*DELETE THIS PAGE*

*The Periodic Safety Update Report (PSUR) template provides required, suggested, and instructional text according to the following key:*

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(Note: Authors may add additional black text for their particular PSUR, if applicable.)

RED TEXT contained in brackets [ ] is information to be Inserted

BLUE TEXT is Optional/Suggested

*GREEN, ITALIC TEXT is Instructional*

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* *Deleting green text and blue boxes (described below)*
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*Throughout this document, tables (example below) provide an alert to authors where there are common sections among PBRERs, RMPs and/or DSURs, and the information presented in these different reports should be consistent. Do not populate the boxes with information or text; blue boxes are similar to instructional text and must be deleted by the applicable Author(s).*

|  |  |  |
| --- | --- | --- |
| *PBRER section* | *RMP section* | *DSUR section* |
|  |  |  |



Marketing Authorisation Holder:

Otsuka Pharmaceutical Development & Commercialization Inc.

2440 Research Boulevard

Rockville, MD 20850

[Generic name]

**PERIODIC SAFETY UPDATE REPORT (PSUR)**

# [RPT #]

IBD: [DD Mmm YYYY]

Reporting Interval: [DD Mmm YYYY] to [DD Mmm YYYY]

Note: This report may contain unblinded clinical trial adverse event data.

Information and data submitted herein contains confidential and proprietary information, and is the property of Otsuka Pharmaceutical Company. Regulatory agencies are not authorised to make this information and data public without written permission from Otsuka.

|  |  |
| --- | --- |
| Signature: | Electronically signed |
|  | [Type Name/Title] - *obtained from Medical Safety Product Lead* |

|  |  |
| --- | --- |
| Signature: | Electronically signed |
|  | [Type Name/Title] - *obtained from EU QPPV* |

# 

# EXECUTIVE SUMMARY

*Lead author(s): Aggregate reporting associate will obtain this information from other sections of the PSUR.*

*Provide a concise summary of the content and the most important information in the report and should contain the following information:*

* *Introduction;*
* *Reporting interval;*
* *Medicinal product(s) - mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s);*
* *Estimated cumulative exposure of clinical trial subjects; interval and cumulative postapproval exposure;*
* *Number of countries in which the medicinal product is approved;*
* *Summary of the overall benefit-risk analysis evaluation (based on subsection 18.2 “benefit-risk analysis evaluation” of the PBRER);*
* *Actions taken or proposed for safety reasons, eg, significant changes to the reference product information, other risk minimisation activities;*
* *Conclusions.*

This is the [#] periodic safety update report (PSUR) for [generic name].

This Periodic Safety Update Report (PSUR) summarises the benefit-risk information received by the Marketing Authorisation Holder (MAH) and any applicable comarketers from worldwide sources during the reporting interval of [DD Mmm YYYY] to [DD Mmm YYYY]. [Generic name] is indicated for the treatment of [add brief description of approved indication(s) and population(s)].

[Generic name] is available as [add formulation(s); dose(s), route(s) of administration and describe therapeutic class (es) and mechanism(s) of action]. [Generic name] was first approved in [Country] on [DD Mmm YYYY] and is currently registered and approved in [#] countries *or* registered in [#] countries and approved in [#] countries.

During the reporting interval of this PSUR, there were approximately [#] patient-years of treatment with [generic name].

*OR*

During the reporting interval of this PSUR, there were approximately [#] patients treated with [generic name].

Cumulatively, there were approximately [#] patient-years of treatment with [generic name].

*OR*

Cumulatively, there were approximately [#] patients treated with [generic name].

Cumulatively, there were approximately [#] patient-years of treatment with [generic name] in MAH-sponsored clinical trials.

*OR*

Cumulatively, there were approximately [#] patients exposed to [generic name] in MAH-sponsored clinical trials.

During the reporting interval of this PSUR, there were [#] safety related updates to the MAH CCDS for [generic name]. *(Briefly note changes at a high level.)*

*Provide a brief summary of benefit-risk from Section 18.2 Benefit-Risk Analysis Evaluation*

*From section 18.2.1 suggested text for conclusion statements:*

*If no new information was received during the PSUR data interval that significantly alters the benefit-risk profile:*

Overall, the previously established favourable benefit-risk profile for [generic name] for the treatment of [approved indication(s)] in [specify population(s)] has been reconfirmed by the efficacy and safety data that have become available during this reporting interval.

*If new efficacy / safety information was received that modifies the benefit-risk profile, but the overall benefit-risk remains positive:*

During the PSUR reporting interval, the MAH has received new, important [efficacy / safety] information that resulted in a modification of the benefit-risk profile of [generic name]. An integrated assessment of the key benefits and risks, considering the full body of the available evidence, indicates that the overall benefit-risk remains positive.

*If more than one indication-specific benefit-risk evaluation, an overall benefit-risk conclusion should be presented for the product as a whole.*

Overall, the previously established favourable benefit-risk profile for [generic name] has been reconfirmed by the efficacy and safety data that have become available during this reporting interval.

*If new efficacy / safety information was received that modifies the benefit-risk profile, but the overall benefit-risk remains positive:*

During the PSUR reporting interval, the MAH has received new, important [efficacy / safety] information that resulted in a modification of the benefit-risk profile of [generic name]. An integrated assessment of the key benefits and risks, considering the full body of the available evidence, indicates that the overall benefit-risk remains positive.

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# LIST OF ABBREVIATIONS, ACRONYMS, AND DEFINITION OF TERMS

***All authors are responsible for updating the abbreviations list as needed.***

| Abbreviation/Acronym | Definition |
| --- | --- |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| CCDS | Company core data sheet |
| CCSI | Company core safety information |
| CSR | Clinical study report |
| CTA | Clinical trial application |
| DIBD | Development international birth date |
| DSUR | Development safety update report |
| FDA | US Food and Drug Administration |
| GPV | Global Pharmacovigilance |
| HCP | Healthcare provider |
| IB | Investigator’s brochure |
| ICSR | Individual case safety report |
| IMP | Investigational medicinal product |
| IND | Investigational new drug |
| MAH | Marketing authorisation holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PASS | Post authorisation safety study |
| PB | Professional brochure |
| PT | Preferred term |
| PSUR | Periodic safety update report |
| RMP | Risk management plan |
| SAE | Serious adverse event |
| SAR | Serious adverse reaction (defined as serious adverse event that is considered drug-related by investigator and/or sponsor) |
| SOC | System organ class |

***GENERAL GUIDANCE NOTE TO AUTHORS:***

***This document is written in accordance with guidelines outlined in the Otsuka Style Guide. If publications and other source documents are cited in this PSUR please enter them as endnotes utilising the guidance in the Otsuka Style guide and mentioned in regional appendix 21.7 of this template***

***Due to the global nature of this document it is to be written in British-style English (as per “English (UK)” option in Word “Spelling &Grammar” check.***

***The use of trial rather than study is preferred. Use trial rather than study, except when referring to a clinical study report, nonclinical study, observation, or epidemiology study***

***A subject is a person with a particular characteristic or behaviour, or a person who undergoes an intervention and is examined in a scientific investigation. Subjects may be used when referring to individuals participating in a clinical trial. Patients may be used when discussing marketed product, eg, as with postmarketing exposure.***

Throughout this document:

* Individual Case Study Reports (ICSRs) may be referred to as 'reports' or 'case reports'.
* The terminology for 'interval' and 'period' may be used interchangeably.
* EU GVP Module VI states that only valid ICSRs should be reported.  An element of a valid ICSR as defined by Module VI is at least a single patient identifier characterised by initials, patient identification number, date of birth, age, age group or gender.  However other regulatory agencies define patient identifiers in broader terms.  Therefore, counts reflected in the report may differ from what was reported as an ICSR to a specific health authority, regulatory agency or licence partner as a result of the differing guidelines.

# Introduction

*Lead author(s): Aggregate reporting associate*

*The PSUR Introduction should include, if applicable:*

* *International birth date (IBD) the date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world;*
* *Reporting interval;*
* *Medicinal product(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);*
* *A brief description of the approved indication(s) and population(s);*
* *A brief description and explanation of any information that has not been included in the PSUR (e.g., when written agreements with a partner company do not provide for exchange of all safety data; product(s)covered in a separate PSUR such as a combination product);*
* *The rationale for submission of multiple PSURs for the medicinal product, if applicable. See guidance for combination therapies in Section 7.5. Please note: wherever possible only one PSUR should be produced.*

This is the [#] periodic safety update report (PSUR) for [generic name].

This PSUR on [generic name], ([IBD of DD Mmm YYYY]), summarises the benefit-risk information received by the MAH and any applicable comarketers from worldwide sources between [ DD Mmm YYYY] to [ DD Mmm YYYY].

[Generic name] is indicated for the treatment of [add brief description of approved indication(s) and population(s)].

[Generic name] is available as [add formulation(s); dose(s), route(s) of administration and describe therapeutic class (es) and mechanism(s) of action].

*If multiple  MAHs and/or business partner(s) for the product exist, please consider including the following:*

This document only reflects data for [generic name] received by the MAH and business partner and not that of other MAHs of [generic name], if applicable. However, if it was not possible to identify the MAH, then Otsuka Pharmaceuticals, Inc. is assumed to be the MAH.

*If excluding any products/formulations from this PSUR, explain why.*

[Generic name, containing the same active ingredient] is [an over-the-counter product, prescription product, fixed combination product, product with multiple indications and/or formulations where multiple PSURs are prepared in agreement with competent authority] and a separate PSUR is prepared for this product.

# Worldwide Marketing Authorisation Status

*The table below describes common sections between PSUR and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 2.0 – Worldwide Marketing Authorisation Status* | *Section 2.0 Worldwide Marketing Approval Status* |

*NOTE Regulatory affairs is responsible for populating this section.*

*Sub-sections for US, EU, Asia and Rest of World (ROW) have been included below. If not applicable, please remove sub-sections and include all text under this main heading in section 2.*

*This section should provide a brief narrative overview including date of first approval, indication(s), approved dose(s), and where approved.*

The product [generic name] was first [approved/authorised] for marketing in [country] on [date] for the indication of [insert indication and also approved doses(s)].

At the time of this report [generic name] has been registered and approved in [#] countries (see Appendix 21.8).

There are no records of any registration being revoked or withdrawn for safety reasons.

*OR*

*Detail any relevant safety action(s) related to medicinal product registration / authorisation.*

## Marketing Authorisation Status (EU)

*This header should only be included if applicable. If not, please put all text in section above (2.0) and refer to the table in Appendix 21.8.*

At the time of this report, [generic name] has been registered and approved in [#] countries within the EU [name of the countries] and is approved for the following indications and doses:

* [mention indication(s) and the approved dose(s)]

## Marketing Authorisation Status (US)

*This header should only be included if applicable. If not, please put all text in section above (2.0) and refer to the table in Appendix 21.8.*

At the time of this report, [generic name] has been registered and approved in the US and is approved for the following indications and doses:

* [mention indication(s) and the approved dose(s)]

## Marketing Authorisation Status (Asia)

*This header should only be included if applicable. If not, please put all text in section above (2.0) and refer to the table in Appendix 21.8.*

At the time of this report, [generic name] has been registered and approved in [#] countries within Asia [name of the countries] and is approved for the following indications and doses:

* [mention indication(s) and the approved dose(s)]

## Marketing Authorisation Status (Rest of World)

*This header should only be included if applicable. If not, please put all text in section above (2.0) and refer to the table in Appendix 21.8.*

At the time of this report, [generic name] has been registered and approved in [#] countries within the rest of world [name of the countries] and is approved for the following indications and approved doses:

* [mention indication(s) and the approved dose(s)]

# Actions Taken in the Reporting Interval for Safety Reasons

*The table below describes common sections between PSUR, RMP and DSUR*

|  |  |  |
| --- | --- | --- |
| *PBRER section* | *RMP section* | *DSUR section* |
| *Section 3 – Actions Taken in the Reporting Interval for Safety Reasons* | *EU RMP:*  *SV.1 Action Taken by Regulatory Authorities and/or Marketing Authorisation Holders for Safety Reasons* | *3.0 Action Taken in the Reporting Period for Safety Reasons* |

*Lead author(s): Regulatory Affairs*

*Sub-sections for US, EU, Asia and Rest of World (ROW) have been included below. If not applicable, please remove sub-sections and include all text under this main heading in section 3.*

*This section should include a description of significant actions related to safety that have been taken worldwide during the reporting interval, related to either investigational uses or marketing experience, by the MAH, sponsor of clinical trial(s), data monitoring committees, ethics committees or competent authorities that had either:*

* *A significant influence on the benefit-risk balance of the authorised medicinal product, and/or*
* *An impact on the conduct of a specific clinical trial(s) or on the overall clinical development Programme.*
* *The reason(s) for each action should be provided, if known, and additional relevant information should be provided when appropriate. Relevant updates to previous actions should also be summarised in this section. Examples of significant actions taken for safety reasons include:*
* *Actions related to investigational drugs:*
* *refusal to authorise a clinical trial for ethical or safety reasons;*
* *partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy (see Section 13);*
* *Note: “Partial suspension” might include several actions (e.g., suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another and/or suspension of a particular dosing regimen in a trial but continuation of other doses).*
* *recall of investigational drug or comparator;*
* *failure to obtain marketing Authorisation for a tested indication including voluntary withdrawal of a marketing Authorisation application;*
* *risk management activities, including:*

*− Protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);*

*− Restrictions in study population or indications;*

*− Changes to the informed consent document relating to safety concerns;*

*− Formulation changes for a safety reason;*

*− Addition by regulators of a special safety-related reporting requirement;*

*− Issuance of a communication to investigators or healthcare professionals; and*

*− Plans for new studies to address safety concerns.*

*Actions related to marketed drugs:*

*Failure to obtain a marketing Authorisation renewal;*

*Withdrawal or suspension of a marketing Authorisation;*

*Actions taken due to product defects and quality issues; including suspension of supply;*

*Risk management activities including:*

*− Significant restrictions on distribution or introduction of other risk minimisation measures;*

*− Significant safety-related changes in labelling documents including restrictions on use or population treated;*

*− Communications to health care professionals; and*

*− New postmarketing study requirement(s) imposed by competent authorities.*

During the reporting period of this PSUR, there have been no regulatory or manufacturer actions related to [generic name] due to safety reasons.

