthedata. Extentofuse(denominator)expressedasnumbersofpatients,patient-time,etc., andprecisionofestimate. Estimateofrelativeriskandprecisionofestimate. Estimateofabsoluteriskandprecisionofestimate. Impactontheindividualpatient(effectsonsymptoms,qualityorlengthoflife). Impactonpublichealth. Riskassociatedwithpatientcharacteristics(e.g.patientfactors(age,pregnancy/lactation, hepatic/renalimpairment,relevantco-morbidity,diseaseseverity,geneticpolymorphism)).

Dose,routeofadministration. Durationoftreatment,riskperiod. Preventability(i.e.predictability,abilitytomonitorfora“sentinel”adverse reactionorlaboratorymarker). Reversibility. Potentialmechanism. Ifapplicable,strengthanduncertaintiesofevidence,includinganalysisof conflictingevidence. Whenmissinginformationconstitutesanimportantrisk,itshouldbeincludedasa safetyconcern.Thelimitationsofthesafetydatabase(intermsofnumberofpatientsstudied, cumulativeexposureorlongtermuse,etc.)shouldbediscussed. ForPBRERsformedicinalproductswithseveralindications,formulations,orroutesof administration,whereetheremaybesignificantdifferencesintheidentifiedandpotentialrisks, itmaybeappropriatetopresentrisksbyindication,formulation,orrouteofadministration. Headingsthatcouldbeconsideredinclude: Risksrelatingtotheactivesubstance. Risksassociatedwithaspecificformulationorrouteofadministration(includingoccupational exposure). Risksrelatingtoaspecificpopulation. Risksassociatedwithnon-prescriptionuse(forbothprescriptionandnon-prescriptionmedicinal products). 2.5.16.5.PBRERsub-section:“Effectivenessofriskminimisationmeasures(if applicable)” Riskminimisationactivitiesarepublichealthinterventionsintendedtopreventthe occurrenceofadversedrugreactionsortoreducetheirseverityshouldtheyoccur.Theaimof riskminimisationactivitiesistoreducetheprobabilityorseverityofanadversedrugreaction. Riskminimisationactivitiesmayconsistofroutineriskminimisationactivities(e.g.SmPC)or additionalriskminimisationactivities(e.g.DirectHealthcareProfessional Communication/educationalmaterials). ThePBRERshouldalsocontaintheresultsofassessmentoftheeffectivenessofrisk minimisationactivitiesrelatedtothebenefit/riskevaluation. Relevantinformationontheeffectivenessand/orlimitationsofspecificrisk minimisationactivitiesforimportantidentifiedriskshathasbecomeavailableduringthe reportingintervalshouldbesummarisedinthissub-sectionofthePBRER.Effectivenessof riskminimisationactivitiesinanycountryorregionmayprovideaninsightforother countriesandregions.Informationmaybesummarisedbyregion,ifapplicableandrelevant. 2.5.17.PBRERsection“Benefitevaluation” PBRERsub-titles17.1(“Importantbaselineefficacyinformationidentifiedduring clinicaltrialsandinthepost-marketingperiod”)and17.2(“Efficacyinformationnewly identifiedduringclinicaltrialsandinthepost-marketingperiod”)providethebaseline informationforsection17.3.Newlyidentifiedbenefitinformationthatsupportthe characterisationofbenefitdescribedinsub-section17.3(“Characterisationofbenefits”) supportsthebenefit/riskevaluationinsection18(“Integratedbenefit/riskanalysisfor authorisedindications”). 2.5.17.1.PBRERsub-section“Importantbaselineefficacyinformationidentified duringclinicaltrialsandinthepost-marketingperiod”

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

Thissub-sectionofthePBRERsummarisesinformationontheefficacyofthemedicinal productatthebeginningofthereportingintervalsoastoprovidethebasisforthebenefit evaluation.Thisinformationshouldrelatetoauthorisedindication(s)ofthemedicinalproduct giveninthereferenceproductinformation(See2.4).

23 Formedicinalproductswithmultipleindications,populationsand/orroutesof administration,thebenefitshouldbecharacterisedseparatelybythesefactorswhererelevant. Thelevelofdetailprovidedinthissub-sectionshouldbesufficienttosupportthe characterisationofbenefitinthePBRERsub-section17.3("Characterisationofbenefits")and thebenefit/riskevaluationinsection18("Integratedbenefit/riskanalysisforauthorised indications").

2.5.17.2.PBRERsub-section"Efficacyinformationnewlyidentifiedduringclinical trialsandinthepost-marketingperiod"

Additionalinformationonefficacyinauthorisedindicationsofsomemedicinalproducts maybecomeavailableduringthereportinginterval.Thiskindofinformationshouldbe presentedinthissub-sectionofthePBRER.Iffeasible,forauthorisedindications,new informationonefficacyunderconditionsofactualuseshouldalsobepresentedinthissub-section.Newinformationonefficacyinusesotherthantheauthorisedindicationsshouldnot beincludedunlessrelevantforthebenefit/riskevaluationintheauthorisedindications. Informationonindicationsnewlyauthorisedduringthereportingintervalshouldbe includedinthissub-section.Thelevelofdetailprovidedinthissectionshouldbesufficientto supportthecharacterisationofbenefitinsub-section17.3("Characterisationofbenefits")and thebenefit/riskevaluationinsection18("Integratedbenefit/riskanalysisforauthorised indications"). Inthissub-section,particularattentionshouldbegiventomedicinalproducts,vaccines, anti-infectiveagentswherechangesinthetherapeuticenvironmentmaychangetheefficacy overtime.

