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Module XVI

Risk minimization measures - selection of tools and effectiveness indicators

Version 1.0

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Module XVI – Risk Minimization Measures: Selection of Tools and Effectiveness Indicators

List of Abbreviations

aRMM	additional Risk Minimization Measure
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
LSR	Local Safety Responsible
MAH	Marketing Authorization Holder
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PASS	Post-Authorization Safety Studies
PPP	Pregnancy Prevention Program
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RMM	Risk Minimization Measure
SmPC	Summary of Product Characteristics

XVI.A. Introduction

Risk management includes the identification, characterization (including quantification), prevention, and minimization of risks. Risk management systems consist of pharmacovigilance activities and interventions intended to prevent the occurrence of risks relating to individual medicinal products, including the assessment of the effectiveness of those activities and interventions. The objectives of risk minimization are achieved through the implementation of Risk Minimization Measures (RMMs) required by the national competent authority and the generation of evidence that these measures are effective.

Effective RMMs and the assessment of their effectiveness should be in place for medicinal products. Monitoring RMM outcomes refers to adherence to RMM by healthcare professionals and patients and achieving the objectives of RMMs. Monitoring and amending RMMs, if warranted, aim at ensuring that the benefits of a particular medicinal product continue to exceed the risks by the greatest achievable margin. The assessment of the effectiveness of RMM is important for risk management with an iterative process of evaluation, correction, and re-evaluation of RMMs, which is integral to the lifecycle benefit-risk assessment of medicinal products.

This GVP Module XVI should be read together with GVP Module V on risk management systems as documented through Risk Management Plans (RMPs) and on details of routine RMM, GVP Module VIII on Post-Authorization Safety Studies (PASS), and GVP Module XV on Safety Communication.

XVI.B. describes criteria for selection, development, implementation, and coordination of RMMs, in particular of “additional RMMs” (aRMMs), and the principles and concepts of the evaluation of RMM effectiveness.

XVI.C. describes the related roles and responsibilities of Marketing Authorization Holders (MAHs). It also reflects the contribution of healthcare professionals and patient representatives.

XVI.B. Structures and processes

XVI.B.1. Definition and principles of risk minimization measures

Risk minimization measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient, should adverse reactions occur.

For all medicinal products, risk minimization is generally addressed by routine RMMs. These include the provision of information and recommendations in the Summary of Product Characteristics (SmPC) and the Package Leaflet (PL), the labelling on the immediate or outer packaging of a medicine, pack size appropriate to the usual treatment duration, and a risk-appropriate legal status of the product (e.g., prescription-only medicine) (see GVP Module V). For some important risks, however, routine RMMs might not be sufficient, and it might be necessary to implement aRMMs.

The risk-benefit balance of a medicinal product can be improved by reducing the burden of adverse reactions or by optimizing benefits, both through patient selection and treatment management (e.g., specific dosing regimen, relevant testing, patient follow-up). RMMs should therefore support the optimal use of a medicinal product in clinical practice with the principal goal of providing the right medicine at the right dose and at the right time to the right patient and with the right information and monitoring.

The selection of RMMs and determining whether only routine or also aRMMs are necessary should be based on the characterization of the safety concerns in the safety specifications of the RMP (see GVP Module V). Each safety concern needs to be considered individually, and the selection of RMMs should take into account the seriousness of the important identified or important potential risk, the severity of the adverse reaction(s), the possible impact of the risk and the RMMs on the patient, the preventability and the clinical actions required to minimize the risk as well as the indication, the route of administration, the target population and the healthcare setting for the use of the product. A safety concern may be addressed by using more than one RMM, and one RMM may address more than one safety concern.

aRMMs should be completely separated from promotional activities.

XVI.B.1.1 Criteria for requiring additional risk minimization measures

Most safety concerns are sufficiently addressed by routine RMM (see GVP Module V).

Careful consideration should be given to whether the risk minimization objectives could be reached with routine measures, and only when not considered sufficient, should it be considered which additional measure(s) is (are) the most appropriate. aRMMs should focus on important safety concerns.

