*\*\*\*\*\*\*\*DELETE THIS PAGE\*\*\*\*\*\*\**

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

BLACK TEXT is required

(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*

*All Authors are responsible for:*

* *Converting* red *and* blue text *to* black text *as appropriate*
* *Deleting unused* red *and* blue text, *and unused alternate* black text.
* *Deleting green text and blue boxes (described below)*
* *Note: Once the report is published, hyperlinked text may appear as* blue text

*Note: If publications and other source documents are cited in this DSUR please enter them as endnotes utilising the guidance in the final Otsuka Style guide.*

*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; boxes are similar to instructional text and must be deleted by the applicable Author(s).*

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

MK-XXXXChemical NameGeneric NameTrade Name1Release DatePrevious Release DatePrevious Edition No



Marketing Authorisation Holder / Sponsor:

Otsuka Pharmaceutical Development & Commercialization Inc.

2440 Research Boulevard

Rockville, MD 20850

[Generic name]

DEVELOPMENT SAFETY UPDATE REPORT (DSUR)

[RPT #]

Reporting Period: [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 Physician* |

|  |  |
| --- | --- |
| 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 DSUR.*

*Provide a concise summary of the important information contained in the report. Together with the title page, it can serve as a “stand-alone” document suitable for submission to ethics committees and other stakeholders, if required by national or regional laws or regulations. Do not include any unblinded information in the Executive Summary.*

*The following information should be included in the Executive Summary:*

* *Introduction- report number and reporting period;*
* *Investigational 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;*
* *Marketing approval(s)? (yes/no)- If yes, number of countries;*
* *Summary of overall safety assessment (based on Section 18 of the DSUR);*
* *Summary of important risks (based on Section 19 of the DSUR);*
* *Actions taken for safety reasons including significant changes to IB;*
* *Conclusions.*

This is the [#] annual development safety update report (DSUR) for [product name], summarising safety data received by Otsuka from [DD Mmm YYYY] to [DD Mmm YYYY]. *(from title page)*

[Product name] is a(n) [mode of action and/or therapeutic class] [indicated/being evaluated] for the treatment of [add indications]. The usual dose of [product name] in subjects is [add all dosing information; grouped by populations, if appropriate]. *(from Section 1)*

Overall, there have been approximately [###] subjects treated with [product name]

*OR*

Overall, there have been approximately *[####]* patient-years of treatment with [product name]. *(from Section 6.1)*

The cumulative number of patients treated with marketed [product name] worldwide from [DD Mmm YYYY] to [DD Mmm YYYY] was approximately [##].

*OR*

Cumulatively, there have been approximately *[####]* patient-years of treatment with marketed [product name]. *(from Section 6.2)*

*AND/OR*

During the reporting period, the number of patients treated with marketed [product name] worldwide was approximately [##]. *(from Section 6.2; include appropriate information as available. If product is not marketed, delete this entire bullet.)*

*OR*

During the reporting period, there were *[####]* patient-years of treatment with marketed [product name].

At the time of this report, [product name] has not been submitted for marketing authorisation. *(from Section 2)*

*OR*

[Product name] was first approved in [add country and date] and is currently registered and approved in [#] countries, *[group by indication/population, if appropriate].*

During the reporting period of this DSUR, there [were/were no] safety related updates to the investigator’s brochure (IB) for [product name]. *If this is the first time that the appended IB includes the RSI section, ONLY include the following statement the first time the IB includes the new RSI section:* In adherence with CT-3 regulations, the IB has been updated to include a reference safety information (RSI) section. *[List only significant changes to IB here]* These updates are discussed in Section 4 Changes to the Reference Safety Information.

The following have been identified as important potential risks: [add cumulative risks from section 19]. *Differentiate what is new for the reporting period versus what was previously identified.*

[Add summary statement from Section 20, conclusions regarding actions that have been or will be taken to address emerging issues]. As with all Otsuka products, the safety profile of [product name] is monitored on a continuing basis. *(from Section 3)*

# TABLE OF CONTENTS

*Aggregate Reporting Associate is responsible for updating the TOC.*

[EXECUTIVE SUMMARY 3](#_Toc447267131)

[TABLE OF CONTENTS 6](#_Toc447267132)

[LIST OF IN-TEXT TABLES 9](#_Toc447267133)

[LIST OF ABBREVIATIONS, ACRONYMS, AND DEFINITION OF TERMS 10](#_Toc447267134)

[1 Introduction 12](#_Toc447267135)

[2 Worldwide Marketing Approval Status 13](#_Toc447267137)

[2.1 Marketing Authorisation Status (EU) 13](#_Toc447267138)

[2.2 Marketing Authorisation Status (US) 14](#_Toc447267139)

[2.3 Marketing Authorisation Status (Asia) 14](#_Toc447267140)

[2.4 Marketing Authorisation Status (Rest of World) 14](#_Toc447267141)

[3 Action Taken in the Reporting Period for Safety Reasons 14](#_Toc447267142)

[3.1 Actions Taken in the Reporting Interval for Safety Reasons (EU) 17](#_Toc447267143)

[3.2 Actions Taken in the Reporting Interval for Safety Reasons (US) 17](#_Toc447267144)

[3.3 Actions Taken in the Reporting Interval for Safety Reasons (Asia) 17](#_Toc447267145)

[3.4 Actions Taken in the Reporting Interval for Safety Reasons (Rest of World) 17](#_Toc447267146)

[4 Changes to Reference Safety Information 17](#_Toc447267147)

[5 Status of Clinical Trials Ongoing and Completed during the Reporting Period 19](#_Toc447267148)

[6 Estimated Cumulative Exposure 20](#_Toc447267149)

[6.1 Cumulative Subject Exposure in the Development Programme 21](#_Toc447267150)

[6.2 Patient Exposure from Marketing Experience 23](#_Toc447267151)

[7 Data in Line Listings and Summary Tabulations 24](#_Toc447267152)

[7.1 Reference Information 25](#_Toc447267153)

[7.2 Interval Line Listings of Serious Adverse Reactions during the Reporting Period 26](#_Toc447267154)

[7.3 Cumulative Summary Tabulations of Serious Adverse Events 26](#_Toc447267155)

[8 Significant Findings from Clinical Trials during the Reporting Period 27](#_Toc447267156)

[8.1 Completed Clinical Trials 28](#_Toc447267157)

[8.1.1 Completed Clinical Trials (EU) 30](#_Toc447267158)

[8.1.2 Completed Clinical Trials (US) 30](#_Toc447267159)

[8.1.3 Completed Clinical Trials (Asia) 30](#_Toc447267160)

[8.1.4 Completed Clinical Trials (Rest of World) 31](#_Toc447267161)

[8.2 Ongoing Clinical Trials 31](#_Toc447267162)

[8.2.1 Ongoing Clinical Trials (EU) 33](#_Toc447267163)

[8.2.2 Ongoing Clinical Trials (US) 34](#_Toc447267164)

[8.2.3 Ongoing Clinical Trials (Asia) 34](#_Toc447267165)

[8.2.4 Ongoing Clinical Trials (Rest of World) 34](#_Toc447267166)

[8.3 Long-term Follow-up 34](#_Toc447267167)

[8.4 Other Therapeutic Use of Investigational Drug 36](#_Toc447267168)

[8.5 New Safety Data Related to Combination Therapies 37](#_Toc447267169)

[9 Safety Findings from Noninterventional Studies 39](#_Toc447267170)

[10 Other Clinical Trial/Safety Information 40](#_Toc447267171)

[11 Safety Findings from Marketing Experience 42](#_Toc447267172)

[12 Nonclinical Data 44](#_Toc447267173)

[13 Literature 46](#_Toc447267174)

