Guideline on Good Pharmacovigilance Practices

Module III- Periodic benefit-risk evaluation report

TURKISH MEDICINES AND MEDICAL DEVICES AGENCY
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PART I
Introduction

1.1.Introduction

Periodic Benefit/Risk Evaluation Report (PBRER), denotes the report comprising the evaluation pertaining to the benefit/risk balance of the pharmaceutical that is prepared by the Marketing Authorisation Holder under a certain pre-established format laid out post-licensing.
Principal questions pertaining to presentation, content and the format of PBRER are presented in the Directives on Drug Safety. This module has been prepared in view of forming a guide towards the preparation, evaluation and reporting PBRER to the authority.
The report known as the Periodic Safety Update Report (PSURs) in the EU has been renamed as the PBRER in our country.
The objective, scope, format and content has been defined in the Structures and Processes section. Details pertaining to the running of the evaluation procedures of the benefits/risk can be found in section three.
Marketing Authorisation Holders are required to prepare their PBRER according to the time tables shown below.

- For PBRER covering the period for up to 12 months, within 70 calendar days (including the full 12-month intervals) from the data lock point
- For PBRER covering the period for over 12 months, within 90 calendar days from the data lock point

The key issues the PBRER is focused on are summary information, scientific safety evaluation and integrated benefit/risk evaluation, so there is no need to include systematically detailed lists of individual cases or case descriptions.
PBRERs are extremely important in terms of providing information on whether or not there are new risks, the risks have changed or there has occured a change in the drugs benefit/risk ratio, and are in this regard related to the risk management plan.
In order to assess the drug safety on a regular basis, marketing authorization holder prepares PBRERs every six months for first two years after MA (marketing authorization) approval in the Turkey, yearly for the subsequent two years then every three years following the MA renewal.

However, if the active ingredient of approved drug is in the current list that exists on the link "List of EURDs and frequency of submission of PSURs" in the EMA's official web site, it can be complied with that list. If some changes related to the safety are required in the summary of product characteristics (SmPC) and package insert (PI) need to be made as a result of prepared PBRERs, a variation application is submitted to the Competent Authority. Also, PBRERs are made available to be shown on inspections carried out by the Competent Authority and it is submitted immediately to Competent Authority upon request. The prepared PBRERs must be submitted to the Competent Authority in 18 months after the drug is released or when the number of patients taking the drug reaches 10,000.

SECTION II Structures and Processes

2.1. The Objective of PBRER

The main objective of PBRER is to evaluate the cumulative information about the risks and benefits, to analyze benefit/risk balance in a comprehensive, short and critical way by considering all of the information those became significant with the new information those emerged or obtained at the first time within this context. By this means, PBRER enables post-registration evaluation of a pharmaceutical at the certain points of its lifecycle.

Since benefit/risk management is a progress that should proceed all through the lifecycle of the pharmaceutical, the evaluation of the risks and benefits related with the daily life use and long term use at post registration stage should be continued.
The populations those were not possible to be investigated during the pre- registration clinical studies and endpoints could be included in the scope of the evaluation. The emergence of more safety information by conducting pharmacovigilance activities could form a different benefit/risk balance. Therefore, MAH should review the benefit/risk balance of the populations those are using the pharmaceutical. This evaluation should be done in the framework of the "ongoing pharmacovigilance" and "risk management" modules intended to optimize the benefit/risk balance by means of effective minimization activities.

PBRER should not be used for prior notification related with an important new safety information or to explain the ways about how to determine the new safety matters or how to announce the new efficacy data as a general rule.

2.2. The Principles Related to the Evaluation of Benefit/Risk Balance and the Scope of Information of the Report

The benefit/risk balance analysis performed during the reporting interval of the pharmaceutical should contain the evaluations related to the safety within the scope of the previous information, efficacy during the clinical studies and current efficacy information.
Risk evaluation should be based on all of the uses of the pharmaceutical. The evaluation should contain safety evaluation in the actual medical practice including the uses those are nonparallel to the unapproved indication and product information. If serious lack of information about the important safety matters relating drug use or populations are detected, this application should be reported in PBRER (e.g. use in pediatric population or during pregnancy). The sources of information for off-label uses could include drug use data, spontaneous reports and the information gathered from the publications in the literature.

The scope of the benefit information should consist of both clinical studies and actual global data related to the approved indications.

Integrated benefit/risk evaluation should be based on all of the approved indications and should comprise risk evaluations of all uses including unapproved indications of the pharmaceutical.
This evaluation should comprise the following aspects:

1. A precise, serious and critical examination to determine whether the information obtained during the reporting interval introduce new signals, detect new or identified risks or makes a significant contribution to the information about previously identified risks.
2. A critical summary of the new information related to the safety, efficacy in the clinical studies or current efficacy those could affect the benefit/risk balance of the pharmaceutical.
3. Integrated benefit/risk analysis for all approved uses based on the cumulative current information starting from the Development International Birth Date (DIBD) which is the first date of approval obtained in any country in order to implement an initiative clinical

study (If DIBD is unknown or MAH cannot access the clinical development data, the nearest available date should be considered as a starting point to include and evaluate the cumulative information).

4. The summary of the risk minimization activities planned to perform and risk minimization activities handled in reporting intervals.
5. A draft of signal and risk evaluation plans including timetables and/or suggestions for additional pharmacovigilance activities.

MAH should decide about the changes and/or actions needed including the consequences of the evaluation in PBRER on the Authority approved SmPC based on cumulative safety data and benefit/risk analysis.

2.3. Principles of PBRER Preparation

Unless otherwise specified by the Authority, a single periodical benefit/risk evaluation report is prepared for all pharmaceuticals containing the same active substance and registered for one single MAH. Periodical benefit/risk evaluation report comprise all indications, uses of administration, dosage forms and dose regimes regardless of being registered under a different name and with separate processes. If relevant, data about a certain indication, dosage form, and use of administration or dose regime are submitted in a separate section of PBRER and all of the safety issues are addressed accordingly.

In the cases like having different formulations for totally different indications, the preparation of a separate PBRER may be in question. In this case Authority approval should be obtained preferably at the stage of registration.

It is not necessary for MAH's to include systematically detailed lists and case descriptions of the individual cases in PBRER. However, when it is needed for the scientific analysis that is performed in concern with a signal and security issue in the related risk evaluation section, case descriptions are included in the relevant risk evaluation sections.

Whenever the data related to those could have significant contribution to safety, benefit and/or benefit/risk analysis is reached to MAH from business associates, these data should be discussed and included in PBRER.

Since PBRER's are the only independent documents containing cumulative data in a certain time interval, bridge summary reports and additional reports will not be accepted.

2.4. Reference information

Risk minimization activities those are evaluated in PBRER include the updates in the product information also.

The reference product information for the PBRER would include "core safety" and "approved indications" components. In order to facilitate the assessment of benefit and benefit-risk by indication in the evaluation sections of the PBRER, the reference product information document should list all approved indications in The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) countries or regions (http://www.ich.org/). When PBRER is introduced to the countries those have locally added indications, those indications could be added to the reference product information while submitted as a local appendix as MAH deemed appropriate.

Benefit evaluation should be based on the PBRER sub section 17.1 (Important Baseline Efficacy/Effectiveness Information obtained during the clinical studies and post marketing

period) where important efficacy information gathered during the clinical studies and post marketing period.

The information related to the specific indications, formulations or uses of administrations should be clearly identified in reference product information.

MAH's could consider the following possible options while choosing the best reference product information for PBRER:

- Company Core Data Sheet (CCDS)
    - It is a common practice for MAHs to prepare their own CCDS, which includes sections relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product. The core safety information contained within the CCDS is referred to as the CCSI. A practical option is for MAHs to use the latest CCDS in effect at the end of the reporting interval as the reference product information for both the risk sections of the PBRER as well as the main approved indications for which benefit is evaluated.
    - When the company core data sheet for a medicinal product does not contain approved indications, the marketing authorizastion holder should clearly specify which document is used as the reference information.
- Other options for the reference product information
    - When there is no CCDS or CCSI for a product, e.g., where the product is approved in only one country or region or for established/generic products on the market for many years, the MAH should clearly specify the reference information being used.
    - If reference information for the approved indication is a document which is separate from the reference safety information (core safety information in the reference product), it should be appendixed to the current version of PBRER at the end of the reporting interval (see 2.5.20).

MAH should continuously discuss about the necessity of any revision for the reference product information/reference safety information in the reporting interval and should ensure that all of the changes made after new information are obtained are included in the appropriate parts of 4th (The Changes in the Reference Safety Information) and 16th sections (Signal and Risk Evaluation) of PBRER. These changes could include the following:

- changes to contraindications, warnings/precautions sections.
- addition of adverse reactions and interactions.
- addition of important new information on use in overdose.
- removal of an indication or other restrictions for safety or lack of efficacy reasons.

MAH should submit the clean copies of all versions of reference product information those are valid at the end of the reporting interval (e.g. different formulations included in the same PBRER) as appendixed to PBRER (see 2.5.20). Reference product information should be dated and versions should be checked.

If available, the parts where the new safety information (e.g. new adverse drug reaction, warning or contraindications) are included in the reference safety information (basic safety information is included in the reference information) should be included in the 14th section ("Late Breaking Information") of PBRER.