2.5.17.3.PBRERsub-section"Characterisationofbenefits"

Thissub-sectionshouldprovidetogetherthebaselinebenefitinformationandthenew benefitinformationobtainedduringthereportinginterval,forauthorisedindications. Theamountofdetailprovidedinthissub-sectionshouldbesufficienttosupportthe benefit/riskevaluationinsection18("Integratedbenefit/riskanalysisforauthorised indications"). Whentherearenonewrelevantbenefitdata,thissub-sectionshouldprovidea characterisationoftheinformationinsub-section17.1("Importantbaselineefficacy informationidentifiedduringclinicaltrialsandinthepost-marketingperiod"). Whenthereisnewpositivebenefitinformationbutnosignificantchangeintherisk profileinthisreportinginterval,thebaselineinformationandnewinformationshouldbe integratedandpresentedsuccinctly.

Thissub-sectionshouldprovideaconcisebutcriticalevaluationofthestrengthsand limitationsofthefindingsonefficacyduringtheclinicaltrialsandinthepost-marketing period,consideringthefollowingwhereapplicable:

Abriefdescriptionofthestrengthofevidenceofbenefit,consideringcomparator, effectsize,statisticalstrength,methodologicaladvantagesanddeficiencies,and consistencyoffindingsfromtrials.

Newinformationthatchallengesthevalidityofasurrogateendpoint,ifused.

Clinicalrelevanceoftheeffectsize.

Generalisabilityoftreatmentresponseacrosstheindicatedpatientpopulation (e.g.informationthatdemonstratestreatmentineffectivenessinasub- population). Adequacyofcharacterizationofdose-response. Durationofeffect. Comparativeefficacy. Adeterminationoftheextenttowhichefficacyfindingsfromclinicaltrialsare generalisabletopatientpopulationstreatedinmedicalpractice.

24 2.5.18.PBRERsection"Integratedbenefit-riskanalysisforauthorisedindications"

ThemarketingauthorisationholdershouldprovideinthisPBRERsectionanoverall evaluationofthebenefitsandrisksofthemedicinalproductasusedinclinicalpractice.As sub-sections16.4("Characterisationofrisks")and17.3("Characterisationofbenefits")

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

presenttherisksandbenefits,thissectionshouldprovideacollectivecriticalanalysisthekey informationpresentedinthepreviussectionsandshouldnotrepeatthebenefitandrisk characterisationspresentedinthesub-sectionsmentionedabove.

2.5.18.1.PBRERsub-section“Benefit/riskcontext(Medicalneedandimportant alternatives)”

Thissub-sectionofthePBRERshouldprovideabriefdescriptionofthemedicalneed forthemedicinalproductintheauthorisedindicationsandasummaryofalternatives(medical, surgicalorother;includingnotreatmentoption).

2.5.18.2.PBRERsub-section“Benefit/riskanalysisevaluation”

Abenefit/riskbalanceisspecifictoanindicationandpopulation.Therefore,for medicinalproductsauthorisedformorethanoneindication,benefit/riskbalancesshould generallybeevaluatedandpresentedbyeachindicationseparately.If,foranindication,there areimportantdifferencesinthebenefit/riskbalanceamongpopulationswithintheindication, thebenefit/riskevaluationshouldbepresentedbypopulation,ifpossible.

Thebenefit/riskevaluationshouldbepresentedanddiscussedinawaytofacilitatethe comparisonofbenefitsandrisksandshouldtakeintoaccountthefollowingpoints:

Previoussectionsandsub-sectionsincludeallimportantbenefitandriskinformation. However,notallbenefitsandriskscontributeimportantlytotheoverallbenefit/risk evaluation.Therefore,thekeybenefitsandrisksconsideredintheevaluationshould bespecified.Thekeyinformationpresentedinthepreviousbenefitandrisk sections/sub-sectionsshouldbecarriedforwardtothissectionforcollective benefit/riskevaluation.

Theconditionofuseofthemedicinalproductshouldbeconsidered:Theconditionto betreated,prevented,ordiagnosed;itsseverityandseriousness;andthepopulation tobetreated(relativelyhealthy;chronicillness,rareconditions).

Withrespecttothekeybenefits,thenature,clinicalimportance,duration,and generalisabilityofthebenefitsaswellasfindingsofefficacyinnon-respondersto othertherapiesandalternativetreatmentsshouldbeconsidered.Ifthereareadifferent elementsofbenefit,allofthemshouldbeconsidered(e.g.fortherapiesfor rheumatoidarthritis:reductionofsymptomsandinhibitionofradiographic progressionofjointdamage).

Clinicalimportanceoftherisk(e.g.natureoftoxicity,seriousness,frequency, predictability,preventability,reversibility,impactonpatients),andwhetheritarose duringclinicaltrialsinunauthorisedindicationsorpopulations,off-labeluse,or misuseshouldbeconsidered.

