Medication Errors

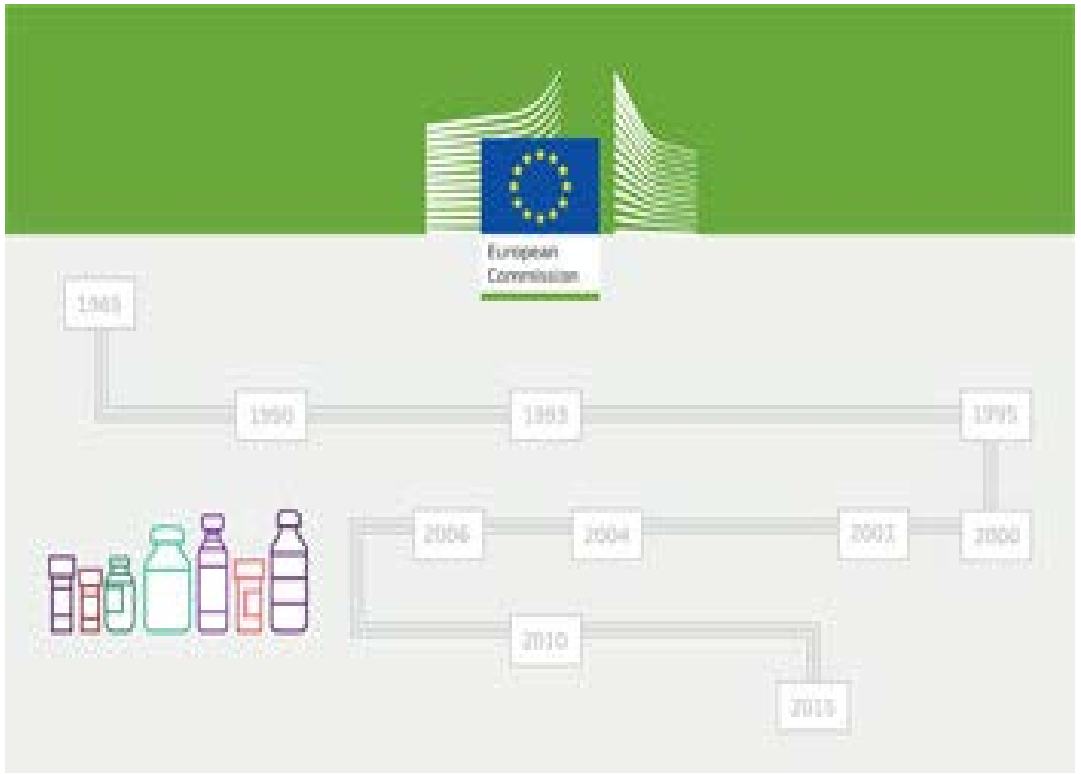
Experience of Pharmacovigilance Risk Assessment Committee with use of regulatory tools

Dr June Raine Chair of PRAC
Medicines & Healthcare products Regulatory Agency, UK

Information Day on Medication Errors
London UK, 20 October 2016

Outline

- **Where have we come from** – new EU regulatory tools for identification & minimisation of medication errors
- **What has been learned so far** - experience to date of applying regulatory tools to medication errors by the Pharmacovigilance Risk Assessment Committee
- **How are we moving forward** – challenges and opportunities to come



- **50** years of medicines regulation
- **21** years of EMA
- **6** years of PhVig legislation
- **4** years of PRAC
- **1 year of Good Practice Guide on medication errors**

3

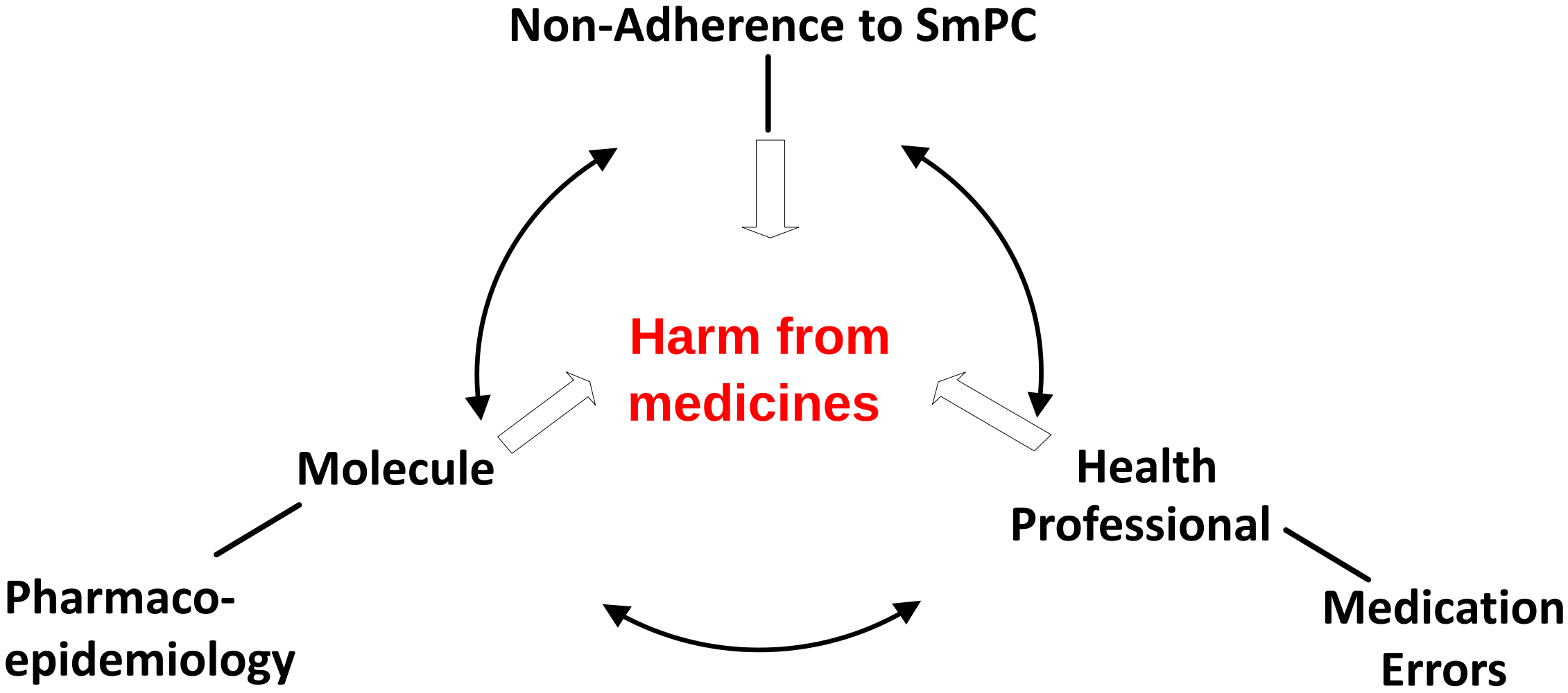
New Definition of Adverse Reaction

Directive 2010/84/EU

*For the sake of clarity, the **definition of the term 'adverse reaction'** should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from*

