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Identification of preventable Adverse Drug Reactions from a regulatory perspective

March 1st 2013, EMA Workshop on Medication Errors

Presented by Almath Spooner, Pharmacovigilance and Risk Management Lead, IMB and Vice Chair, Pharmacovigilance Risk Assessment Committee.

Outline of presentation

1) Role of the regulator.

2) Taking action on drug safety issues – strengthening the link between safety assessment and regulatory action.

3) ‘Preventability’ and Goals for risk management.

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What is the role of the Regulator?

1. Availability of medicines, particularly innovative treatments and technologies, without unnecessary delay

2. Proactive vigilance based on best evidence and prompt risk management

3. As much information to patients and healthcare professionals as possible on benefits and risks

4. Demonstrate that risk has been effectively managed

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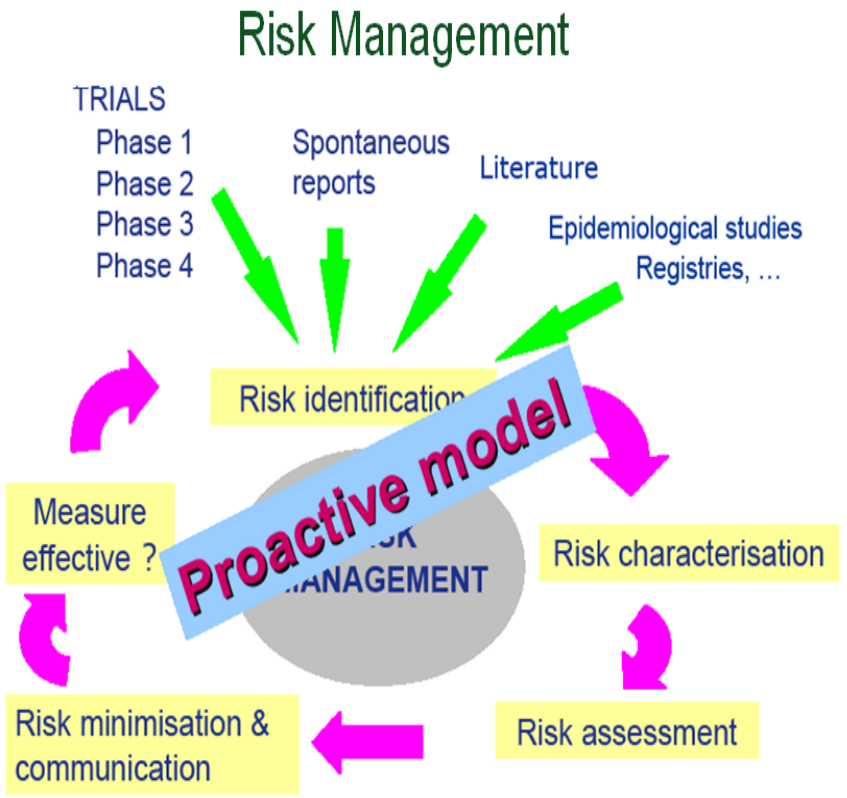
Benefit - Risk Management

Goal - Promote and protect public health by reducing burden of adverse drug reactions through ***effective risk minimisation*** and **optimising use** of medicines – optimise the benefit-risk margin of medicines used in everyday healthcare practice.



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Partners

- Patients and carers
- Healthcare professionals
- Patient safety organisations
- Pharmaceutical industry
- Medicines regulators
- Academics, scientific community.
- Payers

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Ensuring safe and effective use of medicines

Regulatory Framework

-EMA's legal basis for marketing authorisations

' authorisation decisions […] should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned '.

Recital 13, REGULATION (EC) No 726/2004

Medicines Pathway

- Patient history – obtain, document
- Prescribing – select and prescribe
- Transmission/transcription
- Pharmacy – interpret, prepare, dispense, clinical check.
- Patient – concordance + compliance, understanding.
- Monitoring – interpret + response check.

-> **Impact on health outcomes**

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Pharmacovigilance and Risk Management

- Collect and analyse data
- Detect and manage signals
- Evaluate safety issues
- Benefit risk assessment
- Regulatory action / risk minimsation
- Communication
- Audit – check that the measures are effective.

