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Lebanese Guideline on Good Pharmacovigilance Practices (LGVP)

Module VII

Periodic Safety Update Report (PSUR)

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Table of content

Module VII – Periodic Safety Update Report (PSUR)

List of Tables

List of Abbreviations

CCDS:	Company Core Data Sheet
CCSI:	Company Core Safety Information
DIBD:	Development International Birth Date
EMA:	European Medicine Agency
EU:	European Union
EURD:	European Union Reference Dates
MA:	Marketing Authorization
MAH:	Marketing Authorization Holder
PBRER:	Periodic Benefit Risk Evaluation Report
PSUR:	Periodic Safety Update Report
QPPV:	Qualified Person for Pharmacovigilance
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics

VII. A. Introduction

Periodic Safety Update Reports (PSURs) are important pharmacovigilance documents that provide an evaluation of the risk-benefit balance of a medicinal product, to be submitted by Marketing Authorization Holders (MAHs) at defined time points during the post-authorization phase.

This Module provides guidance on the preparation, submission and assessment of PSURs.

MAHs should submit PSURs for their own medicinal products to the national competent authority in Lebanon, which in turn, should assess them to identify any new risk, changes in the risks, or changes in the risk-benefit balance of the product.

A PSUR assessment can determine if further investigations on a specific issue are needed, or if an action concerning the Marketing Authorization (MA) of products containing the same active substance or combination of active substances is necessary to protect public health (e.g. an update of the information provided to healthcare professionals and patients).

This Module outlines the scope, objectives, format and content of PSURs for medicinal products (described in section VII.B), and provides guidance on the purpose and requirements for the submission and assessment of PSURs for medicinal products by MAHs. PSURs for generic medicinal products are required to be submitted.

To note that the required format and content of PSURs in Lebanon presented in this Module are based on those described in the European Good Pharmacovigilance Practices, which in turn, are based on those for the Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH-E2C(R2) guideline (*refer to https://www.ema.europa.eu/en/ich-e2c-r2-periodic-benefit-risk-evaluation-report-scientific-guideline*).

The PBRER format replaces the PSUR format previously described in the ICH-E2C(R1). In line with the European Union (EU) legislation, the report is described as PSUR in the Lebanese GVP Modules.

Further, as this guideline was based on the European Good Pharmacovigilance Practices; the "list of EU reference dates" is adopted in this guideline as well. Hence, the PSURs submitted in Lebanon should follow the dates & frequency stated in the most updated version of this list (see section VII.C).

However, this does not undermine the right of the national competent authority in Lebanon to have additional or altered requirements; and multinational MAHs should be attentive to these requirements and take the necessary measures to comply with them.

VII.B. Structures and processes

VII.B.1. Objectives of the PSUR

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits

The PSUR is a tool for post-authorization evaluation at defined time points in the lifecycle of a product. The primary aim of a PSUR is to present a comprehensive analysis of the risk-benefit balance of a medicinal product, after consideration of emerging safety data. This new data may arise from post-authorization investigations of the medicinal product's profile after evaluation of new populations and endpoints that could not have been investigated in the pre-authorization clinical trials. This structured evaluation should be undertaken in the context of ongoing pharmacovigilance and risk management to facilitate optimization of the risk-benefit balance through effective risk minimization.

VII.B.2. Principles for the evaluation of the risk-benefit balance within PSURs and scope of the information to be included

Benefit-risk evaluation should be carried out throughout the lifecycle of the medicinal product to promote and protect public health and to enhance patient safety through effective risk minimization.

The **risk evaluation** should be based on all uses of the medicinal product. The scope includes evaluation of safety in real medical practice including use in unauthorized indications and use which is not in line with the product information. If use of the medicinal product is identified where there are critical gaps in knowledge for specific safety issues or populations, such use should be reported in the PSUR (e.g. use in pediatric population or in pregnant women). Sources of information on use outside authorization may include drug utilization data, information from spontaneous reports and publications in the literature.

The scope of the **benefit information** should include both clinical trial and real-world data in authorized indications.

The integrated benefit-risk evaluation should be performed for all authorized indications and should incorporate the evaluation of risks in all use of the medicinal product (including use in unauthorized indications).