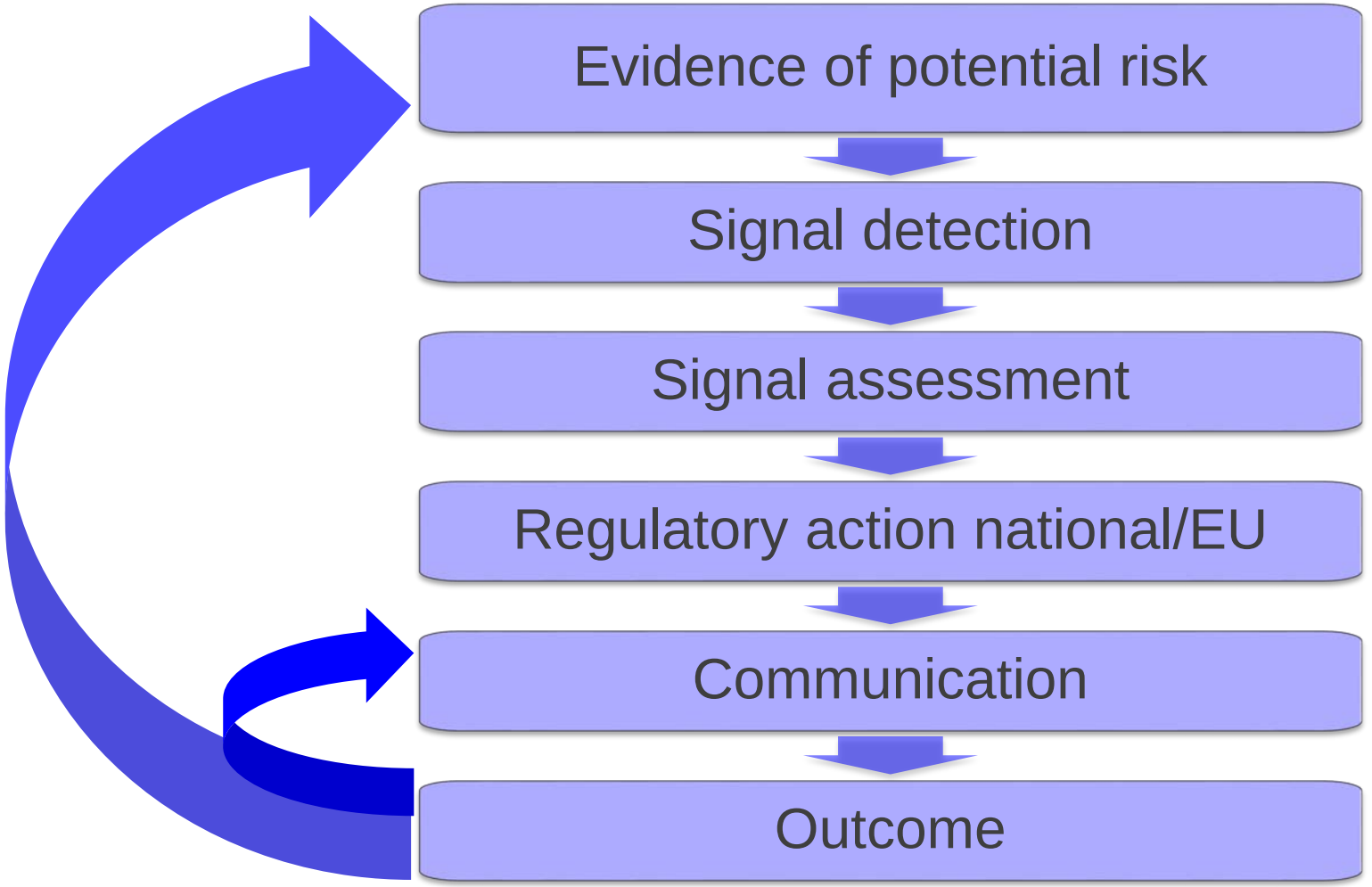
- ***Medication errors***
- *Uses outside terms of marketing authorisation (includes misuse)*

Broader scope of harms associated with medicines



DIA DEVELOP INNOVATE ADVANCE

Pharmacovigilance - a cycle of activities



Pharmacovigilance Risk Assessment Committee

All aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit

What types of decisions does PRAC make?

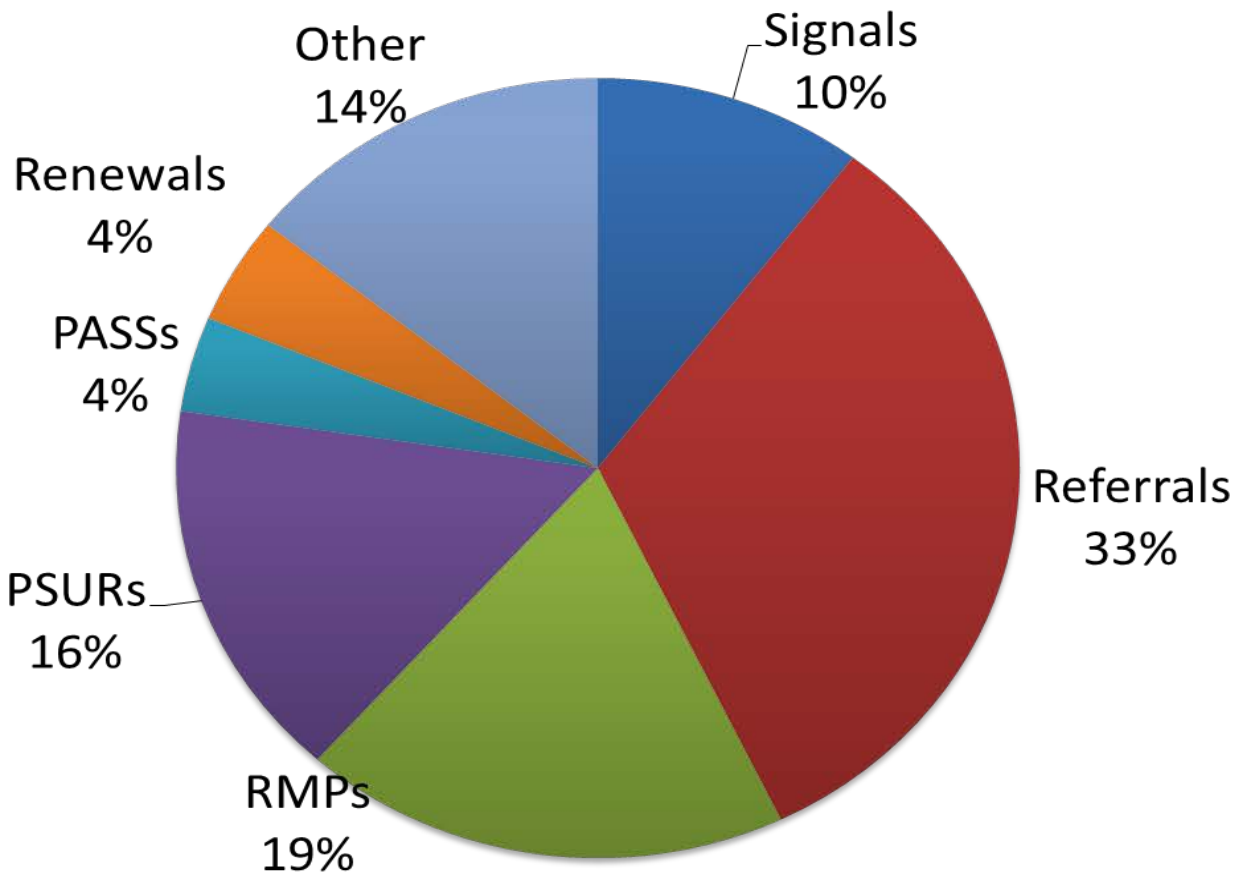
- **Drug safety signals**
  - evaluating signals and advising on action