Whenformulatingthebenefit/riskevaluation,thestrengths,weaknesses,and uncertaintiesoftheevidenceshouldbeconsidered.Howuncertaintiesinthebenefits andrisksimpacttheevaluationshouldbedescribed.Limitationsoftheevaluation shouldbediscussed

Aclearexplanationofthemethodologyandreasoningusedtoimprovethebenefit/risk evaluationshouldbeprovided:

Theassumptions,considerations,anddecisionsorweightingthatsupporttheconclusionsofthe benefit/riskevaluationshouldbeclear.

25 Ifaformalquantitativeorsemi-quantitativebenefit/riskevaluationisprovided,a summaryofthemethodsshouldalsobeincluded.

Economicconsiderations(e.g.cost-effectiveness)shouldnotbeconsideredinthe benefit/riskevaluation. WhenanyimportantnewinformationhasemergedoranadhocPBRERhasbeen requested,adetailedbenefit/riskanalysisshouldbepresentedbasedoncumulativedata.

Conversely,whenlittlenewinformationhasbeenobtainedduringthereportinginterval,the primaryfocusofthebenefit/riskevaluationshouldconsistofanevaluationofupdatedinterval safetydata. 2.5.19.PBRERsection“Conclusionsandactions”

APBRERshouldconcludebyincludingtheimplicationsofanynewinformationthat becameavailableduringthereportinginterval,whenmakinganoverallevaluationof benefit/riskforeachauthorisedindication,aswellasforrelevantsubgroups,ifappropriate.

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

Basedontheevaluationofthecumulativesafetydataandthebenefit/riskanalysis,the marketingauthorisationholdershouldassesstheneedforanychangetothereferenceproduct informationandifany,proposeappropriatechanges.Inadditionandwhereapplicable,the conclusionsshouldincludepreliminaryproposal(s)tooptimiseorfurtherevaluatethe benefit/riskbalanceforfurtherdiscussionwiththeAgency.Thismayincludeproposalsfor additionalriskminimisationactivities.
Formedicinalproductswithapharmacovigilanceorriskmanagementplan,the proposalsshouldbeincorporatedintothepharmacovigilanceplanand/orriskminimisation plan.
Basedontheevaluationofthecumulativesafetydataandthebenefit/riskanalysis,the marketingauthorisationholdershoulddrawaconclusionastotheneedforanychangeand/or action,includingimplicationsfortheapprovedSmPCandpackageleaflet(PL)forthe medicinalproductforwhichthePBRERissubmitted.Theregionalappendixshouldinclude proposalsforproductinformation(SmPCandpackageleaflet)togetherwithinformationon ongoingchanges,ifany. 2.5.20.AppendicestothePBRER AppendicestoaPBRERshouldbenumberedasfollows: 1.Referenceinformation.See2.4. 2.Cumulativesummarytabulationsofseriousadverseeventsfromclinicaltrials,and cumulativeandinterimsummarytabulationsofseriousandnon-seriousadverse reactionsfrompost-marketingdatasources.
3.Tabularsummaryofsafetysignals(Incorporationoftabulationsofsignalsintothe mainbodyofPBRERshouldbepreferred;ifnotincludedinthemainbodyofthe report,itcanbeincludedhere).
4.Listofallthemarketingauthorisationholder-sponsoredinterventionalandnon-interventionalstudieswiththeprimaryaimofidentifying,characterising,or quantifyingasafetyhazardorconfirmingthesafetyprofileofamedicinalproduct, andofnon-interventionalstudiesaimedtomeasuretheeffectivenessofrisk managementmeasures.
5.ListofthesourcesofinformationusedtopreparethePBRER(ifrequestedbythe marketingauthorisationholder). 6.RegionalappendixSection3.4. 2.5.21.MappingsignalsandriskstoPBRERsections/sub-sections
Thefollowingflowchartreflectsthegenerallocationsforthepresentationof informationonsignalsandriskswithinthePBRER.
26 Figure1.PBRERsections/sub-sections-signalsandrisks Safetydatafromavaliableinformationsources Previously recognised risk? New information constitutinga signal Section16.3 Safetysignal detected? Nofurther documentation inthePSUR Safetysignal Section15 Close? Safetysignal ongoing Section15 Section16.2Refutedsignal Newinformationon previoslyrecognised identified/potentialriskor missinginformation Potentialor identifiedrisk Important? Section16.4 Keyto benefit-risk evaluation? Section18.2 Aciton(s) Proposed? Section19 ConsiderupdatetoE2E document,ifapplicable. UpdateRSIasappropriate Nofurther documentation inthePSUR No No No Yes No Yes Yes Yes No Yes No No Yes
27 2.6.Marketingauthorisationholders'qualitysystemsforPBRERs Marketingauthorisationholdersshouldhaveinplaceprocessesandstructuresforthe preparation,qualitycontrol,reviewandsubmissionofPBRERsincludingfollow-upduring andafterevaluation.Thesestructuresandprocessesshouldbedescribedinaccordancewith thewrittenpoliciesandproceduresinthemarketingauthorisationholder’squalitysystem.
Therearevariousareasinthepharmacovigilanceprocessthatcandirectlyimpactthe qualityofPBRERs.Someexamplesincludecasemanagementofspontaneousandstudy reports,literaturescreening,signalmanagement,additionalpharmacovigilanceandpost-marketingresearchactivities,proceduresforintegrationofinformationonbenefitsandrisks fromallavailabledatasourcesandforupdatingofproductinformation.Thequalitysystem shoulddescribethelinksbetweentheresponsibilities,communicationchannelsandthe processeswiththeaimofgatheringallthenecessaryinformationfortheproductionof PBRERs.Thereshouldbedocumentedprocessesincludingqualitycontrolchecksinplaceto