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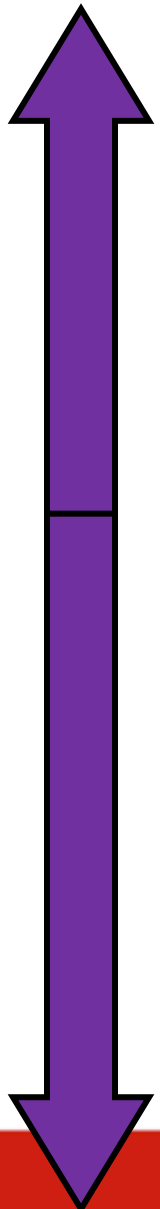
Spectrum of evidence considered

Variable degree of certainty
(e.g. causality, incidence)



- Meta-analysis
- Clinical trial
- Prospective cohort (with controls)
- Case control study
- Observational cohort (no controls)
- Individual case report / case series

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Objectives of the pharmacovigilance legislation

- Clear roles and responsibilities
- Better evidence, more science based.
- **Better link between assessments and regulatory action**.
- Risk based/proportionate
- **Increased proactivity/planning**
- Reduced duplication/redundancy
- Integrate benefit and risk where appropriate
- Ensure robust and rapid EU decision-making
- **Engage patients and healthcare professionals**
- Increase transparency and accountability
- **Provide better information on medicines**

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Strengthening the link between safety assessment and risk management

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Lancet Publication – Dec 1961

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide ('Distaval') with harmful effects on the fœtus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

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Pharmacovigilance – a network effort

REPUBLIC OF CYPRUS

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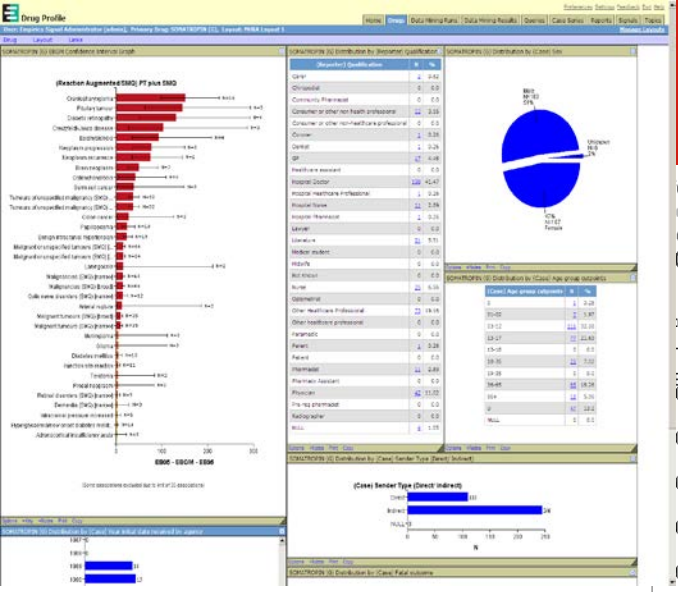


ormin

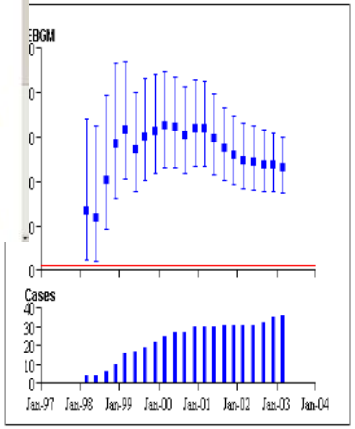
Period Begin: 03/01/1998 End: 03/01/2003

n gap increased (PT)

d gas and acid base analyses (HLT)

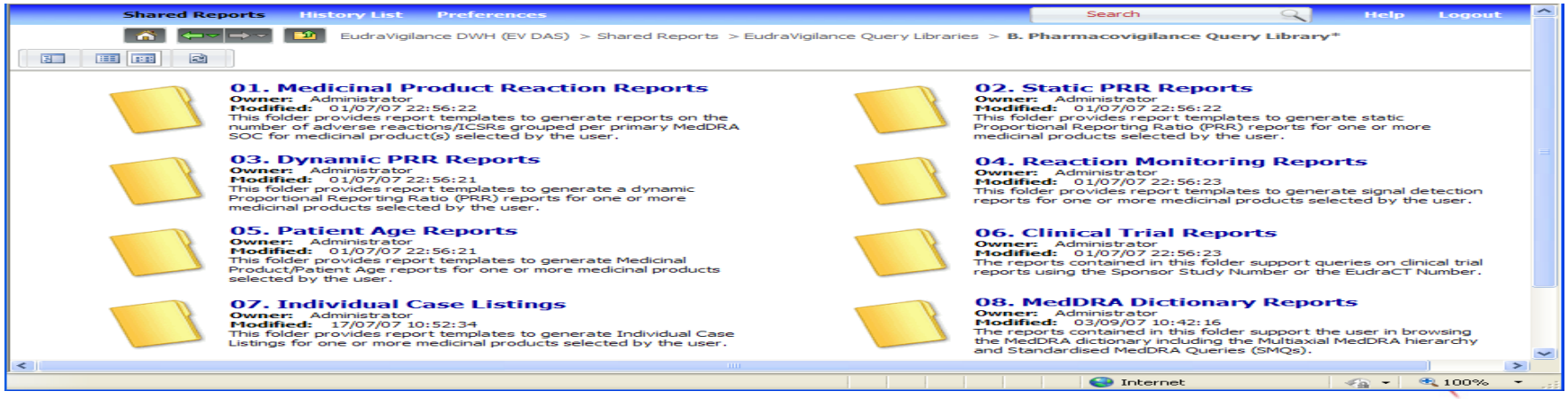
(SOC)

