EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacovigilance – from safety reporting to regulatory action

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The views expressed in this presentation are the presenter's personal views and may not be understood or quoted as being made on behalf of or reflect the position of the European Medicines Agency (EMA) or one of its committees or working parties.

The product information, incl. the package leaflet, is part of the marketing authorisation of the medicinal product

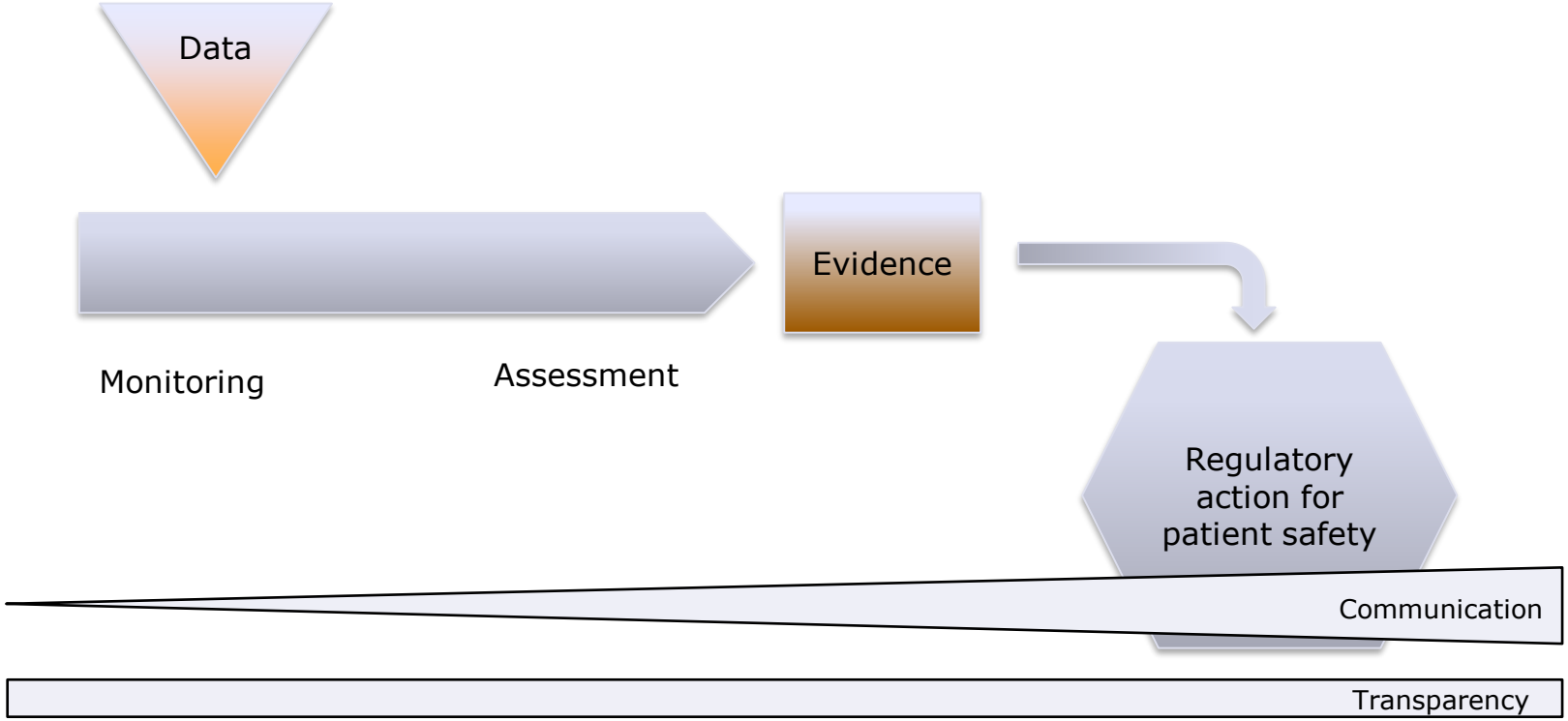
Priya Bahri: Pharmacovigilance © EMA

Pharmacovigilance

= Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem

[World Health Organization (WHO). The importance of pharmacovigilance: safety monitoring of medicinal products. Genève: WHO; 2002.]

