Risk Management Plans (RMPs)

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What is a Risk Management Plan?

- Document to describe the **risk management system** considered necessary to identify, characterize and minimize a medicinal product's important risks.
- It contains:
  - the medicine's safety profile (**safety specification**);
  - how its risks will be prevented or minimized in patients & plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine (**Parmacovigilance plan**);
  - measuring the effectiveness of risk-minimization measures (**Risk Minimization Plan**).

RMP Components

- Safety specification
- Pharmacovigilance plan
- Risk minimization plan

RMP. Purpose

- Describe what is known and not known about the safety profile of a product
- Plan how to characterize further the safety profile of a product
- Implement measures to prevent or minimize risks associated with the product
- Assess the effectiveness of those interventions
- Document the need for efficacy studies and maximize the benefit risk balance of the product

Risk Management Plans. Regulatory Framework

- **EU** --- **EU-RMP** is required with new (or significant change) marketing authorization application.
  - PV legislation in EU
  - GVP Module V rev 2 (Risk management systems)
- **US** --- **Risk Evaluation and Mitigation Strategy (REMS)** may be required depending on the safety profile and benefit-risk evaluation.
  - FDA Amendment Act
  - More use of ETASU (Elements to Assure Safe Use)
- **JP** --- **J-RMP** is required
  - EPPV (Early Post-marketing Phase Vigilance) study: 6 months duration

FDA's Role in Risk Management

- Guidance documents
  - Development of clear standards and definitions
- Support validation of regulatory risk management tools
- Post-marketing surveillance
- Monitor Phase IV studies

Risk Management & Evaluation

Passive/Active Surveillance

- ***AERS***
- ***Data mining***
- ***Death certificates***

Cases of AE / Patients exposed to drug → Cases of AE in defined pop'n / Population exposed/time

Incidence rate of AE

Drug Use data
- ***Outpatient*** (IMS Health, Advance PCS)
- ***Inpatient*** (Premier, CHCA)

Risk management Pre/post metrics
- Health outcomes
- Drug use/concomitancy
- Surrogate outcomes
- Benefit in actual use

- ***VA***
- ***EMR procurement***
- ***Cooperatives***
- ***Kaiser***

Seligman, FDA, 2003

How We Use Epidemiologic Data

8

Assess, quantify and manage risks

Anticipate and prevent risks

Seligman, FDA, 2003

Reactive

- Enhance signal detection using passive/active surveillance
- Place signals in context, make rates with exposure (use) data
- Validate signals in defined population databases
- Evaluate risk management efforts, tools in multiple systems

Seligman, FDA, 2003

Proactive

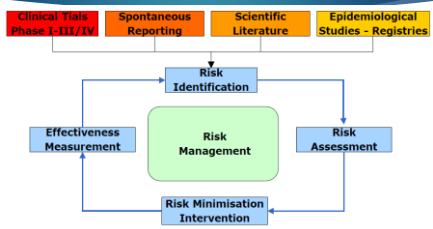
- Decrease medication errors due to name confusion by pre-testing
- Enhance risk communication with label comprehension studies
- Test education materials for cognitive impact
- Enhance risk management effectiveness by assessing feasibility, acceptability of tools

Seligman, FDA, 2003

RMP in the Lifecycle of a Medicine

- RMPs are modified and updated throughout the lifetime of the drug as new information becomes available
- An updated RMP needs to be submitted:
  - at the request of the Health Agency
  - when the risk management system is modified
    - result of new information that may lead to a change of the benefit-risk profile
    - result of an important pharmacovigilance/risk-minimization milestone
- Risk management is a complex process, which needs a governance structure.

Risk Management Cycle



Components of RMP

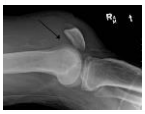
- Safety specification
- Pharmacovigilance plan
- Risk minimization plan

RMP. Definitions

- **Safety specification –** Characterization of risks: epidemiology, disease characteristics, potential mechanism of action, nonclinical / clinical data
- **Pharmacovigilance Activity** – identify and further characterization of the risk (routine or additional)
- **Risk Minimization Measure** – prevent or reduce occurrence or reduce severity of risk (routine or additional)

Safety Concern---- Safety Specification

Tendon Rupture → **What information will you need to characterize it?**



RMP. Definitions

- **Identified Risk** – adequate evidence of causal association
- **Potential Risk** – possible but insufficient evidence for causal association
- **Missing Information** – unknown and clinically significant
- **Important** – potential impact on B-R or public health impact

Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2), dated 28 March 2017.
ICH HARMONISED TRIPARTITE GUIDELINE „PHARMACOVIGILANCE PLANNING E2E „ Current Step 4 version „ dated 18 November 2004.
FMDA Risk Management Plan Guidance, 21 Apr 2012.