In determining whether aRMMs are needed and which measures would be most effective, MAHs/applicants should:

- Consider the target population, frequency, seriousness, severity, context of use, possible impact, and preventability of the risk for which the aRMM is meant to be developed;
- Consider the need for advice to healthcare professionals for appropriate patient selection and excluding patient exposure where the use of the medicinal product is contraindicated, patient monitoring during treatment to prevent adverse reactions, or early detection and management of adverse reactions;
- Assess the potential for effectiveness of the aRMM, including the burden the RMM may impose on the system and possible unintended effects;
- Consider the intended behavioral changes of healthcare professionals and patients during each step of the treatment process; and
- Select the RMM tools that are expected to be:
  - Risk-proportionate and effective on time in minimizing the risk;
  - Practical and not too burdensome for patients or the healthcare system.

XVI.B.2. Categories and tools of additional risk minimization measures

A variety of tools are currently available for use on their own or in a combined manner as aRMMs.

As digital technology advances, the potential of electronic dissemination, such as through web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and healthcare professionals, or for safety systems independent from location, may be considered in addition to paper-based materials.

aRMMs that may be considered in addition to the routine measures include the following:

XVI.B.2.1. Educational programs and tools

Educational programs are a targeted communication tool aiming to improve the use of medicine by positively influencing the actions of healthcare professionals and patients toward minimizing risks. In the context of an educational program, educational tools can include paper, audio, video, web, and in-person training. The content of such materials should bring out additional safety information rather than duplicate the information in the SmPC and leaflet, and should exclude any promotional elements, including logos, product brand colors, suggestive images, and pictures.

Elements to include in an educational tool could provide:

- Guidance on prescribing, including patient selection, testing, and monitoring;
- Guidance on the management of such risks;
- Guidance on how and where to report adverse reactions of special interest.

XVI.B.2.1.1. Educational tools targeting healthcare professionals

Any educational tool targeting a healthcare professional should deliver specific recommendations on the use, contraindications, and warnings associated with the medicine. Other important risks that need aRMMs include patient selection, treatment management such as dosage, testing, and monitoring, special administration procedures, or the dispensing of a medicinal product, and details of information which needs to be given to patients. The format of a particular tool depends on the kind of message to be delivered.

XVI.B.2.1.2. Educational tools targeting patients and/or caregivers

Any educational tool targeting patients should enhance the awareness of patients or their caregivers on the early signs and symptoms of specific adverse reactions causing the need for aRMMs, and on the best course of action to be taken should any of those symptoms occur. If appropriate, a patient‘s educational tool could be used to provide information on the correct administration of the product and to remind the patient about an important activity, for example, a diary for posology or diagnostic procedures that need to be carried out and recorded by the patient and eventually discussed with healthcare professionals, to ensure that any steps required for the effective use of the product are adhered to. A Patient alert card is a tool to be used by patients.

XVI.B.2.2. Controlled access program

A controlled access program consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimization measures. Since the use of such programs should be guided by a clear therapeutic need for the product, controlled access should only be considered as a tool for minimizing a risk with a significant impact on public health or individual patients.

XVI.B.2.3. Other risk minimization measures

XVI. B.2.3.1 Controlled distribution systems

A controlled distribution system refers to the set of measures implemented to ensure the traceability of the medicinal product across the distribution chain. These measures can help prevent the misuse and abuse of medicines.

XVI. B.2.3.2 Pregnancy prevention program

A Pregnancy Prevention Program (PPP) is a set of interventions aiming to minimize pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects. The scope of such a program is to ensure that female patients are not pregnant when starting therapy or do not become pregnant during the course and/or soon after stopping the therapy. It combines the use of educational tools with interventions and controlled access to the product, with the following considerations:

- Educational tools should inform the patients on the measures to minimize teratogenic risk (contraception methods, how long to avoid pregnancy after stopping the treatment…).
- Controlled access should be implemented when prescribing and dispensing the product (carry out a pregnancy test, limit the prescription to a maximum of 30 days).
- Counselling should be offered in the event of an inadvertent pregnancy.
- A pregnancy registry should be implemented to collect pregnancy outcome information.

XVI.B.2.3.3 Direct healthcare professional communication (DHPC)

A Direct Healthcare Professional Communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by a MAH or by the national competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. For example, a DHPC may aim at adapting prescribing behavior to

minimize particular risks and/or to reduce the burden of adverse reactions with a medicinal product. Situations where dissemination of a DHPC should be considered are detailed in Module XV.