[14 Other DSURs 47](#_Toc447267175)

[15 Lack of Efficacy 47](#_Toc447267176)

[16 Region-Specific Information 48](#_Toc447267177)

[17 Late-Breaking Information 49](#_Toc447267178)

[18 Overall Safety Assessment 50](#_Toc447267179)

[18.1 Evaluation of the Risks 50](#_Toc447267180)

[18.2 Benefit-risk Considerations 51](#_Toc447267181)

[19 Summary of Important Risks 52](#_Toc447267182)

[20 Conclusions 55](#_Toc447267183)

[21 Appendices 56](#_Toc447267184)

[21.1 Investigator’s Brochure 56](#_Toc447267185)

[21.1.1 Investigator’s Brochure in Effect at the Start of Reporting Period 56](#_Toc447267186)

[21.1.2 Investigator’s Brochure Revised After Start of Reporting Period 57](#_Toc447267187)

[21.2 Cumulative Table of Important Regulatory Requests 58](#_Toc447267188)

[21.3 Status of Ongoing and Completed Clinical Trials 59](#_Toc447267189)

[21.3.1 Tables of Ongoing and Completed Clinical Trials during the Reporting Period 60](#_Toc447267190)

[21.3.2 Clinical Study Report Synopsis 62](#_Toc447267191)

[21.4 Cumulative Summary Tabulations of Demographic Data 63](#_Toc447267192)

[21.5 Line Listings of Serious Adverse Reactions during the Reporting Period 65](#_Toc447267193)

[21.6 Cumulative Summary Tabulation of Serious Adverse Events 66](#_Toc447267194)

[21.7 Scientific Abstracts 67](#_Toc447267195)

[22 Regional Appendices 68](#_Toc447267196)

[22.1 Cumulative Summary Tabulation of Serious Adverse Reactions 69](#_Toc447267197)

[22.2 List of Subjects who Died during the Reporting Period 70](#_Toc447267198)

[22.3 List of Subjects who Dropped out of Studies during the Reporting Period 71](#_Toc447267199)

[22.4 Significant Phase I Protocol Modifications with Respect to a US IND 72](#_Toc447267200)

[22.5 Significant Manufacturing Changes 73](#_Toc447267201)

[22.6 Description of the General Investigation Plan for the Coming Year with Respect to a US IND 74](#_Toc447267202)

[22.7 Log of Outstanding Business with Respect to a US IND 75](#_Toc447267203)

# LIST OF IN-TEXT TABLES

[Table 4-1 Significant Safety-Related Changes to the Investigator’s Brochure Edition Number[#] 17](#_Toc441052353)

[Table 6.1-1 Cumulative Estimated Subject Exposure in Clinical Studies1, 2 21](#_Toc441052354)

[Table 6.2-1 Cumulative Patient Exposure Units Distributed and Patient Years of Treatment 23](#_Toc441052355)

[Table 12-1 Summary of Nonclinical findings 43](#_Toc441052356)

[Table 19-1 Summary of Important Identified Risks 52](#_Toc441052357)

[Table 19-2 Summary of Important Potential Risks 53](#_Toc441052358)

[Table 21.2-1 Cumulative Table of Important Regulatory Requests 57](#_Toc441052359)

[Table 21.3.1-1 Ongoing Clinical Trials during the Reporting Period 59](#_Toc441052360)

[Table 21.3.1-2 Completed Clinical Trials during the Reporting Period 60](#_Toc441052361)

# LIST OF ABBREVIATIONS, ACRONYMS, AND DEFINITION OF TERMS

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

| Abbreviation/Acronym | Definition |
| --- | --- |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| CCDS | Company core data sheet |
| 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 |
| IB | Investigator’s brochure |
| ICSR | Individual case safety report |
| IMP | Investigational medicinal product |
| IND | Investigational new drug |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PT | Preferred term |
| SAE | Serious adverse event |
| SAR | Serious adverse reaction (defined as serious adverse event that is considered drug-related by the sponsor or investigator) |
| SOC | System organ class |
| SUSAR | Suspected unexpected serious adverse reaction |

***GENERAL GUIDANCE NOTE TO AUTHORS***

***If publications and other source documents are cited in this DSUR please enter them as endnotes utilising the guidance in the final Otsuka Style guide.***

***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. “Subject” 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 safety 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 DSUR Introduction should include, if applicable:*

* *Developmental international birth date (DIBD) or international birth date (IBD) (as applicable);*
* *Reporting period and sequential number of the report;*
* *Investigational product(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);*
* *A brief description of the indication(s) and population(s) being studied;*
* *A short summary of the scope of the clinical trials covered by the report (eg, all trials with the investigational product, indication-specific trials, trials with combination products);*
* *A brief description and explanation of any information that has not been included in the DSUR (eg, when written agreements with a partner company do not provide for exchange of all safety data);*
* *The rationale for submission of multiple DSURs for the investigational product, if applicable. See guidance for combination compounds in Section 8.5.*

This document represents the annual Development Safety Update Report (DSUR) Number [#] for [generic name (preferred) or compound number if no generic name available], herein referred to as [generic name- (may be abbreviated if needed), or compound number if appropriate]. The development international birth date (DIBD) is [DD Mmm YYYY]. *OR, if there is an international birth date for the product, state*: The international birth date (IBD) is [DD Mmm YYYY]. This DSUR summarises the safety data received by Otsuka and any applicable business partners from worldwide sources between [DD Mmm YYYY] and [DD Mmm YYYY].

[Product name] is *[indicated/being evaluated]* for the treatment of [add indications]. This DSUR includes ongoing and completed clinical trials conducted during the DSUR reporting period. The scope of clinical trials in this DSUR include: [describe type of ongoing and completed clinical trials in this DSUR]. The following formulations and doses were included in clinical trials during the DSUR reporting period: [describe formulations/doses included in ongoing and completed clinical trials during the reporting period].

# Worldwide Marketing Approval Status

*Common sections between PBRER and DSUR*

|  |  |
| --- | --- |
| *PBRER section* | *DSUR section* |
| *Section 2 – Worldwide Marketing Authorisation status* | *Section 2.0 Worldwide Marketing Approval Status* |

*Lead Author: 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 2.*

*Provide a brief narrative overview including date of first approval, indication(s), approved dose(s), and where approved, if applicable.*

At the time of this report, [product name] is not authorised for marketing in any country.

*OR*

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, [product name] has been registered and approved in [##] countries.

*OR for non-Otsuka marketed product*

At the time of this report, [product name] has been registered and approved in [##] countries where this clinical trial was executed.