*OR*

During the reporting period of this PSUR, the following regulatory actions related to [generic name] that were taken for safety reasons are described below: [describe safety actions that occurred in the PSUR period via text or by using table below].

*OR*

| Table 3-1 Actions Taken in the Reporting Interval for Safety Reasons | | | | |
| --- | --- | --- | --- | --- |
| Medicinal Product | | Action taken for safety reasons | Reference document concerned (if applicable) | Country |
| Trade name | Active substance |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

## Actions Taken in the Reporting Interval for Safety Reasons (EU)

*This header should only be included if applicable. If not, please put all text in section above (3.0).*

## Actions Taken in the Reporting Interval for Safety Reasons (US)

*This header should only be included if applicable. If not, please put all text in section above (3.0).*

## Actions Taken in the Reporting Interval for Safety Reasons (Asia)

*This header should only be included if applicable. If not, please put all text in section above (3.0).*

## Actions Taken in the Reporting Interval for Safety Reasons (Rest of World)

*This header should only be included if applicable. If not, please put all text in section above (3.0).*

# Changes to Reference Safety Information (RSI)

*Lead author(s): Labelling Team*

*This section should list any significant changes to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, adverse drug reactions (ADRs), overdose, and interactions; important findings from ongoing and completed clinical trials;\* and significant nonclinical findings (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PBRER.*

*A clean version of the reference document that is current at the DLP of the PBRER should be included in Appendix 21.1. A track change version of the reference information is not required. The author is responsible for uploading label to the Report Appendix folder in GEPIC.*

*If CCDS is being used as reference safety information (most often will be the case), please use the following standard text:*

The Company Core Data Sheet (CCDS) contains the MAH indications, dosage, pharmacology, and other product information. This information is based on the MAH’s ongoing review of the safety profile of [generic name]. The CCDS that was current at the end of the reporting interval is included in Appendix 21.1.

Changes to RSI during the Reporting Interval:

During the reporting interval of this PSUR, there were no safety related changes to the CCDS for [generic name].

*OR*

During the reporting interval of this PSUR, the following safety related updates which required a change to the CCDS for [generic name]. Refer to Section 16 for documentation that supported the label change.

*OR*

*If there is no CCDS or CCSI for a product, eg, where the product is approved in only one country or region or for established/generic products on the market for many years, the MAH should clearly specify the reference information being used. This may comprise national or regional product information such as the US Package Insert (USPI) or European Summary of Product Characteristics (SmPC), or the Japanese package insert, as appropriate. For this scenario, please use the following standard text:*

The [EU SmPC / USPI / Japan SPC] was the reference safety information used during the reporting period. The [EU SmPC / USPI / Japan SPC] contains the MAH indications, dosage, pharmacology, and other product information. This information is based on the MAH’s ongoing review of the safety profile of [generic name]. The reference safety information that was current at the end of the reporting interval is included in Appendix 21.1.

*Add other supporting details, eg, CCDS was finalised after the end of the reporting interval, on X date, and will be included in the next PSUR for [generic name].*

Changes to RSI during the Reporting Interval

During the reporting interval of this PSUR, there were no safety related changes to the [EU SmPC / USPI / Japan SPC] for [generic name].

*OR*

During the reporting interval of this PSUR, the following safety related updates which required a change to the [EU SmPC / USPI / Japan SPC] for [generic name]. Refer to Section 16 for documentation that supported the label change.

# Estimated Exposure and Use Patterns

*Sections 5.1 and 5.2 of the PBRER should provide estimates of the size and nature of the population exposed to the medicinal product. This estimate of exposure shall accompany a qualitative and quantitative analysis of actual use, how actual use differs from the indicated us based on all data available to the MAH, including the results of observational or DUS studies. Section 5.1 of the PBRER should provide information on cumulative exposure in clinical trials. Section 5.2 should provide cumulative and interval exposure in the marketed setting. Brief descriptions of the method(s) used to estimate the subject/patient exposure should be provided, as well as the limitations thereof. Consistent methods for calculating patient exposure should be used across PBRERs for the same product. If a change in the method is appropriate, both methods and calculations should be provided in the PBRER introducing the change.*

## Cumulative Subject Exposure in Clinical Trials

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 5.1 Cumulative Subject Exposure in Clinical Trials* | *6.1 Cumulative Subject Exposure in the Development Programme* |

*Lead author(s): Clinical Management for Otsuka-Sponsored clinical trials. Clinical Management reviews the information from the Global Study List from Programme Management and confirms it is consistent with the output data provided by the DSUR coordinator / Clinical Programming..*

*This section should include the following information; in tabular format:*

* *Cumulative number of subjects from ongoing and completed MAH sponsored clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD.*
* *Cumulative subject exposure for ongoing and completed clinical trials should be sub grouped by age range, sex, and racial group for the development programme when the data are available;*
* *Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered*
* *If clinical trials have been or are being performed in special populations (e.g., pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided, as appropriate.*
* *When there are substantial differences in time of exposure between subjects randomised to the investigational medicinal product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years);*
* *Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate;*
* *If the serious adverse events from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available;*

*For individual trials of particular importance, demographic characteristics should be provided separately.*

*Please see the following definitions for what to be included in this section:*

*Started (FPFV in the PSUR period)*

*Active (FPFV before the PSUR period, but FSR not yet completed)*

*Completed (FSR completed in the PSUR period)*

*The table for estimated subject exposure (Table 5.1-1) and demographic tables (Table 5.1-2 and Table 5.1-3) are included below. Cumulative Subject Exposure from the Clinical Trial Programme by Age and Sex, the specific categorisation of age may vary dependent on programme specifics and age categories may overlap. The tables may be separated by indication if appropriate.*

*This section should also include an explanation of the sponsor’s rationale for selecting the method to estimate subject exposure, and the limitations of that method, based on the points above.*

Overall, [####] subjects have been included in the [generic name] clinical programme, of which [####] subjects have received [generic name].   Estimates of overall cumulative subject exposure from completed and ongoing studies are provided in Table 5.1-1.  Cumulative subject exposure from the clinical trial programme by age and sex and by racial group is presented in Table 5.1-2 and Table 5.1-3.  *If complete exposure data is not available, describe those limitations.*

| Table 5.1-1 Cumulative Estimated Subject Exposure in Clinical Trials1, 2 | |
| --- | --- |
| Treatment | Number of subjects3 |
| Medicinal Product |  |
| Placebo |  |
| Comparator Name #1 |  |
| Comparator Name #2 |  |
| **Total** |  |
| 1 *[Choose the following if PSUR is for same reporting period as DSUR]* For ongoing blinded studies, all enrolled patients are counted as “blinded.” For ongoing open studies and completed studies, patient exposure estimates are based on treatment arms. Patients enrolled in multiple studies are counted separately.  *[OR choose the following for all other PSURs]*  Estimates of exposure are based on randomisation schemes for blinded ongoing and treated subjects from open and completed studies.  2 Includes patients and healthy volunteers, as of [DD Mmm YYYY].  3 Includes subjects that have received [product name] and *[choose the following text and amend as appropriate]* other compounds in investigational studies and/or comparators during crossover studies. | |

*Demographic data is cumulative from the ENTIRE clinical development programme can be presented either as one cumulative table or if needed, provide individual tables per study.*

*These tables are only required for the ENTIRE clinical trial programme, both ongoing and completed studies. The specific categorisation of age might be dependent on the subject population and indication.*

| Table 5.1-2 Cumulative Subject Exposure to [Generic Name] from the Clinical Trial Programme by Age and Sex1 | | | | |
| --- | --- | --- | --- | --- |
| Number of Subjects | | | | |
| Age Range (year) | Male | Female | Unknown | Total |
| **<18** |  |  |  |  |
| **18 to 65** |  |  |  |  |
| **66 to 75** |  |  |  |  |
| **>75** |  |  |  |  |
| **Unknown** |  |  |  |  |
| **Total** |  |  |  |  |
| 1 Data from ongoing and completed trials as of [date] | | | | |

| Table 5.1-3 Cumulative Subject Exposure to [Generic Name] from the Clinical Trial Programme by Racial Group1 | |
| --- | --- |
| Racial Group | Number of subjects |
| **Asian** |  |
| **Black** |  |
| **American Indian or Alaska Native** |  |
| **Caucasian** |  |
| **Other** |  |
| **Unknown** |  |
| **Total** |  |
| 1 Data from ongoing and completed trials as of [date] | |

## Cumulative and Interval Patient Exposure from Marketing Experience

*Common sections between PBRER and RMP and DSUR*

|  |  |  |
| --- | --- | --- |
| *PBRER section* | *RMP section* | *DSUR section* |
| *Section 5.2 Cumulative and Interval Patient Exposure from Marketing Experience* | *EU RMP:*  *SV.2 Nonstudy Postauthorisation Exposure* | *6.2 Patient Exposure from Marketing Experience*  *(Note: Cumulative only)* |

*Lead author(s): Aggregate Reporting Associate*

*Contributing Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead; Epidemiology or MSO Delegate(s); Medical Affairs; Sales/Marketing (per region: EU, Japan and US)*

### Postauthorisation (Nonclinical Trial) Exposure

*An overall estimation of patient exposure should be provided. In addition, the data should be routinely presented by sex, age, indication, dose, formulation and region, where applicable. Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment. When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.*

The number of patients/patient-years treated with marketed [product name] worldwide during the period of this PSUR from [DD Mmm YYYY] to [DD Mmm YYYY], was approximately [######].The usual dose of [product name] is [dosage] and the usual duration of therapy is [provide duration], depending on [list dependencies if applicable]. This would imply theoretical lower and upper limits of treatment courses, ranging from [insert appropriate calculations].

A summary of the worldwide distribution of [product name] cumulatively until the data lock point of this PSUR is presented in Table 5.2-1. The estimated patient exposure was based upon [insert assumptions and methodology used for PYT calculation].

This estimate of patient exposure for the cumulative reporting period is based on the availability of monthly product distribution figures; hence, this cumulative estimate has been calculated to [Mmm YYYY]. Patient exposure estimates are based on calculations from product distribution figures, and due to the limitations of this approach, it is not possible to reliably estimate the number of subjects treated with marketed [product name].

