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Lebanese Guideline on Good Pharmacovigilance Practices (LGVP)

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Module VIII

Post-Authorization Safety Study (PASS)

Version 1.0

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Table of content

Module VIII - Post-Authorization Safety Study (PASS)

List of Abbreviations

EMA: European Medicines Agency

ENCePP: European Network of Centers for Pharmacoepidemiology and Pharmacovigilance

GPP: Guidelines for Good Pharmacoepidemiology Practices

IRB/IEC: Institutional Review Board/Independent Ethics Committee

LBCTR: Lebanon Clinical Trials Registry

MAH: Marketing Authorization Holder

MoPH: Ministry of Public Health

MR: Ministerial Resolution

PASS: Post-Authorization Safety Study

PSUR: Periodic Safety Update Report

RMP: Risk Management Plan

VIII.A. Introduction

A Post-Authorization Safety Study (PASS) is defined as any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures.

A PASS may be initiated, managed or financed by a Marketing Authorization Holder (MAH) voluntarily, or pursuant to an obligation imposed by the national competent authority.

This Module concerns PASS which are clinical trials or non-interventional studies and does not address nonclinical safety studies.

A PASS is non-interventional if the following requirements are cumulatively fulfilled:

- The medicinal product is prescribed in the usual manner (including same approved indication, population, dose, and combination as previously studied in clinical trials) in accordance with the terms of the marketing authorization;
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.
- Otherwise, the study is to be considered interventional clinical trial.

Non-interventional studies include:

- Database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort or other study designs making secondary use of data);
- Those involving primary data collection (e.g., prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met.

If a PASS is a clinical trial (i.e., interventional study); the Ministerial Resolution MR #1159/2014 that covers the legal provisions for research submission including requirements for clinical trials/studies/researches approval, and the Ministerial Resolution MR #141/2016 regarding the procedure for authorizing the

national Institutional Review Board/Independent Ethics Committee (IRB/IEC) (both issued by the Ministry of Public Health (MoPH)) shall be followed.

The above-mentioned ministerial resolutions can be accessed through the following links:

https://moph.gov.lb/userfiles/files/HealthCareSystem/Pharmaceuticals/ClinicalTrial/Decision1159-2014.pdf

https://moph.gov.lb/userfiles/files/HealthCareSystem/Pharmaceuticals/ClinicalTrial/Decision141-2016.pdf.

The purposes of this Module are to:

- Provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by MAHs voluntarily or pursuant to an obligation imposed by the national competent authority (section VIII.B.);
- Describe procedures whereby the national competent authority may impose to a MAH an obligation to conduct a clinical trial or a non-interventional study (section VIII.C.2.), and the impact of this obligation on the risk management system (section VIII.C.3);
- Describe procedures that apply to non-interventional PASS imposed as an obligation for the protocol oversight and reporting of results (section VIII.C.4.) and for changes to the marketing authorization following results (section VIII.C.5.).

VIII.B. Structures and processes

VIII.B.1. Scope

The guidance in section VIII.B. applies to non-interventional PASS which are initiated, managed or financed by a MAH and conducted in Lebanon.

This guidance applies to studies that involve primary collection of safety data directly from patients and healthcare professionals and those that make secondary use of data previously collected from patients and healthcare professionals for another purpose.

VIII.B.2. Terminology

- Date at which a study commences: date of the start of data collection.
- Start of data collection: the date from which information on the first study subject is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts. Simple counts in a database to support the development of the study protocol, for example, to inform the sample size and statistical precision of the study, are not part of this definition.
- End of data collection: the date from which the analytical dataset is completely available
- Analytical dataset: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.
- Substantial amendment to the study protocol: *Any amendment to the protocol that is likely to impact the safety, physical or mental well-being of study participants, or that may influence the study results and their interpretation, must be considered. This includes changes to the primary or secondary objectives, study population, sample size, study design, data sources, methods of data collection, definitions of key variables (such as the main exposure, outcome, or confounders), or the statistical analysis plan as described in the study protocol.*

VIII.B.3. Principles

A post-authorization study should be classified as a PASS when it has one of the following objectives:

- To quantify potential or identified risks;
- To evaluate the risks of a medicinal product used in a patient population for which safety information is limited or missing (e.g., pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);
- To evaluate the risks of a medicinal product after long-term use;
- To provide evidence about the absence of risks;
- To assess patterns of drug utilization that add knowledge regarding the safety of the medicinal product (e.g., collection of information on indication, off-label use, dosage, co-medication or medication errors) in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern);
- To measure the effectiveness of a risk minimization measure.

Whereas the PASS design should be appropriate to address the study objective(s), the classification of a post-authorization study as a PASS is not constrained by the type of design chosen as long as it fulfils the criteria set above. For example, a systematic literature review or a meta-analysis may be considered as PASS depending on its aim.