utes: Serious=81%, Death=41%, FDA Category=NONE, Quadrant=A



	Current	Prior	Diff
N	36	35	+1
EB05	34.632	35.568	-0.936
EBGM	45.993	47.435	-1.442
EB95	60.117	62.233	-2.116
PRR	55.101	56.982	-1.881
CHISQ	1455.591	1460.578	-4.987

Reaction SOC / Reaction PT	Metrics	PRR (-)	PRR	PRR (+)	New Total	New EEA	EEA	New Non EEA	Non EEA	New Fatal	Fatal
Blood and lymphatic system disorders											
Agranulocytosis		0.14	0.44	1.35	1	3	0	2	1	1	0	0
Anaemia		1.94	2.31	2.77	7	64	0	10	7	54	1	6
Anaemia megaloblastic		1.05	7.56	54.51	1	1	0	0	1	1	0	0
Aplasia pure red cell		2.44	4.42	8.00	1	10	0	3	1	7	0	1
Bone marrow depression		2.09	3.07	4.52	5	17	0	2	5	14	0	2
Granulocytopenia		0.42	1.32	4.09	1	2	0	1	1	1	0	1
Haemolytic anaemia		1.19	2.15	3.89	1	9	1	3	0	6	0	2
Histiocytosis haematophagic		0.88	3.53	14.18	1	2	0	0	1	2	0	1
Hypoplastic anaemia		1.97	14.43	105.53	1	1	0	0	1	1	1	1
Idiopathic thrombocytopenic purpura		0.08	0.56	3.98	1	1	0	0	1	1	0	0
Leukocytosis		0.32	0.85	2.26	1	4	0	1	1	3	0	0
Leukopenia		1.57	2.12	2.85	2	33	0	7	2	26	0	3
Lymphadenopathy		0.81	1.62	3.24	1	8	0	1	1	6	0	0
Macrocytosis		0.60	4.33	31.01	1	1	0	0	1	1	0	0
Neutropenia		0.75	1.12	1.69	4	20	1	3	3	17	0	1
Normochromic normocytic anaemia		0.32	1.30	5.19	2	2	2	2	0	0	0	0
Pancytopenia		1.31	1.81	2.51	6	30	0	7	6	23	2	7
Red blood cell abnormality		0.89	6.44	46.30	1	1	0	0	1	1	1	1
Thrombocytopenia		0.60	0.88	1.28	5	23	1	7	4	16	0	5
Thrombotic thrombocytopenic purpura		5.17	9.39	17.05	1	10	0	2	1	8	1	3
Cardiac disorders											



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Signal Detection

Alvarez 2010, Drug Safety 33(6), 475-487.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 May 2010
EMA/335078/2010
Press office

Press release

EudraVigilance signal detection methods help detect drug safety issues earlier

Adding EudraVigilance statistical signal detection methods to routine drug safety monitoring methods leads to earlier detection of safety issues

An evaluation of the use of the European Medicines Agency's statistical signal detection method in the adverse drug reaction data collected in the EudraVigilance database has shown a significantly earlier detection of drug safety issues in about 54% of cases where a clinically important adverse drug reaction report was found (compared to 'routine' pharmacovigilance).

The study which was published in Drug Safety, the journal of the International Society of Pharmacovigilance, was carried out by the European Medicines Agency and was conducted in relation to centrally authorised medicines. It provides direct evidence for a strong additive role of EudraVigilance signal detection methods. The study also underlines the importance of established pharmacovigilance systems such as active surveillance, clinical trials or periodic safety update reporting, and concludes that a combination of routine pharmacovigilance and statistical signal detection provides the optimal safety monitoring with earlier detection and better management of safety issues, thereby improving the protection of public health.