Regulatory pharmacovigilance process



Data sources

- Pre-authorisation studies, in particular clinical trials
- Post-authorisation safety studies, including those as per risk management plan or commissioned/conducted by EMA (e.g. using the Data Analysis and Real World Interrogation Network (DARWIN-EU))
- Spontaneous reporting of suspected adverse reactions from patients and healthcare professionals
- Other data sources (e.g. may be published in the scientific literature or obtained from regulatory engagement with patient and healthcare professionals), also on clinical context

How does reporting work?

- Reporting suspected side effects is critical
- Anyone can report to their national competent authority (or the marketing authorisation holder)
- All reports are sent to **EudraVigilance**, the European database of suspected side effects where:
  - the data are collected and analysed to detect new adverse reactions
  - anonymised data are made public: http://www.adrreports.eu/

What happens in response to a spontaneous report?

Databases of national competent authorities, marketing authorisation holders and at EMA in EudraVigilance with over 29.3 million individual case safety reports (ICSRs) relating to 16.9 million case reports by end 2024

All other data

Signals

Evidence

Monitoring

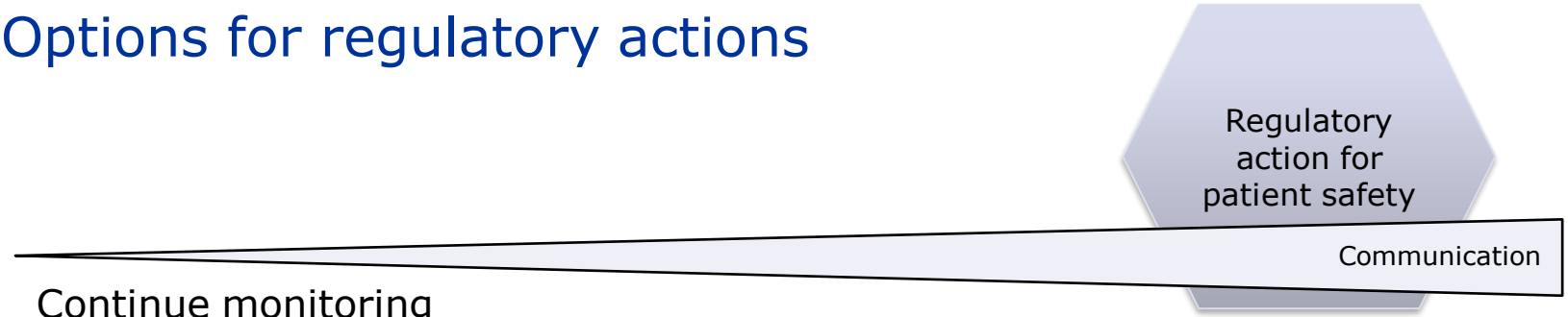
Assessment

Periodic safety update reports

Emerging safety issue

is uncommon

Options for regulatory actions



- Continue monitoring
- Collect or generate more data
- Update the product information (PI) with information on risks and risk minimisation measures (RMM) and/or restrictikon of indications
- Require additional tools for risk minimisation to enhance the RMM in the PI
- Suspend marketing or withdraw the marketing authorisation

Signals at EMA's Pharmacovigilance Risk Assessment Committee (PRAC)