Identify Risk

- ***An untoward occurrence for which there is adequate evidence of a causal association with the drug***
- Examples:
  - an adverse reaction **adequately demonstrated** in non-clinical studies and confirmed by clinical data
  - an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the **magnitude of the difference compared with the comparator group on a parameter of interest, suggests a causal relationship**
  - an adverse reaction suggested by a **number of well-documented spontaneous reports where causality is strongly supported** by temporal relationship and biological plausibility, such as anaphylactic reactions

Label of Chloroquine

Potential Risk

An untoward occurrence for which there is some basis for suspicion of an association with the drug product but where there is currently insufficient evidence to conclude that this association is causal

Examples:

- toxicological findings seen in non-clinical safety studies which have **not been observed or resolved in clinical studies**
- adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a **suspicion of an association, but is not large enough to suggest a causal relationship**
- a **signal** arising from a **spontaneous adverse reaction reporting** system
- an event **known to be associated with other active substances within the same class** or which could be expected to occur based on the properties of the medicinal product

Missing Information

- ***Gaps in knowledge about a drug product, related to safety or use in particular patient populations, which could be clinically significant***
- Information on the safety of a drug product may be limited due to many factors including:
  - relatively small numbers of subjects in clinical trials compared with the intended treatment population
  - restricted population in terms of age, gender and ethnicity
  - restricted co-morbidity
  - restricted co-medication
  - restricted conditions of use
  - relatively short duration of exposure and follow up
  - statistical issues associated with evaluating multiple outcomes
- Examples:
  - populations not studied
  - pregnant women, elderly population, patients with severe renal or hepatic impairment

Missing Information

- Considerations in the definition:
  - gaps in knowledge about the **safety** of a medicinal product for certain **anticipated utilization** or for use in particular patient populations, for which there is **insufficient knowledge** to determine whether the safety profile differs from that characterized so far.
  - The absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern.
  - The risk management plan should focus on situations that might differ from the known safety profile.
  - A scientific rationale is needed for the inclusion of that population as missing information in the RMP.
- Not enough safety data in a defined population

Missing Information

- Evidence of a potential concern in not tested population
  - Suspicion of safety concern in the population insufficiently exposed, but included in the indication (e.g. cardiac safety in elderly; no upper age limit, benefit and safety extrapolated)
- Always has to be relevant for the approved indication
  - e.g. missing information safety in children should not be part of the list of safety concerns if product is not authorised in this population
- Including an item as missing information in RMP usually means activities to further characterize this population are necessary (ie, include in PV plan) or risk minimization activities beyond the routine are needed
- Missing information without additional risk minimization activities is not advisable to be in the RMP

Important. Definition

Risk that could have an impact on the risk benefit balance of the drug product or have implications for public health

- Factors to consider:
  - the impact on the individual
  - the seriousness of the risk
  - the impact on public health
- Any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important

Components of RMP

- Safety specification
- Pharmacovigilance plan
- Risk minimization plan

Pharmacovigilance Plan

The identification of new safety concerns
Further characterisation of known safety concerns including risk factors
Investigation of whether a potential risk is real or not
How important missing information will be sought

- Specific AR Follow up questionnaires are considered routine PhV
- Action plan for safety concerns with additional PhV
- Summary table of additional PhV activities including expected dates of milestones
- For class effects MAHs may be asked to conduct joint studies
- Include additional PhV activities requested by individual MSs

PV Plan--- PV Activities

To characterize and quantify clinically relevant risks, and to identify new adverse reactions (the 'pharmacovigilance plan')

- **Routine PV – generally applies to every drug product**
  - Signal detection system
  - Periodic aggregate safety reports
- **Additional PV – suggested when essential for the safe and effective use of the drug product**
  - Post-authorization safety study (PASS)
  - REMS
  - PMS
  - Patient registry

Attributes of Additional Pharmacovigilance Activities

	Type of activity	In annex II of MA (CAPs only)	Study category (PhV plan)	Status	Supervised under	
					Article 107m	Article 107 n-q
Imposed PASS	"Interventional"*	Yes, in annex IID	1	Mandatory and subject to penalties	No	No
	Non-interventional	Yes, in annex IID			Yes	Yes
Specific obligation	"Interventional"*	Yes, in annex IIE	2	Mandatory and subject to penalties	No	No
	Non-interventional	Yes, in annex IIE			Yes	Yes
Required	"Interventional"*	No	3	Legally enforceable	No	No
	Non-interventional	No			Yes	No

*Clinical interventional studies are subject to the requirements of Directive 2001/20/EC. Non-clinical interventional studies are subject to the legal and ethical requirements related to the protection of laboratory animals, and Good Laboratory Practice as appropriate.

EMA Guideline on good pharmacovigilance practices (GVP) – Module V (Rev 2), 2017

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Safety Concerns & Risk Minimization Measures

Risk Minimization Measures. Definition

- 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.**
- Goal: to optimize the safe and effective use of a medicinal product throughout its life cycle


MEDICATION GUIDE

SEREVENT® DISKUS® [ser' uh vent dis' us]

(salmeterol xinafoate inhalation powder)

Read the Medication Guide that comes with SEREVENT DISKUS before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SEREVENT DISKUS?