- **Regulatory action on benefit risk issues**
  - urgent and non-urgent referrals
  - periodic safety update reports

- **Proactive pharmacovigilance**
  - advising on risk management plans
  - post-authorisation studies

- **Transparency & communication activities**
  - agenda and committee minutes, DHPCs

% of PRAC plenary discussion time 2013, based on total hours



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Data sources routinely used to identify risks

Around 50% signals derive from Eudravigilance ICSRs

Other sources
- PSURs
- RMPs
- post-authorisation safety studies
- published literature

>54% serious safety issues detected earlier if EV used in addition to other resources

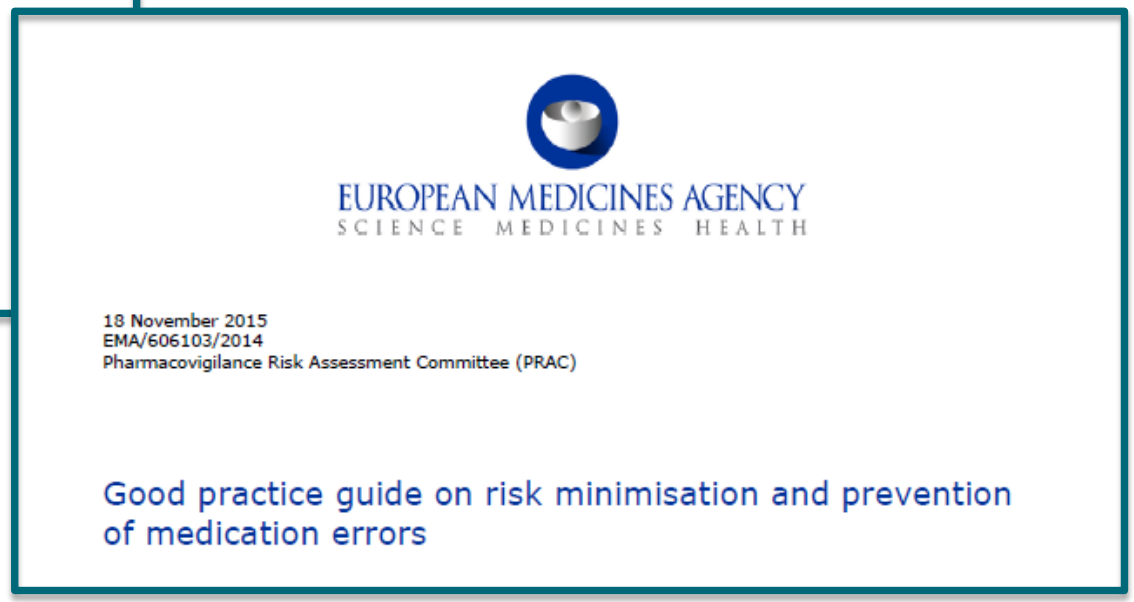
Drug Safety 33(6) 475-487

Medication Errors Good Practice Guides


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2015
EMA/762563/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Good practice guide on recording, coding, reporting and assessment of medication errors


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 November 2015
EMA/606103/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Good practice guide on risk minimisation and prevention of medication errors

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000570.jsp

11

Good Practice Guide on Medication Error - PRAC perspective

- **EU regulatory network in collaborative inter-stakeholder approach**, launching new initiatives for cooperation amongst NCAs & patient safety organisations

- **First ME guidance at EU level combining pharmacovigilance & patient safety** aspects to prevent harm from errors, including new tool - root cause analysis

- **GPG complementary to guidelines on GVP and other EMA guidelines**

  I - to improve **reporting, coding and analysis** of ME resulting in ADRs in EV

  II - to ensure **risk of ME is addressed during entire product life-cycle**

  - **harmonise risk minimisation** & prevention strategies for similar errors
  - product specific addendum on **high strength/fixed combination insulins**

New methodologies for investigating ME error signals

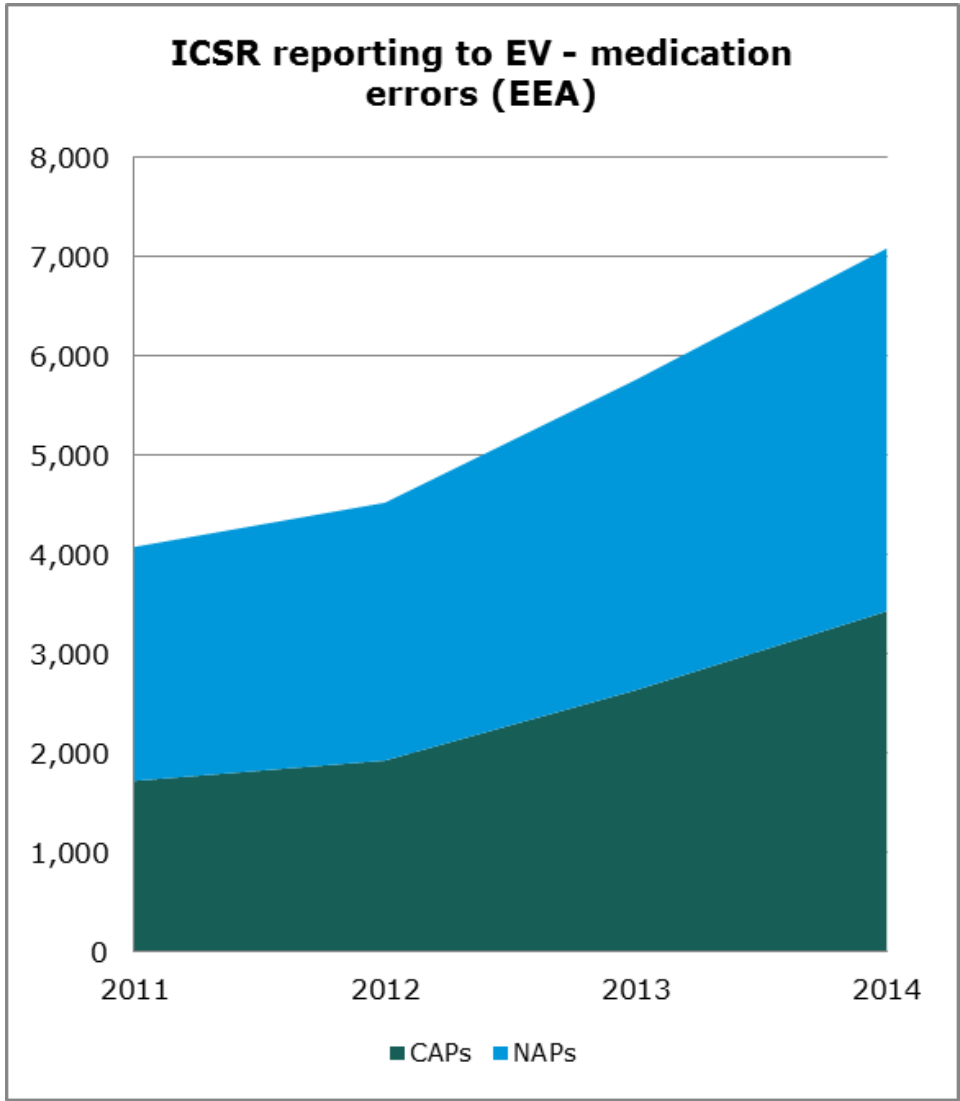
- Systematic approach to evaluation making best use of latest available guidance and methodologies
- ME Signal evaluation to include Root Cause Analysis
- Use of Failure Mode and Effects Analysis Framework