The guidelines below provide relevant scientific guidance that should be considered by MAHs and investigators during the development of the study protocol.

- *The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP): https://www.encepp.eu/standards_and_guidances/index.shtml;*
- *Guidelines for Good Pharmacoepidemiology Practices (GPP): https://www.pharmacoepi.org/resources/policies/guidelines-08027*

To note that non-interventional PASS should not be performed where the act of conducting the study promotes the use of a medicinal product.

VIII.B.4. Study registration

In order to support transparency in all non-interventional PASS and to facilitate the exchange of pharmacovigilance information between the MAH and the NCA (Pharmacy Service, the LNPVP, and other concerned departments), marketing authorization holders (MAHs) should notify these entities of all non-interventional PASS required in the agreed risk management plan or conducted voluntarily, whether in Lebanon or abroad.

For a non-interventional PASS conducted in Lebanon, the study protocol should be submitted to an authorized Institutional Review Board (IRB) for ethical review and exemption, if applicable. Following IRB review, the study should be registered in the Lebanon Clinical Trials Registry (LBCTR). The MAH should inform the NCA (Pharmacy Service, the LNPVP, and other concerned departments) of both the IRB outcome and the LBCTR registration status.

The LBCTR is an online primary registry of clinical trials being undertaken in Lebanon. It will allow registration for investigational (mandatory for some types of interventional studies) as well as observational studies (optional). LBCTR is accessed through the following link for more details concerning the registration procedure for a specific type of study undertaken by MAHs: *https://lbctr.moph.gov.lb/LBCTR/*.

Finally, non-interventional PASS should be exempted by an Institutional Review Board.

VIII.B.5. Study protocol

All PASS must have a written study protocol before the study commences.

The study should follow a scientifically sound protocol developed by individuals with appropriate scientific background and experience. Where present, national requirements shall be followed to ensure the well-being and rights of the participants (see MR#1159/2014).

The MAH is required to submit the study protocol to an authorized Institutional Review Board (IRB) in Lebanon for ethical review and, if applicable, exemption. Once reviewed by the IRB, the national competent authority (Pharmacy Service, the LNPVP, and other concerned departments) should be informed of the IRB's decision and the final version of the protocol. Approval is typically issued by the IRB, while the NCA is notified for regulatory and pharmacovigilance follow-up.

In order to ensure compliance of the MAH with its pharmacovigilance obligations, the Qualified Person responsible for Pharmacovigilance (QPPV) or the Local Safety Responsible (LSR) (see Module I) should be involved in:

For Local Industry:

The Local QPPV is expected to be involved in the protocol clearance process to ensure that:

1. The study adequately addresses relevant safety concerns.
2. The requirements of the Lebanese Good Pharmacovigilance Practices (LGVP) are appropriately applied.

For Multinational MAHs:

The Local Safety Representative (LSR) should be informed of any study conducted within the country. While the LSR is typically not part of the protocol approval process, they should be made aware of any national post-authorization safety studies (PASS) being implemented.

VIII.B.5.1. Format and content of the study protocol

The format and content of the study protocol should follow the format described below:

- Title;
- MAH;
- Responsible parties;

- Abstract;
- Amendments and updates;
- Milestones;
- Rationale and background;
- Research methods;
- Protection of human subjects;
- Management and reporting of adverse reactions;
- Plans for disseminating and communicating study results;
- References.

For more details, refer to Module VIII of the European Medicines Agency (EMA)'s Guideline on good pharmacovigilance practices, through the following link: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#final-gvp-modules-section

VIII.B.5.2. Substantial amendments to the study protocol

The study protocol should be amended and updated as needed throughout the course of the study.

Any substantial amendments to the protocol after the study start should be documented in the protocol in a traceable and auditable way including the dates of the changes. If changes to the protocol lead to the study being considered an interventional clinical trial, the national competent authority (Pharmacy Service, the LNPVP, and other concerned departments) should be informed immediately and the study shall subsequently be conducted in accordance with the aforementioned ministerial resolutions accessed through the links below:

https://moph.gov.lb/userfiles/files/HealthCareSystem/Pharmaceuticals/ClinicalTrial/Decision1159-2014.pdf

https://moph.gov.lb/userfiles/files/HealthCareSystem/Pharmaceuticals/ClinicalTrial/Decision141-2016.pdf.

VIII.B.6. Reporting of pharmacovigilance data to the national competent authority

VIII.B.6.1. Data relevant to the risk-benefit balance of the product

The MAH shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the medicinal product concerned. Any new information that may affect the risk-benefit balance of the medicinal product should be communicated immediately (i.e. once received by the local operating company) in writing as an emerging safety issue to the NCA (Pharmacy Service, the LNPVP, and other concerned departments). Information affecting the risk-benefit balance of the medicinal product may include an analysis of adverse reactions and aggregated data. This communication should not affect information on the result of the study and should be provided by means of PSURs (see Module VII) and in the Risk Management Plan (RMP) updates (see Module V) where applicable.