## Marketing Authorisation Status (EU)

*This header should only be included if applicable. If not, please put all text in section above (2.0).*

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

* [mention indications 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).*

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

* [mention indications 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).*

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

* [mention indications 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).*

At the time of this report, [generic name] has been registered and approved in [#] countries within the Rest of World (ROW) ([name of the countries]) for the following indications and doses:

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

# Action Taken in the Reporting Period for Safety Reasons

*Common sections between PBRER and RMP and DSUR*

|  |  |  |
| --- | --- | --- |
| *PBRER section* | *RMP section* | *DSUR section* |
| *Section 3.0 – 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: Regulatory Affairs*

*Subsections for US, EU, Asia and Rest of World (ROW) have been included below. If not applicable, please remove subsections 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 during the reporting period by the sponsor, regulators, data and safety monitoring boards or ethics committees that had 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. Relevant updates to previous actions should also be summarised in this section (eg, resumption of a clinical trial after suspension).*

*Changes to the investigator’s brochure and company core data sheet should be discussed separately in the “Changes to Reference Safety Information”; see Section 4.*

*Examples of significant actions taken for safety reasons include:*

* *Actions related to investigational products:* 
  + *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 15);*

*Note: “Partial suspension” might include several actions (eg, 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 product or comparator;*
  + *Failure to obtain marketing approval for a tested indication including voluntary withdrawal of a marketing application.*
  + *Risk management activities, including:* 
    - *Protocol modifications due to safety or efficacy concerns (eg, dosage changes, changes in trial inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);*
    - *Restrictions in trial population or indications;*
    - *Changes to the informed consent document relating to safety issues;*
    - *Formulation changes;*
    - *Addition by regulators of a special safety-related reporting requirement;*
    - *Issuance of a communication to investigators or healthcare professionals;*
    - *Plans for new studies to address safety issues.*
* *Actions related to marketed products:* 
  + *Failure to obtain a marketing approval renewal;*
  + *Recall of marketed product;*
  + *Withdrawal or suspension of a marketing approval.*
  + *Risk management activities including:* 
    - *Significant restrictions on distribution or introduction of other risk minimisation measures;*
    - *Significant safety-related changes in labelling documents that could affect the development programme, including restrictions on use or population treated;*
    - *Communications to health care professionals;*
    - *New postmarketing study requirement(s) imposed by regulators.*

*This section should also summarise requests from regulatory authority(ies) that place a specific limitation on current or future development (eg, a request to conduct long-term animal studies before initiating a long-term clinical trial, specification of a maximum dose to be evaluated, a request for specific safety data before initiating trials in paediatric subjects). A cumulative listing of such requests from regulatory authorities should be provided, including any updates if applicable. This should be provided in Appendix 21.2.*

During the reporting period, there were no significant actions related to safety taken for [product name]. In addition, for marketed products, there are no records of any registration being revoked or withdrawn for safety reasons.

*OR*

During the reporting period, the following significant actions for safety reasons were taken: *List any significant actions related to safety and reason for change, if known (for marketed products, include any records of registrations being revoked or withdrawn for safety reasons).*

*OR for non-Otsuka marketed product*

There [were/were no] significant actions taken for safety reasons based on this clinical trial. *List any significant actions related to safety and reason for change, if known.*

A cumulative table of important requests from regulatory authorities regarding limitations on development as described above for the [product name] development programme is provided in Appendix 21.2. *(Regulatory affairs is responsible for completing this table)*

## 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

*Lead Author: Labelling Team / Clinical Management*

*List any significant safety-related changes to the IB or other reference safety information within the reporting period. Such changes might include information relating to exclusion criteria, contraindications, warnings, precautions, serious adverse drug reactions, adverse events of special interest, interactions, and any important findings from nonclinical studies (eg, carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the DSUR.*

During the reporting period of this DSUR, there [were/were no] significant safety-related updates to the Investigator’s Brochure (IB) for [product name].

*As applicable, briefly describe only the* ***significant safety-related changes*** *to the IB (i.e., to safety sections listed in the Summary of Changes Table for your specific product, which includes:**Section 4 (Nonclinical Toxicology), Section 5.4 (Clinical Safety), Section 6 (Summary of Data and Guidance for the Investigator)), or any other changes made for significant safety reasons.*

*NOTE: You may choose to present this information in a table also, see table example 4-1 below:*

***OR***

*If this is the first time that the appended IB includes the RSI section, ONLY include the following statement the first time the IB includes the new RSI section:*

In adherence with CT-3 regulations, the IB has been updated to include a Reference Safety Information (RSI) section. Table 4-1 includes the significant safety-related changes to the IB during the reporting period.

The IB that was in effect at the start of the reporting period is provided in Appendix 21.1.1. If the IB was revised during the reporting period, the revised IB is also provided in Appendix 21.1.2. *If there were no changes to the IB to report, then the statement in blue and Table 4-1 should be deleted.*

| Table 4-1 Significant Safety-Related Changes to the Investigator’s Brochure Edition Number[#] | |
| --- | --- |
| Section | Description of Change |
|  |  |
|  |  |
|  |  |

*OR for non-Otsuka marketed product*

The safety information from this clinical trial did not contribute to any significant safety-related changes to the IB or other reference safety information within the reporting period.

# Status of Clinical Trials Ongoing and Completed during the Reporting Period

*Lead Author(s): Clinical Management (review from Clinical Development). Some information may be obtained from the Global Study List from Programme Management.*

*Provide a brief overview of the clinical trials ongoing and completed by the sponsor in the reporting period, with detailed information presented in a table as an appendix. This information will need to be gathered from multiple sources and hand-tabulated. Separate tables can be provided by indication, formulation, and study population, if appropriate. In addition, where required by national or regional laws or regulations, similar information should be provided for other therapeutic use of an investigational product in the reporting period. The table(s) should include the following information for each clinical trial:*

* *Study ID (eg, protocol number or other identifier*;
* *Phase (1, 2, 3, or 4-use Arabic numerals with reference to phase);*
* *Status:* 
  + *Ongoing (clinical trial has begun; has begun but is currently on hold; has concluded but clinical study report has not been finalised);*
  + *Completed (clinical study report is finalised);*
  + *Countries/regions where there is at least one investigational site for the protocol;*
* *Abbreviated study title;*
* *Design (uncontrolled, controlled, open, single blind, double blind, parallel, cross-over, etc., including treatment arms);*
* *Dose and regimen of investigational product and any comparators:*
* *Trial population as appropriate (age; sex; indication(s); specific patient groups, eg, trial subjects with impaired renal function or trial subjects resistant to treatment);*
* *Date of clinical trial start (as defined by the sponsor, eg, first visit of first patient [FVFP], this may proceed the randomisation visit);*
* *Planned enrolment for trial as a whole.*

*Estimates of cumulative numbers of exposed subjects for each treatment arm, where available. The actual enrolment numbers for open or completed trials, and/or an estimate based on the randomisation scheme for blinded trials should be provided.*

*No further text beyond the standard language below is required in this section, as all data should be in the tables in the appendix.*

Information for ongoing and completed clinical trials during the reporting period can be found in Table 21.3.1-1 and Table 21.3.1-2, respectively in Appendix 21.3.

# Estimated Cumulative Exposure

*Lead Author(s): Clinical Management for Otsuka-sponsored clinical trials. Data outputs for cumulative exposure are provided to Aggregate team by OPCJ Aggregate team. Some information may also be obtained from the global study List from programme management.*

* *An estimation of cumulative subject exposure can help provide context for the cumulative summary tabulations of serious adverse events (SAEs), and the overall assessment of safety. The accuracy of the estimation of clinical trial exposure might be limited because of a number of factors, including the rapidity of subject enrolment and the number of ongoing trials where treatment assignment remains blinded.*
* *The optimal method of data presentation will depend on a number of factors, and the following general points should be considered in the preparation of the estimated exposure for the DSUR:* 
  + *Data should be presented in tabular format;*
  + *When there are important differences among trials in dose, route of administration, or patient population, these differences can be noted in the tables, or separate tables can be considered;*
  + *If the summary tabulations of SAEs are presented by indication, the exposure data should also be presented by indication, when available;*
  + *When there are substantial differences in time of exposure between subjects randomised to the investigational product and comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure data in subject-time (subject-days, -months, or -years);*
  + *Investigational product exposure in healthy volunteers might be less relevant to the overall safety profile, particularly when volunteers are exposed to only a single dose. Such data can be presented separately with explanation, when appropriate. For marketed products that are under clinical investigation, it might not be feasible or useful to obtain precise cumulative clinical trial exposure data, eg, when the product has been marketed for a number of years and/or has many indications. In these circumstances the sponsor should provide an explanation.*