MAH could submit the product information which is approved in Turkey and suggested SmPC in the regional appendix.

2.5. Format and Content of PBRER

PBRER is based on all of the available data related to the benefits and risks where data which is related to the out of indication use and data obtained from the clinical studies also included and comprise the cumulative scientific evaluation of the benefit/risk balance by focusing new information emerged from data lock point of the current PBRER.

Since the clinical development of a medicinal product generally continues after registration, the data obtained from post registration studies or clinical studies related to the unapproved indications or populations should be included in PBRER also. Similarly, since safety information of a medicinal product could be obtained by evaluating the other data related to the out of indication use, these kinds of information should be included in the risk evaluation where relevant and available.

Results of all of the studies and their possible effects on the registration should be evaluated and the summary of the data related to the benefits and risks of the medicinal product should include in PBRER.

The exemplar efficacy and safety sources of information those could be used in PBRER preparation are included:

- Non-clinical trials.
- Spontaneous reports (e.g. the reports present in the safety database of MAH).
- Active monitoring systems
- .Pharmaceutical quality investigations.
- Drug use data.
- Clinical studies including the ones implemented for unapproved indications or populations.
- Empirical studies including registration studies.
- Patient support programs.
- Systematic examinations and meta-analysis.
- Websites supported by MAH.
- The reports from published scientific literature or abstracts including the information presented in scientific meetings.
- Unpublished article drafts.
- Academic institutions and research networks.
- Competent authorities (worldwide).

Above list does not include all of the sources. MAH could use additional data sources to demonstrate safety and efficacy in PBRER and to evaluate benefit/risk balance specific to the medicinal product. MAH could list the data sources used in the appendix of PBRER as he wishes.

The titles, sequences and contents of PBRER sections are as follows.

If no relevant information is available for any section, this should be denoted.

- Part I: Signed title page
- Part II: Executive Summary
- Part III: Table of Contents

1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Interval for Safety Reasons
4. Changes to Reference Safety Information
5. Estimated Exposure and Use Patterns

   5.1. Cumulative Subject Exposure in Clinical Trials

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8. Findings from Non-Interventional Studies
9. Information from Other Clinical Trials and Sources
9.1 Other Clinical Trials
9.2 Medication Errors
10. Non-Clinical Data
11. Literature
12. Other Periodic Reports
13. Lack of Efficacy in Controlled Clinical Trials
14. Late-Breaking Information
15. Overview of New, Ongoing, or Closed Signals
16. Signal and Risk Evaluation
16.1. Summary of Safety Concerns
16.2. Signal Evaluation
16.3. Evaluation of Risks and New Information
16.4. Characterisation of Risks
16.5. Effectiveness of Risk Minimisation (if applicable)
17. Benefit Evaluation
17.1. Important baseline efficacy/effectiveness information identified during Clinical Trials and post marketing period
17.2. Newly identified information on efficacy/effectiveness during Clinical Trials and post marketing period
17.3. Characterisation of Benefits
18. Integrated Benefit-Risk Analysis for Approved Indications
18.1. Benefit-Risk Context (Medical Need and Important Alternatives)
18.2. Benefit-Risk Analysis Evaluation
19. Conclusions and Actions
20. Appendices of Periodic benefit-risk evaluation report

Signed title page of PBRER

The title page should include name of medicinal product/products and drug substance , international birth date, reporting interval, reporting date, detailed information about Marketing Authorisation Holder and any statement on the confidentiality of the information included in the PBRER. Title page should include also signature.

Executive summary

Immediately after the title page, before the table of contents, an executive summary should be presented. The aim of executive summary is to present a concise summary of the content and the most important information contained in the PBRER.

The following information should be included

- Introduction and reporting interval.

- Medicinal product(s), therapeutic class(es), mode(s) of action, indication(s), pharmaceutical formulation(s), dose(s), route(s) of administration,
- Estimated cumulative exposure of clinical trial.
- Estimated interval and cumulative exposure obtained from marketing experience
- Number of countries in which the medicinal product is approved.
- Summary of overall benefit-risk evaluation (Based on subsection of 18.2 "Benefit/risk Analysis Evaluation" of the PBRER).
- Actions taken or proposed for safety reasons (e.g., significant changes to the reference product) information, other risk minimisation activities
- Conclusions.

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The executive summary should be followed by the table of contents.

2.5.1. PBRER's "Introduction" section

The marketing authorization holder should introduce briefly the drug/drugs, so that the PBRER is understandable "alone" and also provides perspective on previous PBRERs and conditions. The following information should be included in the Introduction:

- International birth date and reporting interval.
- Medicinal product(s), therapeutic class(es), mode(s) of action, indication(s), pharmaceutical formulation(s), dose(s), route(s) of administration,
- A short description of the population(s) being studied and being treated.

2.5.2. PBRER's " Worldwide marketing approval status" section

In this section of the PBRER should provide a brief narrative overview including date of first approval, indication(s), approved dose(s), and where approved.

2.5.3. PBRER's " Actions taken in the reporting interval for safety reasons " section

In this section of the PBRER should include a description of significant actions that are carried out across the world related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the MAH, sponsor of a clinical trial(s), data monitoring committees, ethics committees or regulatory authorities that had:

- A significant influence on the benefit-risk profile of the approved medicinal product; and/or
- An impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme. The reason for each action should be provided, if known, and additional relevant information should be provided when appropriate. Relevant updates to previous actions should also be summarised in this section. Examples of significant actions taken for safety reasons include given below:

<u>Actions related to investigational drugs:</u>

- 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 "Partial suspension" might include several actions (e.g., suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another, and/or suspension of a particular dosing regimen in a trial but continuation of other doses).
- Recall of investigational drug or comparator drug.
- Failure to obtain marketing approval for a tested indication, including voluntary

withdrawal of a marketing application.

- Risk management activities including below:
  - protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration).
  - restrictions in study population or indications.
  - changes to the informed consent document relating to safety concerns.
  - Formulation modifications.
  - Addition by competent authorities of a special safety-related reporting requirement
  - Communication with investigators or healthcare professionals.
  - plans for new studies to address safety concerns

Actions related to marketing experience:

- Failure to obtain for a marketing approval renewal or apply for a marketing approval renewal
- Withdrawal or suspension of a marketing approval.
- Activities undertaken due to medication errors and quality problems.
- Suspension of supply by the marketing authorization holder
- risk management activities covering the given below:
  - 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 post-marketing study requirements imposed by competent authorities.

2.5.4. PBRER's " Changes to reference safety information " section

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

2.5.5. PBRER's " Estimated exposure and use patterns "section

The PBRERs will include an accurate estimation of the drug-exposed population, also including all data related to sales volumes and prescription volumes. This exposure estimate will be accompanied, where appropriate, by the qualitative and quantitative analysis of the actual use which, based on all data accessible to the marketing authorization holder, including results obtained from observational studies and from studies on the use of drugs, will show how the indicated use differs from the actual use.

In this section of the PBRER, along with a short description of the method/methods used for calculating exposure of subjects, estimates of the size and nature of the drug-exposed population will be mentioned.

While calculating the exposure of subjects/patients, consistent methods should be used in all PBRERs for the same drug. If a modification of the method is appropriate, both methods and calculations will be presented and the change explained and significant differences between the results obtained using both methods will be highlighted.

2.5.5.1. PBRER's " Cumulative subject exposure in clinical trials " sub section

In this section of the PBRER, the following information about patients studied in clinical

trials supported by the marketing authorization holder should be included, if possible in tabular format:

- Total number of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator products since the DIBD (for "older products", detailed data might not be available).
- More detailed cumulative subject exposure in clinical trials should be presented if available, (e.g., sub-grouped by age, sex, and racial/ethnic group for the entire development programme).
- Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered.
- If clinical trials have been or are being performed in special populations (e.g., pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided, as appropriate.

- When there are substantial differences in duration of exposure between subjects randomised to the investigational medicinal product or comparator(s), or disparities in duration of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or - years).
- Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate.
- If the serious adverse events from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available.
- For individual trials of particular importance, demographic characteristics should be provided separately.

Examples of tabular formats for the calculated exposure in clinical trials are presented in Appendix 1, Table 2, 3 and 4.

2.5.5.2. PBRER's "Cumulative and interval patient exposure from marketing experience" sub section

Separate estimations should be provided for interval exposure (since the data lock point of the previous PBRER) and, when possible, cumulative exposure (since the international birth date). Although obtaining and validating exposure is generally known to be difficult, where possible, the method(s) used to determine the estimation should also be specified along with the number of patients exposed. If it is not possible to predict the number of patients exposed, a justification should be provided. In this case, if available, alternative exposure estimates and the method(s) used to obtain them should be provided. As an example of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a "defined daily dose" may also be used to estimate patient exposure.