VIII.B.6.2. Reporting of adverse reactions/adverse events

Individual cases of suspected adverse reactions should be reported to national competent authority in accordance with the applicable regulations and guidelines discussed in Module VI. Adverse events/adverse reactions collected in studies with primary and secondary data collection should be recorded and summarized in the interim safety analysis and in the final study report. Procedures for the collection, management (including a review by the MAH if appropriate), and reporting of suspected adverse reactions/adverse events should be summarized in the study protocol. If appropriate, reference can be made to the pharmacovigilance system master file (see Module II), but details specific to the study should be described in the study protocol.

VIII.B.6.3. Study reports

VIII.B.6.3.1. Progress report and interim report of study results

The progress report is meant to document the progress of the study, for example, the number of patients who have entered the study, the number of exposed patients or the number of patients presenting the

outcome, problems encountered, and deviations from the expected plan. The progress report may include an interim report of study results.

The timing of the progress reports should be agreed on with the national competent authority and specified in the study protocol when they have been agreed before the study commences. Study progress should also be reported in any Periodic Safety Update Reports (PSURs) (see Module VII) and RMP updates (see Module V), where applicable.

After review of the report, additional information may be requested.

VIII.B.6.3.2. Final study report

The final study report should be submitted as soon as possible within 12 months of the end of data collection.

If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.

The information to be included in the final study report should follow the format described below:

- Title;
- Abstract;
- MAH name and address;
- Investigators;
- Milestones;
- Rationale and background;
- Research question and objectives;
- Amendments and updates to the protocol;
- Research methods;
- Results;
- Discussion;
- Other information;
- Conclusions;
- References.

For more details, refer to Module VIII of the EMA's Guideline on good pharmacovigilance practices, through the following link: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#final-gvp-modules-section.

VIII.B.7. Quality systems, audits and inspections

The MAH shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.

For PASS imposed as an obligation, the MAH shall ensure that the analytical dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection. This provision should also be applied to PASS voluntarily initiated, managed or financed by the MAH. To note, PASS records must be retained for a period of five years after the documents are deemed obsolete, as specified in Module I.

VIII.C. Operations of post-authorization safety studies in Lebanon

VIII.C.1. Scope

Provisions in section VIII.C. refer specifically to PASS initiated, managed or financed by MAHs pursuant to obligations imposed by the national competent authority in Lebanon.

Sections VIII.C.2. and VIII.C.3. apply to **both interventional and non-interventional PASS**.

Sections VIII.C.4. and VIII.C.5. apply to **non-interventional PASS**.

VIII.C.2. Procedure for imposing post-authorization safety studies

PASS pursuant to an obligation imposed by the national competent authority are:

VIII.C.2.1: Situations Where the Conduct of a PASS May Be Mandated by Competent Authority

The conduct of any PASS may be imposed by the competent authority during one of the below situations:

a. Request for a PASS as part of the initial marketing authorization application:

A marketing authorization may be granted by the national competent authority subject to the conduct of a PASS.

b. Request for a PASS during a post-authorization regulatory procedure:

The need for a PASS could be identified by the national competent authority during a post-authorization regulatory procedure, for example, a variation to a marketing authorization.

c. Request for a PASS due to an emerging safety concern:

After the granting of the marketing authorization, the national competent authority, where applicable, may impose on the MAH an obligation to conduct a PASS if there are concerns about the risk of the authorized medicinal product, for example, following evaluation of a safety signal (see EMA GVP, Module IX) link below:

https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/good-pharmacovigilance-practices-gvp).

This obligation shall be duly justified based on benefit-risk considerations, shall be notified in writing and shall include the objectives and timeframe for the submission and conduct of the study.

The request may also include recommendations on key elements of the study (e.g., study design, setting, exposure(s), outcome(s), study population). An overview of study designs and databases frequently used in PASS is provided in EMA GVP Module VIII, Appendix I. Link below:
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf

VIII.C.2.2. Written observations in response to the imposition of an obligation

Within 30 days of receipt of the written notification of the obligation, the MAH may request the opportunity to present written observations in response to the imposition of the obligation.

The national competent authority shall specify a time limit for the provision of these observations. On the basis of the written observations submitted by the MAH, the national competent authority shall withdraw or confirm the obligation.

When the obligation is confirmed, the marketing authorization shall be subject to variation to include the obligation as a condition and the RMP, where applicable, shall be updated accordingly (see Module V).