## Cumulative Subject Exposure in the Development Programme

* *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 OPCJ Aggregate team.*

* *This section should include the following information; in tabular format:* 
  + *Cumulative number of subjects exposed to the investigational product from ongoing and completed clinical trials for the development programme. The number exposed to the investigational product, placebo, and/or active comparator(s) (list separately in each row) since the DIBD (Note: When treatment assignment is blinded, numbers of subjects can be estimated based on the randomisation scheme.);*
  + *Cumulative number of subjects exposed to the investigational product from 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 (Appendix 21.4);*
  + *Demographic characteristics for a single trial, if the trial is of particular importance (eg, a Phase III trial).*
  + *For completed studies (ie, CSR finalised and approved), the CSRs should be the source for exposure. In some cases, filing documents may also be of assistance.*
  + *For ongoing studies that the CSR is in draft, the draft CSR can be consulted to help in estimating exposure. Note: these studies would not be included in the Completed Studies tables (Appendix 21.4).*

*The table for estimated subject exposure (Table 6.1-1) is included in this section and corresponding tables of demographic data (Table 21.4-1 and Table 21.4-2) are included in Appendix 21.4.*

*For Table 21.4-1: Cumulative Subject Exposure for 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 [product name] clinical programme, of which [####] subjects have received [product name]. Estimates of overall cumulative subject exposure from completed and ongoing studies are provided in Table 6.1-1. *If complete exposure data is not available, describe those limitations.*

| Table 6.1-1 Cumulative Estimated Subject Exposure in Clinical Studies1, 2 | |
| --- | --- |
| Treatment | Number of subjects3 |
| IMP |  |
| Placebo |  |
| Comparator name #1 |  |
| Comparator name #2 |  |
| **Total** |  |
| 1 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.  2 Includes subjects 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. | |

An estimate of cumulative exposure to [product name] by age, sex, and racial group from ongoing and completed studies is provided in Appendix 21.4.

## Patient Exposure from Marketing Experience

*Common sections between PBRER, 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(MSO) Associate/Physician; Epidemiology/MSO Delegate(s); Medical Affairs; Sales/Marketing (per region: EU, Japan and US)*

*If the investigational product is marketed by the sponsor, the DSUR should include an estimate of the cumulative patient exposure in the marketed setting. The method for calculating patient exposure for subsequent DSURs and clearly described. If a change in the method is appropriate, then both methods and calculations should be shown in the DSUR introducing the change.*

*OPTIONAL Language for Product that has not been marketed:*

[Product name] is not authorised for sale in any country at the time of this report.

*OPTIONAL Language for Marketed Product:*

The number of patients/patient-years treated with marketed [product name], worldwide during the period of this DSUR 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 DSUR is presented in Table 6.2-1. 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 6.2-1 Cumulative Patient Exposure- Units Distributed and Number of Patients Treated/Patient Years of Treatment | | |
| --- | --- | --- |
| Strength | Number of Units | Number of Patients /Patient-Years of Treatment *(Remove option not used)* |
|  |  |  |
|  |  |  |
|  |  |  |
| **Total** |  |  |

*(Optional text to be used as applicable. Otherwise, please delete sentence):*

The cumulative estimated number of patients treated was not estimated due to variations in dosages and durations of administration.

# Data in Line Listings and Summary Tabulations

*Lead Author: Aggregate Reporting Associate is responsible for providing the tables and listings from clinical trials for Sections 7.1-7.3 (data for the safety tables comes from AVISSO).*

*Interval line listings of the serious adverse reactions (SARs; defined as serious adverse event that is considered drug-related by investigator and/or sponsor) that were reported to the sponsor during the period covered by the DSUR (Appendix 21.5); and*

*Cumulative summary tabulations of serious adverse events that have been reported to the sponsor since the DIBD (Appendix 21.6).*

*Use the preferred term from MedDRA; reference that blinded and unblinded data are included; reference placebo vs comparator data are included.*

Relevant blinded and unblinded safety data are presented using interval line listings for serious adverse reactions (SARs) and cumulative summary tabulations for serious adverse events (SAEs) from clinical trials in tables under Appendix 21.5 and Appendix 21.6, respectively. These tables are generated from the safety database. Case numbers may have different formats associated with former databases, but the differences in format do not imply anything about the content of the case.

*Additional description of output to be added as necessary.*

## Reference Information

*Lead Author: Aggregate Reporting Associate*

*This section of the DSUR should specify the version(s) of the coding dictionary used. If applicable, it should also specify the document and version used as reference safety information for determining expectedness for the tabulations, where required by national or regional laws or regulations.*

This DSUR may contain unblinded and blinded clinical trial adverse event data. Data from the investigational medicinal product (IMP), placebo, comparators, and pretrial and post-trial therapy are included in this report. The ADR terminology used in this DSUR reflects the diagnosis or terminology used by the reporter. The terminology displayed in the line listings and summary tabulations of this DSUR is based on the version [#] of MedDRA that was in use at the time the DSUR line listings and summary tabulations were generated. Due to the mapping of the historic data, changes in MedDRA versions, and evolving coding guidelines and conventions, it is possible that, over time, different Preferred Terms may have been used to identify synonymous reactions.

The status of a SAR as being "expected" or “unexpected” for the placebo or blinded therapy arm involving the IMP will be determined by the reference data Investigator’s Brochure (IB) version [#], release date *(if needed)* DD Mmm YYYY and Investigator’s Brochure version *[#],* release date *(If there is an IB after the start of the reporting period it can be included here)* DD Mmm YYYY for the IMP.

## Interval Line Listings of Serious Adverse Reactions during the Reporting Period

*Lead Author: Aggregate Reporting Associate*

*This section of the DSUR should summarise how case reports were selected for inclusion in the line listings. This section should not serve to provide analyses or conclusions based on the SARs. The line listings should be provided in Appendix 21.5.*

During the reporting period, [##] SAEs were considered related to study product or any other therapy in the case by Sponsor and are considered SARs.

Details of these [##] SARs are provided in Appendix 21.5. Each case report appears only once within the line listing, and is presented in the primary system organ class (SOC) determined by the most serious adverse reaction for the case, as judged by the sponsor. For case reports where the code break has yet to be completed, the product is identified with an IMP of ‘blinded’.

*If there were SAEs but no SARs*

During the reporting period, [##] cases (one patient may have more than one case) were received with [##] SAEs. None of the SAEs were considered possibly related to IMP or any other therapy by the sponsor and therefore, none are considered SARs. A line listing indicating there were no SARs is provided in Appendix 21.5.

*OR*

*If there are no SAEs/SARs*

During the reporting period, no patients experienced any SAEs or SARs; this is reflected in Appendix 21.5.

## Cumulative Summary Tabulations of Serious Adverse Events

*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* |

*Lead Author: Aggregate Reporting Associate*

*This section should refer to an appendix that provides a cumulative summary tabulation of SAEs reported in the sponsor’s clinical trials from the DIBD to the data lock point of the current DSUR. The sponsor should explain any omission of data (eg, clinical trial data might not be available for products marketed for many years or for products acquired through a business merger). The tabulation(s) should be organised by SOC, for the investigational product, as well as for the comparator arm(s) (active comparators, placebo, and treatment unknown due to blinding) used in the programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by protocol, indication, route of administration, or other variables. The line listings should be provided in Appendix 21.6.*

*This section should not serve to provide analyses or conclusions based on the SAEs. Discussion of any significant findings should be presented in Sections 8: Significant Finding from Clinical Trials during the Reporting Period and potentially in the Benefit-Risk and Conclusion sections.*

Appendix 21.6 presents a cumulative table of the number of SAEs that have been reported for the [product name] clinical development programme, from its initiation to the data lock point ([DD Mmm YYYY]), organised by therapy and SOC.