The evaluation should involve:

1. Critically examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks, or contributed to the knowledge of previously identified risks;
2. Critically summarizing relevant new safety, efficacy and effectiveness information that could have an impact on the risk-benefit balance of the medicinal product;
3. Conducting an integrated benefit-risk analysis for all authorized indications based on the cumulative information available since the Development International Birth Date (DIBD), the date of first authorization for the conduct of an interventional clinical trial in any country. For the cases where DIBD that date is unknown or the MAH does not have access to data from the clinical development period, the earliest possible applicable date should be used as a starting point for the inclusion and evaluation of the cumulative information;
4. Summarizing any risk minimization actions that may have been taken or implemented during the reporting interval, as well as risk minimization actions that are planned to be implemented;
5. Outlining plans for signal or risk evaluations including timelines and/or proposals for additional pharmacovigilance activities.

VII.B.3. Principles for the preparation of PSURs

Unless otherwise specified by the national competent authority, the MAH should prepare a single PSUR for all its medicinal products containing the same active substance with information covering all the authorized indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorized under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen, should be presented in a separate section of the PSUR and any safety concerns should be addressed accordingly.

There might be exceptional scenarios where the preparation of separate PSURs might be appropriate, for instance, in the event of different formulations for entirely different indications. In this case, agreement

should be obtained from the national competent authority in Lebanon preferably at the time of authorization.

Case narratives should be provided in the relevant risk evaluation section of the PSUR where integral to the scientific analysis of a signal or safety concern. In this context, the term case narratives refers to clinical evaluations of individual cases.

When data received by the MAH from a partner might contribute meaningfully to the safety, benefit and/or benefit-risk analyses and influence the reporting MAH's product information, these data should be included and discussed in the PSUR.

Each PSUR should include interval as well as cumulative data. As the PSUR should be a single stand-alone document for the reporting interval, based on cumulative data, summary bridging reports and addendum reports, introduced in ICH-E2C(R1) guideline, will not be accepted.

VII.B.4. Reference information

Risk minimization activities evaluated in the PSUR include updates to the product information.

The reference product information for the PSUR should include "core safety" and "authorized indications" components. In order to facilitate the assessment of benefit and risk-benefit balance by indication in the evaluation sections of the PSUR, the reference product information document should list all authorized indications in the country. The basis for the benefit evaluation should be the baseline important efficacy and effectiveness information summarized in the PSUR section VII.B.5.17.1 ("Important baseline efficacy and effectiveness information").

Information related to a specific indication, formulation or route of administration should be clearly identified in the reference product information.

MAHs can refer to the following options to select the most appropriate reference product information for a PSUR:

- Company Core Data Sheet (CCDS):
  - It is common practice for MAHs to prepare their own company core data sheet which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The **core safety information** contained within the CCDS is referred to as the

company core safety information (**CCSI**). A practical option for the purpose of the PSUR is for each MAH to use the CCDS in effect at the end of the reporting interval, as reference product information for both the risk sections of the PSUR as well as the main authorized indications for which benefit is evaluated;

- When the CCDS does not contain information on authorized indications, the MAH should clearly specify which document is used as reference information for the authorized indications in the PSUR.

- Other sources of information:
  - In the absence of CCDS or CCSI for a given product (e.g. for generics, or when the product is authorized in only one country or region), the MAH should clearly specify the reference information being used. This may comprise national information. The document used as reference information should be included as an appendix to the PSUR;
  - The reference product information should be dated and version controlled.

Whenever new safety information is obtained during the reporting interval, the MAH should continuously evaluate the need to revise the reference product information and ensure that significant changes are described in PSUR section VII.B.5.4 ("Changes to the reference safety information") and discussed if applicable in PSUR section VII.B.5.16 ("Signal and risk evaluation"). These changes may include:

- Changes to the contraindications, warnings/precautions sections;
- Addition to 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.

When new information on safety that could warrant changes to the authorized product information has been added to the reference safety information during the period from the data lock point to the submission of the PSUR, this information should be included in the PSUR section VII.B.5.14 ("Late-breaking information") if feasible.

The data lock points included in the "list of EU references dates" enable the synchronization of PSURs submission and permit the single assessment on the national level. These data lock points are fixed on a certain date of the month, and should be used to determine the submission date of the PSUR.

The MAH should provide in the national appendix (see section VII.C.5), information on any final, ongoing and proposed changes to the national or local authorized product information.

