1. OBJECTIVE

These guidelines concern the presentation of a comprehensive review and evaluation of pertinent safety information collected during the reporting period related to an investigational product belonging to clinical trials conducted in our country.

2. DEFINITIONS

In addition to the following definitions, the definitions in the Good Clinical Practice Guidelines and relative regulations are also applicable.

2.1. Identified risk: An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Without being limited, examples of identified risks include:

- an adverse reaction demonstrated in nonclinical studies and confirmed by clinical data
- an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator (placebo or active substance) on a parameter of interest suggests a causal relationship
- an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship or biological plausibility (e.g., anaphylactic reactions or application site reactions)

2.2. Clinical development program: This comprises all clinical trials being conducted with the same investigational product, regardless of indication or formulation.

2.3. Institution: This refers to the Turkish Drug and Medical Device Institution.

2.4. Important identified risk or important potential risk: An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have various implications for public health.

2.5. Anticipated efficacy or benefit: Efficacy or benefit that has not yet been established for the investigational product, but which is anticipated based on knowledge of the class of drugs or data from previous clinical trials or nonclinical studies.

2.6. Adverse event of special interest: An adverse event of special interest is one of scientific and medical concern specific to the sponsor's product or program, for which constant monitoring is necessary and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to the Institution and relevant ethics committee might also be warranted.

2.7. Potential risk: An untoward occurrence for which there is suspicion of a causal relationship with the investigational product but where this relationship has not been confirmed. Without being limited, examples of potential risks include:

- Nonclinical safety concerns that have not been observed or resolved in clinical studies
- Adverse events for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship
- A signal arising from a spontaneous adverse reaction reporting system
- An event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the investigational product.

2.8. Signal: Reports of an event with an unknown causal relationship to treatment, yet is recognized as worthy of further exploration and continued surveillance.

2.9. Development International Birth Date: Date of first approval or authorization for conducting a clinical trial in any country.

2.10. International Authorization Date: This refers to the date on which the first authorization regarding a medicinal product is given to the licensee in any country.

2.11. Data lock point: The date (month and day) designated as the cut-off date for data to be included in a Development Safety Update Report (DSUR) which is based on the Development International Birth Date (DIBD).

3. RESPONSIBILITIES

3.1. The sponsor shall submit all current new safety information emerging during the reporting period as a DSUR as well as reports of adverse events or reactions to a relevant ethics committee and Institution once a year throughout a clinical trial, or upon request. The communication of these reports should be as per the format on the website of the Institution.

3.2. The DSUR shall be clear, straightforward and in the correct format, and shall contain information providing assurance that the sponsors have sufficiently monitored and evaluated the developing safety profile of the investigational product. All safety issues arising during the reporting period shall be discussed in the DSUR.

3.3. In order to promote a comprehensive analysis and presentation of the safety profile of the investigational product, a sponsor should prepare a single DSUR with data pertinent to all dosage forms and strengths, all indications, and all patient populations under study with the investigational product, wherever feasible. If this is not possible, an explanation should be provided in the introduction section of the DSUR.

3.4. The reporting period regarding DSUR begins with the date of first permission for the clinical trial given by the Institution and is finalized with the termination of the trial. The date of the final visit of the last subject in the trial may be identified as the termination of the trial.

3.5. The sponsor should submit the development safety update reports no later than 60 days after the data lock point.

3.6. If more than one sponsor is involved in the clinical trial or drug development program, a single DSUR can be submitted. This includes situations where a sponsor is in a formal co-development or licensing relationship with one or more partners, or where individual clinical trials or a drug development program involve collaboration with public or private institutions, business partners, or other parties. When a single DSUR cannot be arranged, multiple sponsors can agree to prepare separate DSURs for the same investigational product. This can occur where different indications, routes of administration, or formulations are being investigated by different parties. In this situation, the rationale for separate DSURs should be provided in each report.

3.7. A single DSUR may be prepared for clinical trials involving a fixed combination product (i.e., a product consisting of at least two active ingredients in a fixed dose that is administered in a single dosage form). If the sponsor is also conducting clinical trials with individual components of the fixed combination product, separate DSURs should be submitted for each component.