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

checktheaccuracyandcompletenessofthedatapresentedinthePBRERs.Forensuring completenessofdata,adocumentedtemplateorplanfordrawingdatafromvariousdata sourcescanbedeveloped.Theimportanceofanintegratedapproachtobenefit/riskevaluation shouldunderpinprocessesandcrossdepartmentalinputstoPBRERpreparation.
ThePBRERshouldalsocontaintheassessmentofspecificsafetyissuesrequestedby competentauthorities(worldwide).Themarketingauthorisationholdershouldhave mechanismsinplacetoensurethattherequestsmadebycompetentauthorities(worldwide) duringtheirPBRERassessmentareproperlymet.
Theprovisionofthedataincludedinthesummarytabulations(see2.5.6.shouldbe subjecttosourcedataverificationagainstthemarketingauthorisationholder'ssafetydatabase toensureaccuracyofthenumberofevents/reactionspresented.Theprocessforqueryingthe safetydatabase,theparametersusedforaccesstothedataandthequalitycontrolperformed shouldbeproperlydocumented.
Anappropriatequalitysystemshouldbeinplaceinordertoavoidfailuretocomply withPBRERrequirementssuchas:
Failureinsubmission:FailureinsubmissionofPBRERS,submissionoutsidethe correctsubmissionscheduleoroutsidethecorrecttimeframes(withoutprior agreementwiththeAgency). unjustifiedomissionofinformationrequiredby2.5.
Poorqualityreports:Poordocumentationoforinsufficientinformationorevaluation inthereportsprovidedtoperformathoroughassessmentofthenewsafety information,signals,riskevaluation,benefitevaluationandintegratedbenefit/risk analysis,misuseofmedicinalproductsnothighlighted,non-useofstandardised medicalterminology(MedDRA)andinappropriateomissionofcaseswithno reportedriskfactorsincumulativereviews.
SubmissionofaPBRERwherepreviousrequestsfromtheAgencyhavenotbeenaddressed.
Failuretoprovideanexplicitevaluationofthebenefit/riskbalanceofthemedicinalproduct.
Failuretoprovideadequateproposalsforthelocalauthorisedproductinformation.
Anysignificantdeviationfromtheprocessesrelatingtothepreparationorsubmissionof PBRERsshouldbedocumentedandtheappropriatecorrectiveandpreventiveactionsshould betaken.Thisdocumentationshouldbeavailableatalltimes.
Whenthepreparationofthe PBRERisdelegatedbythemarketingauthorisationholder toalicensororacontractedpharmacovigilanceserviceinstitution,themarketingauthorisation holdershouldensurethattherespectivepartyhasaqualitysysteminplacethatiscompliant withthecurrentregulations.Explicitproceduresanddetailedagreementsshouldexist betweenthemarketingauthorisationholderandtherelatedparties.Theagreementsshould specificallyincludeanoptiontoauditthePBRERpreparationprocess.

28 2.7.TrainingofstaffmembersrelatedtothePBRERpreparationprocess

Forallorganisations,itistheresponsibilityofthepersonresponsibleforthe pharmacovigilancesystem(qualifiedpersonresponsibleforpharmacovigilance)toensurethat allthepersonnel,includingpharmacovigilance,medicalandqualitypersonnelinvolvedinthe preparation,review,qualitycontrol,submissionandassessmentofPBRERsareadequately qualified,experiencedandtrainedaccordingtotheapplicableguidelines.Itshouldbeensured thatthequalifiedpersonresponsibleforpharmacovigilanceandifrequired,allother personnelinvolvedinthisprocessreceivespecifictrainingforthedifferentprocesses,tasks andresponsibilitiesrelatingtothePBRER.
Trainingtoupdateknowledgeandskillsshouldalsobeorganizedasnecessary.
Trainingshouldcoverregulations,guidelines,scientificevaluationandwritten proceduresrelatedtothePBRERprocess.Trainingrecordsshoulddemonstratethatthe relevanttrainingwasdeliveredpriortoperformingPBRER-relatedactivities. SECTIONIII
Operationofbenefit/riskevaluationprocess
3.1.Generalprinciplesforthepreparationandsubmissionof PBRERs