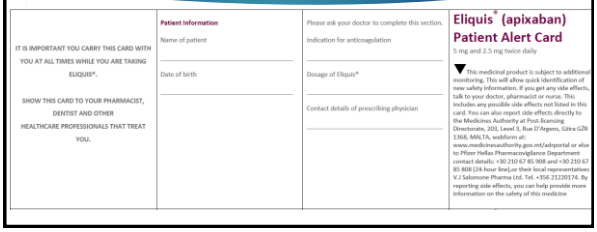
SEREVENT DISKUS can cause serious side effects, including:

- People with asthma who take long-acting beta2-adrenergic agonist (LABA) medicines, such as salmeterol xinafoate (the medicine in SEREVENT DISKUS), have an increased risk of death from asthma problems.
- African-American patients with asthma who take LABA medicines such as salmeterol xinafoate increase the risk of death in people who take LABA.
- Call your healthcare provider if breathing problems worsen over time while using SEREVENT DISKUS. You may need different treatment.
- Get emergency medical care if:
  - your breathing problems worsen quickly
  - you use your rescue inhaler, but it does not relieve your breathing problems.
- Do not use SEREVENT DISKUS as your only asthma medicine. SEREVENT DISKUS must only be used with a long-term asthma control medicine, such as an inhaled corticosteroid.
- SEREVENT DISKUS should be used only if your healthcare provider decides that your asthma is not well controlled with a long-term asthma control medicine, such as an inhaled corticosteroid. When your asthma is well controlled, your healthcare provider may tell you to stop taking SEREVENT DISKUS. Your healthcare provider will decide if you can stop SEREVENT DISKUS without use of asthma control. You will continue taking your long-term asthma control medicine, such as an inhaled corticosteroid.
- Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

Risk Minimization Measures

- **<u>Additional RMM</u> – suggested when essential for the safe and effective use of the drug product**
  - Education program
  - Controlled access program
  - Patient alert cards
  - Healthcare professional communication

Example of Patient Alert Card


IT IS IMPORTANT YOU CARRY THIS CARD WITH YOU AT ALL TIMES WHILE YOU ARE TAKING ELIQUIS®.

SHOW THIS CARD TO YOUR PHARMACIST, DENTIST AND OTHER HEALTHCARE PROFESSIONALS THAT TREAT YOU.

Patient Information

Name of patient

Date of birth

Please ask your doctor to complete this section.

Indication for anticoagulation

Dosage of Eliquis®

Contact details of prescribing physician

Eliquis® (apixaban)
Patient Alert Card
5 mg and 2.5 mg twice daily

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this card. You can also report side effects directly to the Medicines Authority at Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GZR 1368, MALTA, webform at: www.medicinesauthority.gov.mt/adsportal or also to Pfizer Hellas Pharmacovigilence Department contact details: +30 210 67 85 908 and +30 210 67 85 808 (24-hour line),or their local representatives V.J Salomone Pharma Ltd. Tel. +356 21220174. By reporting side effects, you can help provide more information on the safety of this medicine

Risk Minimization Measures

- Needed for all products
- May need more than one
  - Multiple legal status
  - Cross therapeutic areas
  - Different risks for difference target populations
- Clarification of what is routine risk minimisation
- Justify any proposals for additional risk minimisation
- Educational materials:
  - Non promotional
  - Advice to consult communication experts, patients and HCP
  - Similar layout and content may be requested
  - Final version approved by NCA

EU-RMP. Template

Part I	Product(s) overview
Part II	Safety specification
Module SI	Epidemiology of the indication(s) and target population(s)
Module SII	Non-clinical part of the safety specification
Module SIII	Clinical trial exposure
Module SIV	Populations not studied in clinical trials
Module SV	Post-authorisation experience
Module SVI	Additional EU requirements for the safety specification
Module SVII	Identified and potential risks
Module SVIII	Summary of the safety concerns
Part III	Pharmacovigilance plan (including post-authorisation safety studies)
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)
Part VI	Summary of the risk management plan
Part VII	Annexes

Important Considerations

- The RMP focuses on the important risks that are likely to have an **impact on the risk-benefit balance** of the drug product and would usually warrant:
  - Further evaluation as part of the **pharmacovigilance plan**
  - Risk minimisation activities: **product information advising on specific clinical actions to be taken to minimise the risk**, or **additional risk minimisation activities**.
- The aim of RMP is to document the risk management system for important safety risks, rather than provide a 'laundry' list of all ADRs.

Important Considerations

- **Not all ADRs are risks**
  - ADR versus clinical outcome (risk): dizziness (ADR) versus falls (risk), neutropenia, thrombocytopenia (ADRs) versus infections and bleeding (risks).
  - Not always a clear cut!
- **Not all risks are important risks/missing information**
  - Either a risk/missing information is important enough to require risk management activities (PV activities and/or RM activities) beyond the routine, or it is not important enough to include in the RMP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Questions?