aRMM additional Risk Minimisation Measure

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aRMM, Edukační materiály

Guideline on good pharmacovigilance practices (GVP),

- Modul V RMP
- Modul X Additional monitoring
- Modul XV Safety communication
- Modul XVI Risk minimisation measures
- Module XVI Addendum I – Educational materials

GVP Modul XVI Risk Minimisation Measure July 26th, 2024

- applicable to **new applications** for marketing authorization,
- **new risk minimization measures** and **new studies evaluating risk** minimization measures for authorized medicinal products but not immediately applicable to existing risk minimization measures and ongoing activities regarding risk minimization measures;

1. Clarify the role of risk minimization for **risk management planning** and for the impact on the risk-benefit balance of medicinal products, and the role of effectiveness evaluation of risk minimization measures
2. Give more guidance about the **criteria for applying/requesting** additional risk minimization measures
4. Give more guidance on risk minimisation **evaluation parameters** (e.g. implementation, behavioural changes, outcomes),including suitable study designs and data collection methods
5. Recommendations on additional risk minimisation measures within **the lifecycle** of the product
6. Give more details on the **role of healthcare professionals and patients and to clarify possible strategies for their early engagement and role in risk minimisation development, dissemination and evaluation;**

GVP Moduel XVI Risk Minimisation Measure

- **Routine**
  - SmPC – mentioned that aRMM exists
  - PIL - aRMM for patient – PIL should mentioned that aRMM exist and how to access those information
  - Labelling of immediate and outer packaging (including special warnings or precautions or/pictogram)
  - Pack size
  - Classification of the medicinal product (legal status)
- **Additional**
  - Educational/Safety advise tools
    - Guides for RM for patients or HCP
    - HCP check list for risk minimization
    - Risk awareness dialogue form/aid
    - Patient card
    - Patient diary for risk minimization
  - Risk minimization control tools
    - HCP qualification
    - HCP facility accreditation
    - Traceability system for dispatch of the product
    - System for documented exchange of patient information
    - Check of patient certificate of medical intervention if required for prescribing of product

Role of risk minimization measure for risk management planning

- intervention intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicinal product, or to reduce their severity or impact
- **RMM messages**: the key information (i.e. not the full wording) about the risk and the actions intended to be taken by the healthcare professional or the patient for minimising the risk; and
- **RMM tool:** the tool by which the RMM messages are disseminated and adherence to the intended actions for risk minimisation is supported and/or controlled, belonging either to the category of routine or additional RMM tools on the patient should an adverse reaction occur.

Clarify the role of risk communication, dissemination and implementation as a relevant part of any additional risk minimization activity

- Tailoring of materials to target population
- Non promotional
- Dissemination plan develop on national level
- Input from HCP and patient representative to be considered it applicable
- Readability (User testing) testing if applicable

Give more details on the role of healthcare professionals and patients and to clarify possible strategies for their early engagement and role in risk minimisation development, dissemination and evaluation;

- **competent authorities in Member States are responsible** for the approval of nationally tailored additional RMM materials and the agreement of the national RMM dissemination plans
- **differences of the healthcare systems** in Member States and of how particular risk(s) are managed within these systems, some **RMM may need to be implemented differently** in Member States.
- The **national tailoring of RMM** materials should address the specifics of the healthcare systems in Member States, e.g. applicable **subgroups of the target population**, **naming of the RMM tool and full wording of the RMM material** in the **official language(s),** additional information items, **design and formatting**, **dissemination,** with a view to best support the implementation of the RMM in healthcare.
- Competent authorities in Member States are encouraged to, **seek input from healthcare** professional and **patient representatives** request from the marketing authorisation holder **user-testing of additional RMM materials** in the respective official language(s), and consider results from user-testing of RMM when requested from and/or submitted by the marketing authorisation holder.

aRMM, Edukační materiály

- Zákon č. 378/2007 Sb., Zákon o léčivech
- Vyhláška č. 228/2007 Sb., o registraci léčivých přípravků
- Zákon č. 95/2004 Sb.,
- Zákon č. 96/2004 Sb., o nelékařských zdravotnických povoláních

- farmakovigilanční pokyn PHV -7, PHV - 8

Edukační materiály

- sdělení pro zdravotnické pracovníky nebo pacienty a jejich opatrovníky distribuované za účelem **snížení rizik** a tím **zlepšení poměru přínosů a rizik** daného léčivého přípravku.