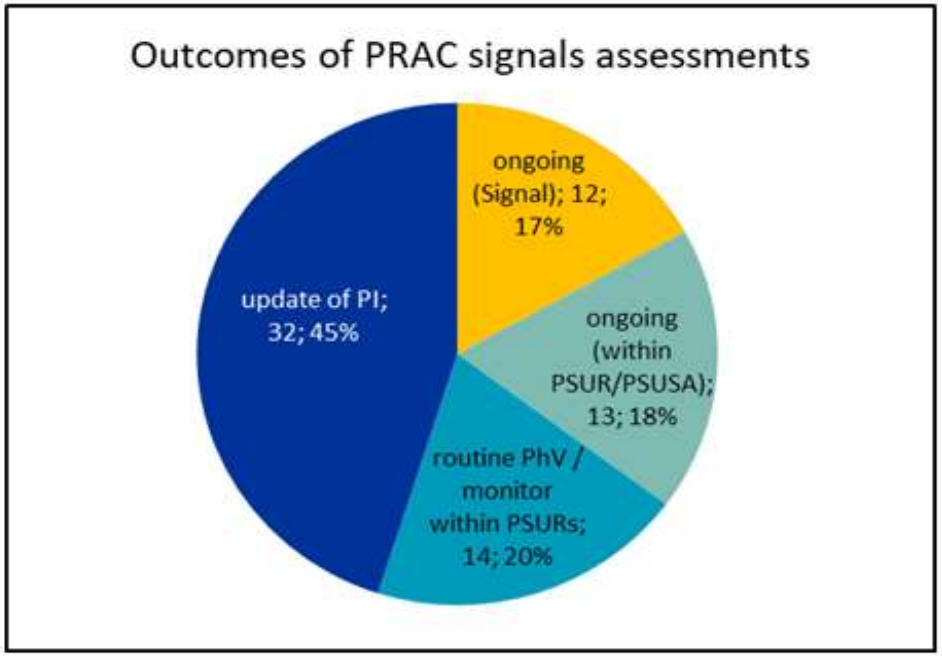
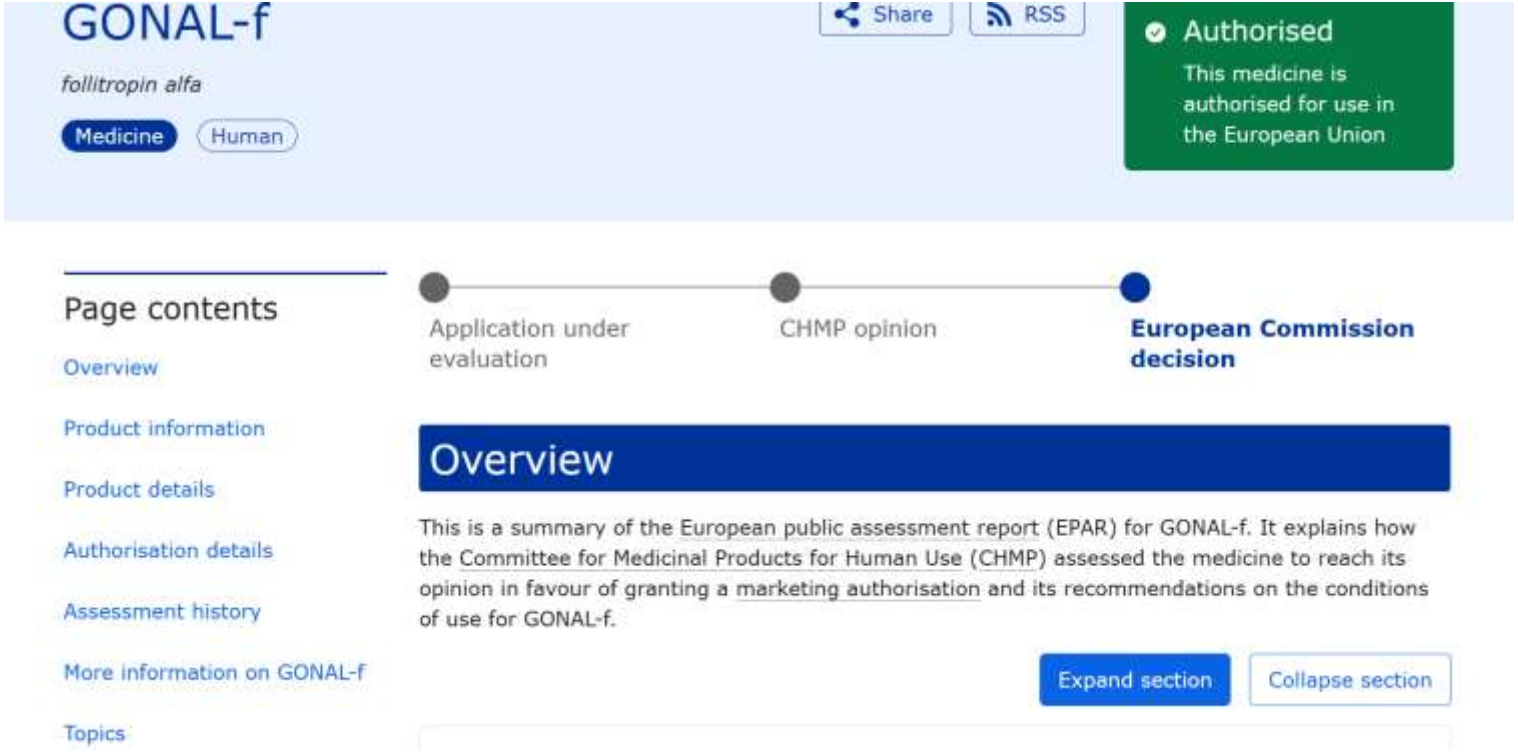


Figure 13. Outcomes of PRAC signal assessments (2024). PI: product information, PSUR: Periodic Safety Update Report, PSUSA: Periodic Safety Update Single Assessment, PhV: pharmacovigilance.