XVI.B.3. Implementation of additional risk minimization measures

Additional RMMs should be implemented sustainably in the target population, with careful consideration to the timing and frequency of the interventions. The potential need for each measure in the future should be assessed at the time of the authorization of the product and should be made clear in the risk minimization plan. While controlled access programs and pregnancy prevention programs will usually apply to all future applications for the same medicinal product, other risk minimization measures, such as training materials and direct contact with healthcare professionals, may not necessarily be needed for all future applications. In all cases, it is important to ensure a clear distinction between the educational tools from any promotional material distributed.

XVI.B.4. Effectiveness of additional risk minimization measures

Periodic evaluation of the effectiveness of aRMMs is necessary to judge the need for corrective actions or even the need to continue with the measures. The most appropriate times to conduct such effectiveness evaluations are after the initial implementation of a risk minimization program, and when evaluating the renewal of marketing authorization (not applicable yet in Lebanon)

The evaluation should address different aspects of risk minimization, including the process itself, its impact on knowledge and behavioral changes in the target audience, and its outcome.

Two categories of evaluation indicators should be considered:

- **Process indicators**: necessary to gather evidence that the implementing steps of aRMMs have been successful.
- **Outcome indicators**: necessary to provide an overall measure of the level of risk control that has been achieved with the RMM in place.

In circumstances where the assessment of outcomes is unfeasible (rare adverse events, insufficient number of exposed patients), the evaluation may be based exclusively on process indicators.

The evaluation can lead to one of the following conclusions:

- The risk minimization should remain unchanged;

- The risk minimization should be modified;
- The risk minimization is insufficient and should be strengthened;
- The risk minimization is disproportionate or lacks a clear focus and could be reduced or simplified.

When presenting the evaluation of the effectiveness of a RMM, the following aspects should be considered:

- The evaluation should provide context by describing the implemented measures, their objectives, and their outcome indicators;
- The evaluation should incorporate relevant analyses of the nature of the adverse reaction(s), including their severity and preventability;
- Outcome indicators should normally be the key endpoint when assessing the attainment of RMMs objectives.

XVI.B.4.1. Process indicators

Depending on the nature of the interventions, various process indicators can be identified for the assessment of their performance.

XVI.B.4.1.1. Reaching the target population

When aRMMs involve the distribution of educational tools to healthcare professionals and patients, the metrics for evaluation should be the assessment of the delivery and reception of the material by the target population.

XVI.B.4.1.2. Assessing clinical knowledge

When educational interventions are adopted as RMMs, the achieved awareness and knowledge level among the target population should be assessed. This can be done through rigorous survey methods with careful consideration of the research objectives, study design, sample size, and representativeness, operational definition of dependent and independent variables, and statistical analysis.

For more information on the methodological aspects to be considered for the design and implementation of a survey, refer to Appendix I within Module XVI 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

The use of advocacy groups or patient support groups to survey knowledge can be considered to be inherently biased and should be avoided.

XVI.B.4.1.3. Assessing clinical actions

In addition to assessing the clinical knowledge of recipients of the educational tools, the resulting clinical actions (i.e., prescribing behavior) should be measured. Drug utilization studies by means of electronic records or through medical chart abstraction are valuable options to quantify clinical actions. By applying appropriate statistical methods to a cohort of medicine users, different aspects of prescribing or use may be assessed, which can provide insights beyond purely descriptive evidence.

XVI.B.4.2. Outcome indicators

Safety outcomes, including the frequency and/or severity of adverse reactions observed in exposed patients in non-interventional settings, are the ultimate measure of success of a risk minimization program. Such an evaluation should involve the comparison of epidemiologic measures of outcome frequency, such as incidence rate or cumulative incidence of an adverse reaction. Ideally, comparison of the frequency before and after the implementation of the RMM should be considered (pre-post design). If unfeasible, comparison may be done against a predefined reference value (i.e., observed versus expected analysis).

The use of spontaneous reporting rates may offer an acceptable approximation of the frequency of the adverse reaction in the treated population, but should be considered with caution because of biases.

XVI.B.5. Coordination

When several medicinal products containing the same active substance, such as generic, have been authorized and require the same additional RMM, their marketing authorization holders are encouraged to collaborate for fulfilling the responsibilities applicable to each individual marketing authorization holder through coordination of a consistent approach to developing, disseminating, evaluating and adapting RMM materials, coordinated and overseen by the national competent authority.

Under these circumstances, advanced planning should ensure that the effectiveness of RMMs can be considered for each individual medicinal product as well as for the products collectively.