- Doplňují, upřesňují či rozšiřují informace o léčivu obsažené v SPC a PIL, které se týkají postupů a opatření nutných pro **bezpečné používání** léčivého přípravku a pro **prevenci** vzniku jeho nežádoucích účinků.

- upřesnění způsobu použití, dávkování
- kontraindikace,
- zvládání kritických situací a nežádoucích účinků,
- opatření týkající se specifických skupin pacientů,
- následného sledování pacientů,
- sdělení, která musí lékař komunikovat s pacientem před, v průběhu nebo po ukončení léčby

Rozhodnuti - kdy a proč?

- EMA (PRAC, CHMP), CMDh
- jiná léková autorita (RMS v MRP/DCP)
- NCAs,
- na návrh držitele rozhodnutí o reg. – pak musí dokázat nutnost tvorby
- aktualizovat RMP

Edukacni materiály- postup schvalování na SUKL

- **emailem na** farmakovigilance@sukl.cz (název LP v předmětu emailu)
- **důvod vzniku + EN originál** (CAP –annex D:
  - Podmínky a povinnosti vyplývající z registrace, nebo Final Overview/EoP u MRP/DCP, nebo RMP)
- **překlad do češtiny**
- **Word formát** (u aktualizací- track verzi)
- **včas před zvažovanou distribucí** (2 měsíce)
- **návrh distribučního plánu** (okruhy, způsob, frekvence opakování)
- distribuce – nelze doplňovat pouze na základě vyžádání lékaře – nutné aktivní zjišťování potřeby
- distribuce není závislá na aktivním promování LP
- **Aktualizace – věcné změny nutno předkládat ke schválení – číslování verzí**

EM – obsah

- důležité bezpečnostní informace
- zdůraznění minimalizace rizik
- dle aktuálního SPC
- jasné, stručné, výstižné
- symbol a prohlášení o následném sledování(▼)
- způsob hlášení NÚ(NCA i MAH)
- Zdůraznit kontext Benefitu LP

Pro lékaře

- nadpis **Edukační pro materiály**
- nepřipouští se loga, kmenové barvy
- Lze v odůvodněných případech povolit EN verzi

Pro pacienty

- bez nadpisu
- připouští se kmenové barvy
- Nelze v EN

EM – nepovolený obsah

- Žádná informace promočního charakteru
- Prvky,, ktere nemají vztah k obsahu
  - Foto
  - Grafy a tabulky
  - Irrelevantni text
  - Odkazyna literaturu
  - Edukativni schemata a obráyky - výjimka

EM - distribuce

- Přímo – ne distributor
- Hard copy, web stranky, email
- Distribuce EMAIL
- Po schválení SUKL
- Jen pro HCP (ne pacienty)
- MAH – seznam jmen a kontatknich emailu
- Process indicators - Inspekce
- Spolupráce více MAHu – účinná látka, PSUSA , referral, generika

Question?

Farmakovigilance od klinických studií až po uvedení produktu na trh

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Early access program

- These programs are also known by various other names
  - such as compassionate use
  - early access,
  - special access, etc.,

  These programs along with clinical trials provide prelaunch access to the investigational drugs. However, there is a difference between a clinical trial and access programs with regards to the entity driving the access and the modality of providing access to the patients.

- A clinical trial is protocol driven, and historically it was the only way for the patients in many countries to obtain preapproved drugs

Compaassionate use-history

- 1962 - After Thalidomide tragedy, FDA implemented a new regulation on clinical trials
- 1962 – early 1980s, access to investigational drugs - informal process governed primarily by telephone
- No written policies
- The advent of AIDS (1980)
- June 1983 : FDA proposed a regulation on the use of investigational drugs for therapeutic purposes, including compassionate use (the final IND regulation was implemented in 1987)
- In France : "l'Agence du Médicament" allows in 1994 compassionate use, after pressures from AIDS patients (= ATU)
- Before 2004 and Article 83 of Regulation (EC) N° 726/2004, only France and Italy had compassionate use programmes

Names and variety

- Compassionate Use
- Expanded Access
- Early Access
- Italy 648 Law
- Authorisatios Temporaires D'Utilisation – ATU
- Unmet medical need programm
- Treatment Use
- Special Use
- Named Patient Programs

CUP – EU legislation

Directive 2001/83/EC provides the legal basis for Member States to implement national programmes

• Article 6 - a medicinal product may not be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State or an authorisation has been granted through a centralized procedure.