*OR*

*If there are no cumulative SAEs*

Cumulatively, no patients experienced any SAEs during the [product name] clinical development programme, from its initiation to the data lock point ([DD Mmm YYYY])*;* this is reflected in Appendix 21.6.

# Significant Findings from Clinical Trials during the Reporting Period

*The information in this section can be provided by indication, when appropriate, and should address the following topics, when applicable. Section 8 represents the interventional clinical development source data for the RSI and therefore must align with Sections 3 and 4 of the DSUR by providing the detailed data for the clinical trial-related safety actions taken by the company and changes made to the RSI during the reporting interval.*

## 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 DSUR should provide a brief summary of clinically important emerging efficacy and safety findings obtained from interventional clinical trials completed during the reporting period.*

*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 DSUR 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 issues, as well as evidence of new safety signals. Noninterventional study information should be provided in Section 10.*

*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 (eg, 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*
  + *IMP 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]. A list of the completed trial(s) for the reporting period is in Appendix 21.3; Table 21.3.1-2.

*[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 completed clinical trials in the period:*

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

*OR*

During the reporting period, data from [#]completed interventional clinical trials for [product name] were analysed. A list of the completed trial(s) for the reporting period is in Appendix 21.3; Table 21.3.1-2.

*[Add 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]*

*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 trial:* Continuing analysis/investigations into emerging *[RISK]* in the *[Abbreviated Protocol Name]* trial, *[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, and the reported deaths (if any), AEs leading to discontinuation, SAEs, and Grade 3/4 events 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 8.1 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 DSUR reporting period.*

*If the sponsor is aware of clinically important information that has arisen from ongoing interventional clinical trials (eg, learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarise the issue(s). It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals. Non interventional trial information should be provided in Section 10.*

*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 (eg, 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*
* *IMP discontinuations because of adverse events, including abnormal laboratory values or investigations*
* *drug–drug and other interactions*

*If an ongoing clinical trial uses the primary Investigational Medicinal Product (IMP), the product which is the focus of the DSUR, in combination with additional IMPs in the therapy regimen, please refer to the directions provided in Section 8.5 when deciding where to include the clinical safety summary. Ongoing clinical trials analysing drug-drug interactions (DDI) or add-on therapy regimens are typically discussed in Section 8.2. Although add-on therapy, primary IMP plus a standard treatment of care (baseline), involves the use of more than one drug to treat the indication, 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 standard of care (baseline) therapy is administered according to its established labelling instructions.*

*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 IMP 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]. Summary information for the ongoing trial(s) can be found in Appendix 21.3; Table 21.3.1-1.

*[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 period 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 8.2 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)*

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

*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 products, particularly advanced therapy products (eg, gene therapy, cell therapy products and tissue engineered products). When the development program 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] trial, [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] trial, [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 trial(s) [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 trial(s) 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 Investigational Drug

*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)*

*This section of the DSUR should include clinically important safety information from other programmes conducted by the sponsor that follow a specific protocol, with solicited reporting as per ICH E2D (eg, expanded access programmes, compassionate use programmes, particular patient use, single patient INDs and treatment INDs).*

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

Expanded access programmes involving [product name] (include as applicable) were completed [list ID Numbers] or ongoing [list ID Numbers] during the reporting period of: [DD Mmm YYYY] to [DD Mmm YYYY].

*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.*

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

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

*OR*

*If this section is not applicable:*

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

*OR*

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

## New Safety Data Related to 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, the product which is the focus of the DSUR, 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.*

*If the DSUR is for an investigational product that is also under development as a component of a fixed combination product or a multidrug regimen, this section should summarise important safety findings from the combination therapy DSUR.*

*Conversely, if this DSUR is for a multidrug therapy or fixed combination product, this section should summarise important safety information arising from trials on the individual components.*

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

*Only ongoing clinical trials are discussed in Section 8.5. If a clinical trial using a combination therapy has been completed (as according to the definition provided in Section 8.1) then the clinical safety summary should be included in Section 8.1.*

*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.

# Safety 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)*

*Contributing Author: 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 summarise relevant safety information from noninterventional studies (i.e., studies for which treatment is prescribed in the usual manner within current standards of clinical practice and not according to a protocol) conducted/sponsored by Otsuka that became available to the sponsor during the reporting period (eg, observational studies, epidemiological studies, registries and active surveillance programmes meeting the definition of noninterventional studies).*

*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 (eg, 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*
* *IMP discontinuations because of adverse events, including abnormal laboratory values or investigations*
* *drug–drug and other interactions*

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

*OR*

*[Add narrative information of relevant safety information]*

# Other Clinical Trial/Safety Information

*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* |

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

*This section should summarise relevant safety information from any other clinical trial/study sources that became available to the sponsor during the reporting period (eg, results from pooled analyses or meta-analyses 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 (eg, 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*
* *IMP discontinuations because of adverse events, including abnormal laboratory values or investigations*
* *drug–drug and other interactions*

No other trials have been conducted with [product name].

*OR*

Although other trials have been conducted with [product name], no important safety findings were noted.

*OR*

The following important safety findings were noted *(include study and safety information):*

# Safety Findings from Marketing Experience

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

*If the investigational product has been approved for marketing in any country, this section should include a concise summary of key safety findings that have arisen from marketing experience and that became available to the sponsor during the reporting period, particularly if the findings resulted in changes to the product labelling, investigator’s brochure, informed consent document or amendments to the product’s risk management plan. This includes not only safety findings relating to approved use but also off-label use, administration to special populations (eg, pregnant women), medication errors, overdose and abuse.*

*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 (eg, 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*
* *IMP discontinuations because of adverse events, including abnormal laboratory values or investigations*
* *drug–drug and other interactions*

*OPTION 1*

There is no marketed data as [product name] is not approved for marketing in any country.

*OR*

*OPTION 2*

The safety profile for this product in the marketed environment is provided in concurrent PSUR *if done concurrently with DSUR or* is reflective of the most recent PSURs provided for the period(s) [DD Mmm YYYY] to [DD Mmm YYYY]. *(NOTE: If most recent is in 2~ 6 month PSURs, they should both be listed)*

During the reporting period of this DSUR, [#] PSURs were provided for the period(s) [DD Mmm YYYY to DD Mmm YYYY]. As noted in the PSUR(s), the following summarises the key safety findings that resulted from monitoring of marketing experience in the reporting period.

There were [#] safety related updates to the CCDS (Company Core Data Sheet) for [product name]. *[If updates occurred]* These updates are summarised below:

*[If the product has a Risk Management Plan]* The Risk Management Plan *[was/was not]* updated during the period of this report.

*[If updates occurred, as appropriate]*

The following newly identified important safety concern(s) and the associated action plan *(was/were)* added to the Risk Management Plan:

*AND/OR*

Important changes to the Risk Management Plan include: *(describe changes)*

*Optional*

The following issues and safety concerns were identified and discussed:

*OR*

*Optional*

The safety profile for this product has not changed *(and/or)* there have been no new safety issues identified with this product.

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

# 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 (eg, carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting period. Implications of these findings should be* *discussed in the Overall Safety Assessment (Section 18).*

*If there are no major safety findings for the study, include “NA” in the appropriate boxes. If there are no nonclinical studies for the product, include “NA” 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 12-1 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 (eg, 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/Physician*

*CSPV Medical Safety Operations Associate/Physician and Aggregate Reporting Associate will review the literature output and draft content for marketed products; Clinical Management will review literature output and draft content for products in development.*

*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 scientific literature or available as unpublished manuscripts, relevant to the investigational product that the sponsor became aware of during the reporting period. This section should include information from nonclinical and clinical studies and, if relevant and applicable, information on products of the same class. It should also summarise significant new safety information presented at a scientific meeting and published as an abstract; the sponsor should provide a copy of the abstract, if possible.*

*If a manuscript or abstract is discussed in this section, a copy should be attached. Note: not all manuscripts or abstracts should be discussed/attached; only those with new or significant safety findings.*

*Example*

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

*Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996 Jun 1;124(11):980-3.*

During the reporting period of this DSUR, there were no published *or available draft* manuscripts or abstracts that described new and potentially important safety information.