The data should be presented according to the following categories:

1. Post-authorisation (non-clinical trial) exposure:

An overall estimation of patient exposure should be provided. In addition to this, the data should be routinely presented by sex, age, indication, dose, formulation, and region, where

applicable. Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment. When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

2. Post-authorisation use in special populations:

Where post-authorisation use has occurred in special populations, actual information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data include non-interventional studies designed to obtain this information, including registries. Populations to be considered for discussion include, but might not be limited to:

- Paediatric population.
- Elderly population.
- Pregnant or lactating women.
- Patients with hepatic and/or renal impairment.
- Patients with other relevant co-morbidity.
- Patients with disease severity different from that studied in clinical trials.
- Sub-populations carrying relevant genetic polymorphism(s).
- Patients of different racial and/or ethnic origins.

3. Other post-authorisation use:

If the marketing authorization holder has information about a drug's pattern of use, which is considered to be important for the interpretation of safety data and may be regional, he should make a brief description in this regard. Examples of such patterns of use may include overdose, misuse, drug abuse and use beyond that recommended in the reference product information (e.g., an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches) If known, the marketing authorization holder may briefly comment on whether use beyond that recommended in the reference product information is supported by clinical guidelines, clinical trial evidence, or an absence of approved alternative treatments. Quantitative use information should be provided, if available.

In order to determine patterns of use beyond reference product information, the marketing authorization holder should use in the appropriate section of the applicable reference product information at the end of the PBRER's reporting interval (e.g., approved indication, contraindications).

Examples of table formats for the exposure calculated from marketing experience are presented in Annex 1, table 5 and 6.

2.5.6. PBRER's " Data in summary tabulations" section

The objective of this section of the PBRER is to present through special tabulations the safety data regarding serious adverse events obtained from clinical trials, serious and non-serious spontaneous reactions obtained from marketing experience (including reports received from health professionals, consumers, scientific literature and the authorities (worldwide)) and serious reactions obtained from non-interventional studies and other demanded non-interventional resources. Graphics can be used for the illustration of certain properties of the data with the initiative of the marketing authorization holder to facilitate the understanding of the data.

When the MedDRA terminology is used for coding the adverse event/reaction terms, the Preferred Term level (PT) and system organ class (SOC) should be presented in the summary tabulations.

The adverse events/reactions severity in the summary tabulations must comply with the definition of serious adverse events/reactions included in the relevant regulations.

When serious and non-serious events/reactions are included in the same individual case safety reports (ICSR), the severity of each reaction must be stated in summary tabulations. The severity should not be changed specifically for the preparation of PBRERs.

2.5.6.1. PBRER's"Reference information" sub section

This section of the PBRER should specify the version/versions of the coding dictionary used for analyses of adverse events/reactions.

2.5.6.2. PBRER's "Cumulative summary tabulations of serious adverse events from clinical trial" sub section

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

The following items should be considered:

- Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all serious adverse events for the investigational drug, active substance controls, and placebo. It may be useful to give rates by dose.
- In general, the tabulation(s) of serious adverse events obtained from clinical trials should include only those terms that were used in defining the case as "serious" or "non-serious".
- The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g., expedited reporting). Sponsors of clinical trials and marketing authorization holders should not unblind data for the specific purpose of preparing the PBRER.
- Certain adverse events in clinical trials can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials). Examples for summary tabulations of serious adverse events obtained from clinical trials are presented in Annex 1, Table 7.

2.5.6.3. PBRER's "Cumulative and interval summary tabulations from post-marketing data sources" sub section

In this subsection of the PBRER, background information regarding the annex that presents cumulative and intermediate summary tabulations of adverse reactions from the international date of birth up to data lock points of the current PBRER, should be presented. The adverse reactions included in this section are obtained from spontaneous ICSRs (received from health professionals, consumers, scientific literature and the authorities (worldwide)) and demanded non-interventional ICSRs including those derived from non-interventional studies.

In addition to serious and non-serious spontaneous reactions obtained from spontaneous sources, serious adverse reactions obtained from non-interventional studies and other demanded non-interventional resources, periodic and cumulative data should be presented side by side in a single tabulation. The tabulation should be organised according to MedDRA system organ class (SOC) (should be listed in internationally agreed order). For specific issues or problems, additional adverse reaction tabulations can be presented according to indication, route of administration or other variables.

For drugs that are being marketed, spontaneously reported adverse events typically suggest that at least one causality is suspected by the rapporteur and should be considered as a suspected adverse reaction.

The analysis performed on the basis of the summary tabulations or results should not be presented in this subsection of the PBRER.

Example for summary tabulations of serious adverse drug reactions obtained from post-marketing data sources are presented in Annex 1, Table 8.

2.5.7. PBRER's "Summaries of significant safety findings from clinical trials during the reporting interval" section

This section of the PBRER should include a summary of important efficacy and safety findings obtained from sources specified in the subsections that are listed below, clinical studies supported by the marketing authorization holder during the reporting interval and which appear clinically significantly. Where possible and relevant, data categorized according to gender and age (particularly pediatric- adult), indication, dose and region should be presented.

In the 15th section of the PBRER ("Overview of new, ongoing, or closed signals"), signals consisting of clinical research sources should be presented in tabulation. The evaluation of rejected signals, terminated in the reporting interval period, whether classified or not, or potential or identified risks should be presented in section 16.2 ("Evaluation of the signal") of the PBRER. New information considered not creating a new defined signal and new information associated with any previously known potential and defined risk, should be respectively evaluated and defined in the subsections 16.3 ("Evaluation of risks and new information") and 16.4 ("Characterisation of risks).

Findings obtained from clinical studies not supported by the marketing authorization holder should be defined in the relevant sections of the PBRER.

When related to the benefit/risk evaluation, information on lack of efficacy obtained from clinical trials for the treatment of non-life-threatening diseases in approved indications should be summarized in this section. Information on lack of efficacy obtained from clinical studies with drugs used to treat or prevent from serious or life-threatening diseases should be summarized in Section 13 ("Lack of efficacy conditions in controlled clinical trials").

In addition, the marketing authorization holder should provide an annex in which interventional post-authorization studies whose main objective is the detection, identification or determination of the size of a safety hazard, or which are supported in order to verify the completed safety profile of a study or which are ongoing in the reporting interval are listed. Following information for each study should be included in the list:

- Information about the study (identification) (eg.; protocol number or other identifier).

- Title of the study (if applicable, abbreviated study title).
- Type of the study (e.g., randomized clinical trial, cohort study, case-control study).
- Population studied including country and other relevant population descriptors, (e.g., paediatric population or trial subjects with impaired renal function);
- Study start (as defined by the marketing authorization holder) and projected completion dates.
- Status: Ongoing (clinical trial has begun) or completed (clinical study report is finalised)

2.5.7.1. PBRER's "Completed clinical trials" sub section

This sub section of PBRER should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

2.5.7.2. PBRER's "Ongoing clinical trials" sub section

If the marketing authorization hold 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 sub section should briefly summarise the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

2.5.7.3. PBRER's "Long-term follow-up" sub section

Where applicable, this sub section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, especially advanced therapy products (eg gene treatments, cell treatment products and tissue engineering products).

2.5.7.4. PBRER's "Other therapeutic use of medicinal product" sub section

This sub section of the PBRER should include clinically important safety information requested from other programmes conducted by the marketing authorization holder that follow a specific protocol, (e.g., expanded access programmes, compassionate use programmes, particular patient use and other organised data collection processes).

2.5.7.5. PBRER's "New safety data related to fixed combination terapies" sub section

The following options are available for the submission of data on combination therapy available:

- When the active ingredient, which is the subject matter of the PBRER, is also being developed or licensed as a component of a fixed combination drug or a multidrug regimen, important safety findings obtained from the use of the combination therapy should be summarized in this subsection.
- If the drug itself is a fixed combination drug, whether licensed or under development or not, important safety information derived from each component should be summarized in this subsection of the PBRER. Specific information of the combination may be included in separate section(s) of the PBRER for all components of the combination or for each component.

2.5.8. PBRER's "Findings from non-interventional studies" section

In this section, information or important safety information derived from the reporting interval, obtained from non-interventional studis supported by the marketing authorization holder and likely to have an impact on the benefit/risk evaluation should be summarized (eg, observational studies, epidemiological studies, records and active surveillance programs). When more than one region is in question, the information obtained from drug usage studies should also be included (for the information the list should contain see 2.5.7).

The marketing authorization holder should provide an additional listing of non-interventional studies he supports in order to detect, identificate or determinate the size of a safety hazard, to verify the drug safety profile or to measure the effectiveness of in the reporting interval ongoing or completed risk management measures.

Final study reports completed in the reporting interval for the work described in the preceding paragraph should also be included in the PBRER's regional annex (see 2.5.20. and 3.4.4).

2.5.9. PBRER's "Information from other clinical trials and sources" section

Data can also be collected from outside the work environment. Event reports that don't result in suspicious adverse reactions or the information obtained from usage patterns can also be included in this subsection 2.5.9.1 and 2.5.9.2 (eg; asymptomatic overdose, drug abuse, use other than that recommended in the reference product information or information obtained from the usage report in special populations). This type of information can be obtained from spontaneous reports, medical information queries, consumer complaints, digital media screenings or other information sources in service of the marketing authorization holder.

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

2.5.9.1 PBRER's "Other clinical trials" sub section

In this subsection, information about the drug's benefit/risk evaluation obtained from other clinical trial sources, including patient support programs accessible to the marketing authorization holder during the reporting interval, should be summarized (eg; combined analysis results of randomized clinical trials, meta-analysis results, safety information obtained from partnerships established during drug development or studies started by researchers).