3.8. For trials involving multi-drug therapy, i.e., combinations of drugs that are not fixed, the sponsor can prepare either:

- A single DSUR focusing on (A+X+Y+Z) for the investigational product (A) + marketed drugs (X, Y, Z) or a single DSUR focusing on (A) including data on the multi-drug therapy
- A single DSUR focusing on (A + B) for two investigational drugs (A) + (B) or two separate DSURs (A) and (B), each including data on the multi-drug therapy
- A single DSUR focusing on the multi-drug therapy (X + Y + Z) for two or more marketed drugs as an investigational drug combination (X, Y, Z).

3.9. The sponsor can delegate the preparation of the DSUR to a third party with a written contract.

3.10. In situations where the sponsor does not have access to information on manufacturing issues, nonclinical data, and marketing status, etc. this should be stated in the DSUR.

3.11. 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 product.

3.12. Even if the sponsor is conducting numerous clinical trials with the same investigational product, the sponsor should separately prepare and submit the safety reports for each each trial, including necessary information regarding all these trials.

3.13. The DSUR should be prepared and submitted in accordance with the format in the appendix of the guidelines.

3.14. All sections within the format defined in the appendix of the guidelines should be completed, and this situation should be specified when there is a lack of information.

3.15. The annual safety report which shall be prepared for observational studies can be provided as specified in the Observational Drug Studies Guidelines, and as line listings if necessary.

4. ENFORCEMENT

These Guidelines are enforced on their approval date.

ANNEX -1: FORMAT OF THE DEVELOPMENT SAFETY UPDATE REPORT (DSUR)

Content

Title Page

The title page of the DSUR should include the following information:

- DSUR number (reports should be numbered sequentially)
- Investigational drugs
- Reporting period
- Date of the report
- Sponsors names and addresses
- Statement on the confidentiality of the information included in the DSUR
- A cautionary statement that the DSUR includes unblinded information, if applicable

Executive Summary

This section should provide a concise summary of the important information contained in the report. The following information should be included in the Executive Summary:

- Introduction — report number and reporting period
- Investigational drugs — modes of action, therapeutic classes, indications, doses, route(s) of administration, formulations
- Estimated cumulative exposure of clinical trial subjects
- Marketing approvals? (yes/no) — If yes, number of countries
- Summary of overall safety assessment
- Summary of important risks
- Actions taken for safety reasons including significant changes to IB
- Conclusions

Table of Contents

1. Introduction

This section should include:

- Development International Birth Date or International Authorisation Date
- Reporting period and sequential number of the report
- Investigational drugs — modes of action, therapeutic classes, routes of administration
- A brief description of the indications and populations being studied
- A short summary of the scope of the clinical trials covered by the report
- A brief description and explanation of any information that has not been included in the DSUR
- The rationale for submission of multiple DSURs for the investigational product, if applicable

2. Worldwide Marketing Approval Status

This section should provide a brief narrative overview including: date of first approval, indications, approved doses, and where approved, if applicable.

3. Actions Taken in the Reporting Period for Safety Reasons

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 monitoring committees (DMC) or ethics committees that had an impact on the conduct of a specific clinical trials or

on the overall clinical development program. The reasons for each action should be provided if known. Relevant updates to previous actions should also be summarized in this section.

Changes to the Investigator's Brochure should be discussed separately in the "Changes to Reference Safety Information".

Examples of significant actions taken for safety reasons include:

- Actions related to investigational products:
  - Refusal to approve or authorize 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
  - Recall of investigational product or comparator
  - Failure to obtain marketing approval for a tested indication including voluntary withdrawal of a marketing application
  - Protocol modifications due to safety or efficacy concerns
  - Restrictions in study 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 other healthcare professionals
  - Plans for new studies to address safety issues
- Actions related to marketed drugs:
  - Failure to obtain a marketing approval renewal
  - Withdrawal or temporary suspension of a marketing approval
  - Significant restrictions on distribution or introduction of other risk minimization measures
  - Significant safety-related changes in labelling documents that could affect the development program, including restrictions on use or population treated
  - Communications to healthcare professionals
  - New postmarketing study requirement(s) imposed by regulators

This section should also summarize requests from regulatory authority(ies) that place a specific limitation on current or future development (e.g., a request to conduct long-term animal studies before initiating a long-term clinical trial, specification of a maximum dose to be evaluated, requests for specific safety data before initiating trials in a paediatric population). A cumulative listing of such requests from health authorities should be provided, including any updates if applicable. This list can be provided as a table, in an appendix, or in this section.