It is important to note that the estimated PYT are not equivalent to the absolute number of patients treated. It should also be noted that the overall PYT estimates are likely to underestimate the true number of patients exposed to [product name], due to the fact that PYT estimates are calculated number of patients who could have been treated for one year based on the tablets distributed. However, since many patients do not stay on therapy for a whole year, even for chronic conditions, the real number of patients is likely to be higher.

| Table 5.2-1 Patient Exposure Doses Distributed and Patient Years of Treatment [Generic name] DD Mmm YYYY to DD Mmm YYYY | | | | |
| --- | --- | --- | --- | --- |
| Strength | Total Number of Doses Distributed | | Number of Patients /Patient-Years of Treatment *(Remove option not used)* | |
|  | Interval  DD Mmm YYYY to DD Mmm YYYY | Cumulative to  DD Mmm YYYY | Interval  DD Mmm YYYY to DD Mmm YYYY | Cumulative to  DD Mmm YYYY |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| **Total** |  |  |  |  |

### Postauthorisation Use in Special Populations

*Where postauthorisation use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data would include clinical trials and noninterventional studies designed to obtain this information, including registries. Populations to be considered for discussion include, but might not be limited to:*

*• Paediatric population;*

*• Elderly population;*

*• Pregnant or lactating women;*

*• Patients with hepatic and/or renal impairment;*

*• Patients with other relevant comorbidity;*

*• Patients with disease severity different from that studied in clinical trials;*

*• Subpopulations carrying relevant genetic polymorphism(s);*

*• Patients of different racial and/or ethnic origins*

*Use the following if no studies conducted:*

There are no data available relating to patient exposure in special populations.

*OR if studies were conducted, use one of the following:*

There was no postauthorisation use in special populations of (compound) (in trials, registries, or noninterventional studies).

*OR*

*Give details of use and data collected.*

### Other Postauthorisation Use

*If the MAH becomes aware of patterns of use of the medicinal product considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include overdose, drug abuse, misuse, and use beyond that recommended in the reference product information (e.g., an antiepileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Such patterns may be regional. If known, the MAH may briefly comment on whether use beyond that recommended in the reference product information is supported by clinical guidelines, clinical trial evidence, or an absence of approved alternative treatments. Quantitative use information should be provided, if available. For purposes of identifying patterns of use outside the terms of the reference product information, the MAH should use the appropriate sections of the reference product information that was in effect at the DLP of the PBRER (e.g., approved indication, contraindications).*

*Use one of the following statements:*

The MAH was not made aware of any patterns of use of (compound).

*OR*

*If the MAH is aware of any patterns of use, describe use here.*

# Data in Summary Tabulations

*When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) should be presented in the summary tabulations. The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH-E2A9 (see Annex IV). When serious and nonserious events/reactions are included in the same ICSR, the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness should not be changed specifically for the preparation of the PSURs*

This section presents the safety data through tabulations of serious adverse events from clinical trials and spontaneous serious and nonserious reactions from marketing experience including reports from HCPs, consumers, scientific literature, worldwide competent authorities, serious reactions from noninterventional studies and other noninterventional solicited source.

Valid cases and cases considered invalid (but which contain at least information on a drug and an event) are entered in the global PV database, and are assessed as part of ongoing signal evaluation activities to support this product. However, only valid cases are presented in the summary tabulations of the report. The results of signalling analyses covering both valid and invalid database cases are therefore built into the preparation of this periodic report, and contribute to its conclusions.

## Reference Information

The coding of adverse events (AE) is based on the MedDRA Version (#) which was current at the time the summary tabulations were generated. Caution is advised when comparing current data, and especially summary tabulations, with those of previous aggregate reports. In addition, the MedDRA term that most closely matches the term used by the reporter is coded. Thus, even within the same reporting period, across reports, the same AE may be captured by synonymous, but not identical, terms.

## Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

*Lead Author: Aggregate Reporting Associate*

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials* | *7.3 Cumulative Summary Tabulations of Serious Adverse Events* |

*This section should provide background for the appendix that provides a cumulative summary tabulation of SAEs reported in the MAH’s clinical trials, from the DIBD to the DLP of the current PBRER. The MAH should explain any omission of data (e.g., clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by system organ class (SOC), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development Programme. Data can be integrated across the Programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by trial, indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the SAEs.*

*The Aggregate Reporting Associate is responsible for uploading this output to Report Appendix folder in GEPIC.*

*The following points should be considered:*

*• In general, the tabulation(s) of SAEs from clinical trials should include only those terms that were used in defining the case as serious; they should not include nonserious events.*

*• When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the Preferred Term level and SOC should be presented in the summary tabulations.*

*• The tabulations should include blinded and unblinded clinical trial data. Unblinded SAEs might originate from completed trials and individual cases that have been unblinded for safety-related ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER) EMA/CHMP/ICH/544553/1998 Page 19/45 reasons (e.g., expedited reporting), if applicable. Sponsors/MAHs should not unblinded data for the specific purpose of preparing the PBRER.*

*• Certain adverse events in clinical trials can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as “exempt” from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).*

*• Causality assessment is generally useful for the evaluation of individual rare ADRs. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all SAEs for the investigational drug, active controls, and placebo. It may be useful to give rates by dose.*

Methods and Reports

The tables in Appendix 21.2 are generated from the safety database.

Presentation of Reports

Summary tabulations for SAEs from clinical trials (Interventional) are provided in Appendix 21.2.

These tables include cumulative (cumulative to DD Mmm YYYY) summary tabulations of SAEs by Preferred Term (PT) from clinical trials (Interventional cases) for [product name] as well as active comparators, and placebo.

## Cumulative and Interval Summary Tabulations from Postmarketing Data Sources

*Lead Author: Aggregate Reporting Associate*

*This section should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the DLP of the current PBRER. As described in ICH Guideline E2D, for marketed medicinal products, spontaneously reported\* adverse events usually imply at least a suspicion of causality by the reporter, and should be considered to be adverse reactions for regulatory reporting purposes. The tabulation should include:*

*• Serious and nonserious adverse drug reactions from spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities;*

*• Serious adverse reactions from noninterventional studies; and*

*• Solicited reports of serious adverse reactions.*

*The tabulation should include interval and cumulative data presented side-by-side), and should be organised by SOC.*

*For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the data presented.*

*The Aggregate Reporting Associate is responsible for uploading this output to Report Appendix folder in GEPIC.*

Methods and Reports

The tables in Appendix 21.3 are generated from the safety database.

Presentation of Reports

Summary tabulations for spontaneous cases and for serious events from noninterventional studies are provided in Appendix 21.3.

These tables include the number of adverse drug reactions by PT from post marketing sources:

* Spontaneous including competent authorities and literature
* Noninterventional post marketing study and reports from other solicited sources

# Summaries of Significant Findings from Clinical Trials during the Reporting interval

*This section of the PBRER should provide a brief summary of clinically important emerging efficacy/effectiveness and safety findings obtained from the MAH’s sponsored clinical trials that became available during the reporting interval of the report. The safety signals arising from clinical trial sources should be tabulated in Section 15 of the PBRER. Evaluation of the signals (whether or not categorised as refuted signals or either potential\* or identified risks\*) that were closed during the reporting interval should be presented in Section 16.2 of the PBRER. New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterised in Sections 16.3 and 16.4, respectively. Findings from clinical trials not sponsored by the MAH should be described in the relevant sections of the PBRER.*

*Section 7 must align with Sections 3 and 4 of the PSUR by providing the detailed data for the clinical trial-related safety actions taken by the company and significant safety-related changes made to the RSI during the reporting interval*

*When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for treatments of nonlife-threatening diseases in approved indications should also be summarised in this section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illnesses should be summarised in Section 13 of the PBRER.*

*When possible and relevant, data categorised by sex and age (particularly children versus adult), indication, dose, and region should be presented.*

*A listing of any MAH-sponsored postmarketing interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval should be included in an appendix. The listing should include the following information for each trial:*

*• Study ID (e.g., protocol number or other identifier);*

*• Study title (abbreviated study title, if applicable);*

*• Study type (e.g., randomised clinical trial, cohort study, case-control study);*

*• Population studied (including country and other relevant population descriptors, e.g., paediatric population or trial subjects with impaired renal function);*

*• Study start (as defined by the MAH) and projected completion dates;*

*• Status:*

*• Ongoing (clinical trial has begun);*

*• Completed (clinical study report is finalised).*

## Completed Clinical Trials

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 7.1 Completed Clinical Trials* | *8.1 Completed Clinical Trials* |

*Lead author(s): Clinical Management (review from Clinical Development)*

*Contributing Author: Information may be obtained from the Global Study List from Programme Management.*

*This section of the PSUR should provide a brief summary of clinically important emerging efficacy and safety findings obtained from MAH sponsored interventional clinical trials completed during the reporting interval.*

*A COMPLETED trial is DEFINED as a clinical trial that has concluded all endpoints (primary, secondary, etc.) and a final Clinical Study Report (CSR)/Addendum report has been issued/submitted/approved by Otsuka within the PSUR reporting period.*

*This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals. Non interventional study information should be provided in Section 8.*

*A safety finding can include but is not limited to following:*

*newly identified safety issues (detailed description of adverse events or reactions; associated laboratory values; risk factors; relationship to dose, duration, time course of the treatment; reversibility; factors that could be useful in predicting or preventing reactions)*

* *meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations)*
* *symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities, for example:*
* *hepatotoxicity*
* *cardiovascular effects, including QT interval prolongation and results from thorough QT/QTc studies*
* *bone marrow toxicity*
* *pulmonary toxicity*
* *renal toxicity*
* *central nervous system toxicity*
* *immunogenicity*
* *hypersensitivity*
* *deaths that are an outcome of an adverse event*
* *study drug discontinuations because of adverse events, including abnormal laboratory values or investigations*
* *drug–drug and other interactions*

*The following introductory sentence can be filled in once all contributions have been received.*

This section summarises the findings for [product name] from [#] completed clinical trials, including [#] Phase 1, [#] Phase 2, and [#] Phase 3 completed trials during the reporting period of: [DD Mmm YYYY] to [DD Mmm YYYY].

*[Provide high level conclusions on efficacy and safety results and summarise emerging efficacy and safety findings, and if so desired, append a synopsis to this report. This list should align with Section 3 (safety actions) and Section 4 (changes to the IB). Describe each finding (per protocol) in one brief sentence.]A bulleted list can be provided, if desired.]*

*OR*

*If there were no completed trials during the period:*

There were no completed interventional clinical trials during the reporting period for [product name].

*OR*

*If a previously characterised or new safety finding from a completed trial has been updated or added, respectively:*

*Updated finding(s):* Based on our review of the data from [#] completed clinical trials [list protocol numbers], the following previously observed relevant safety finding(s) pertaining to [list RISKs] was/were updated.

*[Provide a high level narrative summary or bulleted list of updated safety findings*

*OR*

*Monotherapy study:* Continuing analysis/investigations into emerging *[RISK]* in the *[Abbreviated Protocol Name]* study, *[add protocol #]* confirmed a higher frequency of *[list adverse event(s)]* when subjects [add details, including any actions taken.]

*New finding(s):* Based on our review of the data from [#] completed clinical trials [list protocol numbers], the following new potential/identified safety concern(s) was/were detected.

*[Provide a high level narrative summary or bulleted list of new safety findings.]*

*OR*

*If there are no significant new or updated safety findings:*

Based on our review of the data from completed clinical trials, there were no significant new or updated safety findings. All reported events including events of death, AEs leading to discontinuation, SAEs, and Grade 3/4 events *[this sentence should be customized to include only events of this nature that are included in the report. If none of these types of events are included in report, do not include blue text]* were consistent with the current known safety profile of [product name].

***NOTE: This section can be subdivided using the below headers when applicable. If not applicable, please remove and enter all information in section 7.1 above:***

### Completed Clinical Trials (EU)

### Completed Clinical Trials (US)

### Completed Clinical Trials (Asia)

### Completed Clinical Trials (Rest of World)

## Ongoing Clinical Trials

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 7.2 Ongoing Clinical Trials* | *8.2 Ongoing Clinical Trials* |

*Lead author(s): Clinical Management (review from Clinical Development)*

*Contributing Author: Information may be obtained from the Global Study List from Programme Management.*

*An ONGOING trial is DEFINED as a clinical trial that has 1) reached FPFV, or 2) begun but is currently on hold, or 3) issued a finalised interim CSR but has not concluded, or 4) has concluded all endpoints (primary, secondary, etc.) but has not issued/submitted/approved the overall final (CSR/Addendum) report by Otsuka within the PSUR reporting period.*

*If the MAH is aware of clinically important information that has arisen from ongoing MAH sponsored interventional clinical trials (e.g., learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarise the concern(s). It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals. Non interventional study information should be provided in Section 8.*

*The following introductory sentence can be filled in once all contributions have been received.*

This section summarises the findings for [product name] from [#] Phase 1, [#] Phase 2, and [#] Phase 3 ongoing clinical trials *(If the product is prescribed for multiple indications, then list all indications that were under investigation during the reporting period)* [among *[#]* indications*,* including [list indications], under investigation] during the reporting period [ DD Mmm YYYY] to [ DD Mmm YYYY].