Good Practice Guide on Medication Error - PRAC perspective

- **Clear definition of medication error** including potential, intercepted errors relevant for regulatory decision making
- **Recognition of patterns** or increased frequencies and of causes, contributing factors & clinical consequences of ME, including mitigating actions
- **Expanded MedDRA terminology** version 19.0 in March 2016 and clarifications in PTC documents on coding conventions further increase granularity of ME reporting (ie. type of error, stage of medication use process can now be coded etc.)
- **Electronic Reaction Monitoring Reports** made available to national competent authorities support signal detection activities via new SMQ for ME and separate ME reports (AMOMO)

Medication errors – EU network strategy approach

Deliverable ▸ / Framework ▾	Good Practice Guide Coding & Reporting	Good Practice Guide Risk Minimisation & Prevention	Concept Paper Working Group	Awareness Campaign Reporting	Communi-cation Toolbox
SCOPE (Strengthening Collaboration for Operating Pharmacovigilance in Europe)					
EMA / EU-Regulatory Network (PhV Legislation Implementation)					
MedDRA Points to Consider Working Group					
Patient Safety & Quality of Care Working Group					



Overview of PRAC procedures with ME addressed

ME in PRAC procedures 07/2012 - 07/2016	
Initial MA applications(CAPs, Art. 58)	8
Line extension	1
Signal	3
PSUR, PSUSA	27
RMP (new and updates)	33
PASS (protocols and reports)	5
QRD/NRG issue	2

Signal Fentanyl patch & accidental overdose in children

U.S. Food and Drug Administration
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For Consumers

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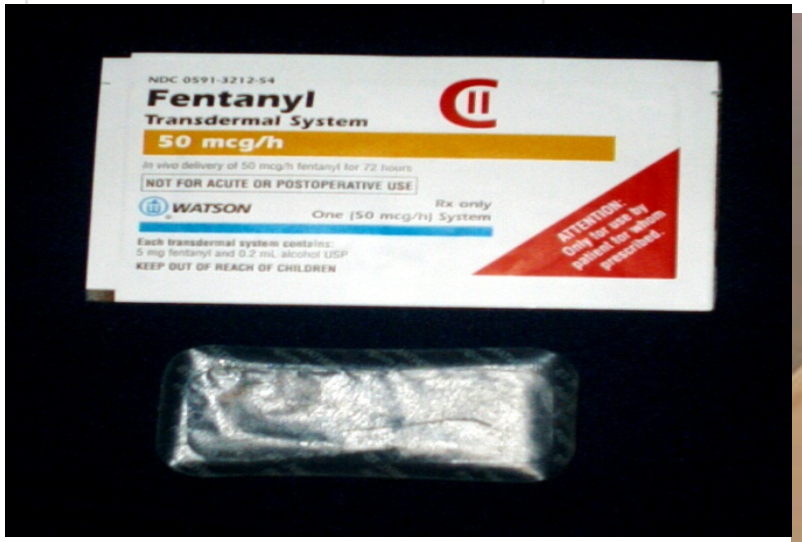
Consumer Updates

Fentanyl Patch Can Be Deadly to Children

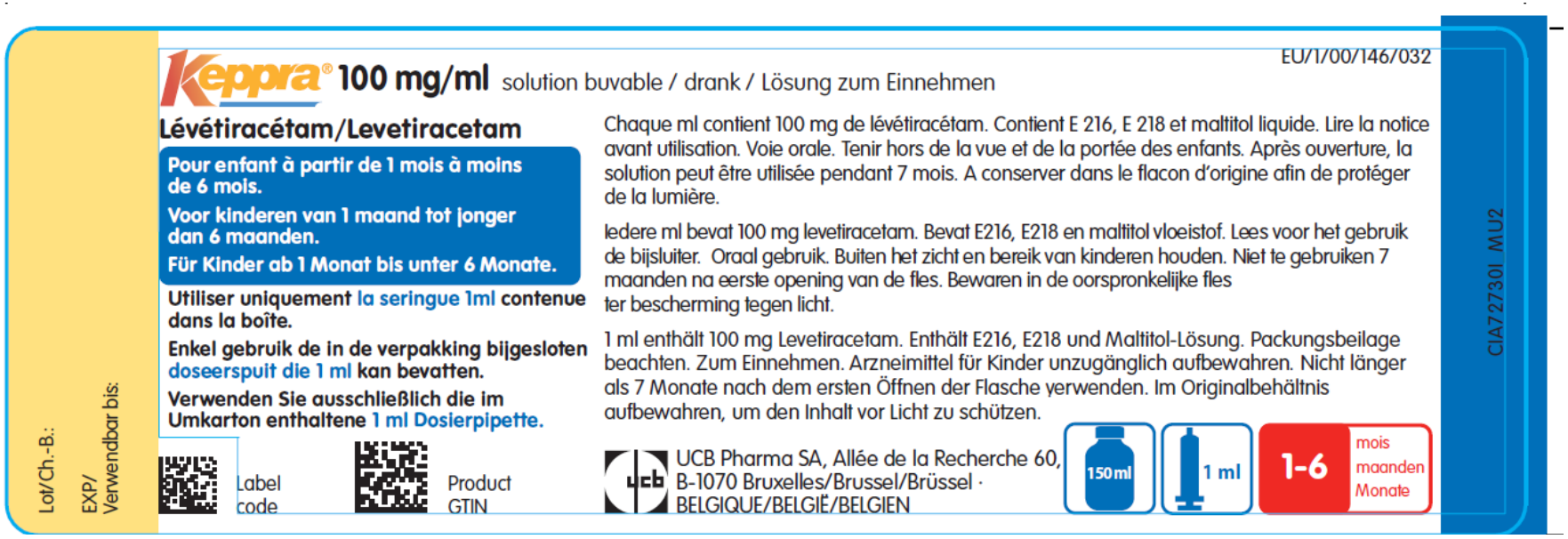


- Signal of overdose in children following inappropriate disposal
- National communications
- New packaging?

