Guideline on Post Authorization Safety Studies (PASS)

NATIONAL MEDICINES REGULATORY AUTHORITY

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Post Authorization Safety Studies (PASS)

1. 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 of measuring the effectiveness of risk management measures

This guidance is concerned with the Non-interventional PASS which are initiated, managed or financed by the MAH or its Local Representative as well as those conducted by a third party on behalf of them, whether voluntarily or upon request of the NMRA.

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

- the medicinal product is prescribed in the usual manner 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.

2. Situations when a PASS may be conducted and its objectives

- to quantify potential or identified risks, e.g. to characterize the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another medicinal product or class of medicinal products as appropriate, and investigate risk factors, including effect modifiers;
- 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 or the effectiveness of a risk management measure (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 management measures.

3. Regulatory procedures during which a PASS may be requested

The NMRA may request the MAH to conduct a PASS as a part of the following procedures:

- Request for a PASS as a part of the initial marketing authorization application
- Request for a PASS during a post authorization regulatory procedure e.g. an extension or a variation to a marketing authorization, a renewal procedure or a PSUR procedure, if there are concerns about the risks of the authorized medicinal product.
- Request for a PASS due to an emerging safety concern for which PASS results would significantly impact on the risk-benefit of the product
- PASS also may be conducted voluntarily by the MAH.

The MAH should include all PASSs in the risk management plan of the medicinal product.

4. Responsibilities of the MAH and reporting of pharmacovigilance data to NMRA

4.1. Study protocol

- The MAH shall develop a study protocol and submit it to the NMRA for review. The study may commence only when the written endorsement from the NMRA has been issued.
- After the study commence, submit any substantial needed amendments to the protocol, before their implementation, to the NMRA.
- The study protocol should have the following content:
    1. Title
    2. MAH
    3. Responsible parties
    4. Abstract

5. Amendments and updates
6. Study Milestones
7. Rationale and background
8. Research question and objectives
9. Research methods
10. Protection of human subjects
11. Management and reporting of adverse events/adverse reactions
12. Plans for disseminating and communicating study results
13. References

For more details, refer to: EMA Guidance for the format and content of the protocol of non-interventional post-authorization safety studies

4.2. Adverse reactions/adverse events collected in these studies

- should be reported to NMRA in accordance national requirements for ICSRs.
- should be recorded and summarized in the interim safety analysis and in the final study report.

4.3. Emerging safety issue

The MAH shall monitor the data generated while the study is being conducted, any new information that may affect the risk-benefit balance of the medicinal product should be communicated immediately in writing as an emerging safety issue to NMRA

4.4. Study Progress report and interim report

MAH may be requested to submit the study progress reports to the NMRA including information about the progress of the study, e.g., 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 interim report of study results is meant to include results of any planned interim analysis of study data before or after the end of data collection.

4.5. Final study report

- Upon completion of the study, the MAH shall submit a final study report, including a public abstract, to the NMRA as soon as possible and not later than 12 months after the

end of data collection, unless a written waiver has been granted by the NMRA. The waiver requested by the MAH should include a justification for such waiver.

- The final study report should have the following content:

    1. Title
    2. Abstract
    3. MAH
    4. Investigators
    5. Study Milestones
    6. Rationale and background
    7. Research question and objectives
    8. Amendments and updates to the protocol
    9. Research methods
    10. Results
    11. Discussion
    12. Other information
    13. Conclusions
    14. References

    For more details, refer to EMA Guidance for the format and content of the final study report of non-interventional post-authorization safety studies

4.6. In addition, the MAH has the following responsibilities:

- ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this fulfilment can be audited, inspected and verified.
- ensure that the study is not a clinical trial, in which case national clinical trial regulation shall apply.
- ensure the well-being and rights of participants in the study.

5. Changes to the marketing authorization following results from a non-interventional post-authorization safety study

The MAH shall evaluate whether the study results have an impact on the marketing authorization and shall, if necessary, submit variation application. In such case, the variation- including an updated summary of product characteristics (SmPC) and package

leaflet- should be submitted to the NMRA with the final study report within 12 months of the end of data collection.

Following the review of the final study report, the NMRA may decide any of the following to the marketing authorization:

- variation,
- suspension, or
- revocation.

The agreed decision – including grounds on which they are based and timetable- shall be sent by NMRA to the MAH and to the relevant departments within the NMRA which should adopt necessary measures to vary, suspend or revoke the marketing authorization.

More urgent action may be required in certain circumstances, for example, based on interim results included in progress reports.

6. Joint post-authorization safety studies

If safety concerns apply to more than one medicinal product, the NMRA shall encourage the MAHs concerned to conduct a joint PASS. This can occur through the following:

- The NMRA should support interactions between the MAHs concerned by sharing contact details among those that wish to participate in a joint study.
- A dedicated meeting with NMRA 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 studies.
- 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 NMRA 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.

7. Study registration

In order to support transparency, tracking and sharing of safety information, the NMRA should establish and maintain studies register for all non-interventional post-authorization studies conducted in Sri Lanka. This register should include at least the following information for each study; the study registration number ID, regulatory procedure relevant to the study request, the concerned MAH(s), concerned medicinal product(s), study title, type, objectives, current status, study protocol, results.

8. Methods for PASS

PASS may adopt different designs depending on their objectives. For description of the main types of studies, as well as the types of data resources available, refer to

EMA Guideline on good pharmacovigilance practices (GVP) Module VIII. Appendix 1. Methods for post-authorization safety studies

ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

For more guidance on the structure, process, methodologies, study protocols & study reports of PASS, refer to

- the *EMA Guideline on good pharmacovigilance practices (GVP) Module VIII*.
- The EMA GVP Modules on Product- or Population-Specific Considerations should also be consulted as applicable to PASS
- ENCePP Guide on Methodological Standards in Pharmacoepidemiology
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