*[Provide high level conclusions on efficacy and safety results and summarise emerging efficacy and safety findings, and if so desired, append a synopsis in Appendix 21.3.2. This list should align with Section 3 (safety actions) and Section 4 (changes to the IB). Describe each finding (per protocol) in one brief sentence.]. A bulleted list can be provided, if desired.]*

*OR*

*If there were no ongoing Clinical Trials in the period:*

There were no ongoing interventional clinical trials during the reporting interval for [product name].

*OR*

*If a previously characterised or new safety finding from an ongoing trial has been updated or added, respectively.*

*Updated finding(s):* Based on our review of available data from [#] ongoing clinical trials [list protocol numbers], the following previously observed relevant safety finding(s) pertaining to [list RISKs] was/were updated.

*[Provide a high level narrative summary or bulleted list of updated safety findings.]*

*OR*

*If there are new significant safety findings:*

*New finding(s):* Based on our review of available data from [#] ongoing clinical trials [list protocol numbers], the following new potential/identified safety concern(s) was/were detected.

*[Provide a high level narrative summary or bulleted list of new safety findings.]*

*OR*

*If there are no significant new or updated safety findings:*

Based on our review of available data from ongoing clinical trials, there are no significant new or updated safety findings, and the reported deaths (if any), AEs leading to discontinuation, SAEs, and Grade 3/4 events were consistent with the current safety profile of [product name].

***NOTE: This section can be subdivided using the below headers when applicable. if not applicable, please remove and enter all information in section 7.2 above:***

### Ongoing Clinical Trials (EU)

### Ongoing Clinical Trials (US)

### Ongoing Clinical Trials (Asia)

### Ongoing Clinical Trials (Rest of World)

## Long-term Follow-up

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 7.3 Long-term Follow-up* | *8.3 Long-term Follow-up* |

*Lead author(s): Clinical Management (review from Clinical Development)*

*A LONG‑TERM FOLLOW‑UP study is DEFINED as a trial that has short-term period upon which primary analyses are done, followed by a long-term period during which the main focus is safety and occasionally durability of action. This follow-up period is not to be confused with an extension cohort where the IMP is being further investigated in an interventional fashion.*

*Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products. (e.g., gene therapy, cell therapy products and tissue engineered products). When the development programme is completed and long-term follow-up is the only ongoing activity generating data for the DSUR, this could be the only section where new information is presented.*

*If long-term follow up was ongoing or completed during the reporting period:*

This section summarises information from long-term follow-up of subject from clinical trials of investigational products. There were [#] trials with subjects in long-term follow-up for [product name] during the reporting period [DD Mmm YYYY] to [DD Mmm YYYY].

[*Present information from ongoing long-term follow-up trials.]*

*OR*

*If the section is not applicable:*

There were no ongoing or completed long-term follow-up studies involving [product name] during the reporting period [DD Mmm YYYY] to [DD Mmm YYYY].

*OR*

*If there are ongoing long‑term follow-up studies and a previously characterised or new safety finding from an ongoing trial has been updated or added, respectively, include the following sentences as appropriate.*

*Updated finding(s):* Based on our review of available data from [#] long‑term follow-up studies [list protocol numbers], the following previously characterised safety finding(s) pertaining to [list RISKs] was/were updated. (*Example text below)*

*[The Clinical representative(s) should provide a high level narrative or bulleted list of updated findings, see example below.]*

* Continuing analysis/investigations into emerging [RISK] in the [Abbreviated Protocol Name] study, [add Protocol #], confirmed a higher frequency of [list adverse event(s)] when subjects [add details, including any actions taken].

*New finding(s):* Based on our review of available data from [#] long‑term follow-up studies [list protocol numbers], the following new potential/identified safety concern(s) was/were detected. (*Example text below)*

*[The Clinical representative(s) should provide a high level narrative or bulleted list of new findings, see example below.]*

* Observations from the [Abbreviated Protocol Name] study, [add Protocol #], revealed [add details] about symptoms when [#] subjects [add details, such as onset, conclusions, or causality].

*OR*

*If there are no significant new or updated safety finding(s):*

After review of available data from long‑term follow-up study (ies) [list PROTOCOLs], there were no significant new or updated finding(s) and the known safety profile of [product name] remained consistent with the current known safety profile of [product name].

*OR*

*If the long term study (ies) were ongoing and/ or completed and were described prior sections 8.1 or 8.2, then please refer to the applicable sections. Do not repeat in this section.*

During the reporting period, there were [#] long term studies [list PROTOCOLs]. Relevant findings are discussed in [cross reference applicable Section(s)].

## Other Therapeutic Use of Medicinal Product

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 7.4 Other Therapeutic Use of Medicinal Product* | *8.4 Other Therapeutic Use of Investigational Drug* |

*Lead Authors: Clinical Management (review from Clinical Development)*

*Contributing Authors:* *GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*NOTE: The GPV Medical Safety Operations Associate is responsible for requesting an adhoc Compassionate Use listing from AVISSO via GSDM and sharing with the authors for this section.*

*This section of the PBRER should include clinically important safety information from other programmes conducted by the MAH that follow a specific protocol, with solicited reporting as per ICH Guideline E2D (e.g., expanded access programmes, compassionate use programmes, particular patient use, single-patient investigational new drug applications [INDs], treatment INDs, and other organised data collection).*

*If expanded access/compassionate use programmes were ongoing or completed during the reporting period:*

[Enter #] [expanded access/compassionate use] programmes involving [product name] were completed [list protocol ID numbers] or ongoing [list protocol ID numbers] during the reporting period of: [DD Mmm YYYY] to [DD Mmm YYYY].

*If applicable, provide high level overview of each programme. The Medical Affairs representative(s) should provide a description of each subject(s) enrolled in the EAP which clarifies why the expanded access was granted. If the volume of subjects is large, then the inclusion criteria should be provided in lieu of individual subject details.*

*Example text below*

**Protocol: XXX-XX-XXX**

**Title:** Compassionate use of delamanid for patients with pulmonary multidrugresistant tuberculosis with limited therapeutic options

**Subject Population**: [Enter inclusion criteria]

**Objective:** [Enter objective]

The compassionate use project (Protocol XXX-XX-XXX) started in February 2014 and is

ongoing.

*[Enter relevant patient enrollment figures or other pertinent patient information].*

*NOTE: Use the Compassionate Use Case Listing provided by GSDM to inform authoring of this section.*

The following [new or updated] important safety information was identified from the [expanded access/compassionate use] programme(s) for [product name] during the reporting period:

*[Provide a high level narrative summary or bulleted list of new or updated safety findings, including discussion of key cases.]*

*OR*

*If this section is not applicable:*

There were no ongoing or completed [expanded access/compassionate use] programmes involving [product name] during the reporting period [DD Mmm YYYY] to [DD Mmm YYYY].

*AND/OR*

No clinically important new or updated safety information from the [expanded access/compassionate use] programme(s) for [product name] was identified during the reporting period.

## New Safety Data Related to Fixed Combination Therapies

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 7.5 New Safety Data Related to Fixed Combination Therapies* | *8.5 New Safety Data Related to Combination Therapies* |

*Lead author(s): Medical Safety Operations Associate/Clinical Management (review from Clinical Development)*

*A COMBINATION therapy is DEFINED as a therapy that involves the primary IMP in combination with one or more additional IMPs. Although add-on therapy, primary IMP plus a standard treatment of care (or baseline), involves the use of more than one drug, this regimen is not typically considered a combination therapy since the baseline therapy is not under investigation or not being used in an interventional fashion (dosage is not controlled by the investigator). In other words, the baseline therapy is administered according to its established labelling instructions.*

*Unless otherwise specified by national or regional regulatory requirements, the following options can be used to present data from combination therapies:*

*• If the product that is the subject of a PBRER is also approved or under development as a component of a fixed combination product or a multidrug regimen, this section should summarise important safety findings from use of the combination therapy.*

*• If this PBRER is for a fixed combination product, this section should summarise important safety information arising from the individual components.*

*The information specific to the combination can be incorporated into a separate section(s) of the PBRER for one or all of the individual components of the combination.*

*The following introductory sentence can be filled in once all contributions have been received.*

This section summarises the findings for [product name] from [#] Phase X trials combining [product name + IMP2], and [#] Phase X trials combining [product name + IMP2 + IMP3], that were ongoing during the reporting period [DD Mmm YYYY] to [DD Mmm YYYY].

*OR*

*If a previously characterised or new safety finding from an ongoing trial has been updated or added, respectively, then the Clinical representative(s) responsible for contributing the clinical safety summary should provide any necessary details to complete this option.*

*Updated finding(s):* Based on our review of available data from [#] combination therapy clinical trials [list protocol numbers], the following previously observed relevant safety finding(s) pertaining to [list RISKs] was/were updated.

*[Provide a high level narrative or bulleted list of updated findings.]*

*OR*

*If there are new significant safety findings:*

*New finding(s):* Based on our review of available data from [#] combination therapy clinical trials [list protocol numbers], [#] new potential/identified safety concern(s) was/were detected.

*[Provide a high level narrative or bulleted list of new findings.]*

*OR*

*If there are no significant new or updated safety findings:*

Based on our review of available data from ongoing combination therapy clinical trials, there were no significant new or updated safety findings, and the reported deaths (if any), AEs leading to discontinuation, SAEs, and Grade 3/4 events were consistent with the current safety profile of [product name].

*OR*

*If not applicable:*

This section is not applicable as [product name] is a monotherapy treatment only.

# Findings from Noninterventional Studies

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 8.0 Findings from Noninterventional Studies* | *Section 9.0* *Safety Findings from Noninterventional Studies* |

*Lead Author(s): Clinical Management (review from Clinical Development); Epidemiology/MSO Delegate(s)*

*Information may be obtained from the Global Study List from Programme Management and the information should pertain to both ongoing and completed trials.*

*This section should also summarise relevant safety information or information with potential impact in the benefit-risk assessment from marketing authorisation holder-sponsored noninterventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when relevant to multiple regions.*

*The marketing authorisation holder should include an appendix listing marketing authorisation holder-sponsored noninterventional studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting interval.*

*Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the EU regional Appendix.*

There is no relevant safety information that became available from noninterventional studies of [generic name] during the reporting interval.

OR

[Add narrative information of relevant safety information].

# Information from Other Clinical Trials and Sources

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 9.0 Information from Other Clinical Trials and Sources* | *Section 10.0* *Other Clinical Trial/Safety Information* |

## Other Clinical Trials/Studies

*Lead author(s): Medical Safety Operations; Clinical Management (review from Clinical Development)*

*This PSUR section should summarise information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources, including patient support programmes, which are accessible by the marketing authorisation holder during the reporting interval (e.g. results from pool analysis or meta-analysis of randomised clinical trials, safety information provided by codevelopment partners or from investigator-initiated trials).*

*Information may be obtained from the Global Study List from Programme Management and the information should pertain to both ongoing and completed trials.*

*The final list selection should be used to evaluate trials for safety findings relevant to the assessment of risk to the trial subject.  A safety finding can include but is not limited to following:*

* *newly identified safety issues (detailed description of adverse events or reactions; associated laboratory values; risk factors; relationship to dose, duration, time course of the treatment; reversibility; factors that could be useful in predicting or preventing reactions)*
* *meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations)*
* *symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities, for example:*
* *hepatotoxicity*
* *cardiovascular effects, including QT interval prolongation and results from thorough QT/QTc studies*
* *bone marrow toxicity*
* *pulmonary toxicity*
* *renal toxicity*
* *central nervous system toxicity*
* *immunogenicity*
* *hypersensitivity*
* *deaths that are an outcome of an adverse event*
* *study drug discontinuations because of adverse events, including abnormal laboratory values or investigations*
* *drug–drug and other interactions*

This section summarises the findings for [product name] from [#] Phase X trials combining [product name + IMP2], and [#] Phase X trials combining [product name + IMP2 + IMP3], that were ongoing during the reporting period [DD Mmm YYYY] to [DD Mmm YYYY].

*OR*

*If a previously characterised or new safety finding from an ongoing trial has been updated or added, respectively, then the Clinical representative(s) responsible for contributing the clinical safety summary should provide any necessary details to complete this option.*

*Updated finding(s):* Based on our review of available data from [#] combination therapy clinical trials [list protocol numbers], the following previously observed relevant safety finding(s) pertaining to [list RISKs] was/were updated.

*[Provide a high level narrative or bulleted list of updated findings.]*

*OR*

*If there are new significant safety findings:*

*New finding(s):* Based on our review of available data from [#] combination therapy clinical trials [list protocol numbers], [#] new potential/identified safety concern(s) was/were detected.