4. Changes to Reference Safety Information

This section should 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. Specific information relevant to these changes should be provided in the appropriate sections of the DSUR.

5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

This section should 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. Separate tables can be provided by indication, formulation, and study population, if appropriate. In addition, similar information are 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 (e.g., protocol number or other identifier)
- Phase of the study
- Status of the study (e.g., ongoing, completed)
- Centres where there study is conducted
- Abbreviated study title, if available
- Design of the study (controlled, randomised, open-label, etc.)
- Dose and regimen of investigational product and comparator
- Study population as appropriate (age; sex; indication(s); specific patient groups, e.g., trial subjects with impaired renal function or trial subjects resistant to treatment)
- Date of clinical trial start
- Total number of subjects in all the centres planned to enrol in the trial
- Estimates of cumulative numbers of exposed subjects for each treatment arm, where available (The actual enrolment numbers for open or completed trials, or an estimate based on the randomization scheme for blinded trials, should be provided.).

6. Estimated Cumulative Exposure

The DSUR should provide information on cumulative exposure. An estimation of cumulative subject exposure may be useful 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. 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 randomized 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 drugs that are under clinical investigation, it might not be feasible or useful to obtain precise cumulative clinical trial exposure data (e.g., when the drug has

been marketed for a number of years or has many indications). In these circumstances, the sponsor should provide an explanation.

6.1. Cumulative Subject Exposure in the Development Program

This section should include the following information, in tabular format:

- The cumulative number of subjects from ongoing and completed clinical trials; the number of subjects exposed to the investigational product, placebo, or active comparator(s) since the DIBD (When treatment assignment is blinded, the numbers of subjects can be estimated based on the randomization scheme.)
- Cumulative number of subjects exposed to the investigational product from ongoing and completed clinical trials, subgrouped by age range, sex, and racial group for the development program when the data are available
- Demographic characteristics for a single trial if the trial is of particular importance (e.g., a pivotal Phase III trial).

The specific categorization of age might be dependent on the subject population or indication. 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.

6.2. Patient Exposure from Marketing Experience

If the investigational product is marketed by the sponsor, the DSUR should include an estimate of the cumulative patient exposure in the marketed setting, with an explanation of the method(s) used to determine the estimate.

7. Data in Line Listings and Summary Tabulations

DSUR should present important clinical safety information through:

- Interval line listings of the SARs that were reported to the sponsor during the period covered by the DSUR; and
- Cumulative summary tabulations of serious adverse events that have been reported to the sponsor since the DIBD.

Although the evaluation of individual rare adverse drug reactions (ADRs) and causality assessment for making decisions regarding expedited reporting is generally useful, individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations in a DSUR should include all SAEs and not just SARs for the investigational product and comparators.

The line listings and tabulations should include blinded and unblinded clinical trial data. Unblinded data might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g., expedited reporting), if applicable. Sponsors should not unblind data for the specific purpose of preparing the DSUR. At the sponsor's discretion, graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

If the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the Preferred Term level should be presented in the line listings and summary tabulations. In general, the tabulation(s) of SAEs should include only those terms that were used in defining the case as serious; they should not include nonserious events.

Certain adverse events can be excluded from the line listings and summary tabulations, but

such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database, and those that are integral to efficacy endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

7.1. Reference Information

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 regional laws or regulations.

7.2. Line Listings of Serious Adverse Reactions During the Reporting Period

This section of the DSUR should summarize 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 an appendix.

The line listings should provide key information on all SARs (blinded and unblinded) reported from the sponsor's clinical trials during the reporting period. The data should be organized by trial and then by System Organ Class (SOC).

Where possible the line listing(s) should include each subject only once regardless of how many SAR terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (sign, symptom, or diagnosis), as judged by the sponsor. It is possible that the same subject could experience different SARs on different occasions. Under such circumstances, the SARs can be listed separately, and a single subject can be included in a line listing more than once.