*OR*

During the reporting period of this DSUR, the following new and significant safety findings were published, available as draft manuscripts/abstracts or presented at scientific meetings:

The abstracts/manuscripts presented above are attached in Appendix 21.7. *(Lead Authors:Upload approved manuscripts to Report Appendix folder in GEPIC or provide pathways for approved manuscripts and notify the Aggregate Reporting Associate)*

*[Describe safety findings from literature.]*

# Other DSURs

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

*A sponsor should prepare a single DSUR for a single investigational product. However, if a sponsor prepares multiple DSURs for a single investigational product (eg covering different indications, development programmes, or formulations), this section should summarise significant findings from the other DSURs, if they are not presented elsewhere within this report.*

*When available, the sponsor should summarise significant findings from DSURs provided by other sponsors conducting clinical trials with the same investigational product during the reporting period.*

*In this section, use executive summary of other DSURs including those from other sponsors.*

This report represents the only DSUR for [product name].

*OR*

It was agreed between [Company Name] and Otsuka that there would be multiple DSURs for [product name] due to [describe rationale]. The Company Name DSUR Number [#]issued [Mmm YYYY] contains information [describe what is unique].

*Add executive summary from other DSURs here.*

# Lack of Efficacy

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

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

*OR*

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

# Region-Specific Information

*Lead Author: Aggregate Reporting Associate*

*See appendices for specific contributions.*

*The information in this section can be used to comply with national or regional requirements and can be provided in appendices to the DSUR. Sponsors should refer to national or regional requirements to determine which of the following sections should be included, as well as the scope of clinical trials that should be covered by these sections. Examples include:*

* *Cumulative summary tabulation of serious adverse reactions (Appendix 22.1). This cumulative summary tabulation of all SARs should specify the number of SARs by: a) SOC, b) adverse reaction term and c) treatment arm, if applicable. Unexpected adverse reaction terms should be identified.*
* *List of subjects who died during the reporting period (Appendix 22.2). The list of subjects who died during participation in the clinical trials should include the following information at a minimum: case number, assigned treatment (could still be blinded), and cause of death of each subject. Any safety issues identified from a review of these deaths should be addressed in section 18 of the DSUR as appropriate.*
* *Significant manufacturing changes (Appendix 22.5). This section should include a summary of significant manufacturing or microbiological changes during the reporting period and discuss potential safety issues arising from these changes in Section 18 of the DSUR, if applicable.*

For further regional specific information, please refer to the following appendices:

* Appendix 22.1 Cumulative Summary Tabulation of Serious Adverse Reactions
* Appendix 22.2 List of Subjects who Died during the Reporting Period
* Appendix 22.3 List of Subjects who Dropped out of Studies during the Reporting Period
* Appendix 22.4 Significant Phase 1 Protocol Modifications with Respect to a US IND
* Appendix 22.5 Significant Manufacturing Changes
* Appendix 22.6 Description of the General Investigational Plan for the Coming Year with Respect to a US IND
* Appendix 22.7 Log of Outstanding Business with Respect to a US IND

# 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/Physician; Aggregate Reporting Associate*

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

*This section should summarise information on potentially important safety findings that arise after the data lock point but while the DSUR is in preparation. Examples include clinically significant new case reports, important follow-up data, clinically relevant toxicological findings and any action that the sponsor, a DMC, or a regulatory authority has taken for safety reasons. The Overall Safety Assessment (see Section 18) should also take these new data into account.*

There was no important or new late-breaking information that would alter the currently known safety profile as described in the current IB of [product name].

*OR*

The following important or new late-breaking information became available after the reporting end date: *[describe]*

# Overall Safety Assessment

*The overall safety assessment should be a concise, integrated evaluation of all new relevant clinical, nonclinical, and epidemiologic information obtained during the reporting period relative to previous knowledge of the investigational product. This assessment should consider cumulative experience, new information collected in the period covered by the DSUR and, for investigational products with a marketing approval, clinically significant postmarketing data. It should not summarise or repeat information presented in previous sections of the DSUR, but should provide an interpretation of the information and its implications for the clinical trial population and the development programme. If appropriate, separate assessments can be provided by therapeutic area, route of administration, formulation, and/or indication.*

## Evaluation of the Risks

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

*In evaluating the risks, particular emphasis should be placed on interpretation of data related to newly identified safety concerns or providing significant new information relative to previously identified safety concerns. Relevant points to consider include (where applicable):*

* *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 (eg, 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 and hypersensitivity;*
* *deaths that are an outcome of an adverse event;*
* *IMP discontinuations because of adverse events, including abnormal laboratory values or investigations;*
* *drug–drug and other interactions;*
* *important nonclinical safety findings;*
* *manufacturing issues that could affect risk;*
* *lack of efficacy where this would place trial participants at risk;*
* *any specific safety issues related to special populations, such as the elderly, children, patients with hepatic or renal impairment, or any other at-risk groups (eg, slow or fast metabolisers);*
* *pregnancy and lactation exposure and outcomes;*
* *safety findings arising from experience with long-term treatment;*
* *evidence of clinically significant medication errors;*
* *evidence of lack of patient compliance;*
* *experience with overdose and its treatment;*
* *occurrences of drug misuse and abuse;*
* *any safety issues resulting from procedures required by the protocol (eg, bronchoscopy, biopsy, central line insertion) or associated with the conduct or design of a particular study (eg, inadequate subject monitoring schedule, excessive period without active treatment); and*
* *Potential impact of significant new safety issues identified with another drug in the same class.*
* *For most products (including all marketed products), the RMP should be used as the source for this information. If the product does not have an RMP, the IB may provide appropriate information.*

## Benefit-risk Considerations

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

*This section should provide a succinct statement on the perceived balance between risks that have been identified from cumulative safety data and anticipated efficacy/benefits and should note whether there have been any changes in this balance since the previous DSUR. This section is not intended to be a full benefit-risk assessment of the investigational product.*

# Summary of Important Risks

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

*NOTE: CSPV Medical Safety Operations Associate/Physician should align with Clinical Management on Phase I/II development products for this section.*

*This section should provide a concise, cumulative, issue-by-issue list of important identified and potential risks, eg, those that might lead to warnings, precautions, or contraindications in labelling (i.e., drug-drug interactions). Such risks might include, for example, toxicities known to be associated with a particular molecular structure or drug class (i.e., class effect), or concerns based on accumulating nonclinical or clinical data. Each risk should be re-evaluated annually and resummarised as appropriate, based on the current state of knowledge. New information should be highlighted. The appropriate level of detail is likely to be dependent on the stage of drug development.*

*The information in this section could provide the basis for the safety specification of a risk management plan (RMP) (ICH E2E). When an RMP is already in place, this section should align with the RMP or draft RMP (Important Identified Risks and Important Potential Risks are defined as identified risks, potential risks or missing information that could impact on the risk-benefit balance of the product or have implications for public health).*

*Risks that have been fully addressed or resolved should remain in the summary and be briefly described, eg, findings from toxicology studies or early clinical trials that were not borne out by later clinical data.*

This section summarises the important identified and/or potential risks that have been recognised during the conduct of the [product name] clinical development programme.