VII.B.5. Format and contents of the PSUR

The PSUR should be based on all available data and should focus on new information which has emerged since the data lock point of the last PSUR. Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment. Because clinical development of a medicinal product frequently continues following MA, relevant information from post-authorization studies or clinical trials in unauthorized indications or populations should also be included in the PSUR. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of other data associated with off-label use, such knowledge should be reflected in the risk evaluation where relevant and appropriate. The PSUR should provide summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the MA. Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSURs include the following:

- Non-clinical studies;
- Spontaneous reports (e.g. on the MAH's safety database);
- Active surveillance systems (e.g. sentinel sites) ;
- Investigations of product quality;
- Product usage data and drug utilization information;
- Clinical trials, including research in unauthorized indications or populations;
- Observational studies, including registries;
- Patient support programs;
- Systematic reviews and meta-analyses;
- MAHs sponsored websites;
- Published scientific literature or reports from abstracts, including information presented at scientific meetings;
- Unpublished manuscripts;
- Licensing partners, other sponsors or academic institutions and research networks;
- Medicines authorities (worldwide).

The above list is not intended to be all inclusive, and additional data sources may be used by the MAH to present safety, efficacy and effectiveness information in the PSUR and to evaluate the risk-benefit balance, as appropriate to the product and its known and emerging important benefits and risks. When desired by

the MAH, a list of the sources of information used to prepare the PSUR can be provided as an appendix to the PSUR.

A PSUR should be prepared following the full modular structure set out below in this GVP Module [Part I, Part II and Part III (section 1 to section 20)].

For the purposes of this Module, sources of information include data regarding the active substance(s) included in the medicinal product, or the medicinal product that the MAH may reasonably be expected to have access to and that are relevant to the evaluation of the safety, and/or risk-benefit balance. It is therefore recognized that while the same format (as defined in this GVP Module) should be followed for all products, the extent of the information provided may vary where justified according to what is accessible to the MAH. For example, for a MAH-sponsored clinical trial, there should be access to patient level data while for a clinical trial not sponsored by the MAH, only the published report may be accessible.

The level of detail provided in certain sections of the PSUR should depend on known or emerging important information on the medicinal product 's benefits and risks. This approach is applicable to those sections of the PSUR in which there is evaluation of information about safety, efficacy, effectiveness, safety signals and risk-benefit balance. When preparing the PSUR, the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)) on PBRER should also be applied. Guidance on the titles, order and content of the PSUR sections is provided in sections VII.B.5.1. to VII.B.5.20.

When no relevant information is available for any of the sections, this should be stated under the section, but do NOT omit any section. The PSUR should follow the below design:

- Part I: Title page including signature
- Part II: Executive Summary
- Part III: Table of Contents
    1. Introduction
    2. Worldwide marketing authorization status
    3. Actions taken in the reporting interval for safety reasons
        a. Actions related to investigational uses
        b. Actions related to marketing experience
    4. Changes to reference safety information
    5. Estimated exposure and use patterns
        5.1. Cumulative subject exposure in clinical trials

18.1. Benefit-risk context – Medical need and important alternatives

18.2. Benefit-risk analysis evaluation

19. Conclusions and actions

20. Appendices to the PSUR.

The MAH is required to make direct use of the EU Guideline on Good Pharmacovigilance Practices, Module VII on PSURs.

The structure and content for the PSUR should be formulated in accordance with the details provided in Module VIII of the European Medicines Agency (EMA)'s Guideline on good pharmacovigilance practices, accessed through the following link: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#final-gvp-modules-section.

VII.B.6. Training of staff members on the PSUR process

For all organizations, it is the responsibility of the person responsible for the pharmacovigilance system to ensure that the personnel, including pharmacovigilance, medical and quality personnel involved in the preparation, review, quality control, submission and assessment of PSURs are adequately qualified, experienced and trained according to the applicable guidelines (e.g. ICH E2C(R2) and this GVP Module VII. When appropriate, specific training for the different processes, tasks and responsibilities relating to the PSUR should be in place.

Training to update knowledge and skills should also take place as necessary.

Training should cover legislation, guidelines, scientific evaluation and written procedures related to the PSUR process.

Training records should demonstrate that the relevant training was delivered prior to performing PSUR-related activities.