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

Iftheactivesubstanceofamedicinalproductforwhichmarketingauthorisationisheld isincludedinthelistofEuropeanUnionreferencedatesandfrequencyofsubmissionof PBRERs,themarketingauthorisationholdershallpreparethePBRERsincompliancewith thislistfollowingitsreceiptofmarketingauthorisationinTurkey.Inthiscase,thelistshould beprintedoutandPBRERshouldbepreparedaccordingtothedatesannouncedinthelist.It istheresponsibilityofthemarketingauthorisationholdertofollow-uptheupdatedlist.
Iftheactivesubstanceofthemedicinalproductisnotincludedinthislist,themarketing authorisationholdercontinuetoevaluatethesafetyofitsmedicinalproductsregularlyby preparingonceineverysixmonthsduringthefirsttwoyears;onceayearduringthe subsequenttwoyearsandonceineverythreeyearsfollowingextensionofthevalidityperiod ofauthorisation. If,asaresultoftheevaluation,newsafetyinformationhasemergedthataffect benefit/riskprofileorSmPC/PL,itistheessentialresponsibilityofthemarketing authorisationholdertosubmitavariationbeforerequestedbytheAgencyandthesaidreports neednotbesubmittedtotheAgencyroutinely.However,themarketingauthorisationholder shallmakethePBRERsavailabletobeprovidedduringtheauditsconductedbytheAgency andsubmitthemtotheAgencyimmediatelyuponrequest.
Inaddition,medicinalproductsthatareinthephaseofextensionofvalidityperiodof marketingauthorisationandneverplacedonthemarketinTurkeyhavetosubmit18-month datafromthedatetheyareplacedonthemarkettotheAgency.
3.2.PBRERstatusduringextensionofvalidityperiodofmarketingauthorisation
PBRERshallbesubmittedtotheAgencyduringextensionofvalidityperiodof marketingauthorisationinlinewiththeprovisiononsubmissionschedulesetoutinthe RegulationonAuthorisationofMedicinalProductsforHumanUsepublishedintheOfficial GazetteNo.31686dated11/12/2021.
Medicinalproductsthatareinthephaseofextensionofvalidityperiodofmarketing authorisationandneverplacedonthemarketinTurkeyhavetosubmit18-monthdatafrom thedatetheyareplacedonthemarkettotheAgency.
29 3.3.RelationshipbetweenPBRERandriskmanagementplan
DuringthepreparationofaPBRER,themarketingauthorisationholdershouldconsider whetheranyidentifiedorpotentialrisksdiscussedwithinthePBRERisimportantand requiresanupdateoftheRMP.Insuchacase,updatedrevisedRMPincludingthenew importantsafetyconcernshouldbesubmittedwiththePBRER.
IfimportantsafetyconcernsareidentifiedbytheAgencyduringtheevaluationofa PBRERandnoupdatedRMPornoRMPhasbeensubmitted,recommendationsshouldbe madetosubmitanupdateoranewRMPwithinadefinedtimeline.
3.3.1.PBRERandriskmanagementplan–commonmodules
TheproposedmodularformatsforthePBRERandtheRMPaimtoaddressduplication andfacilitateflexibilitybyenablingcommonPBRER/RMPsectionstobeutilised interchangeablyacrossbothreports.Commonsectionsmentionedaboveareidentifiedin Table1:
30 Table.1.CommonsectionsofPBRERandRMP PBRERSection RMPSection Section3–“Actionstakenin thereporting intervalforsafetyreasons” PartII,moduleSV–“Post-authorisation experience”,section“Regulatoryauthorityand marketingauthorisationholderactionforsafety reasons” Sub-section5.2–“Cumulativeandinterval patientexposurefrommarketingexperience” PartII,moduleSV–“Post-authorisation experience”,section“Non-studypost- authorisationexposure” Sub-section16.1–“Summaryofsafetyissues”PartII,moduleSVIII–“Summaryofthesafety issues”(asincludedintheversionoftheRMP whichwascurrentatthebeginningofthe PBRERreportinginterval)
Sub-section16.4–“Characterisationofrisks”PartII,ModuleSVII–“Identifiedandpotential risks"
Sub-section16.5–“Effectivenessofrisk minimisation(ifapplicable)” PartV–“Riskminimisationmeasures”,section “Evaluationoftheeffectivenessofrisk