2.5.9.2 PBRER's "Medication errors" sub section

Even if not related to adverse outcome, information on potential drug misuse and improper drug use patterns should be summarized in this subsection. Potential drug misuse is a description of situations, in which the patient is or is not included, that may lead to the misuse of the drug. This information may be related to the drug's overall benefit/risk evaluation or the interpretation of safety data. Medication errors may occur at any stage of the medication and patients, consumers and health professionals may be involved in this event.

2.5.10. PBRER's "Non-clinical data" section

This section should summarise major safety findings from non-clinical in vivo and in vitro studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designed to address specific safety concerns should be included in the PBRER, regardless of the outcome.

2.5.11. PBRER's "Literature" section

This section of the PBRER should include a summary of unpublished drafts the marketing authorisation holder became aware of in the reporting interval or new and significant safety findings in literature published in peer-reviewed scientific journals.

Literature review for the PBRER should be more comprehensive than individual cases

of adverse reactions, as it includes other drugs containing the same active substance and studies reporting the safety outcomes in voluntary groups.

Special types of safety information which can not be found with a search created to identify individual cases, but should be included, should include the following:

- Pregnancy outcomes not obtained by adverse results (including abortion).
- Use in the pediatric population.
- Early access to drugs, off-label drug use.
- Lack of efficacy.
- Asymptomatic overdose, drug abuse or misuse.
- Medication errors without adverse events.
- Important non-clinical safety results.

If relevant and applicable, information about other active substances included in the same class should be taken into consideration.

Publication reference must be submitted in Vancouver Convention style.

2.5.12. PBRER's "Other periodic reports" section

This section of the PBRER is only applicable in certain circumstances regarding fixed combination drugs or drugs with more than one indication and/or formulation where a compromise is reached with the Institution and more than one PBRER is prepared. In general, the marketing authorization holder must prepare one PBRER for a single active ingredient unless otherwise specified by the Authority; however, if more than one PBRER is prepared for a single drug, it is necessary to summarize the major findings related to other PBRERs in this section, if they are not provided elsewhere in the report.

Where present, in accordance with written agreements, the marketing authorization holder should summarize the significant findings obtained by other parties (eg; sponsors, other marketing authorisation holders) from the periodic reports submitted during the reporting interval.

2.5.13. PBRER's "Lack of efficacy conditions in controlled clinical trials" section

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

2.5.14. PBRER's "Late-breaking information" section

In this section of the PBRER, the marketing authorization holder will summarize potentially important findings of safety and efficacy obtained after the data lock point, during the preparation period of the PBRER. Examples include clinically relevant new publications, important follow-up data, clinically significant toxicological findings and an activity carried out by the marketing authorization holder, a data monitoring committee or or a competent authority (worldwide) due to safety. A case which will not constitute an important indicator (e.g.; the first example of an important event) or a safety signal which will not constitute an important indicator or in cases where additional information cannot be provided to the evaluation of safety issues already in the PBRER, new individual case reports should not be included routinely (e.g; a well-documented case of aplastic anemia in a drug known to be associated with adverse effects on the bone marrow in the absence of possible alternative causes).

In this section of the PBRER should be included, if possible, any significant change (e.g; new adverse reactions, warnings or contraindications) suggested for the reference product information resulting from this reporting period (see. 2.4).

The data presented in this section also should be considered during the evaluation of risks

and new information (see. 2.5.16.3).

2.5.15. PBRER's "Overview of new, ongoing, or closed signals" section

The location where information related to risks and signals included in the PBRER is presented is shown in Figure 1. The purpose of this section is to provide, as in signals whose evaluation is ongoing at the end of the reporting period, an overview of a high level for signals whose closure was made during the reporting period (e.g; the completed evaluation). When the first step screening is made or the netting phase is entered, the signal should be included in the PBRER and determination to carry out further evaluation should be shown by the marketing authorization holder. (The here mentioned signal is a validated signal). Because the validation step is required, it should be considered that a safety signal is not equivalent to the disproportionate reporting statistics of a specific drug/event combination. Signals may be qualitative (ivotal individual case safety reports, case series) or quantitative (e.g., a disproportionality score, findings of a clinical trial or epidemiological study).Signals may arise in the form of an information request or inquiry on a safety issue from a competent authority.

Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation involve medical judgement and scientific interpretation of available data, which is presented in Section 16 ("Signal and risk evaluation") of the PBRER.

The new signal represents a signal detected in the reporting interval. When clinically significant new information about a previously closed signal is found in the PBRER's reporting interval, this also can be considered as a new signal, because it is necessary to carry out additional activities to confirm the new feature of the previously rejected signal or identified risk. New signals can be closed or classified as continuing at the end of the PBRER's reporting period, depending on the signal evaluation status.

New information on the previous signals will be included in the following examples for new signals:

- Re-opened closed or dismissed signal.
- Identified risks with the new information showing that there is a significant clinical difference in the frequency or severity of the risk (e.g; transient increase in liver enzymes are identified risks and new information pointing towards more severe consequences such as liver failure was found or neutropenia is a defined risk and in the absence of possible alternative causes a well-documented case report of agranulocytosis was received).
- Identified risk with a newly discovered higher frequency or severity (e.g; in the indicated subpopulation).
- If verified, potential risk that requires a new alert, measure, a new contraindication or restriction in indication(s) or the population the drug is used by or other risk minimizing activities.

The marketing authorization holder should list all at the end of the reporting period closed or ongoing signals in a tabular in this section or as an attachment. This table should contain the following information:

- a brief description of the signal.
- date when the MAH became aware of the signal.
- status of the signal at the end of the reporting interval (closed or ongoing).
- source of the signal, if available.
- source of the signal.
- a brief summary of key data.
- plans for further trial.
- actions taken or planned.

An example of the tabular of the signals can be found in Appendix 2.

Details of signal evaluation for closed signals should be presented in the PBRER's subsection 16.2 ("Signal evaluation") instead of this section.

New information considered not creating a new signal and previously known identified and potential risks should be presented in the PBRER's subsection 16.3 ("Evaluation of risks and new information").

If the competent authority (worldwide) wants the reporting and follow-up of a specific subject (not considered as a signal) in the PBRER, the marketing authorization holder should summarize the results of the analysis in this section in case the results are found negative. If a specific issue becomes a signal, the signal should be added to the signal tabular and be discussed in subsection 16.2 ("Signal evaluation").

2.5.16. PBRER's "Signal and risk evaluation" section

The purpose of this section of the PBRER is to provide:

- A brief summary of what is known about important identified and potential risks and important missing information at the beginning of the reporting interval covered by the report (2.5.16.1);
- An evaluation of all signals closed during the reporting interval (2.5.16.2);
- An evaluation of new information with respect to previously recognised identified and potential risks (2.5.16.3);
- An updated characterisation of important potential and identified risks, where applicable (2.5.16.4);
- A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions (2.5.16.5).

The flowchart creating a map of the signals and risks in the PBRER's specific sections/subsections can be found in 2.5.21.

This evaluation subsections should include a perspective for identifying the risk profiles considered to be significant and an interpretation and critical evaluation of the information, instead of repeating or summarizing the information presented in the PBRER's previous sections. In addition, as a general rule, the PBRER's evaluation sections are not required to include individual case histories, however, a clinical evaluation of pivotal or illustrative cases (e.g; first suspicious case of agranulocytosis seen with the active substance belonging to a class of drugs known to potentially cause agranulocytosis) should be presented when they are part of a scientific analysis of a signal or risk (See 2.3).

2.5.16.1. PBRER's "Summary of safety concerns" sub section

The purpose of this sub section is to provide a summary of safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For drugs with current safety specifications, this section will probably be derived from or the same as the safety specification summary which was current at the beginning of the PBRER's reporting interval.

The following safety information should be presented:

- Important identified risks.
- Important potential risks.
- Important missing information.

The following factors should be considered when determining whether or not a risk is important:

- medical seriousness of the risk, including the impact on individual patients.
- its frequency, predictability, preventability, and reversibility.
- potential impact on public health (frequency; size of treated population).

- Potential to refrain from the use of drugs with protective benefits because the risk is perceived disproportionately by the population (e.g; vaccines).

For drugs that don't have a current safety specification, significant identified and potential risks associated with the use of the drug based on the pre- and post-authorization experience, as well as information about the missing important information should be presented in this section.

Important identified and potential risks may include:

- important adverse reactions.
- interactions with other medicinal products.
- interactions with foods and other substances.
- medication errors.
- effects of occupational exposure.
- pharmacological class effects.

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

2.5.16.2. PBRER's "Signal evaluation" sub section

In this subsection of the PBRER, the evaluation results of all safety signals closed in the reporting interval (whether classified as important or not) should be summarized. A safety signal may be closed after the evaluation because it was refuted or identified as a potential or identified risk. There are two main classifications that should be included in this subsection:

1. Signals rejected after the evaluation on the grounds of being erroneous signals in light of the scientific evaluation of available information and medical opinion.
2. Signals categorized as potential or identified risk after the evaluation, including inefficiency.