No other clinical trials/studies have been conducted with [generic name].

*OR*

Although other clinical trials/studies have been conducted with [generic name], no important safety findings were noted.

*OR*

The following important safety findings were *noted (include clinical trial/study and the safety findings):*

## Medication Errors

*Lead author(s): Medical Safety Operations; Clinical Management (review from Clinical Development)*

*Contributing Author: GPV Medical Safety Operations/Medical Safety Product Lead*

*This subsection should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient. Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product. A medication error may arise at any stage in the medication use process, and may involve patients, consumers, or healthcare professionals.*

*This information may be received by the MAH via spontaneous reporting systems, medical information queries, customer complaints, screening of digital media, patient support programmes, or other available information sources.*

*Signals or risks identified from any information source and/or category of reports should be presented and evaluated in the relevant section of the PBRER.*

No information from other sources outside of a study environment has been received for [generic name].

*OR*

Although information from other sources outside of a study environment has been received for [generic name], no important safety findings were noted.

*OR*

The following important safety findings were noted *(identify other source and the safety findings):*

## Other Sources Outside of the Study Environment

*When Regulatory Agencies request inclusion within a PSUR of reviews of postmarketing data that do not fit into the concept of a safety “topic” or “signal” (for example, a Regulatory Agency may request a review of all events from an entire MedDRA SOC), it is not appropriate to place these reviews in PSUR section 16.  Instead, these reviews should be placed in this section, and introduced with the following suggested standard introductory text. If the Agency request requires detailed presentations of individual case report narratives, it may be appropriate to summarise the data in this section, and place the individual case report narratives in a PSUR Appendix, with an appropriate cross-reference to the Appendix.*

No information from other sources outside of a study environment has been received for [generic name].

*OR*

Although information from other sources outside of a study environment has been received for [generic name], no important safety findings were noted.

*OR*

The following important safety findings were noted *(identify other source and the safety findings):*

*AND, if applicable based on Regulatory Agency request for inclusion within PSUR:*

Additional postmarketing data have been reviewed per agency request. *Include here a brief summary  (key points/conclusions) of a topic (s) that has (have) been reviewed per agency request but not deemed as signals by the RMST thereby not addressed in 16.2 section; cross-reference supplemental appendix 20.1X should you consider including detailed review there.*

# Nonclinical Data

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 10.0 Nonclinical Data* | *Section 12.0 Nonclinical Data* |

*Lead Author(s): Nonclinical*

*This section should summarise major safety findings from nonclinical in vivo and in vitro studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designed to address specific safety concerns should be included in the PSUR, regardless of the outcome. Implications of these findings should be discussed in Section 16 and 18, as warranted.*

*If there are no major safety findings for the study, include “n/a” in the appropriate boxes. If there are no nonclinical studies for the product, include “n/a” in the table below. Please note the table format must be used when populating this section.*

There were [X] completed and [X] ongoing nonclinical studies during the reporting period.

| Table 10-1 Summary of Nonclinical findings | | | | |
| --- | --- | --- | --- | --- |
| Study No. / Report No. | Study Title | Study Ongoing or Complete | Major Safety Findings in Non-  clinical Studies  Yes / No | Summary of Major Safety Findings in Nonclinical Studies |
| **Efficacy Pharmacology Studies** | | | | |
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| **Safety Pharmacology Studies** | | | | |
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| **Pharmacokinetic Studies** | | | | |
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| **Toxicity Studies** | | | | |
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|  |  |  |  |  |

*A major safety finding can include but is not limited to following:*

* *Newly identified safety issues (detailed description of adverse events or reactions; associated laboratory values; risk factors; relationship to dose, duration, time course of the treatment; reversibility; factors that could be useful in predicting or preventing reactions)*
* *Meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations)*
* *Symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities, for example:* 
  + *hepatotoxicity*
  + *cardiovascular effects, including QT interval prolongation*
  + *bone marrow toxicity*
  + *pulmonary toxicity*
  + *renal toxicity*
  + *central nervous system toxicity*
  + *immunogenicity*
  + *deaths that are an outcome of an adverse event*
  + *drug–drug and other interactions*

# Literature

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 11.0 Literature* | *Section 13.0 Literature* |

*Lead author(s): Aggregate Reporting Associate*

*Contributing Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*GPV Medical Safety Operations Associate/Medical Safety Product Lead and Aggregate Reporting Associate will review the literature output and draft content;*

*Literature Search: Literature search is performed by the Information Resource Centre (IRC).*

*This section should summarise new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, relevant to the approved medicinal product that the MAH became aware of during the reporting interval. Literature searches for PBRERs should be wider than those for individual adverse reaction cases, and include studies reporting safety outcomes in groups of subjects. If relevant, information on active substances of the same class should be considered.*

*The special types of safety information that should be included, but which may not be found by a search constructed specifically to identify individual cases, include:*

*• Pregnancy outcomes (including termination) with no adverse outcomes;*

*• Use in paediatric populations;*

*• Compassionate supply, named patient use;*

*• Lack of efficacy;*

*• Asymptomatic overdose, abuse or misuse;*

*• Medication error where no adverse events occurred;*

*• Important nonclinical safety results.*

*If no published literature that described new and potentially important safety information is identified:*

During the reporting interval of this PSUR, there was no published literature that described new and potentially important safety information on [generic name].

*If published literature that described new and potentially important safety information is identified:*

There was [X] publication(s) identified during the time interval of this PSUR that described new and potentially important safety information on [generic name].

*Include abstract and publication references here for all selected publications and summarise and comment on the safety issue (if applicable).*

*Example*

*List the first six authors followed by et al.*

1. Vega KJ, Pinna I, Kerensky B. Heart transplantation is associated with an increased risk for pancreato-biliary disease. Ann Intern Med 1996 Jun 1; 124(11):980-3.

**Abstract/Summary**:

**Company Comment**:

1. .....

# Other Periodic Reports

*Lead author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*Unless otherwise specified by national or regional regulatory requirements, the MAH should prepare a single PBRER for a single active substance. However, if an MAH prepares multiple PBRERs for a single active substance (e.g., covering different indications, or formulations), this section should summarise significant findings from the other periodic reports if they are not presented elsewhere within this report.*

*When available, based on contractual agreements, the MAH should summarise significant findings from periodic reports provided during the reporting interval by other parties (e.g., sponsors, MAHs, other contractual partners).*

*If no other periodic reports have been created during the interval the following statement should be inserted in this section:*

The MAH has not submitted any PSURs for other products containing the same active substance during the reporting interval either as a single medicinal product or in a fixed combination product.

# Lack of Efficacy in Controlled Clinical Trials

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 13.0 Lack of Efficacy in Controlled Clinical Trials* | *Section 15.0 Lack of Efficacy* |

*Lead Author: Clinical Management (review from Clinical Development)*

*Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy (ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new antiplatelet drug for acute coronary syndromes) could reflect a significant risk to the treated population and should be summarised in this section.*

This section is not applicable, as there are no clinical trial data indicating lack of efficacy for [generic name].

OR

[Include lack of efficacy conditions that reflect risks for subject in clinical trials].

# Late-Breaking Information

*Common sections between PBRER and DSUR, if reports cover same period and submitted at same time*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 14.0 Late-Breaking Information* | *Section 17.0 Late-Breaking Information* |

*Lead Author(s): GPV Medical Safety Operations/Medical Safety Product Lead; Aggregate Reporting Associate*

*The Aggregate Reporting Associate* *will send an email to all contributors requesting late breaking information, and the Medical Safety Operations/Medical Safety Product Lead will complete this section as appropriate with the received information.*

*This section should summarise information on potentially important safety and efficacy / effectiveness finding that arise after the DLP but while the PBRER is in preparation. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the MAH, a data monitoring committee, or a regulatory authority has taken for safety reasons. New individual case reports should not be included unless they are considered to constitute an important index case (i.e., the first instance of an important event), an important safety signal, or where they may add information to the evaluation of safety concerns already presented in the PBRER (e.g., a well-documented and unconfounded case report of aplastic anaemia in a medicinal product known to be associated with adverse effects on the bone marrow).*

*Any significant change proposed to the reference product information which has occurred after the DLP of the report but before submission should also be included in this section, where feasible. Such changes could include a new contraindication, warning/precaution, or new adverse drug reaction.*

*The data presented in this section should also be taken into account in the evaluation of risks and new information.*

*If there was no important or new late-breaking information during the reporting period:*

There was no important or new late-breaking information during the reporting period that would alter the currently known safety profile as described in the current CCDS.

*OR*

*Describe relevant late breaking information here.*

# Overview of Signals: New, Ongoing, or Closed

*Lead Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*The purpose of this section is to provide an overview of signals detected, under review, and evaluated during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval. The scope includes signals detected from any source (for example from spontaneous reports, published literature, clinical trials, epidemiological study findings) using quantitative and/or qualitative methods. It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting as a validation step (evaluation of the data supporting the detected signal) is required.*

*For the purposes of the PSUR, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the marketing authorisation holder.*

*Only signals as defined by the signalling team or GPV Medical Safety Product Lead can be included in the PSUR.*

*"Newly identified" refers to a signal that has been identified during the PSUR reporting interval, or to a previously closed signal, where the new clinically significant information became available during the reporting interval.*

*Examples of "new clinically significant information on a previously closed signal" might include:*

* *information suggesting a clinically significant difference in the severity or frequency of the risk*
* *A higher frequency or severity of the risk is newly found in an indicated subpopulation.*
* *Information which warrants a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimisation activities.*

*"Ongoing" refers to a signal that was identified prior to the PSUR reporting interval, and is still under evaluation at the data lock point.*

*"Closed" refers to a signal for which an evaluation was completed during the reporting interval. Signals that are both newly identified and closed during the reporting interval should be handled as closed signals. The detailed signal evaluations should be included in Section 16.2 “Signal evaluation” while the high level overview of signals should be provided in this section.*

The MAH has an established process to identify, evaluate, validate, or refute possible safety signals. Data sources are screened for new safety information related to [generic name], and any new safety topics identified are reviewed by a team of scientists from multiple disciplines, including nonclinical, clinical and pharmacovigilance personnel. Following initial review of the available data, a determination is made on the basis of the nature and the quality of the new information whether further investigation is warranted, at which point those topics referred for further investigation are considered “validated signals.” Potential data sources include: safety data from MAH-sponsored clinical trials and other studies, spontaneous adverse event reports, published literature, and communications from external sources, including regulatory agencies, and (if applicable) business partners.

During the reporting interval of this PSUR, there were [X] safety signals for [generic name] that were either newly identified, ongoing or closed. These safety signals are listed below:

| Table 15-1 Overview of Signals Detected, under Review, and Evaluated during the Reporting Interval | |
| --- | --- |
| **New (newly-detected signals currently undergoing evaluation** | * [new signal#1] * [new signal#1] * *etc*. |
| **Ongoing (previously-identified signals currently undergoing evaluation)** | * [ ongoing signal #1 ] * [ ongoing signal #2 ] * *etc*. |
| **Closed (newly detected or previously identified signals for which evaluation was completed during the reporting interval)** | * [ ongoing signal #1 ] * [ ongoing signal #2 ] * *etc*. |

See Appendix 21.4 Tabular Summary of Safety Signals and Table 21.4-1 Tabulation of Signals that are New, Ongoing, and Closed during the Reporting Interval for details of signals detected, under review and evaluated during the reporting interval.

See Section 16.2 Signal Evaluation for details of the evaluations of signals that were closed during the reporting interval.