DIA DEVELOP INNOVATE ADVANCE

Signal – levetiracetam & paediatric overdose

- Case reports of paediatric overdose with oral solution leading to coma & respiratory depression, mostly in paediatric patients aged 3 m to 15 years
- Different container sizes and dosing syringes for 1ml, 3ml, 10ml marketed
- 20% cases associated with misuse of syringe/dosing spoon
- Readability of PIL to be assessed especially where most reports originated
- Proposals for outer packaging adding weight range along with age range



Levetiracetam oral solution - communications

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Direct Healthcare Professional Communication

27 September 2016 *to be actualized*

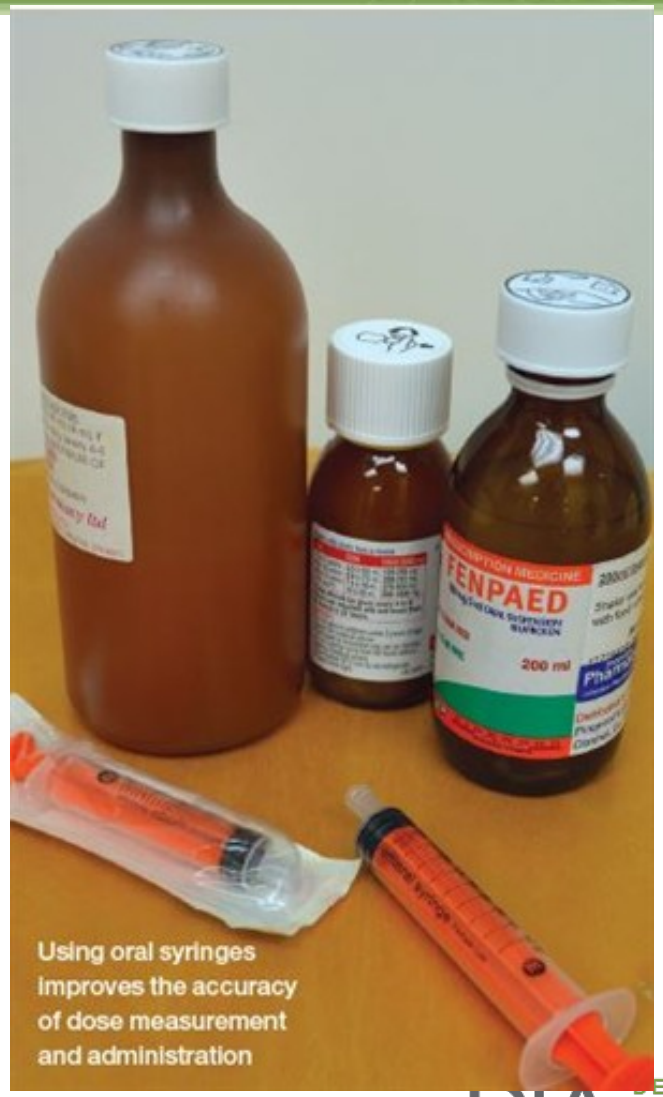
Levetiracetam containing products 100 mg/ml oral solution presentations: Risk of medication errors associated with overdose

Dear Healthcare Professional,

UCB[1] *<name of local affiliate>* in agreement with the European Medicines Agency and the *<National Competent Authority >* would like to inform you of the following:

Summary

- Cases of an up to 10-fold accidental overdose with Keppra (levetiracetam) oral solution have been reported. The majority of cases occurred in children aged between 6 months and 11 years. The use of an inadequate dosing device (e.g. confusion between a 1ml and a 10ml syringe, resulting in a 10-fold overdose) was identified as an important cause



Levetiracetam oral solution - communications

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 October 2016
EMA/668736/2016

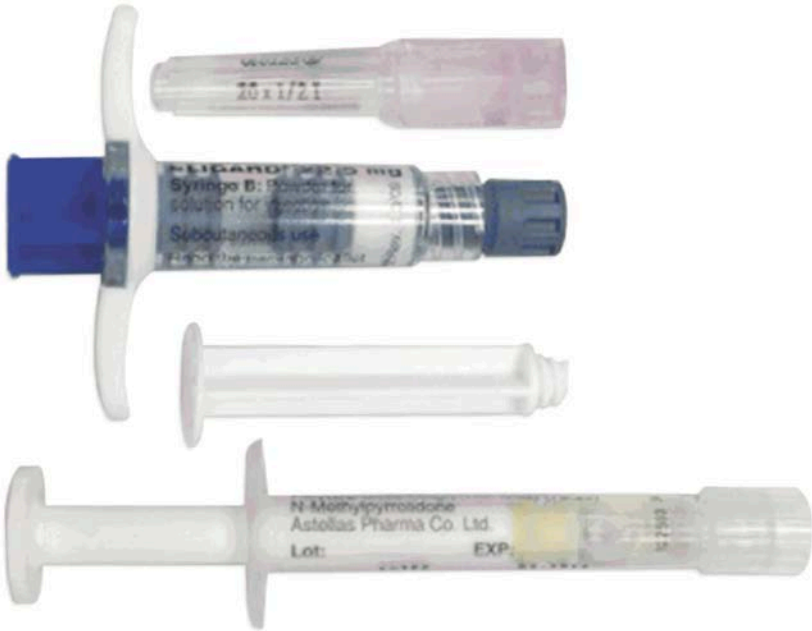
EMBARGO – DO NOT PUBLISH BEFORE
TODAY, FRIDAY 14 OCTOBER 2016, 12:00 HRS UK TIME

EMA recommends measures to ensure safe use of Keppra oral solution

Medicine should only be used with dosing syringe included in the package

Signal – leuprorelin wrong administration technique

- 11 cases from ES FEDRA database raised signal of wrong technique in administration process potentially leading to inadequate dose
- Cumulative review, including root cause analysis - ME during preparation, mixing & administration
- Risk minimisation measures, DHPC & communication plan informing on correct reconstitution & administration
- Periodic surveys of targeted healthcare providers
- Parallel consideration of development of improved presentation