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

minimisationactivities” 3.4.EU-specificrequirements
Thescientificevaluationofthebenefit/riskbalanceofthemedicinalproductincludedin thePBRERshouldbebasedonallavailabledata,includingdatafromclinicaltrialsin unauthorisedindicationsandpopulationsdetailedin2.5.
TheEU-specificrequirementsformedicinalproductsauthorisedinEUshouldbe includedinthePBREREUregionalappendix.
3.4.1.PBREREUregionalappendix,sub-section“Proposedproductinformation”
IntheEU,duringthePBRERassessmentprocedure,itisalsodeterminedwhetherany amendmenttotheproductinformationisneeded.Theopiniongivenontheactiontakenbythe authorityshouldincluderecommendationsforupdatestoproductinformationwhereneeded.
Marketingauthorisationholdersshouldprovidethenecessarysupportivedocumentationand referenceswithinthePBRERtofacilitatethis.
Themarketingauthorisationholderisrequiredtoreviewcarefullytheimpactofthedata andevaluationspresentedwithinthePBRERonthemarketingauthorisation.Basedonthe evaluationofthecumulativesafetydataandthebenefit/riskanalysis,themarketing authorisationholdershoulddrawconclusionsinthePBRERastotheneedforanyactions and/orchangestotheSmPC(s)forthemedicinalproduct(s)forwhichaPBRERissubmitted.
Inthissub-section,themarketingauthorisationholdershouldprovidetheproposalsfor productinformation(SmPC/PL)basedontheabovementionedevaluation.Theseshouldbe basedonallEUauthorisedindications.
Forsubmissionofavariationbasedonthereviewandconclusionsofthe PBRER, changestotheproposedSmPC/PLshouldbemarkedonthepageusingtrackchangefor providingclarificationsonthechangesmadeontherighthandsideofthepage.Allthe SmPCs/PLspreparedasaresultofPBRERshouldreflecttheappropriateinformation accordingtothecumulativedataincludedandanalysedinthePBRER.
31 Amendmentstotheproductinformationshouldnotbepostponedordelayeduntilthe PBRERsubmission.Amendmentsthatarenotrelatedtotheinformationpresentedinthe PBRERshouldnotbeproposedwithinthePBRERprocedure.Itistheobligationofthe marketingauthorisationholdertosubmitavariationforthenecessaryamendmentstothe SmPC/PL.
Abriefdescriptionofongoingprocedures(e.g.variations)toupdatetheproduct informationshouldbeprovidedinthissection.
3.4.2.PBREREUregionalappendix,sub-section“Proposedadditional pharmacovigilanceandriskminimisationactivities”
Thissub-sectionshouldincludeproposalsforadditionalpharmacovigilanceand additionalriskminimisationactivitiesbasedontheconclusionsandactionsofthePBRER, includingastatementofintentiontosubmitanRMPoranupdatedRMP.
3.4.3.PBREREUregionalappendix,sub-section“Summaryofongoingsafety issues”
Inordertosupporttheinformationprovidedinthe PBRERsub-section16.1“Summary ofsafetyissues”(see2.5.16.1.),atable“Summary–Ongoingsafetyissues”shouldbe includedinthisPBRERsub-section.Thistableshouldbederivedfromtheversionof RMP availableatthebeginningofthePBRERreportinginterval(SeeRiskManagementModule).
3.4.4.PBREREUregionalappendix,sub-section“Reportingoffindingsfrompost-authorisationsafetystudies”
Findingsfrombothinterventionalandnon-interventionalpost-authorisationsafety studiesshouldbereportedinthePBRER.Whilethemarketingauthorisationholdershould informcompetentauthoritiesinMemberStatesandtheEuropeanMedicinesAgencyas applicableaboutanynewinformationthatmayaffectthebenefit/riskbalanceimmediately, thePBRERshouldprovidecomprehensiveinformationonthefindingsofallpost-authorisationsafetystudies,bothinterventionalandnon-interventional,inPBRERsections7 and8respectively. Finalstudyreportsforstudiesconductedwiththeprimaryaimofidentifying, characterisingorquantifyingasafetyhazard,confirmingthesafetyprofileofthemedicinal

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

product,orofmeasuringtheeffectivenessofriskmanagementmeasureswhichwere completedduringthereportingintervalshouldalsobeincludedasanannextothePBRER. Forsuchstudiesdiscontinuedduringthereportinginterval,thereasonsforstoppingthestudy shouldalsobeexplained. Ifanimportantsafetyconcernisidentifiedinthecourseofastudy,regardlessof whetherithasbeendetectedthroughpre-specifiedmethodsandwhetherthestudyis consideredapost-authorisationsafetystudy,themarketingauthorisationholderand specificallythequalifiedpersonresponsibleforpharmacovigilanceshallimmediatelyinform therelevantcompetentauthoritiesinMemberStates.
PBRERsshouldnotbeusedastheinitialcommunicationmethodforthesubmissionof finalstudyreportstothecompetentauthoritiesinMemberStatesorforthenotificationofany newinformationthatmightinfluencetheevaluationofthebenefit/riskbalance.
3.4.5.PBREREUregionalappendix,sub-section“Effectivenessofriskminimisation”
Riskminimisationactivitiesarepublichealthinterventionsintendedtopreventthe occurrenceofanadversedrugreaction(s)associatedwiththeexposuretoamedicinalproduct ortoreduceitsseverityshoulditoccur.Thesuccessofriskminimisationactivitiesin achievingtheseobjectivesshouldbeevaluatedthroughoutthelife-cycleofamedicinal producttoensurethattheburdenofadversereactionsisminimisedandthus,theoverall benefit/riskbalanceisoptimised.Inaccordancewithsection2.5.16.5.,evaluationofbroad globalexperiencewouldbereflectedintheentirebodyofthereport.