VII.C. Operations of PSURs in Lebanon

VII.C.1. Routine submission of PSURs in Lebanon

Since the main objective of a PSUR is to present a comprehensive analysis of the risk-benefit balance of the medicinal product taking into account all new or emerging information from all countries, the PSUR can be described as a global pharmacovigilance document. The required format and content of PSURs in Lebanon are based on those for the PBRER described in the ICH-E2C(R2) guideline.

Therefore, for the purpose of not reinventing the wheel and as this guideline was based on the European Good Pharmacovigilance Practice; the "list of EU reference dates" (EURD) is adopted in the context of this guideline. Hence the PSURs submitted in Lebanon should follow the dates & frequency stated in the most updated version of the list; this does not undermine the right of the competent authority in Lebanon to request the submission of PSURs at any time or to change as appropriate the submission frequency on the national level.

VII.C.1.1. Summary of the list of European Union reference dates and frequency of submission of PSURs

The EURD list is a comprehensive list of active substances and combinations of active substances contained in medicinal products subject to different MAs, together with the corresponding EU reference dates, frequencies for submission of periodic safety update reports and related data lock points (the date designated as the cut-off date for data to be included in a PSUR).

The EURD list aims to standardize the timing and frequency of PSUR submissions for the same active substances or combinations. It prioritizes submissions based on risk factors, new product information, significant product changes, vulnerable patient populations, and other safety considerations, with the list subject to updates based on emerging information and changes in criteria. This list will become effective through a regulation issued by the competent authority in Lebanon.

The EU reference dates list can be accessed through the following link:

https://www.ema.europa.eu/documents/other/list-european-union-reference-dates-frequency-submission-periodic-safety-update-reports-psurs_en-0.xlsx

VII.C.1.2. Application of the "EURD" to the routine submission of PSURs in Lebanon

VII.C.1.2.1. Submission of PSURs for medicinal products: general requirement

For products included in the EURD list, MAHs are expected to follow the dates and frequency stated in the most updated version of the list when submitting PSURs for the respective products containing those active substances or combinations.

Unless otherwise specified in the EURD list, or agreed with the competent authority, a single PSUR should be prepared for all medicinal products containing the same active substance and authorized for one MAH.

VII.C.1.2.2. Submission of PSURs in case of active substances not included in the EURD list

For medicinal products containing an active substance or a combination of active substances **NOT** included in the EU reference dates list, PSURs should be submitted (if there is no specific concern about the safety) based on the following standard submission schedule to define the frequency and date of PSURs submission for those substances:

- At 6 months' intervals once the product is authorized, even if it is not marketed;
- Once a product is marketed, PSUR submission every 6 months should be continued following initial placing on the market for 2 years, then once a year for the following 2 years and thereafter at 3-yearly interval.

VII.C.1.2.3. Medicinal products with conditioned PSURs submission frequency in the marketing authorization

Currently, in Lebanon, when a Marketing Authorization (MA) is granted for a medicinal product, there is no requirement or condition imposed regarding the specific timing or frequency for submitting Periodic Safety Update Reports (PSURs).

VII.C.1.2.4. Submission of PSURs for generic and well-established use of medicinal products

As a general rule, PSURs for generic and well-established use medicinal products are required to be submitted in Lebanon.

The national competent authority will enact regulation governing the PSURs submission details of such products.

VII.C.1.2.5. Submission of PSURs for fixed dose combination products

Unless otherwise specified in the "list of EU reference dates and frequency of submission", if the substance that is the subject of the PSUR is also authorized as a component of a fixed combination medicinal product, the marketing authorization holder should either submit a separate PSUR for the combination of active substances authorized for the same marketing authorization holder with cross-references to the single-substance PSUR(s), or provide the combination data within one of the single-substance PSURs.

VII.C.1.2.6. Publication of the list

The list is expected to be published monthly by the European Medicines Agency (EMA). The list should also then be adopted and become effective through a regulation issued by the competent authority in Lebanon.

The EU reference dates list can be accessed through the following link: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs#submission-requirements-and-eu-reference-dates:-the-eurd-list-section.

VII.C.2. Submission of PSURs on demand of the national competent authority (ad hoc request)

In addition to the routine PSUR submission, MAHs should submit PSURs immediately upon ad hoc request from the competent authority in Lebanon. When the timeline for submission has not been specified in the request, to be submitted within 90 calendar days of the data lock point.