[EudraVigilance Report 2024]

European public assessment report (EPAR)



[Extract from EMA website]

Engagement of patients

- Direct patient reporting of spontaneous reporting of suspected adverse reactions, or not direct via a healthcare professionals
- Participation in studies
- Participation in regulatory engagement options: e.g., membership in board/committees/working parties/working groups; public hearings/ad hoc expert meetings/scientific advisory groups (SAGs); targeted and public written consultations

Quantitative review of PRAC engagement events 2015-2019

Engagement events total: 130

Engagement products total: 71

Engagement products with repeated events in a given year total; range: 28; 2-4

Engagement events per year: 2015: 17 (14 products); 2016: 24 (17 products); 2017: 33 (21 products), 2018: 36 (20 products); 2019: 20 (13 products)

130 engagement events per engagement type: Safety communication review: 50; DHPC reviews: 36; Written consultation: 22; Scientific Advisory Group meeting: 4; Ad hoc expert group meeting: 8; Stakeholder meeting: 5; Teleconference: 2; Public hearing: 2; Scientific publication: 1

= 44 engagement events (excl. DHPC and safety communications review) for 28 products

[Bahri P & Pariente A, 2021]

Engagement of patient and healthcare professional representatives for risk minimisation

- Provide general/product-specific input on RMM options, regarding e.g. tools, messages, target populations and implementability, to support regulatory decisions on RMM
- Contribute to the development of tailored RMM materials, also e.g. through user-testing of RMM materials, and to the development of RMM dissemination plan

- Support the dissemination via multiple channels, incl. those outside regulatory oversight, to address the media preferences of the target populations and to support the implementation of RMM in healthcare
- Provide input on and participate in the evaluation of RMM effectiveness

[EU-GVP Module XVI]

Pivotal cases of collaborations with patient representatives

Risk of lipodystrophy with medicines used for highly active antiretroviral therapy (HAART): First-time engagement of patient and healthcare professional representatives in a multi-stakeholder oversight committee for research requested by EMA for an adverse reaction suspected and notified by patients themselves (1999)
Risk of potential carcinogenicity with contaminated nelfinavir-containing products: First-time engagement of EMA where a patient representative was contacted by EMA immediately after a marketing authorisation holder's notification of a quality defect and before the risk assessment could be started (Note: The risk assessment demonstrated that the exposure of patients had been below the toxic threshold.) (2007)
Risk of teratogenicity with thalidomide: First-time engagement of EMA where victim and patient representatives were brought together at a dedicated meeting (2007)
Risk of progressive multifocal leukoencephalopathy (PML) with natalizumab: First-time invitation of patient representatives in a Scientific Advisory Group (SAG) meeting at EMA regarding a risk of an authorised medicine (2008)
Risk of venous thromboembolism (VTE) with combined hormonal contraceptives (CHCs): First-time dedicated meeting with patient and healthcare professional representatives for EMA's Pharmacovigilance Risk Assessment Committee established in July in 2012 under then new legislation (2013)
Risk of teratogenicity with valproate: First-time public hearing at EMA's Pharmacovigilance Risk Assessment Committee (PRAC) (2017)

[Bahri & Pariente 2021]

Public hearing for valproate in 2017

- Antiepileptic medicine which can cause birth defects and long-term development problems for the child exposed during pregnancy
- Concerns over ineffectiveness of previous risk minimisation measures/lack of implementation
- Written consultation, public hearing and a dedicated meeting
- Input from patients and healthcare professional was instrumental for regulatory decision making by EMA's Pharmacovigilance Risk Assessment Committee (PRAC)
- Updates to product information and additional risk minimisation measures, i.e. restrictions of use in female patients and a comprehensive programme for avoiding exposure during pregnancy, which includes individualised care, communication and disease management.
- Positive feedback from stakeholders and regulators on the public hearing

Valproate public hearing case study – Pilotable proposals for PRAC

A) Agreeing on appropriate RMM with stakeholders and catalysing healthcare leadership for implementation