In order to clearly define the grounds for refuting or accepting the signal as a potential or identified risk, a short and concise description of each signal evaluation should be presented by the marketing authorization holder for both categories of the closed signals.

The level of detail presented in the definition of the signal evaluation should be reflecting the medical significance of the signal (eg, severe, irreversible, causing increased morbidity or mortality), the impact on public health (e.g; common use, frequency, usage significantly other than recommended in the product information) and the scope of existing evidence. In case more than one evaluation is included for both classifications on closing signals, they may be presented in the following order:

- closed and refuted signals;
- closed signals that are categorised as important potential risks;
- closed signals that are categorised as important identified risks;
- closed signals that are potential risks not categorised as important; and
- closed signals that are identified risks not categorised as important.

If valid, the evaluation of the closed signal may be presented according to indication or population.

Definitions of signal evaluation may be included in this subsection of the PBRER or as an attachment. The following information should be included as appropriate in each evaluation:

- source of the signal;
- Background relevant to the evaluation;

- method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms [e.g., PTs, HLTs, SOCs, etc.] or Standardised MedDRA Queries [SMQs] that were reviewed), and analytical approaches;
- results – a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an ICSR, e.g., an index case of well documented agranulocytosis or Stevens Johnson syndrome;
- discussion; and
- conclusion.

2.5.16.3. PBRER's "Evaluation of risks and new information" sub section

In this subsection, new information not yet included in the sub section 16.2 ("Signal evaluation") and associated with the previously noticed information should be critically evaluated.

New information generating a signal regarding a previously noticed risk or a previously refuted signal (if this signal is also closed in the PBRER's reporting interval), should be evaluated and presented in the signal tabular (see 2.5.15) in subsection 16.2 ("Signal evaluation").

Updated information for previously noticed risks that don't create a signal should be included in this subsection. Examples may include information confirming that a potential risk is an identified risk or information that allows a previously noticed risk to be further defined.
New information can be organised as follows:

1. new information on important potential risks;
2. new information on important identified risks;
3. new information on other potential risks not categorised as important;
4. new information on other identified risks not categorised as important;
5. update on important missing information.

New information obtained during the PBRER's reporting interval should be in the focus of the evaluation(s). The evaluation should be short and concise, but its impact on the understanding of the risk and its identification, if present, should be interpreted at the same time. The evaluation will be the basis for updating the identification of important potential and identified risks in section 16.4 ("Characterisation of risks") of the report. It is recommended that the level of detail of the evaluation included in this subsection is commensurate with the reachable evidence of risk, the medical importance of the risk and its relation with public health.

The evaluation of updating new knowledge and incomplete information may be included in this subsection of the PBRER or presented as an attachment.

The following information should be included as appropriate in each evaluation:

- source of the new information;
- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria, and analytical approaches;
- results – a summary and critical analysis of the data considered in the risk evaluation;

- discussion;
- conclusion including whether or not the evaluation supports an update of the characterisation of any of the important potential and identified risks in Section 16.4 ("Characterisation of the risks") of the PBRER.

Any new information about exposed populations or information obtained earlier to resolve missing information should be critically evaluated in this subsection. Unsolved concerns and uncertainties should be disclosed.

2.5.16.4. PBRER's "Characterisation of risks" sub section

Important identified and potential risks should be defined based on cumulative data (not limited to the reporting interval) and important information that is missing should be disclosed in this subsection.

Depending on the nature of the data source, where applicable, the identification of risk may include the following:

- frequency;
- numbers of cases (numerator); precision of estimate, taking into account the source of the data;
- extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- estimate of relative risk; precision of estimate;
- estimate of absolute risk; precision of estimate;
- impact on the individual patient (effects on symptoms, quality or quantity of life);
- public health impact;
- patient characteristics relevant to risk (e.g., age, pregnancy/lactation, disease severity, hepatic/renal impairment, relevant co-morbidity, genetic polymorphism);
- dose, route of administration;
- duration of treatment, risk period;
- preventability (i.e., predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker);
- reversibility;
- potential mechanism;
- strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information presents a significant risk, it should be included as a safety concern. Limitations of the safety database (in the context of the number of patients studied, cumulative exposure or long-term use and so on) should be discussed.

It may be appropriate to present risks according to indication, formulation or route of administration in PBRERs for drugs with significant differences in identified and potential risks, a variety of indications, formulations or routes of administration. Titles that may be

considered include:

- Risks relating to the active substance.
- Risks related to a specific formulation or route of administration (including occupational exposure).
- Risks relating to a specific population.
- Risks associated with non-prescription use (for substances that are available as both prescription and non-prescription products).

2.5.16.5. PBRER's "Effectiveness of risk minimisation (if applicable)" sub section

Risk minimization activities are public health initiatives carried out in order to prevent the occurrence of adverse drug reactions or to reduce their severity. The purpose of risk minimization activities is to reduce the probability of occurrence of adverse drug reactions or to reduce their severity. Risk minimization activities may consist of routine risk minimization activities (e.g; SmPC) or additional risk minimization activities (e.g; Information Letters/training material for Doctors).

The PBRER should include results regarding the evaluation of the effectiveness of risk minimization associated with the benefit/risk evaluation.

Information about effectiveness and/or limitations of specific risk minimization activities regarding significant identified risks obtained in reporting intervals should be summarized in this sub section of the PBRER. The effectiveness of risk minimization activities in any country or region may set an example for other countries and regions. If valid and relevant, information can be summarized by region.

2.5.17. PBRER's "Benefit evaluation" section

The sub sections 17.1 ("Important baseline efficacy information identified during Clinical trials and post-marketing period") and 17.2 ("Important baseline efficacy information newly identified during Clinical trials and post-marketing period") provide basic information for section 17.3 of the PBRER. The new identified benefit information supporting the identification of benefits defined in sub section 17.3 ("Benefit evaluation"), supports the benefit/risk evaluation in section 18 (Integrated benefit-risk analysis for approved indications).

2.5.17.1. PBRER's "Important baseline efficacy information identified during Clinical trials and post-marketing period" sub section

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

For drugs with more than one indication, population and/or route of administration, the benefit should be defined separately based on these elements, if relevant.

The details presented in this sub section should be at a level sufficient to support the identification of benefit in sub section 17.3 ("Characterisation of benefits") and the benefit/risk evaluation in section 18 ("Integrated benefit-risk analysis for approved indications") of the PBRER.

2.5.17.2. PBRER's "Important baseline efficacy information newly identified during Clinical trials and post-marketing period" sub section

Additional information regarding the effectiveness of some approved indications of the

drug may be obtained during the reporting interval. This type of information should be presented in this sub section of the PBRER. If possible, new information about the effectiveness under real conditions of use in approved indications should be presented in this sub section. If not associated with benefit/risk evaluation in approved indications, new information about the effectiveness regarding the use in unapproved indications should not be presented.

Information on newly approved indications during the reporting interval should also be included in this sub section. The detail provided in this sub section should be sufficient to support the benefit/risk evaluation in Section 17.3 ("Characterisation of benefits") of PBRER and in Section 18 ("Integrated benefit-risk analysis for approved indications") of PBRER.

Special attention should be given to drugs, vaccines and anti-infective agents whose efficacy might be changed over time by changes in therapeutic environment in this sub section.

2.5.17.3. PBRER's "Characterisation of benefits" sub section

The initial benefit information should be presented together with the new benefit information obtained during the reporting interval in this sub section.

The amount of detail presented in this sub section should be enough to support the benefit/risk evaluation in section 18 ("Integrated benefit-risk analysis for approved indications").

This sub section should ensure the identification of the information in sub section 17.1 ("Important baseline efficacy information identified during Clinical trials and post-marketing period") in the absence of new related benefit data.

In cases where new positive benefit information is found during this reporting interval, but the risk profile doesn't change significantly, the initial information and the new information should be submitted briefly and combined.

A short but critical evaluation of strengths and limitations of the findings related to efficacy during clinical trials and in the post-marketing period should be presented taking also into account, if valid, the following:

- a brief description of the strength of evidence of benefit, considering comparator, effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials;
- new information that challenges the validity of a surrogate endpoint, if used.
- Clinical relevance of the effect size.
- Generalizability of treatment response across the indicated patient population (e.g., information that demonstrates lack of treatment effect in a sub-population
- adequacy of characterization of dose-response.
- duration of effect.
- comparative efficacy in the clinical trials.
- A determination of the extent to which efficacy findings obtained from clinical trials are generalizable to patient populations treated in medical practice.

2.5.18. PBRER's "Integrated benefit-risk analysis for approved indications" sections

In this section of the PBRER, the marketing authorization holder should provide an overview of the benefits and the risks of the drug as used in clinical practice. As benefits and risks are presented in sub sections 16.4 ("Characterisation of risks") and 17.3 ("Characterisation of benefits"), a critical analysis of the key information presented in the previous section should be presented collectively and the benefit and risk definitions presented in the above subsection should not be repeated in this section.