VII.C.3. Timelines for PSUR submission

Each MAH should be responsible for submitting PSURs for its own products to the national competent authority according to the following timelines:

- Within 70 calendar days of the data lock point (day 0) for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and
- Within 90 calendar days of the data lock point (day 0) for PSURs covering intervals greater than 12 months;

- The timeline for the submission of ad hoc PSURs requested by the national competent authority will normally be specified in the request, otherwise the ad hoc PSURs should be submitted within 90 calendar days of the data lock point.

VII.C.4. Relationship between PSUR and risk management plan

The general relationship between the Risk Management Plan (RMP) and the PSUR is described in Module V, while an overview of the common RMP/PSUR modules is provided in below.

During the preparation of a PSUR, the MAH should consider whether any identified or potential risks discussed within the PSUR is important and requires an update of the RMP.

In these circumstances, updated revised RMP including the new important safety concern should be submitted with the PSUR and assessed in parallel. If important safety concerns are identified by the national competent authority during the assessment of a PSUR and no updated RMP or no RMP has been submitted, recommendations should be made to submit an update or a new RMP within a defined timeline.

VII.C.4.1. PSUR and risk management plan – common modules

The proposed modular formats for the PSUR and the RMP aim to address duplication and facilitate flexibility by enabling common PSUR/RMP sections to be utilized interchangeably across both reports. Common sections with the above-mentioned reports are identified in Module V, Table V.2.

VII.C.5. National appendix requirements for PSURs

The scientific evaluation of the risk-benefit balance of the medicinal product included in the PSUR detailed in section VII.B.5. should be based on all available data, including data from clinical trials in unauthorized indications and populations.

The multinational MAHs should submit the PSUR with relevant national appendix as well as the EU-regional appendix of the PSUR submitted in EU as appropriate.

This national appendix should include the following:

VII.C.5.1. PSUR national appendix, sub-section "Current national product information"

- This section should contain a clean copy of the national product information approved in Lebanon and which is in effect at the end of the reporting interval;
- A clean copy of all versions of the reference product information in effect at the end of the reporting interval (e.g. different formulations included in the same PSUR) were provided in appendix 1 of the PSUR (see section VII.B.5.20.).

  When a meaningful difference exists between this reference safety information (e.g. CCDS or CCSI) and the safety information in the national product information (national Summary of Product Characteristics (SmPC) and package leaflet) approved in Lebanon, a brief comment should be prepared by the company, describing these local differences with track change version;
- The reference product information document should list all authorized indications in ICH countries or regions. When there are additional locally authorized indications in Lebanon, these indications may be either added to the reference product information or handled in the national appendix as considered most appropriate by the marketing authorization holder and the competent authority in Lebanon.

VII.C.5.2. PSUR national appendix, sub-section "Proposed product information"

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

Within the PSUR, the MAH is required to consider the impact of the data and evaluations presented within the report, on the MA. Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the MAH should draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved SmPC(s) for the product(s) for which the PSUR is submitted.

In this sub-section, the MAH should provide the proposals for product information (SmPC and package leaflet) based on the above-mentioned evaluation. These should be based on all authorized indications in Lebanon.

A track change version of the proposed SmPCs and package leaflets based on the assessment and conclusions of the PSUR should be provided.

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

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

VII.C.5.3. PSUR national appendix, sub-section "Proposed additional pharmacovigilance and risk minimization activities"

This sub-section should include proposals for additional pharmacovigilance and additional risk minimization activities based on the conclusions and actions of the PSUR, including a statement of the intention to submit a RMP or an updated RMP when applicable.

VII.C.5.4. PSUR national appendix, sub-section "Summary of ongoing safety concerns"

In order to support the information provided in the PSUR section 16.1 "Summary of safety concerns" (see section VII.B.5.16.1.), Table "Summary – Ongoing safety concerns" should be included in this PSUR sub-section. This table should be extracted from the version of RMP available at the beginning of the PSUR reporting interval (see Module V).

VII.C.5.5. PSUR national appendix, sub-section "Worldwide marketing authorization status table"

In addition to the PSUR section worldwide MA status (VII.B.5.2.), a cumulative table with the following information should be provided for any indication, for all countries where a regulatory decision about MA has been made.