32 Thissub-sectionshouldadditionallyprovideanevaluationoftheeffectivenessof routineand/oradditionalriskminimisationactivitiesspecificallyrelevanttoanEUcontext. Resultsofanystudytoassesstheimpactorotherformalassessmentofriskminimisation activitiesintheEUshouldalsobeincludedwhenavailable.Aspartofthiscriticalevaluation, themarketingauthorisationholdershouldmakeobservationsonfactorscontributingtothe successorweaknessofriskminimisationactivities.Ifaparticularriskminimisationstrategy provesineffective,thenalternativeactivitiesneedtobeputinplace.Incertaincases,itmay bejudgedthatriskminimisationcannotcontroltheriskstotheextentpossibletoensurea positivebenefit/riskbalanceandthatthemedicinalproducteitherneedstobewithdrawnfrom themarketorrestrictedtothosepatientsinwhomthebenefitsoutweightherisks.More extensiveguidanceonmonitoringtheeffectivenessofriskminimisationactivitieswillbe publishedinaseparatemodule.Asaprinciple,themarketingauthorisationholdershould distinguishintheirevaluationbetweenimplementationsuccessandattainmentoftheintended outcome. 3.5.RequirementsspecifictoourcountryPointsmentionedintheEU-specificrequirementssectionshouldalsobeprepared separatelyforourcountryandarchivedwiththePBRER.
3.6.QualitysystemsandrecordmanagementsystemsforPBRERs
3.6.1.Qualitysystemsandrecordmanagementsystemsatthelevelofthemarketing authorisationholder
Themarketingauthorisationholdershouldputinplacespecificqualitysystem proceduresandprocessesinordertoensuretheupdateofproductinformationinthelightof scientificknowledge,includingtheunion/associationannouncementsreleasedbyTITCK. Themarketingauthorisationholdersareresponsibleforcheckingregularlythelistof EUreferencedatesandfrequencyofsubmissionpublishedintheEMAweb-portaltoensure compliancewiththePBRERreportingrequirementsfortheirmedicinalproducts. Formedicinalproductsforwhichthesubmissionofan RMPisnotrequired,the marketingauthorisationholdershouldmaintainonfileaspecificationofimportantidentified risks,importantpotentialrisksandmissinginformationinordertosupportthepreparationof thePBRERs. Themarketingauthorisationholdershouldhaveproceduresinplacetofollowthe requirementsestablishedbytheAgencyforthesubmissionofPBRERs.
Thequalifiedpersonresponsibleforpharmacovigilanceshallberesponsibleforthe establishmentandmaintenanceofthepharmacovigilancesystemandthereforeshouldensure thatthepharmacovigilancesysteminplaceensuresthecompliancewiththerequirements

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

establishedfortheproductionandsubmissionofPBRERs.Inrelationtothemedicinal productscoveredbythepharmacovigilancesystem,specificadditionalresponsibilitiesofthe qualifiedpersonresponsibleforpharmacovigilanceinrelationtoPBRERsshouldincludethe following: Ensuringthenecessaryquality,includingtheaccuracyandcompleteness,ofthedata submittedinthePBRERs;
Ensuringfullresponseaccordingtothetimelinesandwithintheprocedureagreed(e.g. nextPBRER)toanyrequestfromtheAgencyrelatedtoPBRERs,
Awarenessoftheunion/associationandotherimportantdecisionsinordertoensure thatappropriateactionistaken.
TherecordretentiontimesforproductrelateddocumentsinModuleIVshallalsoapply toPBRERSandsourcedocumentsrelatedtothecreationofPBRERS,includingdocuments relatedtoactionstakenforsafetyreasons,clinicaltrialsandpost-authorisationstudies, relevantbenefitinformationanddocumentsusedforthecalculationofpatientexposure.

33 APPENDICES

Appendix1.Examplesoftablesforestimatedexposureandadverseevents/reactions data Table2.Estimatedcumulativesubjectexposureinclinicaltrials
Estimatesofcumulativesubjectexposure,baseduponavailabledatafromcompletedclinical trialsandtheenrolment/randomisationschemesforongoingtrials. Treatment Numberofsubjects Drug Comparator Placebo Table3.Cumulativesubjectexposuretoinvestigationaldrugincompletedclinicaltrials byageandsex Numberofsubjects Agerange Male Female Total Datafromcompletedtrialsasof[date] Table4.Cumulativesubjectexposuretoinvestigationaldrugincompletedclinicaltrials byracial/ethnicgroup Racial/ethnicgroup Numberofsubjects Asian Black White Other Unknown Total Datafromcompletedtrialsasof[date] Table5.Cumulativeexposureinmarketingexperience Indication Sex Age(years) Dose Formulation Region MaleFemale2 to ≤ 16 >16 to 65 >65Unknown<40≥ 40 UnknownIntravenousOralEUJapanTurkeyUSA/CanOther Total Depression Migraine Table5.Includescumulativedataobtainedfromday/month/yeartoday/month/year,where available

34 Table6.Intermittentexposureinmarketingexperience Indication Sex Age(years) Dose Formulation Region MaleFemale2 to ≤ 16 >16 to 65 >65Unknown<40≥ 40 UnknownIntravenousOralEUJapanTurkeyUSA/CanOther Depression Migraine Table6includesdatainaparticularintervalfromday/month/yeartoday/month/year
Table7.Cumulativetabulationofseriousadverseeventsthatoccurredinclinicaltrials SystemOrganClass (SOC) Preferred Term(PT) Investigational Medicinal Product Blinded Activecomparator Placebo BloodandLymphatic SystemDisorders n n n n Anemia n n n n BoneMarrowNecrosis n n n n CardiacDisorders n n n n Tachycardia n n n n Ischaemic Cardiomyopathy n n n n Table8.Numberofadversereactionsfrompost-authorisationsources*codedwith"preferred term". SOC MedDRA PT Spontaneousreportings,includingthosefromcompetent authorities(worldwide)andliterature Non-interventional post-marketingstudy andreportsfrom othersolicited sources** Serious Non-serious Total spontaneous Serious IntervalCumulativeIntervalCumulativeCumulative IntervalCumulative <SOC1> <PT> <PT> <PT> <SOC2> <PT> <PT> <PT> <PT> <PT>
*Non-interventionalpost-authorisationstudies,reportsfromothersolicitedsourcesand spontaneousICSRs(e.g.reportsfromhealthcareprofessionals,consumers,competent authorities(worldwide),andscientificliterature) **Doesnotincludeinterventionalclinicaltrials.