2.5.18.1. PBRER'nin "Benefit-risk context (medical need and important alternatives)"sub section

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

2.5.18.2. PBRER's "Benefit-risk analysis evaluation" sub section

A benefit-risk profile is specific to an indication and population. For this reason, for products approved for more than one indication, benefit/risk profiles should be evaluated and presented for each indication individually. If there are important differences in the benefit/risk profiles among populations within an indication, benefit-risk evaluation should be presented by population, if possible.

The evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks, and should take into account the following points:

- Previous sections will include all important benefit and risk information. But not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections/sub sections should be carried forward for integration in the benefit/risk evaluation.
  - Usage status of the drug should be considered: The condition that is to be treated, prevented or diagnosed, the severity and severity of the condition and the population to be treated (partially healthy, chronically ill, rare cases).
  - In terms of basic benefits; the structure of benefits, clinical significance, duration and generalizability, as well as effectiveness findings in those not responding to other therapies and alternative practices and effect size should also be considered. If different benefit items are available, all must be considered (eg; for the treatment of rheumatoid arthritis: Prevention of radiographic progression of joint damage and reducing symptoms).
  - The clinical significance of the risk (eg, toxicity structure, severity, frequency, predictability, preventability, reversibility, impact on patients) with unapproved indications or whether it occurs during clinical trials conducted in populations, off-label use or improper drug use or not should be considered.
  - While formulating the benefit/risk evaluation, the strengths, weaknesses and uncertainties of the evidence should be considered. How uncertainties about the benefits and risks affect the evaluation should be defined. Limitations of the evaluation should be discussed.

The methods and reasons used to improve the benefit/risk evaluation should be explained clearly:

- Assumptions supporting the results of the benefit/risk evaluation, considerations taken into account and decisions or their severity should be clear.
- If a formal quantitative or semi-quantitative benefit/risk evaluation has been submitted, summaries of the methods should be included.
- Economic considerations (eg, cost-effective) should be taken into account during the benefit/risk evaluation.

A detailed benefit/risk analysis based on cumulative data should be presented when important new information arises or a PBRER is requested for a specific purpose. On the contrary, if less new information is obtained during the reporting interval, the main focus of the benefit/risk evaluation should consist of the evaluation of the updated intermediate safety data.

2.5.19. PBRER's "Conclusions and actions"section

A PBRER should be finalized by including the effects of the new information obtained in the range of reporting while making, where appropriate, a general benefit/risk evaluation for the corresponding sub-group in addition to all approved indications.

The Marketing Authorization Holder should, based on the cumulative safety data and benefit/risk analysis evaluation, evaluate whether changes in the reference product information need to be made or not, and if applicable, propose the appropriate changes. In addition, if valid, the results should include preliminary suggestions/proposals for an optimization of the benefit/risk ratio or for further assessment. This may include recommendations for further studies towards minimizing the risk.

Recommendations for medications containing a pharmacovigilance or risk management plan should be included in the pharmacovigilance plan and/or risk minimization plan.

Upon evaluation of the cumulative safety data and benefit/risk analysis, the Marketing Authorization Holder should come to a conclusion as to whether changes and/or action are needed or not, including conditions affecting the approved SmPC and PI of the drug. The Regional annex should include information about ongoing changes, if applicable, along with the proposals for the product information (SmPC and PI).

2.5.20. ***Appendices to the PBRER***

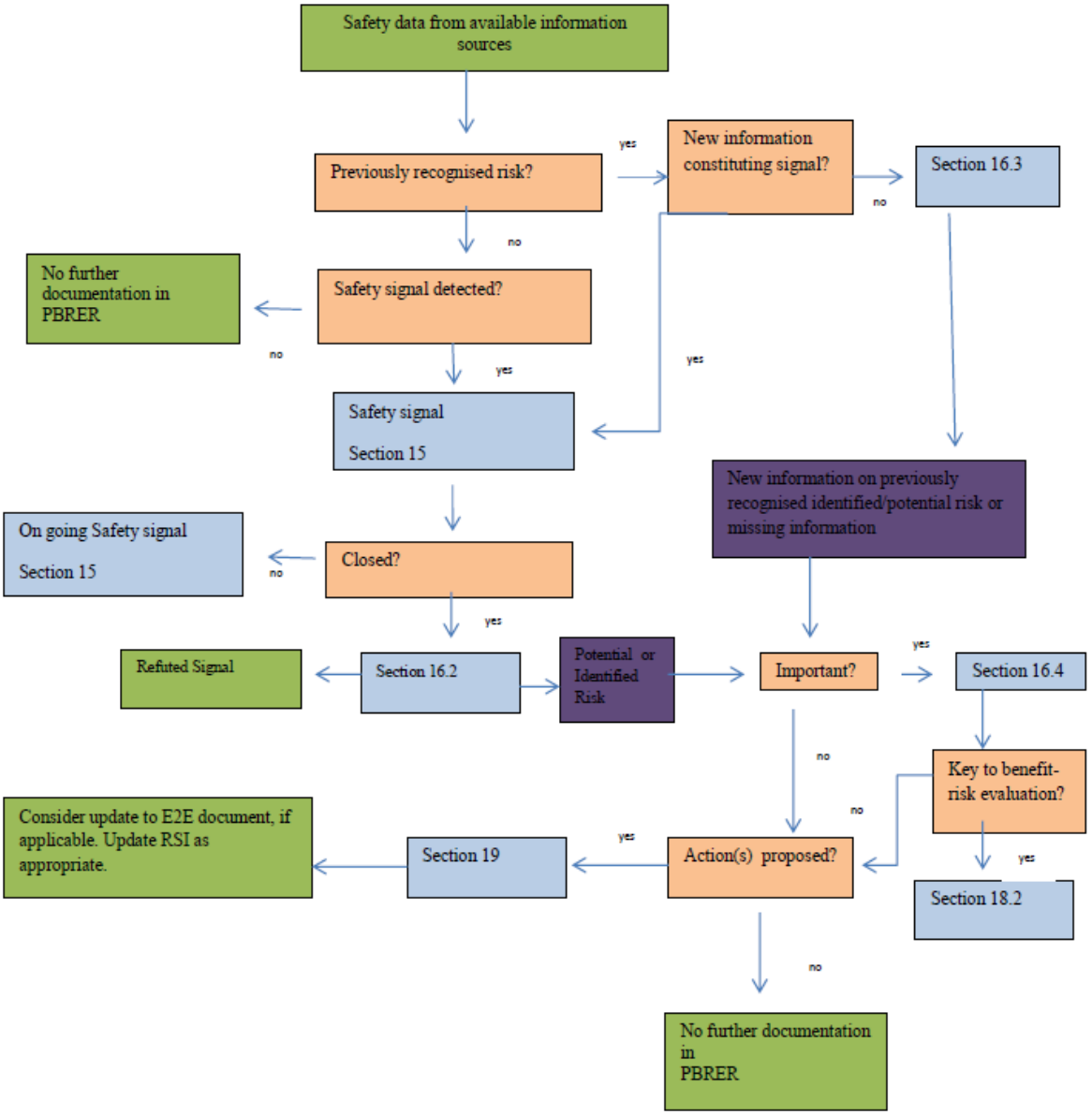
Appendices of the PBRER should be numbered as follows:

1. Reference Information see section 2.4.
2 Cumulative summary tables of serious adverse events from clinical trials and cumulative and intermediate summary tables for serious and non-serious adverse reactions obtained from post-marketing data source.
3. Tabular Summary of Safety Signals (Including the signal tables in the PBRER's main report should be preferred; if they are not included in the main report they may be included here.)
4. A list of all interventional and non-interventional studies that are supported by the Marketing Authorization Holder and whose main purpose is the detection, identification or determination of the extent of the drug's safety risk or the verification of its safety profile and non-interventional studies carried out to measure the effectiveness of risk management measures
5. List of the Sources of Information Used to Prepare the PBRER (when desired by the marketing authorization holder).
6. Regional appendix: Section 3.4.

2.5.21. The place of signals and risks in the PBRER's sections/sub-sections

The following diagram shows the general locations where information about signals and risks will be presented in the PBRER.

Figure 1. PBRER sections/subsections – signals and risks



2.6. Marketing Authorization Holders' quality systems for the PBRERs

Marketing Authorization Holders should have processes and structures for the preparation, quality control, inspection and submission of PBRERs, including monitoring during and after the evaluation. These structures and processes should be defined in accordance with the written policies and procedures of the registration holder's quality system.

There are various fields in the pharmacovigilance process that might directly affect the PBRER's quality. Some examples are case management of spontaneous reports and work-oriented reports, literature review, signal management, additional pharmacovigilance and post-marketing research activities, operations for the integration of benefit and risk information received from all data sources available and updating product information. The quality system should define the connections between responsibilities, communication channels and processes in order to combine all information required for forming PBRERs. In order to check the accuracy and completeness of the data presented in the PBRERs, documented processes including quality control must exist. A documented template or plan for the reception of data from various sources can be generated to ensure that the data is complete. The importance of an integrated approach towards the benefit/risk evaluation should support the processes for preparing a PBRER and inter-sectional input.

The PBRER should also include an evaluation of specific safety problems that are to be discussed in a PBRER according to the competent authorities (worldwide). The marketing authorization holder should posses the necessary mechanisms to ensure during the PBRER evaluation that the requests made by the competent authorities (worldwide) are adequately met.