• Article 5 - defines an exception to this requirement under defined circumstances [A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive [requirement for a marketing authorisation] medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an **authorised health-care professional and for use by an individual patient under his direct personal responsibility]**

Article 83 – defines use of unauthorized **product in group of patients**

Guideline scope – article 83

- The use of Article 83 is applicable to unauthorised medicinal products for human use
  - For patients with a **chronically** or **seriously debilitating disease**, or a **life threatening disease**, and who cannot be treated satisfactorily by an authorised medicinal product
  - **Group** of patients
  - The medicinal product is either "the subject of an application for a **centralised marketing authorisation** in accordance with Article 6 of Regulation (EC) No 726/2004 or
  - is **undergoing clinical trials**" in the European Union or elsewhere

- Article 83 is not applicable
  - Medicinal products which are **not eligible** for the Centralised Procedures
  - Compassionate use on a **named patient basis**
  - A medicinal product, which has **already been authorised** via the Centralised Procedure

Compassionate use ≠ clinical trials

Compassionate use ≠ clinical trials

Compassionate use is not a substitute for properly conducted trials

Patients should always be considered for inclusion in clinical trials before being offered compassionate use programmes

Compassionate use ≠ off-label use

Compassionate use does not refer to the use of an authorised medicinal product for an indication different from the one mentioned in section 4.1 of the summary of product characteristics (SPC), i.e. off-label use

Compassionate use – Eu guideline

- This guideline is designed to
  - Facilitate and improve access to compassionate use programmes by patients in the EU
  - Favour a common approach regarding
  - The conditions of use
  - The conditions for distribution
  - The patients targeted for the compassionate use of an unauthorised new medicines
- Increase transparency between Member States in terms of treatment availability

Compassionate use – EU guideline

- European legal framework foresees two situations of exceptional application of a non-licensed medicinal product to patients.

  Those applicable for a cohort (group) of patients
  "Named Patient Use" (also referred to as Named Patient Programme, NPP)

- Substantial heterogenity in EU with regard to requirements for CU programmes

Named patient program

- Named Patient Program (NPP) provides patients and physicians access to medicines that are not available to them in their own country. These drugs must be approved in at least one country, from which it can be imported into the patient's country under a NPP.
- These may be drugs that are:
  - Approved, but not yet commercially available to be prescribed in the patient's country
  - Approved and available in one country but not approved and available in the patient's country
  - Discontinued in the patient's country but not another
  - In shortage in the patient's country but not another
- To be eligible for an NPP, a patient must have a physician who is willing to prescribe the medicine on the patient's behalf.

CUP, RAP, NPP

Comparison of EAPs in the US to CUP and NPP in the EU

Criteria	EAP (US)	CUP (EU)	NPP (EU)
Legislation in place	• Expanded Access Programs (FDA, 1997)	• Article 83 (1) of Regulation (EC) No 726/2004	• Article 5 of Directive 2001/83/EC
Who initiates the Program?	• Manufacturer • Physician	• Manufacturer/Group of physicians (e.g. in Italy)	• Physician
Criteria to define/select target population is set by	• Manufacturer/FDA	• Manufacturer/CHMP	• Manufacturer/Physician
Who can benefit from Program? Limitation in Use?	• Group of patients (treatment INDs & treatment protocols) • Named patients (single patients INDs)	• Group of patients i.e. more than one (permission is granted to a clinic or hospital as opposed to a particular patient)	• Only named patients for whom physician has made a request
Liability	• Manufacturer	• Manufacturer	• Prescribing physician
Medicinal product should be undergoing clinical trials or awaiting marketing authorization?	✓	✓	×
Is off label use permitted?	×	×	×
Are Physicians paid for taking part in the program	✓	×	×
Are drugs in the program priced	×	×	✓

Source:[9] Yazdani Morteza, Boggio Francesca-Initiating early access programs in Europe: Five things to consider: Executive insights. http://www.executiveinsight.ch/sites/default/files/publication_pdfs/Early%20Access%20programmes_5_things%20to%20consider.pdf. EAPs = Early access programs, NPP = Named patient program, CUP = Compassionate use program

Question?

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