# Signal and Risk Evaluation

*The purpose of this section is to provide:*

*• A succinct summary of what is known about important identified and potential risks and missing information\* at the beginning of the reporting interval covered by the report (16.1);*

*• An evaluation of all signals closed during the reporting interval (16.2);*

*• An evaluation of new information with respect to previously recognised identified and potential risks (16.3);*

*• An updated characterisation of important potential and identified risks, where applicable (16.4); and*

*• A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions (16.5).*

## Summary of Safety Concerns

*Common sections between PBRER and RMP*

|  |  |
| --- | --- |
| *PBRER section* | *RMP section* |
| *Subsection 16.1 – “Summary of safety concerns”* | *EU RMP:*  *SVIII – “Summary of the safety concerns”* |

*Lead Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*The purpose of this section is to provide a summary of the product-specific important safety concerns at baseline, i.e., the beginning of the reporting interval, against which new information and evaluations can be made.*

*For products with a Risk Management Plan (RMP), extract the list of important safety concerns from the table in Section 1.10 "Summary – Ongoing Safety Concerns" (for RMPs prepared according to the 2006 CHMP RMP template), or in Module SVIII "Summary of the Safety Concerns" (for RMPs prepared according to the 2014 EMA Guideline, GVP Module V). The safety concerns should correspond to those included in the version of the RMP that was in effect at the beginning of the PSUR reporting interval.*

A list of the product-specific important safety concerns (identified and potential risks, and missing information) at the beginning of the PSUR reporting interval, as described in Part II Module SVIII of the [product] EU RMP version [X], is presented in Table 16.1-1.

| Table 16.1-1 Summary of Safety Concerns | |
| --- | --- |
| **Important identified risks** | * [ important potential risk #1 ] * [ important potential risk #2 ] * [drug-drug interaction] * *etc.* |
| **Important potential risks** | * [ important potential risk #1 ] * [ important potential risk #2 ] * [drug-drug interaction] * *etc.* |
| **Missing information** | * [Missing information #1 ] * [Missing information #2 ] * *etc.* |

*If there are updates to the RMP Summary of Safety Concerns (RMP Section 2.8) after the start of the reporting period:*

During the reporting period, RMP version [X] was approved by the EMA with the following changes:

* *list changes*
* *......*

*OR*

*If there are only minor editorial changes or updates to data that does not impact the overall safety profile:*

Although RMP version [X] was updated during the reporting period, these changes did not impact the Summary of Safety Concerns listed in RMP version [X] [effective [DD Mmm YYYY].

*OR*

*If no new version of the RMP was published during the reporting interval:*

There were no changes to RMP version [X] during the reporting period.

*For products without an RMP, list the product-specific important safety concerns (identified and potential risks, and missing information), based on data that were available at the beginning of the reporting interval. What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health. Normally, any risk which is clinically important and which is included in the contraindications or warnings and precautions sections of the prescribing information should be included here. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person’s life, and which could lead to serious consequences if untreated should also be considered for inclusion (risks include not only adverse reactions but other safety concepts, such as: drug/food interactions, occupational exposure, class effects, medication errors including unintended exposures to the product).*

*The summary of missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.*

## Signal Evaluation

*Lead Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*This section should summarise any completed signal evaluations that resulted in a signal being closed during the PSUR reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a risk, following evaluation. The two main categories to be included in this section are:*

* *Those signals that, following evaluation, have been categorised as a potential or identified risk, including lack of efficacy.*
* *Those signals that, following evaluation, have been rejected as false signals based on a scientific evaluation of the currently available information.*

*As described in Section 15.0 Overview of Signals: New, Ongoing or Closed, only validated signals should be included in the PSUR.*

*If there were no signals that were closed during the reporting interval, use the following standard statement:*

There were no signal evaluations that were completed during the PSUR reporting interval.

*If signal evaluation(s) was/were completed during the reporting interval and the signal(s) was/were closed, present a summary of the evaluation for each such signal as demonstrated below.*

This section summarises the results of evaluations of safety signals that were closed during the reporting interval.

*For both categories of closed signals, a sufficient description of each signal evaluation should be included in order to clearly describe the basis upon which the signal was either rejected or considered to be a risk by the marketing authorisation holder. The level of detail provided in the description of the signal evaluation should be proportionate to the medical significance and public health importance of the signal, and the extent of the available evidence. For each closed signal, provide the following specific information:*

| Table 16.2-1 Signal Evaluation for [name of signal #1] | |
| --- | --- |
| **Source / Trigger of signals** | *eg nonclinical study results, clinical study results, post marketing data* |
| **Background** | *e.g., description of the "signal" condition, background epidemiology, possible mechanism(s) of toxicity, etc.* |
| **Method(s) of Evaluation** | *Include data source(s), search criteria and analytical methods: e.g., meta-analysis of clinical trial data, case-level evaluation of post marketing adverse event reports, pharmacoepidemiological study, etc.* |
| **Results** | *provide a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an individual (index) case* |
| **Discussion** |  |
| **Conclusion** | *SIGNAL WAS CONFIRMED*  *When the conclusion of the signal evaluation is that the topic should be considered a product-specific safety concern (i.e., the signal has been “confirmed”), choose the appropriate text to characterise the disposition of the signal.*  Based on this evaluation, [name of signal #1] has been categorised as a/an [important identified / important potential / identified / potential] risk for [generic name].  The MAH has updated [the CCDS (see Section 4, Changes to Reference Safety Information) / the Risk Management Plan (see Section 4, Changes to Reference Safety Information) and the RMP] with this new information.  *SIGNAL WAS REFUTED*  *When the conclusion of the signal evaluation is that the evidence does not support an association with the product (i.e., the signal has been “refuted”), use the following standard text to document this conclusion.*  The available scientific evidence does not support an association between [generic name] and [name of signal #1]. |

## Evaluation of Risks and New Information

*Lead Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*New information relating to a previously known risk, that is not considered to constitute a signal, should be discussed in this section. (New information relating to a previously known risk that constitutes a signal should be evaluated in Section 16.2 Signal Evaluation).*

*This section should provide a critical appraisal of new information for known risks, both important risks and those not categorised as important. The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PSUR. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Include information that provides insight on a new aspect of a known risk but which does not require further action to verify. Examples might include:*

* *new information from spontaneous reports leading to addition of new information regarding a previously identified safety concern to the prescribing information, but the risk is not categorised as important*
* *new information that confirms an association with the product, resulting in recategorisation of a potential risk as an identified risk*
* *Information that indicates a change in frequency of a known risk.*

*If no new information relating to a previously known risk was received during the reporting interval, use the following standard statement:*

No new information relating to a previously known risk was received during the PSUR reporting interval.

*If new information relating to a previously known risk was received during the reporting interval, present a summary of the new information for each risk as demonstrated below.*

*The level of detail provided in the description of the risk evaluation should be proportionate to the medical significance and public health importance of the risk, and the extent of the available evidence.*

| Table 16.3-1 Risk Evaluation for [name of risk #1] | |
| --- | --- |
| **Source of New Information** | *e.g., nonclinical study results, clinical study results, post marketing data* |
| **Background** | *e.g., description of the risk condition, background epidemiology, possible mechanism(s) of toxicity, etc.* |
| **Method(s) of Evaluation** | *Include data source(s), search criteria and analytical methods: e.g., meta-analysis of clinical trial data, case-level evaluation of post marketing adverse event reports, pharmacoepidemiological study, etc.* |
| **Results** | *provide a summary and critical analysis of the data considered in the risk evaluation; where integral to the assessment, this may include a description of a case series or an individual (index) case* |
| **Discussion** |  |
| **Conclusion** | *for important risks, state whether or not the evaluation supports an update of the characterisation of an important potential / identified risk in Section 16.4 “Characterisation of risks”* |

*This section should also include an update on missing information. Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this section. Unresolved concerns and uncertainties should be acknowledged.*

## Characterisation of Risks

*Common sections between PBRER and RMP*

|  |  |
| --- | --- |
| *PBRER section* | *RMP section* |
| *Subsection 16.4 – “Characterisation of risks”* | *EU RMP:*  *SVII.3 Details of Important Identified and potential risks from clinical development and post authorisation experience* |

*Lead Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead; Epidemiology/MSO Delegate(s)*

*Characterise important identified and potential risks based on cumulative data (i.e. not restricted to the reporting interval), and describe missing information.*

*For products with an RMP, the information on important identified and potential risks presented in this section should be consistent with that in RMP Section 1.5.2 "Details of important Identified and potential risks" (for RMPs prepared according to the 2006 CHMP RMP template), or RMP Module SVII subsection "Details of Important Identified and Potential Risks from Clinical Development and Postauthorisation Experience" (for RMPs prepared according to the 2014 EMA Guideline, GVP Module V). The information should correspond to the version of the RMP that is in effect at the end of the* *PSUR reporting interval. Authors should import the tables from the RMP into this section and correct/renumber table captions to be consistent with rest of the PSUR.*

*For products without an RMP, the important safety concerns presented in this section should include those listed in Section 16.1 Summary of Safety Concerns and also add to those the new important safety concerns that were identified during the PSUR reporting interval (i.e. the closed signals from section 16.2 Signal Evaluation that had a disposition of "categorised as an important identified or important potential risk"). An example table format for presenting this information is provided below.*

*Also, for older products without RMPs, GPVand Clinical should work together to identify important risks to be included in the table. Most risks will come from the Contraindications and Warnings and Precautions sections of the RSI, although others can be included (e.g., drug-drug interactions) at the discretion of GPV and Clinical. When preclinical information is not readily available, the team may choose to use an alternate table where risks are combined into a single ‘Identified Risks’ category, without delineating between ‘Important’ and ‘Potential’ risks.”*

*For each important risk, provide the following information (for older products, the level of detail provided may be adjusted in accordance with the extent of the available data):*

*Example table:*

| Table 16.4-1 Details of Important [Identified / Potential] Risk: [name of identified / potential risk #1] | |
| --- | --- |
| **Identified/Potential Risk** | MedDRA Preferred Term(s): *provide a list of MedDRA Preferred Terms to be included in risk concept* |
| **Frequency** | *For identified risks: provide incidence of the adverse experience(s) from studies (clinical trials or epidemiological studies) as either an incidence proportion (denominator in units of persons) or incidence rate (denominator in units of person-time), including excess incidence (compared to the comparator group(s)). Confidence intervals are also required. Time to event data should be summarised using survival techniques. Cumulative hazard functions may also be used to represent the cumulative probability of occurrence of an adverse reaction in the presence of competing events.*  *For potential risks: the background incidence / prevalence in the target population(s) should be provided.* |
| **Public Health Impact** | *Provide information on severity and seriousness / reversibility / outcomes.* |
| **Impact on the Individual Patient** | *Provide information on effect of product on quality of life.* |
| **Risk Factors** | *Include patient factors, dose, at risk period, additive or synergistic factors.* |
| **Preventability** | *Describe the predictability/preventability/reversibility of the risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness.* |
| **Potential Mechanism** |  |
| **Evidence Source(s) and Strength of the Evidence** |  |

*For products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration.*

Detailed information characterising the Important Identified and Potential Risks, and a description of the Missing Information (when constituted as an important risk) have been extracted from version[XX] of the [generic name] RMP.

## Effectiveness of Risk Minimisation (if Applicable)

*Do not delete header if not applicable.*

*Common sections between PBRER and RMP*

|  |  |
| --- | --- |
| *PBRER section* | *RMP section* |
| *Subsection 16.5 – “Effectiveness of risk minimisation (if applicable)”* | *EU RMP:*  *Part V Risk minimisation measures* |

*Lead Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*Risk minimisation activities are public health interventions intended to prevent the occurrence of adverse drug reaction associated with a medicinal product or to reduce their severity. Risk minimisation activities may consist of routine risk minimisation (labelling) or additional risk minimisation activities (e.g., Healthcare Professional and/or patient communication / education).*

*The PSUR shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the benefit-risk assessment. Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this section.*

*Insights into the effectiveness of risk minimisation activities that may be applicable across multiple regions are of particular interest. Information may be summarised by region, if applicable and relevant.*

*If this PSUR is going to EU, place regional information in EU Regional Appendix 20.5.*

*For products with an RMP, the information presented in this section should be consistent with that in RMP section 4.0 (for RMPs prepared according to the 2008 CHMP Template) or RMP Part V Risk minimisation measures (for RMPs prepared according to the 2014 EMA Guideline, GVP Module V). The information should correspond to the version of the RMP that is in effect at the end of the PSUR reporting interval.*

*When no new relevant information regarding the effectiveness of risk minimisation became available during the PSUR reporting interval, the following standard statement should be used:*

No new information regarding the effectiveness of risk minimisation activities relevant to the benefit-risk assessment were received during the PSUR reporting interval.

# Benefit Evaluation

*Lead Author(s) for Section 17.1 to 17.3: Clinical Management/Clinical Development)*

## Important Baseline Efficacy and Effectiveness Information

*This section summarises information on the efficacy/effectiveness of the medicinal product as of the beginning of the reporting interval, and provides the basis for the benefit evaluation. This information should relate to the approved indication(s) of the medicinal product listed in the reference product information (see Section 2.4).*

*For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors, where relevant.*

*The level of detail provided in this section should be sufficient to support the characterisation of benefit in PBRER Section 17.3 and the benefit-risk assessment in Section 18.*

This section summarises baseline efficacy/effectiveness information for [generic name] by indication and population for use at the beginning of the current reporting interval [DD Mmm YYYY].