PSUSA Paediatric iv paracetamol

- Accidental overdose of neonates and infants following confusion between mg and ml led to product information updates
- Based on cumulative reported cases, safety concern of medication errors considered an “important identified risk” in risk management plan
- National communications and ongoing monitoring
- Effectiveness of risk minimisation measures MAHs and cumulative analysis in the next PSUR

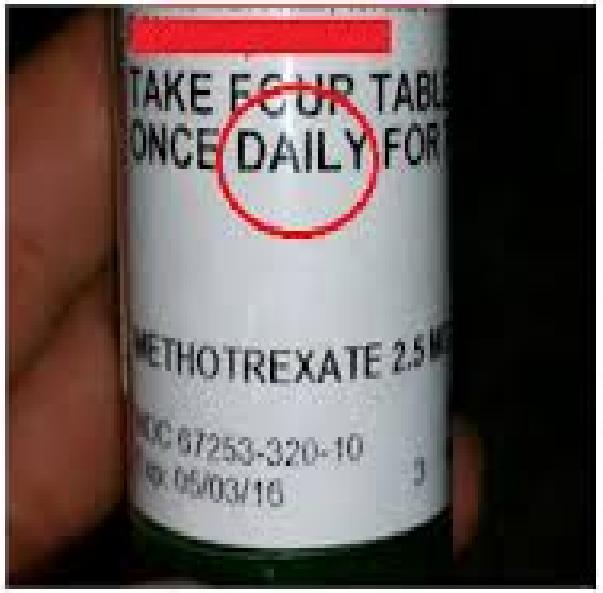
Risk Management Plan - Methotrexate

- **Product information text in PIL and SmPC**
  - Instructions in section 4.2

- Other **risk minimisation measures –**
  - Pack size and design
  - “Methotrexate is usually taken once a week”

- Pharmacist patient medication record systems to flag up warning to dispensing staff?

- Confusion between different tablet strengths?



The above image illustrates an error with methotrexate. The doctor wrote for the patient to take 4 tablets weekly. But the pharmacy instructed the patient to take 4 tablets daily.

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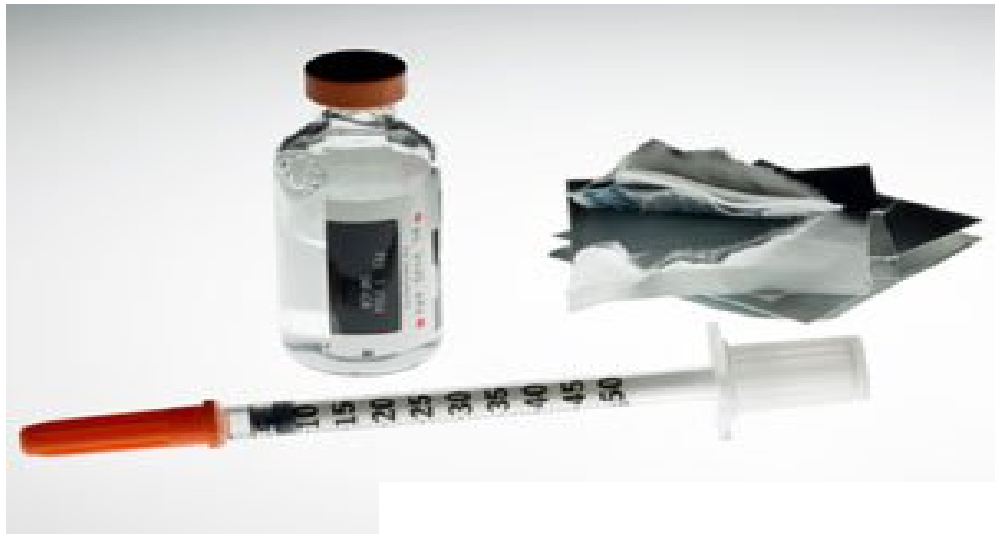
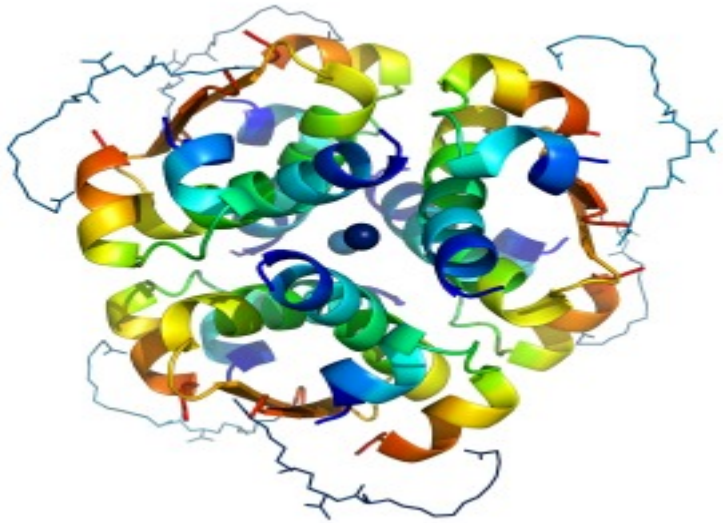
Risk management plans - insulins