*For marketed products with an RMP, use this verbiage:* The information in this section is consistent with Part II Module SVIII of the [product name] EU RMP version [X] [effective- DD Mmm YYYY].

*If there are no important identified risks, but there are potential risks, use this verbiage:* At present, all are considered as potential risks, with none characterised as identified risks associated with the administration of [product name].

*OR*

*If there are no important identified or potential risks, use this verbiage:*

At present, no important potential or identified risks have been associated with the administration of [product name].

Details for all important identified and/or potential risks, if any, are provided in Tables 19-1 and 19-2 below: New or updated risks are footnoted.

*(Include table even if there are no identified risks, as noted in first row below “Identified Risks- None Identified”) Include drug-drug interactions if documented as an important identified risk.*

| Table 19-1 Summary of Important Identified Risks | | | |
| --- | --- | --- | --- |
| Potential Risks | Nonclinical Data | Clinical Data | Actions |
| None identified | Not applicable | Not applicable | Not applicable |
| Irritability | 28-day dog study:  Irritability in moderate-dose dogs.  12-month dog study:  Irritability not observed at same dose.  Rat studies:  Irritability not observed. | Phase I-II clinical studies:  Irritability not observed.  No longer considered a potential risk. | The status of this potential risk will be confirmed by the outcome of ongoing Phase III clinical trials. |
| Liver toxicity1 | 12-month dog study:  ZB3579 may be associated with mild hepatic inflammation. | Phase I-II clinical studies:  Liver injury not evident. | The relatively short duration of therapy in Phase I/II studies means that longer duration clinical studies are necessary to place the dog findings into context.  Phase III clinical trial protocols have been amended to manage potential risk of liver injury to trial subjects:  additional exclusion criteria  enhanced LFT monitoring  stopping rules  Data Monitoring Committee established |
| Identified Drug-drug Interaction CYP3A4 Inhibitors | If available provide IC50 data | In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased product X AUC and Cmax by 63% and 37%, respectively.  If applicable, also provide class effect data | When  concomitant administration or product X with ketoconazole occurs, the dose of product X should be reduced to approximately one-half of the prescribed dose. |
| Identified Alcohol-Drug Interaction |  |  | Due to the primary CNS effects of product X,  caution should be used when taken in combination with alcohol or other CNS  medicinal products with overlapping undesirable effects, such as sedation. |
| New or updated risk. | | | |

*(Include table even if there are no potential risks, as noted in first row below “Potential Risks- None Identified) Include drug-drug interactions if documented as an important potential risk.*

| Table 19-2 Summary of Important Potential Risks | | | |
| --- | --- | --- | --- |
| Potential Risks | Nonclinical Data | Clinical Data | Actions |
| None identified | Not applicable | Not applicable | Not applicable |
| Irritability | 28-day dog study:  Irritability in moderate-dose dogs.  12-month dog study:  Irritability not observed at same dose.  Rat studies:  Irritability not observed. | Phase I-II clinical studies:  Irritability not observed.  No longer considered a potential risk. | The status of this potential risk will be confirmed by the outcome of ongoing Phase III clinical trials. |
| Liver toxicity1 | 12-month dog study:  ZB3579 may be associated with mild hepatic inflammation. | Phase I-II clinical studies:  Liver injury not evident. | The relatively short duration of therapy in Phase I/II studies means that longer duration clinical studies are necessary to place the dog findings into context.  Phase III clinical trial protocols have been amended to manage potential risk of liver injury to trial subjects:  additional exclusion criteria  enhanced LFT monitoring  stopping rules  Data Monitoring Committee established |
| Potential Drug-drug Interaction CYP3A4 Inhibitors | If available provide IC50 data | In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased product X AUC and Cmax by 63% and 37%, respectively.  If applicable, provide class effect data | When  concomitant administration or product X with ketoconazole occurs, the dose of product X  should be reduced to approximately one-half of the prescribed dose. |
| Potential Alcohol-Drug Interaction |  |  | Due to the primary CNS effects of product X, caution should be used when taken in combination with alcohol or other CNS medicinal products with overlapping undesirable effects, such as sedation. |
| New or updated risk. | | | |

# Conclusions

*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/Physician*

*The conclusion should briefly describe any changes to the previous knowledge of efficacy and safety resulting from information gained since the last DSUR. The conclusion should outline actions that have been or will be taken to address emerging safety issues in the clinical development programme.*

# Appendices

*All information below here is related to children documents a part of the vDOC (delete text when finalising document)*

## Investigator’s Brochure

### Investigator’s Brochure in Effect at the Start of Reporting Period

*Clinical Management is responsible for providing the IB in effect at the start of the reporting period and uploading to Report Appendix folder in GEPIC. The investigator’s brochure (IB) in effect at the start of the reporting period should serve as the reference safety information to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug.*

### Investigator’s Brochure Revised After Start of Reporting Period

*Clinical Management is responsible for providing a final clean copy of the revised version and uploading to Report Appendix folder in GEPIC.*

*If the IB has been revised during the reporting period and not previously submitted to the relevant regulatory authority, the sponsor should provide a copy of the current version of the IB as an attachment to the DSUR.*

*If there were no revisions please state in this section of the template: "Not applicable"*

## Cumulative Table of Important Regulatory Requests

*Lead author(s): Regulatory Affairs- The responsible author for this section should enter the information directly into this template, and the Aggregate Reporting Associate will then create an appendix. Please note the table below has example data and should be updated accordingly based on product.*

*This table should include a cumulative listing of requests (including any updates) from regulatory authority(ies) that place a specific limitation on current or future development (eg, a request to conduct long-term animal studies before initiating a long-term clinical trial, specification of a maximum dose to be evaluated, a request for specific safety data before initiating trials in paediatric subjects). Information entered here should be in line with- or at least complementary to actions noted in section “Action Taken in the Reporting Period for Safety Reasons” of the DSUR.*

| Table 21.2-1 Cumulative Table of Important Regulatory Requests | | | |
| --- | --- | --- | --- |
| Date of Request | Agency/Country | Request Description | Status |
| [DD Mmm YYYY] | FDA/USA | *Conduct a trial to evaluate dose X in the following population before initiating trials in paediatric subjects.* | *Study Completed – no significant findings* |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
| FDA = US Food and Drug Administration  USA = United States of America | | | |

*OR*

Not applicable.

## Status of Ongoing and Completed Clinical Trials

*Lead Author(s): Clinical Management populates the Tables 21.3.1-1(ongoing trials during reporting period) and 21.3.1-2(completed trials during reporting period) within this template (using data extracted from Global Study List by Programme Management, uploaded in Supporting documents folder).*

*The Aggregate Reporting Associate will create a separate appendix 21.3 (prior to sending for management review) by using the text entered in the tables 21.3.1-1 and 21.3.1-2 below by Clinical 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 Report Associate assigned to the DSUR. The Aggregate Reports Associate will work with programme management to get the tables corrected and then inform the team.***