To ensure the accuracy of the presented incident/reaction number, the data contained in the summary table (See Fig. 2.5.6.) and the marketing authorization holder's safety data base will be subject to source data verification. The safety database query process, the parameters used for access to data and quality control work carried out should be documented appropriately.

As mentioned below, to avoid a lack of compliance with the PBRER requirements a suitable quality control system is required:

- Application cannot be made: The PBRER application cannot be made, applications are made outside the correct application plan or outside the correct time periods (without previous agreement of the institution).
- The unjustified removal of the information 2.5. requires.
- Poor quality of reports: Reports for the comprehensive evaluation of new safety information, signals, risk evaluation, benefit evaluation and integrated benefit/risk analysis are poorly documented, contain insufficient information or are submitted with insufficient evaluation, failure to emphasize the misuse of drugs, failure to use standard medical terminology (MedDRA) and improper removal of cases without risk factors reported in cumulative reviews.
- Submission of a PBRER that does not respond to the earlier demands of the institution.
- The drug's benefit/risk balance has not clearly been evaluated.
- Failure to make sufficient proposals for local-approved product information.

Significant deviations that occur in processes related to the preparation or presentation of PBRERs should be documented and appropriate corrective and preventive actions should be carried out. This document must be accessible at all times.

When the task of the preparation of a PBRER is given to a license issuer or to a contracted pharmacovigilance service provider, the Marketing Authorization Holder should ensure that the interested party has a quality system in accordance with current regulations. There should be clear procedures and detailed contracts between the Marketing Authorization Holder and the interested parties. Especially an option regarding supervision of the PBRER preparation process should be included in the contracts.

2.7. Training of the staff regarding the PBRER preparation process

In all Organizations, the person responsible for the pharmacovigilance system (pharmacovigilance authority) is responsible of ensuring that all the related staff, including pharmacovigilance, medical and quality staff involved in the preparation, inspection, quality control, submission and evaluation of the PBRER, possess the valid guidelines, necessary qualifications, experience and training. Special training for different processes, tasks and responsibilities regarding the PBRER should be provided to pharmacovigilance officials and, if necessary, other staff involved in this process.

Also, trainings should be organized as necessary to keep knowledge and skills up to date.

Regulations, manuals, scientific evaluations and written processes regarding the PBRER process should be included in the training. Before conducting activities related to PBRER, having received the relevant training should be proven with training records.

SECTION III
Operation of benefit/risk evaluation process

3.1. General principles for preparation and submitting PBRER

After receiving a licence in Turkiye, Marketing Authorisation Holder (MAH) continues to evaluate the safety of medicinal products periodically by preparing PBRERs every six months for two years, once a year for the next two years, and also once every three years after renewal of the licence. However, if the active substance of the licenced product is included in the current list provided in the "List of EURDs and frequency of submission of PSURs" on the official website of EMA, this list can be complied. PBRER is prepared according to the dates declared in the list. Following the current list is the responsibility of the licence holder.

As a result of the evaluation, in the event of new safety information affecting benefit/risk profile or Summary Product Characteristics/Packaging Leaflet, performing a variation submission is the primary responsibility without any request by the Authority and it is not necessary to submit the related reports to Authority routinely. However, 18 months after the drug release on market or numbers of patient reach 10.000, PBRERs should be submitted to the Authority. The aforementioned application is applicable for the all products released on/after the date of 15.04.2014.

3.2. Preparation and submission schedule of PBRERs

If the MAH prepares PBRERs every six months for two years, once a year for the next two years after receiving a licence in Turkiye, and also once every three years after renewal of the licence or if the active substance is not included in the current list provided in the "List of EURDs and frequency of submission of PSURs" on the official website of EMA, the following steps are performed to prepare PBRER.

During the benefit/risk evaluation to be performed after receiving a licence of the product and subsequent preparation of PBRER, zero-day is the licence date of the product. In the six-month reports, data is locked after six months from the licence date. This date is data lock point. Report is prepared within 70 clendar days from the data lock point (eg. for the medicinal product licenced 01 January 2013, fist six-month report should involve the date between 01.01.2013 to 30.06.2013; the date of 30.06.2013 should be accepted as a data lock point and report should be prepared within the 70 calendar days following this date. A second annual report for the same medicinal product should involve between 01.01.2016 to 31.12.2016. For this report, 31.12.2016 should be accepted as a data lock point and report should be prepared within the 70 calendar days following this date). The report period in three-year report to be prepared after renewal should comprise three-year data and should be prepared within 90 calendar days.

If more than three years have passed from the date of the last PSUR submitted before the date of 15.04.2014 (since the submission of the 3-year report will have passed), report should be prepared as five-year report and PSUR format and archieved. If less than three years have passed from the date of the last PSUR submitted before the date of 15.04.2014, 3-year PBRER should be prepared and archieved. For example, if the last report has been submitted on the date of 01.04.2009; since more than 3 years pass from this date, PSUR/National Report including 5-year period should have been prepared (Since it belongs to the period before the Regulation, submission of National Report is allowed. National Report is described in "Pharmacovigilance Guideline to MAH revoked on the date of 15.04.2014). After that, PBRER should be prepared and archieved at three-year intervals.

For example, if the last report has been submitted on the date of 01.04.2012; PBRER should have been prepared on the date of 01.04.2015. After that, preparation of PBRER is continued at three-year intervals (When added three years to this date, it corresponds to the date of 01.04.2015. Since Regulation has been issued prior to this date, 3-year report should be prepared).

If the active substance of the licenced product is included in the current list provided in the "List of EURDs and frequency of submission of PSURs" on the official website of EMA and will be complied this list; PBRER should have been prepared within 70 calendar days from the data lock point for PBRERs comprising intervals up to 12-month (including exactly 12-month intervals) and 90 calendar days from the data lock point for PBRERs comprising intervals exceeding 12-month. The release date of the drug is

There should be no spaces in terms of the date among the PBRERs prepared.

18 months after the drug release on market in our country or when numbers of patient reach 10.000, PBRERs to be submitted to the Authority can be submitted cumulative evaluation of the first three six-month PBRERs if the drug is released on the licenced date. Release date of the drug is the date of declaration of manufacture of import to Drug Monitoring System (DMS). When numbers of patient reach 10.000 in our country, MAH who wants to make presentation can use "International Reporting of Periodic Drug-Safety Update Summaries, Final Report of CIOMS Working Group II, Geneva, 1992" report to calculate exposure.

3.3. Relationship between PBRER and risk management plan

During the preparation of PBRER; the MAH should evaluate if any identified or potential risk discussed within PBRER is important and if update of RMP is necessary or not. In

that case, updated and revised RMP including new significant safety concern should be submitted along with PBRER. During the evaluation of a PBRER, if significant safety concerns are identified and updated RMP or any RMP is not submitted; recommendations should be as submission of RMP that is new or updated at a specific time interval.

3.3.1. PBRER and RMP – common modules

The anticipated modular format for PBRER and RMP aims to provide to make copy and to facilitate flexibility by encouraging the use of common PBRER/RMP sections to be used as a modified format in both report.
The common sections mentioned abouve are identified in Table-1.

Table.1. Common sections of PBRER and RMP

PBRERs Section	RMPs section
Section 3 – "**Actions taken in the reporting interval for safety reasons**"	Part II, module SV – "Post authorisation experience", section "Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons"
Sub Section 5.2 – "**Cumulative and interval patient exposure from marketing experience**"	Section II, modül SV – "Post authorisation experience", section "Non-study post-authorisation exposure"
Sub section 16.1 – "**Summary of safety concerns**"	Section II, module SVIII – "Summary of the safety concerns" (As included in the RMP version current at the beginning of the PBRER reporting interval)
Sub section 16.4 – "**Characterisation of risks**"	Section II, Module SVII – "Identified and potential risks"
Sub section 16.5 – "**Effectiveness of risk minimisation (if applicable)"**	Section V – "Risk minimisation measures", section "Evaluation of the effectiveness of risk minimisation activities"

3.4. Specific requirements of EU

Scientific evaluation of benefit/risk ratio of the medicinal product included in PBRER should be based on the all available data including data obtained from non-approved indications detailed in Section 2.5 and clinical studies conducted on populations. Specific requirements of EU for the medicinal products licenced in EU should be added to EU ragion appendices of PBRER.

3.4.1. PBRER EU ragional appendices, "Proposed Product Information" subsection

During PBRER evaluation procedure in EU, it should be decided if changes in product information are necessary or not. Opinion to be provided by Authority or action to be taken, if required, includes the recommendation for the update of product information. In order to facilitate this, MAHs should submit supportive documentation and references required within PBRER.

MAH should examine closely the effect of data and evaluations within PBRER on regulatory. Based on the evaluation of the cumulative safety data and the benefit/risk analysis; MAH should come to the conclusion in terms of if changes in approved SPC and/or action are necessary for drug(s) whose PBRER is(are) submitted.

In this subsection, MAH should privde proposals for product information (SPC/PIL) based on the evaluation mentioned above. These are based on the all indications approved in EU. In variation submission to be performed based on the evaluation and results of the PBRER; changes to be done in proposed SPC/PIL should be marked in related pages and the explanations of the changes should be described at the right side of the page.