B) Building-up stakeholder input on all elements critical to RMM implementation

C) Collaborating with all stakeholders for monitoring implementation and evaluating RMM

[Bahri P et al 2020]

Example from recent PRAC decisions – May 2025

Review of medicines containing finasteride and dutasteride concluded

Finasteride and dutasteride tablets: Measures to minimise risk of suicidal thoughts

Following an EU-wide review of available data on finasteride and dutasteride medicines, EMA's safety committee (PRAC) has confirmed suicidal ideation (suicidal thoughts) as a side effect of finasteride 1 and 5 mg tablets but concluded that the benefits of finasteride and dutasteride medicines continue to outweigh their risks for all approved uses. The frequency of the side effect is unknown, meaning that it is not possible to estimate it from available data.

A warning about mood changes, including depression, depressed mood and suicidal ideation, is already included in the product information for finasteride medicines. Patients who experience mood changes should seek medical advice and, if taking finasteride 1 mg, should also stop treatment.

Most cases of suicidal ideation were reported in people using 1 mg finasteride to treat hair loss due to male hormones. The product information for finasteride 1 mg will now also alert patients about the need to seek medical advice if they experience problems with sexual function (such as decreased sex drive or erectile dysfunction) that have been reported to contribute to mood alterations and suicidal ideation in some patients. A patient card will be included in the 1 mg finasteride package to remind patients of these risks and to advise them about the appropriate course of action.

Data assessed by the PRAC

In reaching its conclusion, the PRAC assessed available information on the effectiveness and safety of finasteride and dutasteride medicines, including data from clinical trials, EudraVigilance (the European database of reported suspected side effects), literature case reports and studies in the scientific literature.

The review identified 325 relevant cases of suicidal ideation in EudraVigilance, 313 reported for finasteride and 13 for dutasteride (with 1 case reported for both). These cases were considered either probably or possibly related to treatment, and most cases concerned patients treated for alopecia. These numbers were considered in the context of an estimated exposure of around 270 million patient years for finasteride and around 82 million patient years for dutasteride (1 patient year is the equivalent of one patient taking the medicine for one year).

The Committee also considered information received during the review from patients or their relatives, healthcare professionals, academics, and patient and consumer organisations, who shared their experiences with finasteride treatment and/or provided additional data on finasteride use.

[Extract from EMA website]

Example from recent PRAC decisions – November 2024

Doxycycline: currently available evidence not supporting link with risk of suicidality

EMA's safety committee (PRAC) has concluded that the currently available evidence is not sufficient to establish a causal relationship between the use of the antibiotic doxycycline and the risk of suicidality.

Doxycycline is a broad-spectrum antibiotic, widely used to treat a wide range of infections caused by bacteria such as acne, urinary and lower respiratory tract infections, dental infections, and skin infections. It is also used to prevent the development of certain infections, such as malaria.

A safety signal on the risk of suicidality, suicidal thoughts or actions with doxycycline was raised based on cases reported to the Finnish national competent authority, as well as further cases reported to EudraVigilance, the centralised European database of suspected side effects reports, and the medical literature.

The PRAC started its review in November 2023 and requested the marketing authorisation holders for doxycycline to perform a cumulative review of the data from all relevant sources.

The PRAC also requested a study based on real-world evidence, which includes data from electronic health records and disease registries, through DARWIN EU to facilitate the assessment of the signal. After reviewing all available evidence from spontaneous reports, the literature, the discussion on possible mechanisms and the study performed via DARWIN EU, the PRAC considered that the evidence is not sufficient to establish a causal relationship and that no update to the product information of doxycycline is warranted.