### Tables of Ongoing and Completed Clinical Trials during the Reporting Period

| Table 21.3.1-1 Ongoing Clinical Trials during the Reporting Period | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study ID | Phase | Country | Study Title | Study design | Dosing regimen | Study population | FVFP | Planned enrolment | Subject exposure |
| 1234A-016 | III | Europe | Assessment of safety and efficacy in patients with GERD | Randomised, double-blind, parallel, active-controlled | ZB3579 10-20 mg or esomeprazole 40 mg po od 12 weeks | Males/females Age: 18-90 GERD patients | 02Aug09 | ZY 10 mg: 500 ZY 20 mg: 500 Esomeprazole: 500 | ZY 10 mg: 136 ZY 20 mg: 136 Esomeprazole: 136 |
| 1234A-017 | III | USA Canada | Assessment of safety and efficacy in patients with GERD | Randomised, double-blind, parallel, active-controlled | ZB3579 10-20 mg or esomeprazole 40 mg po od 12 weeks | Males/females Age: 18-90 GERD patients | 03Aug09 | ZY 10 mg: 500 ZY 20 mg: 500 Esomeprazole: 500 | ZY 10 mg: 145 ZY 20 mg: 145 Esomeprazole: 145 |
| 1234A-018 | I | UK | Renal impairment study | Randomised, double-blind, parallel | ZB3579 10 mg od po 7 days | Males/females Age: 18–65 Renally impaired patients | 04Dec09 | ZB3579: 18 | ZB3579: 12 |
| 1234A-019 | I | UK | Hepatic impairment study | Randomised, double-blind, parallel | ZB3579 10 mg od po 7 days | Males/females Age: 18–65 Hepatically impaired patients | 24Nov09 | ZB3579: 18 | ZB3579: 8 |
| 1234A-020 | III | Europe | Assessment of safety and efficacy in patients with GERD | Randomised, double-blind, parallel, active-controlled 12 weeks | ZB3579 10-20 mg or lansoprazole 30 mg po od 12 weeks | Males/females Age: 18-90 GERD patients | 13Sep09 | ZY 10 mg: 500 ZY 20 mg: 500 Lansoprazole: 500 | ZY 10 mg: 56 ZY 20 mg: 56 Lansoprazole: 56 |
| 1234A-021 | I | UK | Bioavailability study (Phase II vs III formulations) | Randomised, double-blind, cross-over | ZB3579 10-20 mg po od (x2 formulations) | Males Age: 18-45 Healthy volunteers | 05Dec09 | ZB3579: 12 | ZY 10 mg: 6 ZY 20 mg: 6 |
| FVFP = First visit first patient  based upon total number of patients recruited as of [DD Mmm YYYY] and applied randomisation schemes. | | | | | | | | | |

| Table 21.3.1-2 Completed Clinical Trials during the Reporting Period | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study ID | Phase | Country | Study Title | Study design | Dosing regimen | Study population | Subject exposure |
| 1234A-013 | II | Europe | Dose-response study of safety and efficacy in patients with GERD | Randomised, double-  blind, parallel, active-  controlled  6 weeks | ZB3579: 5-40 mg po od  Esomeprazole: 40 mg  po od | Males/females  Age: 18-90  GERD patients | ZY 5 mg: 224  ZY 10 mg: 236  ZY 20 mg: 228  ZY 40 mg: 219  Esomeprazole: 225 |
| 1234A-014 | II | USA  Canada | Dose-response study  of safety and  efficacy in patients  with GERD | Randomised, double-  blind, parallel, active-  controlled  6 weeks | ZB3579: 5-40 mg po od  Esomeprazole: 40 mg  po od | Males/females  Age: 18-90  GERD patients | ZY 5 mg: 186  ZY 10 mg: 192  ZY 20 mg: 182  ZY 40 mg: 198  Esomeprazole: 184 |
|  | | | | | | | |

*If there were no completed trials during the reporting period, delete Table 21.3.1-2 and include the following text:*

There were no completed clinical trials during this reporting period.

### Clinical Study Report Synopsis

*Append CSR synopsis, if any, per Section 8.1, directly into this template and the Aggregate Reporting Associate will then create an appendix. This section should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the 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 issues, as well as evidence of new safety signals.*

## Cumulative Summary Tabulations of Demographic Data

*Lead Author(s): Aggregate Reporting Associate*

*These tables are provided by the OPCJ Aggregate Reports team. These tables are 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. Due to variations in study designs across a programme, there may be overlapping age ranges.*

*The Aggregate Reporting Associate will create the appendix by converting the file to PDF.*

| **Cumulative Subject Exposure to [Product Name] from the Clinical Trial Programme by Age and Sex**1 | | | | |
| --- | --- | --- | --- | --- |
|  |  | 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] | | | | |

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

*OR If tables are not relevant*

To date, no studies have been completed.

## Line Listings of Serious Adverse Reactions during the Reporting Period

*Lead Author: 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 table to the Safety Data Output folder..*

## Cumulative Summary Tabulation of Serious Adverse Events

*Lead Author: 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 table to the Safety Data Output folder.*

## Scientific Abstracts

*Lead Author: Clinical Management (review from Clinical Development) for products in development; GPV Medical Safety Operations/Physician for products marketed.*

No presentations relevant to [product name] were made during the reporting period.

*OR*

*Provide PDFs of the abstracts/manuscripts and upload to Report Appendix folder in GEPIC, or provide pathways for approved manuscripts, and notify the Aggregate Reporting Associate and notify the Aggregate Reporting Associate*

# Regional Appendices

## Cumulative Summary Tabulation of Serious Adverse Reactions

*Lead Author: 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 table to the Safety Data Output folder.*

*OR*

No reports identified.

## List of Subjects who Died during the Reporting Period

*Lead Author: 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 table to the Safety Data Output folder.*

*OR*

No reports identified.

## List of Subjects who Dropped out of Studies during the Reporting Period

*Lead Author: Aggregate Reporting Associate*

*OPCJ Aggregate team provides the table/list and sends to Aggregate Report Team. The Aggregate Reporting Associate will then upload the table to the Report Appendix folder.*

*OR*

No reports identified.

## Significant Phase I Protocol Modifications with Respect to a US IND

*Lead Author: Clinical Management and Clinical Development. The responsible author for this section should enter the information directly into the IND template located in GEPIC.*

*Note to Aggregate Reporting Associate: If being submitted to the FDA, content will be provided for this section and it will be a stand-alone document and submitted to the FDA as a link to the DSUR package. Please inform Regulatory of the separate document once the report has been finalised. The main document/appendix should always state the following sentence:*

For US FDA submissions only: refer to eCTD Section 1.13.2 - Summary of Clinical Pharmacology Information of the US IND.

## Significant Manufacturing Changes

*Lead Author: Regulatory Affairs with Chemistry, Manufacturing and Control (CMC). The responsible author for this section should enter the information directly into the IND template located in GEPIC.*

*Note to Aggregate Reporting Associate: If being submitted to the FDA, content will be provided for this section and it will be a stand-alone document and submitted to the FDA as a link to the DSUR package. Please inform Regulatory of the separate document once the report has been finalised. The main document/appendix should always state the following sentence:*

For US FDA submissions only: refer to eCTD Section 1.13.5 - Summary of Manufacturing Changes of the US IND.

## Description of the General Investigation Plan for the Coming Year with Respect to a US IND

*Lead Author: Clinical Management and Clinical Development. The responsible author for this section should enter the information directly into the IND template located in GEPIC.*

*Note to Aggregate reporting associate: If being submitted to the FDA, content will be provided for this section and it will be a stand-alone document and submitted to the FDA as a link to the DSUR package. Please inform Regulatory of the separate document once the report has been finalised. The main document/appendix should always state the following sentence:*

For US FDA submissions only: refer to eCTD Section 1.13.9 - General Investigational Plan of the US IND.

## Log of Outstanding Business with Respect to a US IND

*Lead Author: Regulatory Affairs. The responsible author for this section should enter the information directly into the IND template located in GEPIC.*

*Note to Aggregate Reporting Associate: If being submitted to the FDA, content will be provided for this section and it will be a stand-alone document and submitted to the FDA as a link to the DSUR package. Please inform Regulatory of the separate document once the report has been finalised. The main document/appendix should always state the following sentence:*

For US FDA submissions only: refer to eCTD Section 1.13.14 - Log of Outstanding Regulatory Business of the US IND.