New generation of insulins

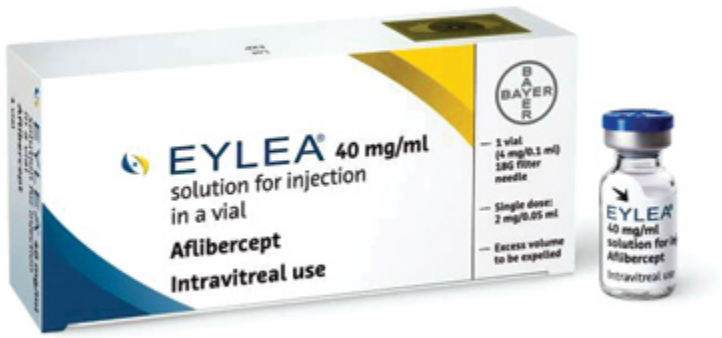
Potential risk of error

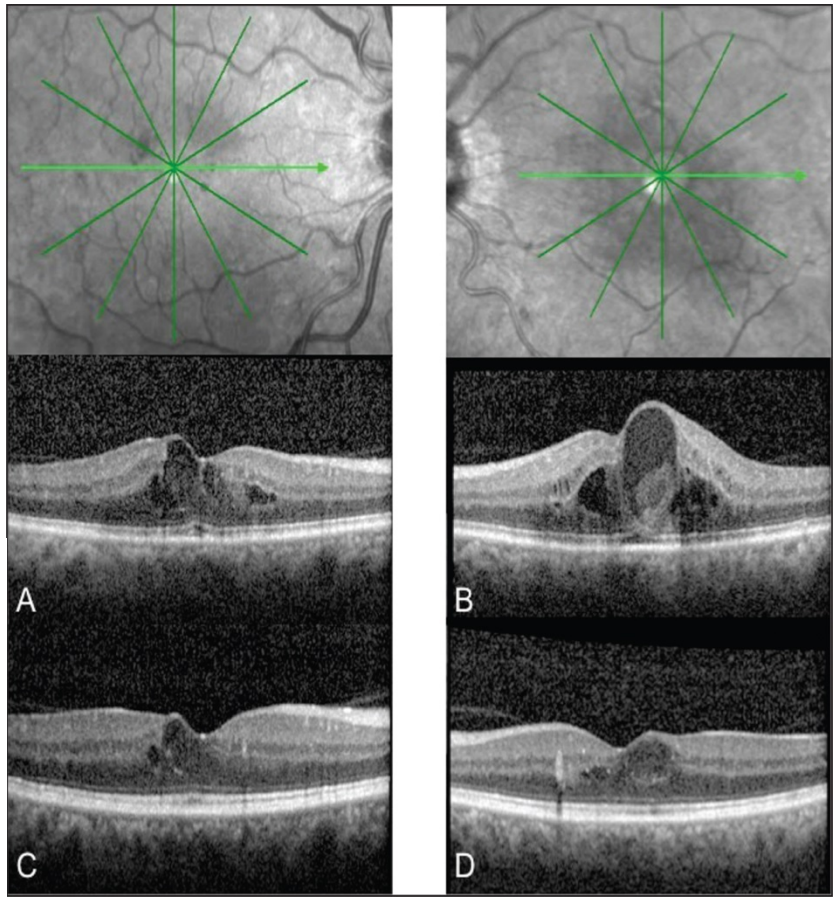
- higher strengths
- new combinations

Addendum to GPG supports consistent approach

PASS study – aflibercept overdose

- Extension of indication of indication for central retinal vein occlusion
- Potential risk of medication errors (overdose due to pre-filled syringe)
- Observational PASS to evaluate physician and patient knowledge of safety and safe use information





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Effectiveness of risk minimisation measures - bivalirudin

- ME including reports describing patients receiving bolus without subsequent infusion with risk of ischaemic events included in RMP
- Educational materials with dosing instructions
- Eurovision 2 PASS to assess current drug utilisation patterns for percutaneous coronary intervention following implementation of new risk minimisation measures (HCP dosing card, slide deck, training programme).
- To assess frequency of bolus-only dosing without subsequent infusion and frequency of dose adjustment in renally impaired patients.

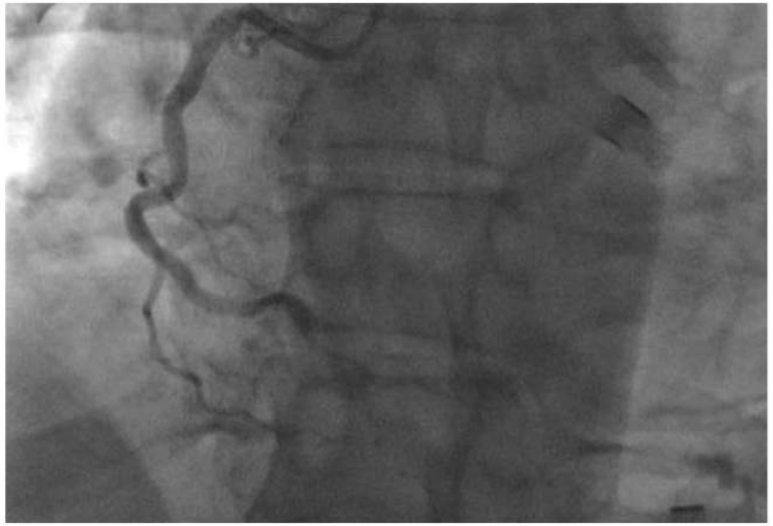
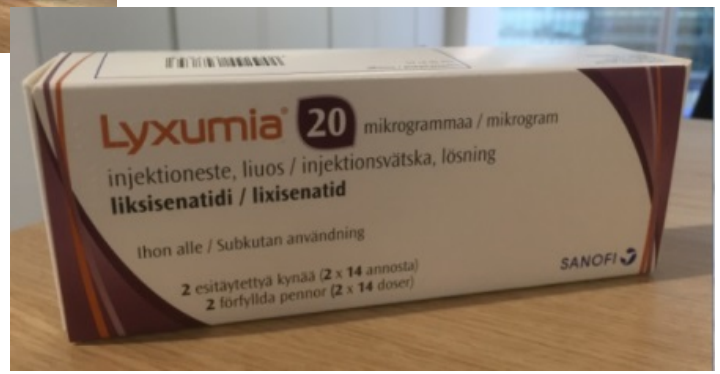


Figure 3. 100% RCA occlusion (Ikari Right 1.0).

Request from CHMP for advice



Lysanxia - prazepam

anxiety & delirium tremens

Lixiana - edoxaban

prevention of stroke & systemic embolism

Lyxumia - lixisenatide

Type 2 diabetes

27

EMA communications on medication errors

- To promote the safe use of medicines, EMA systematically communicates to patients & HCPs on any additional measure decided upon at EU level on dedicated webpage
- **Aim:** prevent medication errors, increase awareness of additional risk minimisation measures recommended by PRAC and CHMP
- Ensure medicines are used correctly and reduce risk of medication errors
- Communications are accessible via the European public assessment reports (EPARs) of these medicines and via webpage

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DIA DEVELOP INNOVATE ADVANCE

Communication	Published
EMA warns **Noxafil** tablets & oral suspension have different doses, not interchangeable	24/06/2016
Educational brochure for healthcare professionals, diary for patients using **Uptravi**	31/05/2016
Measures to avoid medication errors with **Exjade**	22/04/2016
Educational brochure & video to be given to HCPs to ensure **Obizu**r is used correctly	15/12/2015
Measures to avoid medication errors with **Blincyto**	08/12/2015
Measures to ensure that Ionsys is handled and used correctly	30/11/2015
Compliance card to be given to patients using **Farydak** to ensure correct use	27/11/2015
Guidance on prevention of medication errors with **diabetes medicines** containing insulin and a non-insulin active substance	27/11/2015
Guidance on prevention of medication errors with **high-strength insulins**	27/11/2015
EMA recommends measures to ensure safe and effective use of **Strensiq**	26/06/2015
Q & As on recommendations to prevent administration errors with **Velcade**	20/01/2012