*For each indication and population for use, [e.g. "Osteoporosis in postmenopausal women, "Hypertension in adults"] provide the following information.*

| Table 17.1-1 [Indication and population for use] | |
| --- | --- |
| **Epidemiology and Natural History of the disease** | *Present a brief summary of the epidemiology and natural history of the disease, including information on incidence, prevalence, morbidity and mortality of the disease. Potential source document: RMP, epidemiology of the target disease section.* |
| **Nature of the benefit** | *Describe the benefit (s) of the therapy (e.g., diagnostic, preventive, symptomatic, or disease modifying treatment). CCDS – source document. Please consider using the CCDS version which is current at the beginning of the reporting period of the PSUR.*  *Example*  *Treatment with [product X] reduces the risk of vertebral and hip fractures in postmenopausal women with osteoporosis*  *The efficacy of [product X], specifically the effects on bone mass and fracture incidence in postmenopausal women, were examined in two phase 3 efficacy studies of 2 or 3 years duration as well as in a large placebo controlled trial, using [product X] daily (5 mg daily for two years and 10 mg daily for either one or two additional years).* |
| **Important endpoints that support the benefit** | *Present principal results with regard to the main endpoints supporting the benefit. Typically, this information is well summarised in the product label, section Clinical Studies*  [ endpoint #1]  *Example: effect on bone mineral density*  *In the initial efficacy studies, the mean bone mineral density (BMD) increases with product X 10 mg/day relative to placebo at three years were 8.8%, 5.9% and 7.8% at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. Increases in BMD were evident as early as 3 months and continued throughout the entire 3 years of treatment*  *[endpoint #2]*  *Example: effect on fracture incidence*  *In the initial efficacy studies, there was a 48% reduction ([product X 3.2% vs placebo 6.2%) in the proportion of patients treated with [product X experiencing one or more vertebral fractures relative to those treated with placebo.*  *In a three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture, [product X] daily reduced the incidence of ≥1 new vertebral fracture by 47% ([product X 7.9% vs. placebo 15.0%). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1% vs. 2.2%, a reduction of 51%).*  *In a four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37% of the global population who correspond with the above definition of osteoporosis) in the incidence of hip fractures ([product X] 1.0% vs. placebo 2.2%, a reduction of 56%) and in the incidence of ≥1 vertebral fracture (2.9% vs. 5.8%, a reduction of 50%).* |
| **Evidence of efficacy and effectiveness by comparator** | *Summarise efficacy of alternative treatments focusing on the same endpoints as in the above section.* |
| **Trends, patterns and/or evidence of benefit in important subgroups,** | *e.g. age, sex, ethnicity, disease severity, or genetic polymorphism*  *Specify subpopulations for which the efficacy of the product has not been demonstrated*  *If subgroup efficacy analyses did not identify differences with regard to product efficacy, consider the following text*  There is currently no evidence of differential benefit for any particular subgroup. |

## Newly Identified Information on Efficacy and Effectiveness

*New information on efficacy/effectiveness in approved indications that may have become available during the reporting interval should be presented in this section. For approved indications, new information on efficacy/effectiveness under conditions of actual use should also be described in this section, if available. New information about efficacy/effectiveness in uses other than the approved indication(s) should not be included, unless relevant for the benefit-risk evaluation in the approved indication. Information on indications approved during the reporting interval should also be included in this section. The level of detail provided in this section should be sufficient to support the characterisation of benefit in Section 17.3 and the benefit-risk assessment in Section 18.*

*New information on efficacy/effectiveness might also include changes in the therapeutic environment that could impact efficacy/effectiveness over time, e.g., vaccines, emergence of resistance to anti-infective agents.*

During this reporting interval, there has been no new important information on efficacy or effectiveness that significantly alters the benefit-risk profile of [generic name]. See Section 17.1 Important Baseline Efficacy and Effectiveness Information for a summary of the established efficacy profile for this product.

*OR*

*If new information became available during the reporting interval, summarise the information as follows:*

This section summarises newly identified information on efficacy/effectiveness of [generic name] presented by indication.

## Characterisation of Benefits

*This subsection provides an integration of the baseline benefit information and the new benefit information that became available during the reporting interval for authorised indications.*

*When there are no new relevant benefit data provided, and no significant change in risk profile, this subsection should refer to PSUR subsection 17.1 (Important Baseline Efficacy and Effectiveness Information).*

No new benefit data for [generic name] for the treatment of [add approved indication (s)] has become available during the reporting interval. For this indication, the product baseline efficacy and effectiveness information remains unchanged (see Section 17.1).

*When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this section should be succinct.*

*In the case when the new information suggests benefit is significantly less than originally demonstrated, provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following, when applicable:*

*• a brief description of the strength of evidence of benefit; considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;*

*• New information that challenges the validity of a surrogate endpoint, if used;*

*• Clinical relevance of the effect size;*

*• Generalisability of treatment response across the indicated patient population (e.g., information that demonstrates lack of treatment effect in a subpopulation);*

*• Adequacy of characterisation of dose-response;*

*• Duration of effect;*

*• Comparative efficacy; and*

*• A determination of the extent to which efficacy findings from clinical trials are generalisable to patient populations treated in medical practice.*

This section presents the changes to the baseline efficacy profile of [generic name], with new information highlighted.

*Insert and update the baseline efficacy table for each indication (that is the table (s) in Section 17.1) incorporating the new benefit information (underline or shade) that is detailed in Section 17.2.*

# Integrated Benefit-risk Analysis for Authorised Indications

*Lead Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*Whereas PBRER Sections 16.4 and 17.3 present the risks and benefits, respectively, Section 18 should provide an integration and critical analysis of the key information in these sections as described below. Section 18 provides the benefit-risk analysis, and should not simply duplicate the benefit and risk characterisation presented in Sections 16.4 and 17.3.*

The MAH has prepared an integrated benefit-risk analysis for [generic name] within the authorised indications. This analysis incorporates a critical evaluation of the benefit-risk balance.

## Benefit-risk Context-Medical Need for Important Alternatives

*Lead Authors: Clinical Management; Clinical Development*

*This section should provide a brief description of the medical need for the medicinal product in the approved indications, and summarise alternatives (medical, surgical, or other; including no treatment).*

## Benefit-Risk Analysis Evaluation

*Lead Author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead; Clinical Management; Clinical Development*

*A benefit-risk profile is specific to an indication and population. For products approved for more than one indication, benefit-risk profiles should be evaluated and presented for each indication individually. If there are important differences in the benefit-risk profiles among populations within an indication, benefit-risk evaluation should be presented by population, if possible. The evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks, and should take into account the following points:*

*• Whereas previous sections will include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections should be carried forward for integration in the benefit-risk evaluation.*

*• Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated.*

*• With respect to key benefit(s), consider its nature, clinical importance, duration, and generalisability, as well as evidence of efficacy in nonresponders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g., for therapies for arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).*

*• With respect to risk, consider its clinical importance, e.g., nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients, and whether it arose from off-label use, a new use, or misuse.*

*• The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.*

*Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:*

*• The assumptions, considerations, and judgment or weighting that support the conclusions of the benefit-risk evaluation should be clear.*

*• If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.*

*Economic considerations (e.g., cost effectiveness) should not be included in the benefit-risk evaluation.*

*When there is important new information or an ad hoc PBRER has been requested, a detailed benefit-risk analysis is warranted.*

*Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.*

The benefit-risk evaluation is developed from a careful review of all available relevant data on the key benefits and key risks of [generic name] considered in the context of the medical need within the indication population(s), and the clinical profile(s) of the available alternative therapy (ies). Key benefits and risks are identified on the basis of relevance and medical importance. The key benefits and risks are incorporated into an integrated assessment using a structured framework that allows qualitative evaluation on the basis of features such as effect size, medical importance / seriousness, duration, and quality of the supporting evidence. Product-specific considerations include:

* [Generic name] is indicated for the treatment of [add indication], [add key characteristics of target disease that justify the medical need for the treatment] (Example: a serious condition with a high mortality rate and limited alternative treatment options).
* The measures of benefit [list main endpoints] are not directly comparable to the measures of risk [list key risks].

### Overall Benefit-risk Conclusion

*Lead author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead; Clinical Management; Clinical Development*

*If no new information was received during the PSUR data interval that significantly alters the benefit-risk profile:*

Overall, the previously established favourable benefit-risk profile for [generic name] has been reconfirmed by the efficacy and safety data that have become available during this reporting interval.

*If new efficacy / safety information was received that modifies the benefit-risk profile, but the overall benefit-risk remains positive:*

During the PSUR reporting interval, the MAH has received new, important [efficacy / safety] information that resulted in a modification of the benefit-risk profile of [generic name]. An integrated assessment of the key benefits and risks, considering the full body of the available evidence, indicates that the overall benefit-risk remains positive.

# Conclusions and Actions

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 19.0 Conclusions and Actions* | *Section 20.0 Conclusions* |

*Lead author(s): GPV Medical Safety Operations Associate/Medical Safety Product Lead*

*The PSUR should conclude with the implications of any new information that arose during the reporting interval in terms of the overall evaluation of benefit-risk for each authorised indication, as well as for relevant subgroups, if appropriate.*

*Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the marketing authorisation holder should assess the need for changes to the reference information/reference safety information and propose changes as appropriate.*

*In addition and as applicable, the conclusions should include preliminary proposal(s) to optimise or further evaluate the risk-benefit balance for further discussion with the relevant competent authority (ies). This may include proposals for additional risk minimisation activities.*

*For products with a pharmacovigilance or risk management plan, the proposals should be incorporated into pharmacovigilance planning together with the risk minimisation plan.*

Analysis of the data contained within this PSUR supports the adequacy of the current CCDS for [generic name] in terms of product safety.

*If the product has a RMP also include the following sentence:* Analysis of these data contained within this PSUR supports the adequacy of the current Risk Management Plan for [generic name].

Examination of the data contained within this PSUR supports the conclusion that the overall benefit-risk balance for [generic name] continues to be positive.

As with all MAH products, the safety profile of [generic name] is closely monitored on a continuing basis.

# Regional Appendix

*The information included in this appendix should be used to comply with national or regional requirements*

***Lead author: See below***

## EU Regional Appendix

### Proposed Product Information

*Lead Author(s): Regulatory Affairs Europe*

*The assessment of the need for amendments to the product information is incorporated within the PSUR assessment procedure in the EU. The regulatory opinion/position should include recommendations for updates to product information where needed. Marketing authorisation holders should provide the necessary supportive documentation and references within the PSUR or in this appendix to facilitate this.*

*Within the PSUR, the marketing authorisation holder is required to consider the impact of the data and evaluations presented within the report, on the marketing authorisation. Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved SmPC(s) for the product(s) for which the PSUR is submitted [IR Art 34 (5)].*

*In this subsection, the marketing authorisation holder should provide the proposed amendments for product information (SmPC and package leaflet) based on the above mentioned evaluation. These should be based on all EU authorised indications.*

*A track changes version of the proposed amended parts ONLY of the SmPCs and package leaflets based on the assessment and conclusions of the PSUR should be provided. For centrally authorised medicinal products, the proposed updates to the product information should also be submitted to Module 1.3.1 of the Electronic Common Technical Document (eCTD).*

*All the SmPCs and packages leaflets covered by the PSUR and in effect at the data lock point should be reviewed to ensure that they reflect the appropriate information according to the cumulative data included and analysed in the PSUR.*

*Amendments to the product information should not be postponed or delayed until the PSUR submission and amendments not related to the information presented in the PSUR, should not be proposed within the PSUR procedure. It is the obligation of the marketing Authorisation holder to submit a variation in accordance with the Regulation (EC) No 1234/2008 on variations to the terms of a marketing Authorisation.*

*A brief description of ongoing procedures (e.g. variations) to update the product information should be provided in this section.*

***Lead author: Regulatory Affairs Europe***

During and after the reporting period of this PSUR, there were no safety variation application(s) submitted or approved to propose a change to the product information [SmPC and/or package leaflet] for [generic name].

*OR*

[During and after the reporting period of this PSUR *OR* During the reporting period of this PSUR *OR* After the reporting period of this PSUR], there were safety variation application(s) approved to propose a change to the product information [SmPC and/or package leaflet] for [generic name]:

AND/OR

[During and after the reporting period of this PSUR *OR* During the reporting period of this PSUR *OR* After the reporting period of this PSUR], there were safety variation application(s) submitted and not yet approved to propose a change to the product information [SmPC and/or package leaflet] for [generic name]:

*[List the variations: variation procedure number; scope of variation]*

Considering the impact of the data and evaluations, presented within this PSUR, the MAH concludes that there is no need to amend the product information [SmPC and/or package leaflet] for [generic name].