The following information should be included in the line listings:

- Study identification number
- Subject identification number
- Sponsor's adverse reaction case reference number
- Country in which case occurred
- Age and sex of trial subject
- Treatment group (identified as "blinded" if the blind has not been broken)
- Dose and dosing interval of investigational product (and, when relevant, dosage form and route of administration)
- Date of onset or time to onset of the most serious adverse reaction
- Dates of treatment or best estimate of treatment duration
- Serious adverse reaction(s) (when MedDRA is used, the Preferred Term should be presented)
- Outcome (e.g., resolved, fatal, improved, sequelae, unknown). This field should indicate the consequences of the reaction(s) for the patient (using the worst of the different outcomes for multiple reactions).
- Comments, if relevant (e.g., causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drugs)

7.3. Cumulative Summary Tabulations of Serious Adverse Events

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. The tabulation(s) should be

organized by SOC, for the investigational product, as well as for the comparator arm(s) used in the program. Data can be integrated across the program. Alternatively, when useful and feasible, tabulations of SAEs can be presented by protocol, indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the SAEs.

8. 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.

8.1. Completed Clinical Trials

This section of the DSUR 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 also be presented as a synopsis. It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals.

8.2. Ongoing Clinical Trials

If the sponsor is aware of clinically important information that has arisen from ongoing clinical trials (e.g., learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarize the issues. It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals.

8.3. Long-term Follow-up

Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational products, particularly advanced therapy 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.

8.4. Other Therapeutic Use of Investigational Drug

This section of the DSUR should include clinically important safety information from other programs conducted by the sponsor that follow a specific protocol, with solicited reporting as per relative regulations (e.g., expanded access programs, compassionate use programs, particular patient use).

8.5. New Safety Data Related to Combination Therapies

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

Conversely, if this DSUR is for a multi-drug therapy or fixed combination product, this section should summarize 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.

9. Safety Findings from Noninterventional Studies

This section should summarize relevant safety information from noninterventional studies that became available to the sponsor during the reporting period.

10. Other Clinical Trial/Study Safety Information

This section should summarize relevant safety information from any other clinical trial/study sources that became available to the sponsor during the reporting period (e.g., results from pooled analyses or meta-analyses of randomized clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

11. Safety Findings from Marketing Experience

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, or informed consent document or amendments to the product's risk management plan). This section includes not only safety findings relating to approved use but also off-label use, administration to special populations, medication errors, overdose and abuse.

12. Nonclinical Data

This section should summarize major safety findings from nonclinical in vivo and in vitro studies ongoing or completed during the reporting period. Implications of these findings should be discussed in the Overall Safety Assessment.

13. Literature

This section should summarize 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 drugs of the same class. It should also summarize 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.

14. Other DSURs

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

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

15. Lack of Efficacy

Data indicating lack of efficacy, or lack of efficacy relative to established therapies, for investigational products intended to treat serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) could reflect a significant risk to clinical trial subjects and should be summarized in this section.

16. Region-Specific Information

The information in this section can be used to comply with regional requirements and can be provided in appendices to the DSUR. Sponsors should refer to 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: This cumulative summary tabulation of all SARs should specify the number of SARs by SOC, adverse reaction term, and treatment arm, if applicable. Unexpected adverse reaction terms should be identified.
- List of subjects who died during the reporting period: 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 the DSUR as appropriate.
- List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period:
  This list should include all subjects who dropped out of clinical trials in association with adverse events during the reporting period, whether or not thought to be drug-related. Any safety issues identified from a review of these withdrawals should be addressed in the DSUR as appropriate.
- Significant Phase I protocol modifications: This section should include significant Phase I protocol modifications made during the reporting period, if not previously submitted as a protocol amendment.
- Significant manufacturing changes: 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 the DSUR, if applicable.
- Description of the general investigation plan for the coming year: This section should outline an investigational plan to replace that submitted for the previous year.

17. Late-Breaking Information

This section summarizes 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 should also take these new data into account.