VIII.C.2.3. Joint post-authorization safety studies

If safety concerns apply to more than one medicinal product, the national competent authority in Lebanon may if applicable encourage the MAHs concerned to conduct a joint PASS. This can occur through the following:

- The national competent authority in Lebanon should support interactions between the MAHs concerned; Upon request from the MAHs, a dedicated pre submission meeting with national competent authority in Lebanon may be organized to support interactions between the MAHs and to provide suggestions for the joint study proposal and core elements for the study protocol.

Submissions of joint PASS follow the same requirements as single study.

A single contact person for the submission should be appointed amongst all MAHs concerned and specified in the cover letter. This person will be the primary contact point on all interactions with national competent authority in Lebanon and will receive the documentation relevant for the procedure.

The responsibility to communicate with the rest of the participants in the joint study lies with the appointed contact person as per the specific contractual arrangements among MAHs.

The cover letter should include the full list of medicinal products and MAHs concerned by this joint PASS.

VIII.C.3. Impact on the risk management system

All PASS imposed as a condition to the marketing authorization will be described in the RMP (see Module V) and their results provided in the PSUR following completion of the final report, where applicable (see Module VII).

All relevant sections/modules of the RMP should be amended to document the conduct of the study, including the safety specification, the pharmacovigilance plan, the RMP, and the summary of activities, as appropriate.

A copy of the study protocol approved by the national competent authority and conducted in Lebanon should be provided in Annex 6 of the national display of the RMP. The protocol of PASS conducted outside Lebanon will be presented as part of the core RMP.

When a RMP does not exist, a new RMP should be developed, referring to the PASS.

Other non-interventional PASS that are not obligations or required studies in the RMP but which could provide relevant information on the safety profile of the product should be listed in the RMP Part III – "Summary table of additional pharmacovigilance activities".

VIII.C.4. Regulatory supervision of non-interventional post-authorization safety studies

Non-interventional PASS conducted voluntarily or pursuant to obligations imposed by the competent authority are supervised and assessed by the NCA (Pharmacy Service, the LNPVP, and other concerned departments) in Lebanon. Necessary exemption from IRB/REC should be obtained as well. Below is the link to access the list of authorized IRBs in Lebanon:

https://moph.gov.lb/userfiles/files/HealthCareSystem/Pharmaceuticals/ClinicalTrial/ListofAuthorizedIRBs.pdf.

VIII.C.4.1. Roles and responsibilities of the marketing authorization holder

Following the imposition of the obligation to conduct a non-interventional PASS in Lebanon as a condition to the marketing authorization, the MAH shall:

- Develop a study protocol according to the format and content specified in section VIII.B.5, and submit it to the national competent authority as appropriate. Prior to submission of the protocol, the MAH may submit a request for a pre-submission meeting in order to clarify specific aspects of the requested study (such as study objectives, study population, definition of exposure, and outcomes) and to facilitate the development of the protocol in accordance with the objectives determined by the national competent authority.
- Prove that the study is not a clinical trial;
- The study may start only when the written endorsement from the national competent authority has been issued.
- National requirements should be followed to ensure the well-being and rights of participants in the study (see MR#1159/2014After the study commence, the MAH shall submit any substantial needed amendments to the protocol (i.e., any amendments from the original protocol), before their implementation, to the national competent authority in Lebanon (section VIII.B.5.2);

- Follow the requirements outlined in section VIII.B.6 for reporting pharmacovigilance data to the national competent authority;
- The MAH shall submit study results as specified in section VIII.B.6.3.
- The final study report shall be submitted to the national competent authority in Lebanon within 12 months of the end of data collection unless a written waiver has been granted.

VIII.C.5. Changes to the marketing authorization following results from a non-interventional PASS

The MAH shall evaluate whether the study results have an impact on the marketing authorization and shall, if necessary, submit to the national competent authority an application to vary the marketing authorization. In such case, the variation should be submitted to the national competent authority with the final study report within 12 months of the end of data collection.

Following the review of the final study report, the national competent authority may decide on the variation, suspension or revocation of the marketing authorization. The decision shall mention any divergent positions and the grounds on which they are based and include a timetable for the implementation of this agreed action.

The agreed decision shall be sent to the MAH and to the relevant departments within the national competent authority which should adopt necessary measures to vary, suspend or revoke the marketing authorization in line with the implementation timetable stated in the decision.

In case a variation is agreed upon, the MAH shall submit to the national competent authority an appropriate application for a variation, including an updated Summary of Product Characteristics (SmPC) and package leaflet within the determined timetable for implementation.

The type and requirements of the variation is decided based on the variations section listed Decree # 571/2008 “Application of the provisions of Articles 3 and 5 of Law No 530 promulgated on July 16, 2003 (conditions of registering, importing, marketing and classifying pharmaceuticals)”.
https://moph.gov.lb/files/media/docs/1460629329Marsoum5712008.pdf.

More urgent actions may be required in certain circumstances, for example, based on interim results included in progress reports (see also section VIII.B.6.3.1).