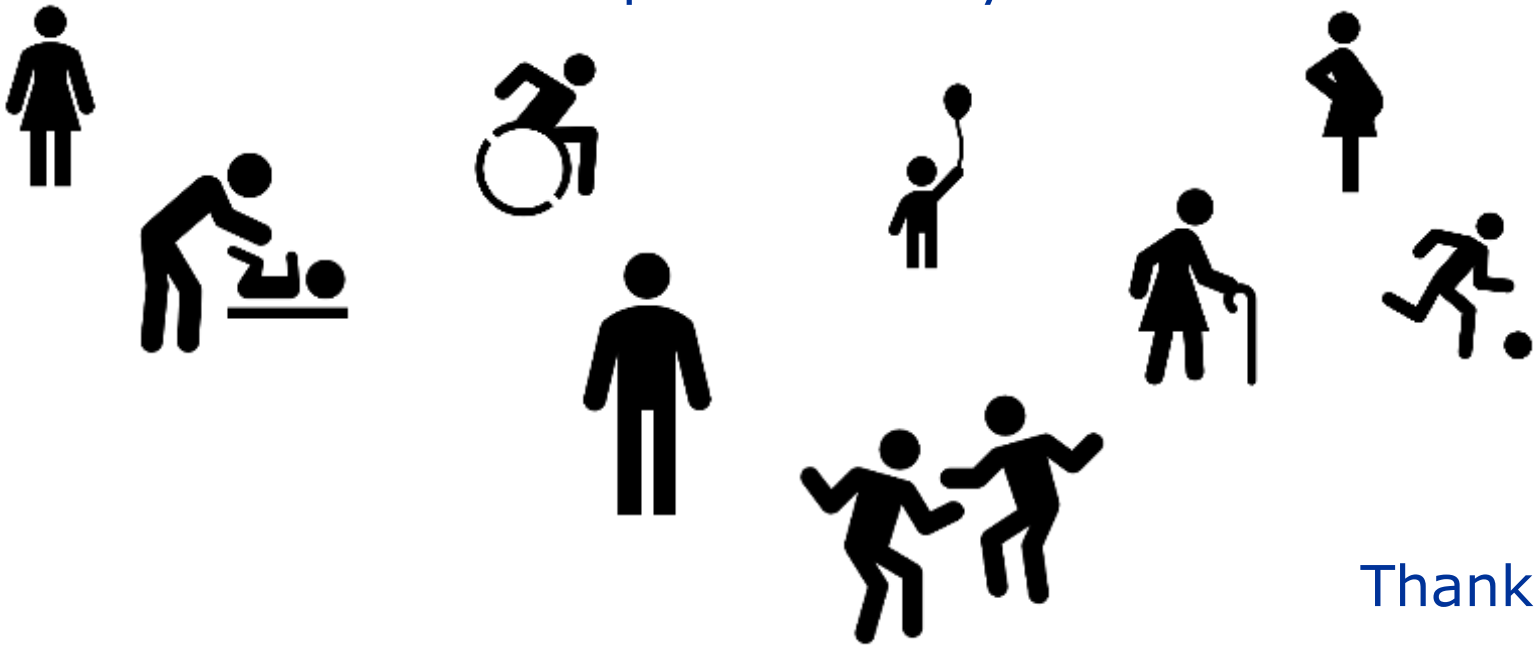
Suicide-related events in relation to doxycycline will be closely monitored and any new evidence will be discussed in the Periodic Safety Update Reports (PSURs).

[Extract from EMA website]

Implementation pathway of risk minimisation measures

[EU-GVP Module XVI rev 3]

Let’s work together from regulation through healthcare for patient safety!



Thank you!!!

References and further reading

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Some more details on risk minimisation measures

Risk minimisation measures

Control tools

Educational/safety advice tools

Package leaflet (PL)

Summary of product characteristics (SmPC)

Additional RMM tools enhance the SmPC/PL messages and are to be mentioned in the SmPC/PL

Tools for risk minimisation measures (RMM)

Routine (r)RMM tools:

- Product information
  - Package leaflet
  - Summary of product characteristics
  - Labelling of outer and inner packaging
- Legal status
- Pack size
- Design of packaging

Additional (a)RMM tools:

- Educational/safety advice tools
  - Guides for patients or healthcare professionals
  - Healthcare professional checklist
  - Risk awareness dialogue form
  - Patient card
  - Patient diary
- Risk minimisation control tools (e.g. qualification, certificate, traceability)

[EU-GVP Module XVI]

Intended actions for risk minimisation, e.g.

- Observe indications and contraindications
- Follow recommended dosing and schedule
- Minimise potential for medication errors
- Avoid risk factors, e.g. alcohol, medicines with adverse interactions
- Take measures to protect against adverse reactions, e.g. add medication, request a pregnancy test, postpone blood donation
- Monitor for early signs and symptoms of adverse reactions
- Manage adverse reactions to limit their impact, possibly stop using the medicine

Frequency categories of adverse reactions

Very common (≥1/10 patients)

Common (≥1/100 to <1/10 patients)

Uncommon (≥1/1,000 to <1/100 patients)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

"Frequency not known (cannot be estimated from the available data)"

[SmPC Guideline]

Thank you

Further information

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