XVI.B.6. Quality systems for risk minimization measures

The final responsibility for the quality, accuracy, and scientific integrity of risk minimization measures lies with the MAH and its Qualified Person for Pharmacovigilance (QPPV) or Local Safety Responsible (LSR). The MAH is responsible for updating the RMP when new information becomes available. Any document on aRMMs, the risk minimization tools, and the results of studies or analyses for evaluation of effectiveness may be subject to inspection.

XVI.C. Operations of risk minimization measures in Lebanon

XVI.C.1. Responsibilities of the marketing authorization holder/applicant

The MAH/applicant should:

- Clearly define the objectives of any proposed aRMM and the indicators to assess their effectiveness. Any additional risk minimization intervention should be developed in accordance with the general principles outlined in XVI.B.1 and XVI.B.2 and should be fully documented in the RMP (see Module V);
- Implement the measures adopted in the RMP at the national level after agreement with the national competent authority.

  In the implementation of web-based tools, the MAH/applicant should apply requirements specific to Lebanon, with particular consideration of potential issues linked to accessibility, recognizability, responsibility, and privacy and data protection.
- Provide information regarding the status of implementation of aRMMs as agreed with the national competent authority and keep them informed of any changes, challenges, or issues encountered in the implementation of the aRMMs. Any relevant changes to the implementation of the tools should be agreed with the national competent authority before implementation.

- For generic products, the MAH/applicant should develop RMMs in line with the scope, content, and format of the tools used for the reference medicinal product. Scheduling and planning of interventions should be carefully coordinated in order to minimize the burden on the healthcare systems.

  For generic products, the effectiveness of RMMs should be assessed by MAHs in close cooperation with the national competent authority.
- Monitor the outcome of all RMMs. General principles for effectiveness evaluation are provided in XVI.B.4.
- Report the evaluation of the impact of additional risk minimization activities when updating the RMP;
- Report in the Periodic Safety Update Report (PSUR) the results of the assessment of the effectiveness of RMMs, which might have an impact on the safety or risk-benefit assessment.
- Ensure timely communication with the national competent authority for relevant regulatory evaluation and actions, as appropriate (see also XVI.C.2 and Modules V and VII).

XVI.C.1.1 Submission of educational materials

The following should be submitted to the national competent authority:

- A cover letter including the following information:
  - The contact details of the MAH and, if applicable, another organization to which it has subcontracted the submission (at least names and e-mail addresses);
  - The regulatory procedure which has led to the need for the educational material(s) with supportive documents (e.g., authority decision/ request, approved RMP, assessment report identifying the need for this aRMM);
- A detailed implementation plan for the educational material with the following information:
  - Target population(s);
  - Dissemination method (e.g., paper, e-mail, via social media, learned societies and/or patient associations, publication on websites, other digital methods);
  - Time point when dissemination is anticipated to start and frequency of further disseminations;
  - Estimated date of launch or date of start of the marketing of the product (in the case of a new marketing authorization);

- Draft educational material as documents in a common open text-processing electronic format of the proposed materials in the language(s) required by the national competent authority in Lebanon;
- The intended layout and, where applicable, images and graphic presentations of the information (e.g., pictures, charts, diagrams, video).

When changes of the risk and/or the need for aRMM have been identified and changes in the key elements and/or in the content of the educational material(s) have been agreed with the national competent authority in Lebanon, the MAH should submit revised proposals of the educational material after changes for assessment and approval. In the revised educational material, the changes should be highlighted against the materials previously approved by the national competent authority in Lebanon.

XVI.C.2. Responsibilities of healthcare professionals and patients

While healthcare professionals and patients hold no legal obligations with respect to the implementation of the PV legislation, their cooperation is paramount to the success of aRMMs in order to optimize the risk-benefit balance of a medicinal product.

XVI.C.3. Impact of risk minimization measures effectiveness on the RMP/PSUR

The outcome of the implemented aRMMs should be included in the RMP and PSUR as follows:

- The RMP should focus on how this informs risk minimization and/or PV planning, and should include the results of the effectiveness evaluation of the measures.
- The PSUR should evaluate how the implemented measures impact the safety profile and/or risk-benefit balance of the product.

Changes to the product information should not be proposed via a stand-alone RMP update; rather, a variation application should be submitted. A PSUR can also result directly in an update to product information.