18. 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, clinically significant postmarketing data for investigational products with a marketing approval. It should not summarize 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 program. If appropriate, separate assessments can be provided by therapeutic area, route of administration, formulation or indication.

18.1. Evaluation of the Risks

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 (e.g., increased frequency or severity, outcome)
- symptoms, findings, and laboratory evidence of newly and previously identified clinically significant toxicities (e.g., hepatotoxicity, bone marrow toxicity, pulmonary toxicity, immunogenicity and hypersensitivity)
- deaths that are an outcome of an adverse event
- study drug discontinuations because of adverse events, including abnormal laboratory values or investigations
- drug–drug interactions 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
- 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 or associated with the conduct or design of a particular study
- potential impact of significant new safety issues identified with another drug in the same class

18.2. Benefit-risk Considerations

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.

19. Summary of Important Risks

This section should provide a concise, cumulative, issue-by-issue list of important identified and potential risks (e.g., those that might lead to warnings, precautions, or contraindications in labelling). Such risks might include, for example, toxicities known to be associated with a particular molecular structure or drug class, or concerns based on accumulating nonclinical or clinical data. Each risk should be re-evaluated annually and re-summarized as appropriate, based on the current information. New information should be highlighted. The appropriate level of detail is likely to be dependent on the stage of drug development. For example, summaries covering drugs in early development might include information on individual cases, whereas in later development, as more knowledge and perspective are gained, the information on each risk might be less detailed.

The information in this section could provide the basis for the safety specification of a risk management plan.

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

20. Conclusions

The conclusion should briefly describe any changes to the previous knowledge of efficacy and safety data 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 program.

21. Appendices to the DSUR

The DSUR should be accompanied by the following appendices, as appropriate, numbered as follows:

- Investigator's Brochure
- Cumulative Table of Important Regulatory Requests
- Status of Ongoing and Completed Clinical Trials
- Cumulative Summary Tabulations of Demographic Data
- Line Listings of Serious Adverse Reactions
- Cumulative Summary Tabulation of Serious Adverse Events
- List of subjects who died during the reporting period
- List of subjects who dropped out of studies during the reporting period
- Significant Phase I protocol modifications
- Significant manufacturing changes
- Description of the general investigation plan for the coming year
- Log of outstanding business
- Scientific Abstracts

APPENDIX 2 - EXAMPLES OF TABLES AND TABLE HEADINGS FOR CLINICAL TRIAL LISTINGS

TABLE 1: Status of Ongoing and Completed Clinical Trials

Overview of Ongoing Studies [Study Drug]

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	FVFP (first visit first patient)	Planned enrollment	Subject exposure*

* Based upon total number of patients recruited as of [date] and applied randomization schemes

Status of Clinical Studies Completed During the DSUR Period [Study Drug]

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	Subject/patient patient exposure per treatment arm (M/F)

TABLE 2: Estimated Cumulative Subject Exposure

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment or randomization schemes for ongoing trials

Treatment	Number of subjects
Drug	
Comparator	
Placebo	

TABLE 3: Cumulative Subject Exposure to Investigational Product from Completed Clinical Trials by Age and Sex*

	Number of subjects		
Age range	Male	Female	Total

* Data from completed trials as of [date]

TABLE 4: Cumulative Subject Exposure to Investigational Product from Completed Clinical Trials by Racial Group*

Racial group	Number of subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

* Data from completed trials as of [date]

TABLE 5: Examples of Headings for Interval Line Listings of Serious Adverse Reactions

Interval Line Listings of Serious Adverse Reactions

Study ID	Subject Initials Subject No.*	Country Gender Age	Serious adverse drug reactions (SARs)	Outcome	Date of Onset Time to Onset**	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments

*Study/center/patient
**Primary serious adverse drug reaction only

TABLE 6: Examples of Cumulative Tabulations of Serious Adverse Events

Example of Cumulative Summary Tabulation of Serious Adverse Events

System Organ Class	Total up to 21/10/2015			
Preferred Term	[Study drug]	Blinded	Active comparator	Placebo
Investigations	18	4	7	2
Alanine aminotransferase increased	9	2	4	1
Aspartate aminotransferase increased	9	2	3	1
Nervous system disorder	2	2	4	7
Syncope	2	2	4	7