*OR*

Considering the impact of the data and evaluations, presented within this PSUR, the MAH provides the following proposals for product information [SmPC and/or package leaflet] for [generic name]:

*[List the proposed changes to the product information]*

*Provide the comparison table in the template and label it as “Reference Information Comparison European Union”.*

### Proposed Additional Pharmacovigilance and Risk Minimisation Activities

*Lead author: GPV Medical Safety Operations/Medical Safety Product Lead*

*Considering the provision established in IR Art 34 (5), this subsection should include proposals for additional pharmacovigilance and additional risk Minimisation activities based on the conclusions and actions of the PSUR, including a statement of the intention to submit a RMP or an updated RMP when applicable.*

*If there are no new proposed pharmacovigilance and risk minimisation activities, insert the following statement:*

The MAH concludes that based on review of the available data, including new safety information received during the current PSUR reporting interval that the current pharmacovigilance and risk minimisation activities are adequate to address the product-specific safety concerns and no new additional pharmacovigilance and/or additional risk minimisation activities are required.

*OR*

*If new additional pharmacovigilance and/or additional risk minimisation activities are proposed, provide a description of the new activity (ies) below*

*For products with an RMP, the plan to include the proposed new activity (ies) in the RMP should also be described, for example:*

The [generic name] Risk Management Plan has been updated to incorporate the new additional pharmacovigilance / additional risk minimisation] activity (ies), and [is provided with this PSUR] *or* will be provided on [planned date of submission].

### Summary of Ongoing Safety Concerns

*Lead author: GPV Medical Safety Operations/Medical Safety Product Lead*

*The content of PSUR section 16.1 "Summary of safety concerns" should be copied and pasted into this Appendix.*

| Table 20.1.3-1 Summary of Safety Concerns | |
| --- | --- |
| **Important identified risks** | * [ important identified risk #1 ] * [ important identified risk #2 ] * [Drug-Drug Interaction]   *etc.* |
| **Important potential risks** | * [ important potential risk #1 ] * [ important potential risk #2 ] * [Drug-Drug Interaction]   *etc.* |
| **Missing information** | * [Missing information #1 ] * [Missing information #2 ]   *etc.* |

### Reporting of Results from Postauthorisation Safety Studies (PASS)

*Lead Author(s): Epidemiology/MSO Delegate(s) (for noninterventional studies) and Clinical Management (for interventional studies) with input from Global Study List (Programme Management).*

*Findings from both interventional and noninterventional (for further guidance see Module VIII) postauthorisation safety studies (PASS) should be reported in the PSUR. While the marketing authorisation holder should inform competent authorities in Member States and the Agency as applicable about any new information that may impact on the risk-benefit balance immediately, the PSUR should provide comprehensive information on the findings of all PASS, both interventional and noninterventional, in PSUR sections 7 and 8 respectively.*

*Final study reports for studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed during the reporting interval should also be included as an annex to the PSUR. For such studies discontinued during the reporting interval, the reasons for stopping the study should also be explained.*

*If an important safety concern has been identified in the course of a study, regardless of whether it has been detected through prespecified methods and whether the study is considered a PASS, the marketing authorisation holder and specifically the qualified person responsible for pharmacovigilance (QPPV) will have informed the relevant competent authorities in Member States immediately.*

*PSURs should not be used as the initial communication method either for the submission of final study reports to the competent authorities in Member States or for the notification of any new information that might influence the evaluation of the risk-benefit balance.*

| Table 20.1.4-1 Completed Study Reports for Interventional and Noninterventional PASS | | | |
| --- | --- | --- | --- |
| Protocol title | EU PAS register no. (if applicable) | Report date | Reasons for stopping the study (if applicable) |
|  |  |  |  |
|  |  |  |  |

*If there are no applicable study reports, insert the following statement:*

There are no new study reports from noninterventional PASS during the reporting interval.

There are no new study reports from interventional PASS during the reporting interval.

### Effectiveness of Risk Minimisation

*Lead author: GPV Medical Safety Operations/Medical Safety Product Lead*

*Risk Minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The success of risk Minimisation activities in delivering these objectives needs to be evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall risk-benefit balance is optimised. In accordance with section VII.B.5.16.5., evaluation of broad global experience should be reflected in the body of the report, when provides insights into the effectiveness of risk Minimisation activities in any country or region that may have utility in other countries or regions are of particular interest.*

*This subsection should additionally provide an evaluation of the effectiveness of routine and/or additional risk Minimisation activities specifically relevant to an EU context. This should take account of regulatory imposed obligations for implementation of risk Minimisation measures in addition to the overall requirement for monitoring of safety and benefit-risk. Results of any studies to assess the impact or other formal assessment(s) of risk Minimisation activities in the EU should be included when available. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk Minimisation activities. If a particular risk Minimisation strategy proves ineffective, then alternative activities need to be put in place. In certain cases, it may be judged that risk Minimisation cannot control the risks to the extent possible to ensure a positive risk-benefit balance and that the medicinal product needs to be withdrawn either from the market or restricted to those patients in whom the benefits outweigh the risks. More extensive guidance on monitoring the effectiveness of risk Minimisation activities is included in Module XVI. As a principle, the marketing authorisation holder should distinguish in their evaluation between implementation success and attainment of the intended outcome.*

*When no new results of assessments of effectiveness of risk minimisation became available during the PSUR reporting interval, the following standard statement should be used:*

No new results of assessments of the effectiveness of risk minimisation activities relevant to the benefit-risk assessment were received during the PSUR reporting interval.

# Appendices

All documents after here are related to children documents a part of the vDOC (delete text when finalising document)

## Reference Information

*Lead author(s): Labelling*

*Provide a clean copy of all versions of the reference information in effect at the end of the reporting interval (e.g. different formulations included in the same PSUR). The reference information should be dated and version controlled and uploaded to Report Appendix folder in GEPIC.*

## Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

*Lead Author: GPV Aggregate Reporting Associate*

*The safety tables come from AVISSO and are provided to the Aggregate Reporting Associate. The Aggregate Reporting Associate will then upload the tables to the Safety Data Output folder in GEPIC.*

*OR*

No reports identified.

## Cumulative and Interval Summary Tabulations of Adverse Reactions from Postmarketing Data Sources

*Lead Author: GPV Aggregate Reporting Associate*

*The safety tables come from AVISSO and are provided to the Aggregate Reporting Associate. The Aggregate Reporting Associate will then upload the tables to the Safety Data Output folder in GEPIC.*

## Tabular Summary of Safety Signals

*Lead Author(s): GPV Medical Safety Operations/Medical Safety Product Lead - The responsible author(s) should enter the information/table into this template directly, and the Aggregate Reporting Associate will then create an appendix.*

| Table 21.4-1 Tabular summary of safety signals new, ongoing or closed during the reporting interval | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Signal term | Date detected | Status | Date closed | Source or trigger of signal | Reason for evaluation and summary of key data | Method of signal evaluation | Action(s) taken or planned |
|  | [DD Mmm YYYY] | [ new / ongoing / closed ] | [DD Mmm YYYY] | *e.g., nonclinical study, clinical study, postmarketing data* | *brief summary of key data and rationale for further evaluation* | *e.g. meta-analysis of clinical trial data, case-level evaluation of post marketing adverse event reports, etc.* | *e.g. no action required, adverse reaction added to prescribing information, etc.* |
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|  |  |  |  |  |  |  |  |

*Signal status:*

* *New: signal was first identified during the PSUR reporting interval, and is still under evaluation at the end of the interval*
* *Ongoing: signal was identified prior to the PSUR reporting interval and is still under evaluation at the end of the interval*
* *Closed: (both newly and previously identified) signals for which signal evaluation was completed during the PSUR reporting interval*
* *If no data, include an appropriate statement.*
* *Date detected (month/year): the month and year when a topic is identified as a validated signal by the MAH. For example:*
* *For an internally generated signal: the date when the evaluating team makes the determination that the available information about the topic sufficiently supports the possibility of a new potential causal association (or a new aspect of a known risk) so that further evaluation of the signal is warranted*
* *For a signal generated by a health authority: the date when the health authority communication / inquiry is received*
* *Date closed (month/year): the month and year when the signal evaluation was completed*

## Listing of all Marketing Authorisation Holder-sponsored Postmarketing Interventional Trials

*Lead Author(s): Clinical Management (obtain information from Global Study List from Programme Management). The Aggregate Reporting Associate will create an appendix from the tables provided by Programme Management. Include trials that were completed or ongoing during the reporting interval.*

*Note: Please do not attempt to modify data or add any comments to the documents in the supporting documents folder. If data received from programme management (GSL) needs to be corrected, please contact the Aggregate Reports Associate assigned to the report. The Aggregate Reports Associate will work with programme management to get the tables corrected and then inform the team.*

*The listing should include the following information for each trial:*

* *Study ID (e.g., protocol number or other identifier);*
* *Study title (abbreviated study title, if applicable);*
* *Study type (e.g., randomised clinical trial, cohort study, case-control study);*
* *Population studied (including country and other relevant population descriptors, e.g. Paediatric population or trial subjects with impaired renal function);*
* *Study start (as defined by the MAH) and projected completion dates;*
* *Status:*
* *Ongoing (clinical trial has begun);*
* *Completed (clinical study report is finalised).*
* *If no data, include an appropriate statement.*

## Listing of all Marketing Authorisation Holder-sponsored Noninterventional Studies

*Lead Author(s): Clinical Management (obtain information from Global Study List from Programme Management).**The Aggregate Reporting Associate will create an appendix from the tables provided by Programme Management.*

*Note: Please do not attempt to modify data or add any comments to the documents in the supporting documents folder. If data received from programme management (GSL) needs to be corrected, please contact the Aggregate Reports Associate assigned to the report. The Aggregate Reports Associate will work with programme management to get the tables corrected and then inform the team.*

*Use RMP Appendix 4 "Synopsis of Ongoing and Completed Pharmacoepidemiological Study Programme," and select for inclusion only those noninterventional studies that meet the criteria for this PSUR Appendix (i.e., targeted safety studies and studies intended to evaluate the effectiveness of risk minimisation), and were completed or ongoing during the reporting interval.*

*If no data, include an appropriate statement.*

## List of the Sources of Information Used to Prepare the PSUR (When Desired by the Marketing Authorisation Holder)

***If not including a list of sources please include the following statement:***

Not applicable.

***OR if references are utilised in the report, please add them as endnotes using the below instructions. If including a references list (optional) instructions are also below and in final Otsuka style guide.***

***HOW TO ADD REFERENCES TO AN OST FORMATTED DOCUMENT***

* *Publications and other source documents cited in this PSUR should be entered into the template as endnotes.*
* *An index of references can be included in this appendix (optional). If so, authors are advised to use the styles/formats as specified in the latest Otsuka Style Guide to link references to text.*

***NOTE****: References must be verified by the author(s) against the original documents.*

*General Rules:*

* *Use the customised Insert Citation function of the Otsuka Style Template (located on the Otsuka Refs Toolbar) to insert reference (endnote) citations.*
* *To use the Insert Citation feature, authors must first create or select a list of references in an Excel spreadsheet format. This spreadsheet should contain 2 columns, Full Citation and Short Title. The style for Full Citation when citing published literature is a modified version of the Vancouver Style. A Short Title should be associated with each Full Citation that is unique but descriptive and can simply be the first author and year published/issued, or report number or some other short but descriptive designator.*
* *In reference lists created using the Insert Citation feature, references are identified by Arabic numbers, 1-n, and numbered consecutively in the order in which they are first mentioned in the text. The original number assigned to the reference is reused each time the reference is cited in the text, regardless of its subsequent position in the text.*

***Sample index of references format expected is as below.***

*1 Halpern SD, Umbel PA, Copland AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25; 347(4):284-7.*

*2* *Rose ME, Herbing MB, Mesick J, Marion DW, Palmer AM, Shading JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002; 935(1-2):40-6.*

*3 author5, author6, short title...*

## Table Listing Worldwide Marketing Authorisation Status

*Lead Author(s): OPCJ Regulatory Affairs**will provide this information in tabular format to the Aggregate reporting team, and the Aggregate Reporting Associate will then create an appendix and upload to GEPIC.*

| Table 21.8-1 Worldwide Marketing Authorisation Status | | | |
| --- | --- | --- | --- |
| Country | Date of Approval/  Authorisation | Approved Indication | Approved Dosage |
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|  |  |  |  |
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*OR if multiple products are included within the same report, provide a Table for each product.*