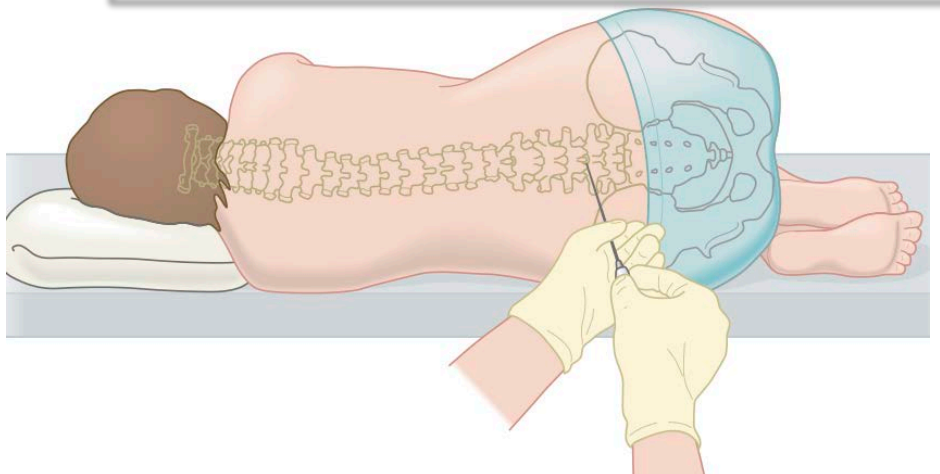
Communications – bortezomib intrathecal administration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 January 2012
EMA/34910/2012
EMEA/H/C/000539

Questions and answers

Recommendations to prevent administration errors with Velcade (bortezomib)



- When possible, different connectors for medicines to be administered via intrathecal or intravenous route
- When possible, intrathecal chemotherapy should be administered at different time than any other parenteral chemotherapy
- Syringes should be clearly labelled with name of medicine and route of administration
- Procedures for double checking labelling of syringes before administration
- Intravenous and intrathecal injections should be handled only by suitably trained HCPs
- HCPs involved in administration or management of cancer chemotherapy should be trained and informed of dangers of intrathecal administration of Velcade and measures to prevent this

30

Challenges

- ADR reporting – definition of ME for pharmacovigilance purposes, MedDRA coding concepts (e.g. off-label use, abuse, misuse, etc.) sometimes difficult to distinguish
- Encouraging HCP reporting of ME and overcoming legal aspects with regards to liability in some MS - no blame reporting culture
- Consolidation of information from patient safety (incident) reporting systems for regulatory purposes (Art 107 (5)a) - this is in the remit of Member States' competent authorities, further collaborative work is required to improve exchange of information on ME between pharmacovigilance and patient safety world
- Harmonisation of error prevention strategies for therapeutic areas across MS e.g. labelling and colour coding conventions for certain therapeutic areas

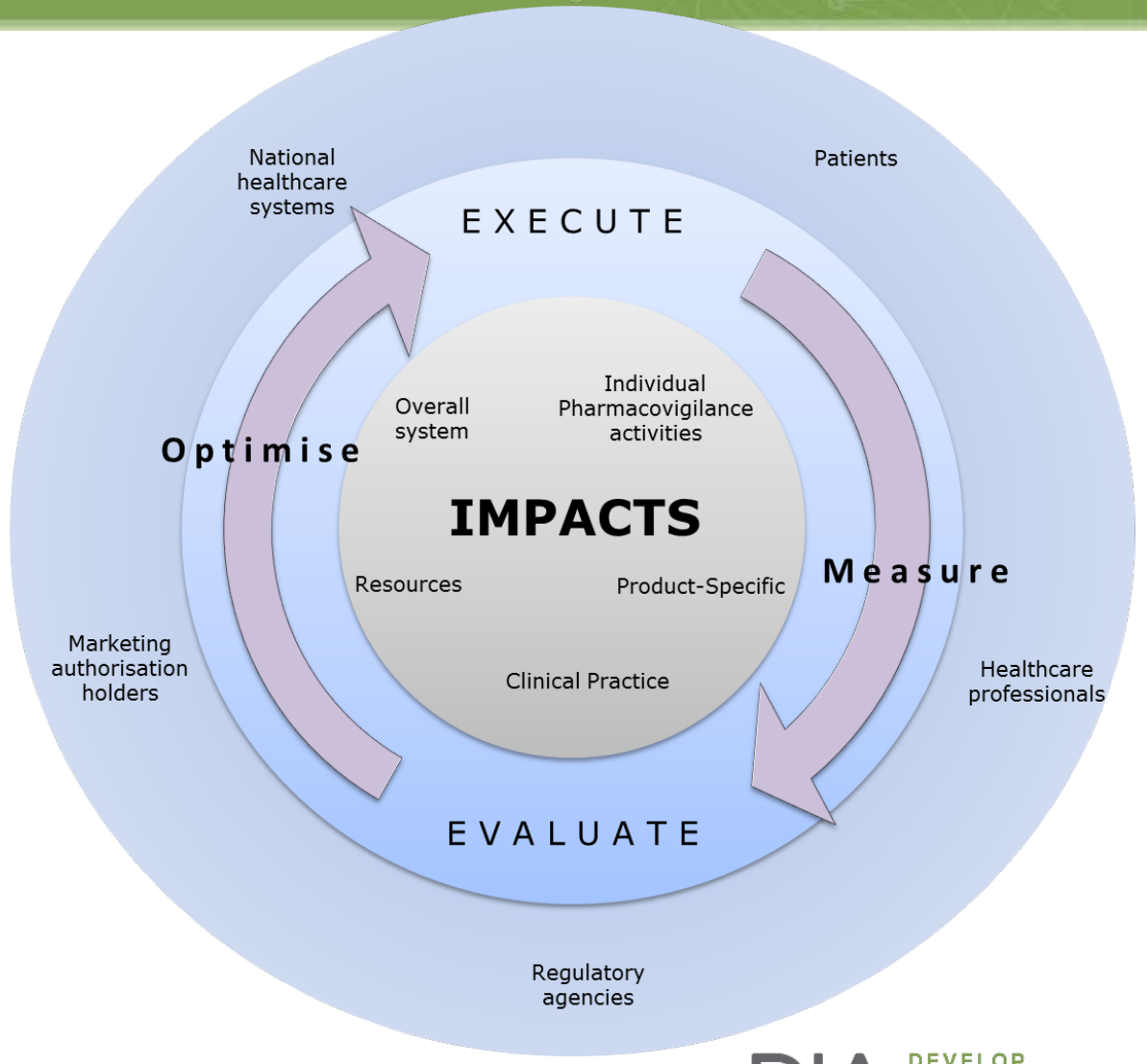
Opportunities

- Optimal use of regulatory tools
  - additional monitoring “black triangle”
  - improved labelling
  - protocols for HCPs?
- New data sources
- PRAC Impact strategy

PRAC Strategy for measuring impact

PRAC strategy includes a three year work plan underpinned by collaboration with industry through the quarterly platform meetings with EU associations, and is:

- ✓ Health-focused;
- ✓ Science-based;
- ✓ Leverage ongoing work by:
  - EMA
  - NCAs
  - Academia
  - Industry
- ✓ Prioritise key tools and methods



33

Conclusions

PRAC is committed to reducing the burden of medication error

Regulatory tools and new methodologies are yet to be optimally used

Patient and healthcare professional members of PRAC play a central role

Key to success is collaboration by all stakeholders

Thank you for your attention!

Ask