35 Appendix2.Exampleoftabularsummaryofsafetysignalsthatwereongoingorclosed duringthereportinginterval Thetablebelowhasbeenconfiguredforafictitiousmedicinalproduct. Table9.Tabularsummaryofsafetysignalsongoingorclosedduringthereporting interval Reportinginterval:DD-MMM-YYYYtoDD-MMM-YYYY Signal term Date detected Status (ongoing orclosed) Dateclosed (forclosed signals) Sourceof signal Reasonfor evaluationand summaryofkey data Methodofsignal evaluation Action(s)taken orplanned StrokeMMM/ YYY OngoingMMM/ YYY

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g

Meta-analysis (published trials) Statistically significantincrease infrequency Reviewofmeta-analysesand availabledata. Pending. SJS MMM/ YYY Closed MMM/ YYY Spontaneous casereports Rashisalready amongidentified risks. SJSwasnot reportedinpre- authorisation clinicaltrials. 4reportswithinthe first6monthsof authorisation; reasonabletimefor theonsetof reaction;no alternativecauses. Targetedfollow- upofreportswith avisittoa hospital. Reviewofcases bythemarketing authorisation holder's dermatologistand literaturesearch. Updateof warnings/precauti onssectionof referencesafety information. Sendingdirect healthcare professional communication. Planning effectiveness survey6months afterdistribution ofletters. UpdateofRMP. ExplanatoryNotes Signalterm: Abriefdescriptivenameofamedicalconceptforthesignal.Thismaybedeveloped andarrangedasthesignalisevaluated.Theconceptandscopemayormaynotbe limitedtospecificMedDRAterms,dependingonthesourceofsignal. Datedetected: Monthandyearthemarketingauthorisationholderbecameawareofthesignal Status: Ongoing:Signalsstillunderevaluationatthedatalockpointofthe PBRER.Ifknown,anticipated completiondateshouldbeprovided.

36 Closed:Signalforwhichevaluationwascompletedbeforethedatalockpointof thePBRER. Note:Anewsignalofwhichthemarketingauthorisationholderbecameawareduringthe reportinginterval;maybeclassifiedasclosedorongoing,dependingonthestatusofthe signalevaluationattheendofthereportingintervalofthePBRER. Dateclosed(month/year): Monthandyearwhenthesignalevaluationwascompleted. Sourceofsignal: Dataorinformationsourcefromwhichasignalarose(e.g.spontaneousreports, clinicaltrialdata,scientificliterature,non-clinicalstudyresults,informationrequestor inquiriesfromcompetentauthorities(worldwide)). Reasonforevaluationandsummaryofkeydata: Abriefsummaryofkeydataandrationaleforfurtherevaluation. Action(s)takenorplanned: Statewhetherornotaspecificactionhasbeentakenorisplannedforallclosedsignals thathavebeenclassifiedaspotentialoridentifiedrisks.Ifadditionalactionsare plannedfornewlyorpreviouslyidentifiedsignalsunderevaluationatthedatalock point,theseshouldbeincludedinthelist,otherwise,thispartshouldbeleftblankfor ongoingsignals.

37 Periodcoveredbythisreport: From<date>to<date>(e.g.datalockpoint) DateofthisReport: <Date> Appendix3.CoverletterforPBRERSubmission PERIODICBENEFIT/RISKEVALUATIONREPORT ACTIVESUBSTANCE(S):<Name(s)> ATCCODE(S):<Code(s)> MEDICINALPRODUCTSCOVERED: Medicinal productname(s) Marketing authorisationnumber(s) Marketing authorisationdate(s) Marketing AuthorisationHolder <> <> <> <> <> <> <> <> INTERNATIONALBIRTHDATE:<Date> OTHERINFORMATION:
<Otheridentifyingordescriptiveinformation,dependingontherequestofthemarketingauthorisation holder> MARKETINGAUTHORISATIONHOLDER'SNAMEANDADDRESS: <Name> <Address> NAMEANDCONTACTDETAILSOFTHEQUALIFIEDPERSONRESPONSIBLEFOR PHARMACOVIGILANCE: <Name,surname> <Address> <Phone> <Fax> <E-mail> “Iherebydeclareandundertakethatthepharmacovigilancedataarecorrect." SIGNATURE:<signature> DISTRIBUTIONLIST <Authority> <Numberofcopies>

sion published by the Turkish Medicines and Medical Devices Agency (TİTCK), imported from the AIFD Legislation Portal archive. In the event of any discrepancy, the Turkish original text (mevzuat.g