Below is a cumulative table; accordingly, entries must not be removed from the table e.g. if the product is no more authorized; instead the MAH should change the relevant information in the table. Fictious examples for different cases are shown in the Table VII.1. below.

Typically, indications for use, populations treated (e.g. children vs. adults) and dosage forms will be the same in many or even most countries where the product is authorized. However, when there are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures.

If more convenient and useful, separate regulatory status tables for different product uses or forms should be utilized.

Table 1: Worldwide marketing authorization status table

First approval date/application date	Country	Local trade name	Dosage form	Indication	Current authorization status and date	Date	Current marketing status and date	Application refusal (if any)	Refusal date	Comments/explanation
2-3-1990	UK	<name>	Tablet	<indication>	authorized	2-3-1995 renewal	Marketed 7-9-1990			
9-1-1991	France	<name>	Tablet	<indication>	withdrawn	4-6-2000				<reason for withdrawal>
4-9-1991	KSA	<name>	Tablet	<indication>	suspended	5-8-1998				<reason for suspension>
4-5-2005	Japan	<name>	Capsule	<indication>				refused	9-11-2005	<reason for refusal>
3-1-2007	Egypt	<name>	Tablet	<indication>	authorized		Not marketed 4-8-2010			<reason for not marketing>
1-3-2009	Jordan	<name>	Tablet	<indication>	authorized		Never launched			<reason for not launching>

Patient exposure in the Lebanon: information about the cumulative and interval patient exposure from marketing experience in Lebanon

National data in Summary tabulation: Cumulative and interval summary tabulations for ADRs (serious and non-serious) received in Lebanon form different post-marketing data sources

VII.C.6. Quality and record management systems for PSURs at the level of MAHs

Specific quality system procedures and processes should be in place in order to ensure the update of product information by the MAH in the light of scientific knowledge, including the assessments and recommendations.

It is the responsibility of the MAH to check regularly the list of EU reference dates and frequency of submission.

Systems should be in place to schedule the production of PSURs according to:

- The list of EU reference dates and frequency of PSURs submission; or
- The conditions laid down in the national MA; or
- As defined by the national competent authority as applicable (without any conditions in their MA or not included in the list of EU references dates and frequency of submission; or
- Ad hoc requests for PSURs by the national competent authority.

For those medicinal products where the submission of an RMP is not required, the MAH should maintain on file a specification of important identified risks, important potential risks and missing information in order to support the preparation of the PSURs.

The MAH should have procedures in place to follow the requirements established by the competent authority for the submission of PSURs.

The Qualified Person for Pharmacovigilance (QPPV) should be responsible for the establishment and maintenance of the pharmacovigilance system and therefore should ensure that the pharmacovigilance system in place enables the compliance with the requirements established for the production and submission of PSURs. In relation to the medicinal products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV in relation to PSURs should include:

- Ensuring the necessary quality, including the correctness and completeness, of the data submitted in the PSURs;
- Ensuring full response according to the timelines and within the procedure agreed (e.g. next PSUR) to any request from the competent authority related to PSURs;
- Awareness of the PSUR and assessment report conclusions and the decisions of the competent authority in order to ensure that appropriate action takes place.

The record retention times for product-related documents in Module I, also apply to PSURs and source documents related to the creation of PSURs, including documents related to actions taken for safety

reasons, clinical trials and post-authorization studies, relevant benefit information and documents utilized for the calculation of patient exposure.

The responsibilities for preparation and submission of PSURs should be clearly specified in written agreements when MAHs are involved in contractual arrangements, and when the preparation is delegated to third parties, explicit procedures and detailed agreements should exist between the MAH and third parties.

VII.D. Appendices

Appendix 1. Examples of tabulations for estimated exposure and adverse events/reactions data

Marketing authorization holders can modify these examples tabulations to suit specific situations, as appropriate.