All SPC/PILs prepared as a result of PBRER should reflect information in accordance with the cumulative data analysed and incorporated to the PBRER.

Changes in the product information should not be postponed or delayed until the PBRER submission. Changes not related to the information submitted in the PBRER, should not be proposed within the PBRER process. To apply the variation submission related with the changes need to be done in the SPC/PIL is the responsibility of MAH.

3.4.2. PBRER EU regional appendices, "Proposed additional pharmacovigilance and risk minimization activities" subsection

This subsection should contain additional pharmacovigilance and risk minimization actions based on the result of the PBRER including declaration of intention to submit a RMP or updated RMP.

3.4.3. PBRER EU regional appendices, "Summary of ongoing safety concern" subsection

In order to support the information presented in 16.1 sub section "Summary of safety concern" of PBRER (see section 2.5.16.1), a table named "Summary – Ongoing safety concern" should be added to this subsection of PBRER. This table will be obtained from the available version of RMP at the initial of the PBR report date range (see Risk Management Module).

3.4.4. PBRER EU regional appendices, "Reporting of findings obtained from post-authorisation safety studies" subsection

Findings from both interventional and non-interventional post-authorisation safety studies should be reported in PBRER. While MAH should inform competent authorities in EU member-state countries and EMA if applicable for the any new information that would instantly affect benefit/risk ratio, PBRER should provide compherensive information with regard to the findings of the overall interventional and non-interventional post-authorisation safety studies included in section 7 and 8 of PBRER, respectively. Final study reports for the studies conducted with the primary aim of identifying of safety profile of the medicinal product or quantifying the effectiveness of the risk management precautions identified during the reporting period, determining, identifying or quantifying a safety hazard, should also be included as an appendices of PBRER. For such studies discontinued to conduct at report interval, disconitunation reasons of the study should also be explained.

If significant safety concern is identified during the study, MAH and especially pharmacovigilance responsible immediatey inform related competent authorities in member-state countries, even if it is determined by predefined methods or the study is a

post-authorisation safety study. PBRERs should not be used as a primary communication method to submit final study reports or to inform any new information that would affect the evaluation of benefit/risk ratio to related competent authorities.

3.4.5. PBRER EU regional appendices, "Effectiveness of risk minimisation"subsection

Risk minimization activities are public health interventions aimed to prevent the occurrence of adverse drug reaction(s) related with an exposure to a medicinal product or minimize the severity if occurred. The success of the risk minimization activities in fulfilling these objectives should be evaluated during the lifecycle of the medicinal product to ensure the reduction of the burden of the adverse reactions and thus optimization of the general benefit/risk profile. In accordance with Section 2.5.16.5, assessment of the broad global experience will be reflected in the full report.

In addition to this subsection, especially in accordance with EU contents, an assessment of the effectiveness of the routine and/or additional risk minimization activities should also be provided. Findings of any studies conducted to evaluate the effectiveness of risk minimization activities or other official assesments in EU should also be included, if available. As a part of this critical evaluation, MAH should observe the factors contributing to success or weak sides of risk minimization activities. If it proves that a specific risk minimization strategy is not effective, alternative activities should be found out. In some cases, it could be judged that the risk minimization could not totally control the risks to assure the positive benefit/risk ratio and the medicinal product should have to be withdrawn from the market or should have to be restricted with patients in whom the benefits greater than the risks. A more detailed guideline will be issued as a separate module with regard to the monitoring of the effectiveness of risk minimization activities. In a principle, MAH should discriminate between the application success and intented result.

3.5. Requirements according to our country

Matters included in the EU-specific requirements section should also be prepared for our counry and archieved along with PBRER.

APPENDICES

Annex 1. Examples of summary tabulations for estimated exposure and adverse events/reactions

Table 2. Estimated Cumulative Subject Exposure from Clinical Trials

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

Treatment	Number of subjects
Medicinal product	
Comparator	
Placebo	

Table 3. – Cumulative Subject Exposure to Investigational Drug 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 Drug from Completed Clinical Trials by Racial Group

Racial group	Number of subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

Data from completed studies as of [date]

Table 5. Cumulative Exposure from Marketing Experience

Indica	Sex		Age (year)				Dose			Formul		Region				
	Male	Female	2 -≤16	>16 -65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	AB	Japan	Turkey	USA/Canada	Other
Total																
Depres																
Migrai																

Table 5 includes cumulative data obtained from month/day/year through month/day/year.

Table 6. Interval Exposure from Marketing Experience

Indica	Sex		Age (years)				Dose			Formul		Region				
	Male	Female	2 - ≤16	>16 - 65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	EU	Japan	Turkey	USA/Canada	Other
Depres																
Migrai																

Table 6 includes interval data obtained from month/day/year through month/day/year.

Table 7. Cumulative Tabulations of Serious Adverse Events occurred during Clinical Trials

System Organ Class (SOC) ~~Preferred Term (PT)~~	Investigational Product	Blinded	Active comparator	Placebo
Blood and lymphatic system	n	n	n	n
Anemia	n	n	n	n
Bone marrow necrosis	n	n	n	n
Cardiac Disturbances	n	n	n	n
Tachicardia	n	n	n	n
Ischemic cardiomyopathy	n	n	n	n

Table 8. Numbers of adver drug reacions coded with “obtained from the post-authorisation source*” and “preferred terms*”

SOC MedDRA PT	Spontaneous, including competent authority and literature (worldwide)					Non-interventional post-marketing study and reports from other solicited *	
	Serious		**Non serious**		**Total spontaneou**	**Serious**	
	Interv	**Cumul**	**Interv**	**Cumul**	**Cumulativ**	**In**	**Cumulativ**
<SOC							
<PT>							
<PT>							
<PT>							
<SOC							
<PT>							
<PT>							
<PT>							
<PT>							
<PT>							

*Post-authorisation non-interventional studies, reports collected from other requested sources and spontaneous BOGRs (eg; reports obtained from health professionals, consumers, competent authorities (global) and scientific literatures)
** Not contains interventional clinical studies.

Annex 2: Example of a tabular summary of safety signals that were ongoing or closed during the reporting interval

The following table is fictionalized for an imaginary drug.

Table 9. Tabular summary of safety signals that were ongoing or closed during the reporting interval

Reporting Interval: DD-MMM-YYYY to DD-MMM-YYYY

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	MMM/YYY	On going	MMM/YYY	Meta-analysis (published trials)	statistically significant increase in frequency	review meta-analysis and available data	pending
SJS	MMM/YYY	closed	MMM/YYY	Spontaneous case reports	Rash already an identified risk SJS not reported in pre authorisation clinical trials. 4 reports within 6 months of approval; plausible time to onset, no alternative reason.	targeted follow up of reports with site visit to one hospital. Full review of cases by marketing authorization holder dermatologist and literature searches	Reference summary information updated with a Warning and Precaution section. Planning of an effectiveness research for 6 months after the distribution of letters. RMP's update

Explanatory notes

Signal term

- A brief descriptive name of a medical concept for the signal. The description may evolve and be refined as the signal is evaluated. The concept and scope may, or may not, be limited to specific MedDRA terms, depending on the source of signal.

Date detected:

- Month and year the marketing authorization holder became aware of the signal

Status:

- Ongoing: Signal under evaluation at the data lock point of the PBRER. Provide anticipated completion date, if known.
- Closed: Signal for which evaluation was completed before the data lock point of the PBRER.

Note: A new signal of which the marketing authorization holder became aware during the reporting interval may be classified as closed or ongoing, depending on the status of signal evaluation at the data lock point of the PBRER.

Date closed (month/year):

- Month and year when the signal evaluation was completed.

Source of signal:

- Data or information source from which a signal arose (eg; spontaneous reports, clinical trial data, scientific literatures, non-clinical study results, or information requests or inquiries from a regulatory authority).

Reason for evaluation and summary of key data:

- A brief summary of key data and rationale for further evaluation

Action(s) taken or planned:

- State whether or not a specific action has been taken or is planned for all closed signals that have been classified as potential or identified risks. If any further actions are planned for newly or previously identified signals under evaluation at the data lock point, these should be listed. Otherwise leave blank for ongoing signals.

Annex 3. Cover page on PBRER's submission

PERIODIC BENEFIT-RISK EVALUATION REPORT
DRUG SUBSTANCE(S):<Name(s)>
ATC CODE/CODES: <Code(s)>

MEDICINAL PRODUCTS COMPROMISED:

Name(s) of the drug	Authorisation number/numbers	Registration date(s)	Marketing Authorisation Holder
<>	<>	<>	<>
<>	<>	<>	<>

DEVELOPMENT BIRTH DATE: <Date>

Period of this method: **From the date <date> to the date <date> (eg;data lock point)** Date of this report: **<Date>**

OTHER INFORMATION:
<Other determinants or expalanatory information depending on the request of marketing authorization holder>

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:
<Name>
<Address>

NAME AND CONTACT INFORMATION OF PHARMACOVIGILANCE RESPONSIBLE:
<Name, surname>
<Address>
<Phone number>
<Fax number>
<E-mail>

"I declare and commit the accuracy of the pharmacovigilance data."

SIGNATURE: <signature>

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