Table VII.2. Estimated cumulative subject exposure from clinical trials

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

Treatment	**Number of Subjects**
Medicinal product	
Comparator	
Placebo	

Table VII.3. Cumulative subject exposure to investigational drug from completed clinical trialsby age and sex

Number of subjects			
Age range	Male	Female	Total

Data from completed trials as of <*insert date*>

Table VII.4. Cumulative subject exposure to investigational drug from completed clinical trialsby racial/ethnic group

Racial/ethnic group	**Number of subjects**
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

Data from completed trials as of <*insert date*>

Table VII.5. **Cumulative** exposure from marketing experience

Indication	**Sex**		**Age (years)**				**Dose**			**Formulation**		**Region**					
	Male	Female	2 to ≤16	>16 to 65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	Arab country concerned	EU	Japan	Colombia	US/Canada	Other
Overall																	
e.g. Depression																	
e.g. Migraine																	

Table VII.5 includes cumulative data obtained from day/month/year throughout day/month/year, where available

Table VII.6. Interval exposure from marketing experience

Indication	**Sex**		**Age (years)**				**Dose**			**Formulation**		**Region**					
	Male	Female	2 to ≤16	>16 to 65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	Arab country concerned	EU	Japan	Colombia	US/Canada	Other
e.g. Depression																	
e.g. Migraine																	

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

Table VII.7. Cumulative tabulation of serious adverse events from clinical trials

System Organ Class Preferred Term	**Investigational medicinal product**	**Blinded**	**Active comparator**	**Placebo**
Blood and lymphatic system disorders				
Anemia				
Bone marrow necrosis				
Cardiac disorders				
Tachycardia				
Ischemic cardiomyopathy				
<SOC>				
<PT>				

Table VII.8. Numbers of adverse reactions by preferred term from post-authorization sources*

MedDRA SOC PT	**Spontaneous, including medicines authorities(worldwide) and literature**					**Non-interventional post-marketing study and reports from other solicited sources ****	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
<SOC 1>							
<PT>							
<PT>							
<SOC 2>							
<PT>							
<PT>							

* Non-interventional post-authorization studies, reports from other solicited sources and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, medicines authorities (worldwide), and scientific literature)

** This does not include interventional clinical trials

Appendix 2. Example of tabular summary of safety signals thatwere ongoing or closed during the reporting interval

Table VII.9. The tabular summary below is a fictitious example of tabular summary of safety signals 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/YYYY	Ongoing	MMM/YYYY	meta-analysis (published trials)	Statistically significant increase in frequency	Review meta-analysis and available data	Pending
SJS	MMM/YYYY	Closed	MMM/YYYY	Spontaneous case reports	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 reports within 6 months of authorisation; plausible time to onset and no possible alternative causes.	Targeted follow up of reports with site visit to one hospital. Full review of cases by MAH dermatologist and literature searches	RSI updated with a warning and precaution DHPC sent Effectiveness survey planned 6 months post DHPC. RMP updated

Explanatory notes:

- **Signal term:**

A brief descriptive name of a medical concept for the signal. This may evolve and be refined asthe signal is evaluated. The concept and scope may or may not be limited to specific MedDRA term(s), 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 PSUR. Anticipated completion date, if known, should be provided.

Closed: Signal for which evaluation was completed before the data lock point of the PSUR.

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

- **Date closed:**

Month and year when the signal evaluation was completed.

- **Source of signal:**

Data or information source from which a signal arose. Examples include, but may not be limitedto, spontaneous reports, clinical trial data, scientific literature, and non-clinical study results, or information request or inquiries from a medicines authority (worldwide).

- R**eason 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 havebeen 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.

Appendix 3. Template: Cover page of periodic safety update report(PSUR)

PERIODIC SAFETY UPDATE REPORT

for

ACTIVE SUBSTANCE(S): <INN>

ATC CODE(S): <Code(s)>

MEDICINAL PRODUCTS COVERED:

Invented name of the medicinal product(s)	Marketing authorization number(s)	Date(s) of authorization *(Underline the International Birth Date)*	Marketing authorizationholder
<>	<>	<>	<>
<>	<>	<>	<>

INTERNATIONAL BIRTH DATE (IBD): <Date>

EUROPEAN UNION REFERENCE DATE (EURD): <Date>

INTERVAL COVERED BY THIS REPORT:

From <date> to <date (i.e. data lock point)>

DATE OF THIS REPORT:

<Date>

OTHER INFORMATION:

<Other identifying or clarifying information if necessary>

MARKETING AUTHORIZATION HOLDER'S NAME AND ADDRESS:

<Name>

<Address>

<E-mail address> **(contact person for the PSUR procedure)**

NAME AND CONTACT DETAILS OF THE QPPV:

<Name>

<Address>

<Telephone number>

<Fax number>

<E-mail address>

SIGNATURE (QPPV or designated person): <Signature>