Signal Management by PRAC

- PRAC prioritises according to the available information, strength of evidence and public health context.
- Where appropriate, signals escalated to a formal EU safety referral.
- Activity reflected in agendas and minutes.

Adverse (Drug) Reaction

- *‘A response to a medicinal product which is noxious and unintended’*

- Regulatory action outside the 'normal conditions of use‘ - Dir 2010/84/EU, amended articles 116 and 117 (deletion of 'normal conditions of use')

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Regulatory action to safeguard public health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 January 2013
EMA/PRAC/731552/2012
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)
Draft agenda of meeting 7-10 January 2013

2. EU Referral Procedures for Safety Reasons: Urgent EU Procedures

2.1. Newly triggered procedures

2.1.1. Tetrazepam (NAPs)

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. Exenatide – BYETTA (CAP), **BYDUREON** (CAP); **Liraglutide – VICTOZA** (CAP)

- Signal of gastrointestinal stenosis and obstruction

Status: *for initial discussion*

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

5.1.1. Afatinib (dimaleate)

- Evaluation of the RMP in the context of an initial Marketing Authorisation Application procedure

Status: *for discussion and agreement of advice to CHMP*

6. Assessment of Periodic Safety Update Reports (PSURs)

6.1.1. 5-aminolevulinic acid hydrochloride – AMELUZ (CAP)

- Evaluation of a PSUR procedure

Status: *for discussion and agreement of recommendation to CHMP*

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2013

CONCEPT OF ‘PREVENTABILITY’ AND RISK MANAGEMENT GOALS

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UK

- 6.5% hospital admissions in UK
- ADRs were responsible for death of 0.15%
- **72% were classified as avoidable**

Pirmohamed et al

2004 BMJ 329; 15-19

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Germany

- Incidence of hospitalization due to at least ‘possible’ serious outpatient ADRs - 3.25%
- Average treatment costs of a single ADR €2250
- Total costs - €434 million per year for Germany
- **Preventable cases** 20.1% - potential saving of €87m per year

Rottenkolber 2011 Pharmacoepi & Safety; 20: 626 -634

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Ireland

EMJ Online First, published on February 6, 2013 as 10.1136/emermed-2012-201945

Original article

Determining the frequency and preventability of adverse drug reaction-related admissions to an Irish University Hospital: a cross-sectional study

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ABSTRACT

Background Adverse drug reactions (ADR) cause considerable morbidity and mortality.

Methods This 4-week study was undertaken in Cork University Hospital, Ireland, for all admissions from the emergency department (ED). A panel independently reviewed patients with suspected ADRs. Causality assessment was performed using the Naranjo ADR probability scale and the Hallas criteria was used to assess preventability of the ADRs.

Results During the study period, 1258 patients were admitted from the ED; of these, 856 patients were included in the study; 75 patients (8.8%) had an ADR-related admission. Over half were deemed to be 'possibly' or 'definitely' avoidable. The level of agreement between reviewers using the Naranjo and Hallas criteria was very low.

In the ADR group (n=75), 50.7% were men compared with 53.1% in the non-ADR group (n=781)

are responsible for more than 100 000 deaths annually in the USA.[2]

Estimates for the incidence of ADRs in the literature vary, depending on the definition of ADR used, study setting and study population.[5] In addition, the incidence of ADR-related admissions is often underestimated due to the lack of documentation in patient medical notes.[4 6]

In a 2010 systematic review on ADR-related admissions, 95 studies were included.[7] These studies estimated a prevalence of ADR-related admission of 0.1% to 54%, and the authors identified that there was a higher prevalence reported in studies that examined all hospital admissions compared with those only in acute hospitals.[7] There is also wide variation in the reported figures for preventability of ADRs in the literature ranging from 3.9% to 92%.[8 9]

Although several studies have been performed in the UK, other European countries and the USA

Preventable adverse drug reactions

Literature suggests no common understanding of the concept of preventability.

Harms from

- Medication errors?
- Intentional abuse or misuse?
- Intentional overdose?
- Unintended/occupational exposure?
- Drug quality problems?

Inconsistent use of terminology and different perspectives .....unified by a common risk management goal?

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Risk Minimisation Activity

A public health intervention intended **to prevent or reduce the probability of the occurrence of an adverse reaction** associated with the exposure to a medicine or to **reduce its severity should it occur**.

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 June 2012
EMA/838713/2011

Guideline on good pharmacovigilance practices (GVP)
Module V – Risk management systems

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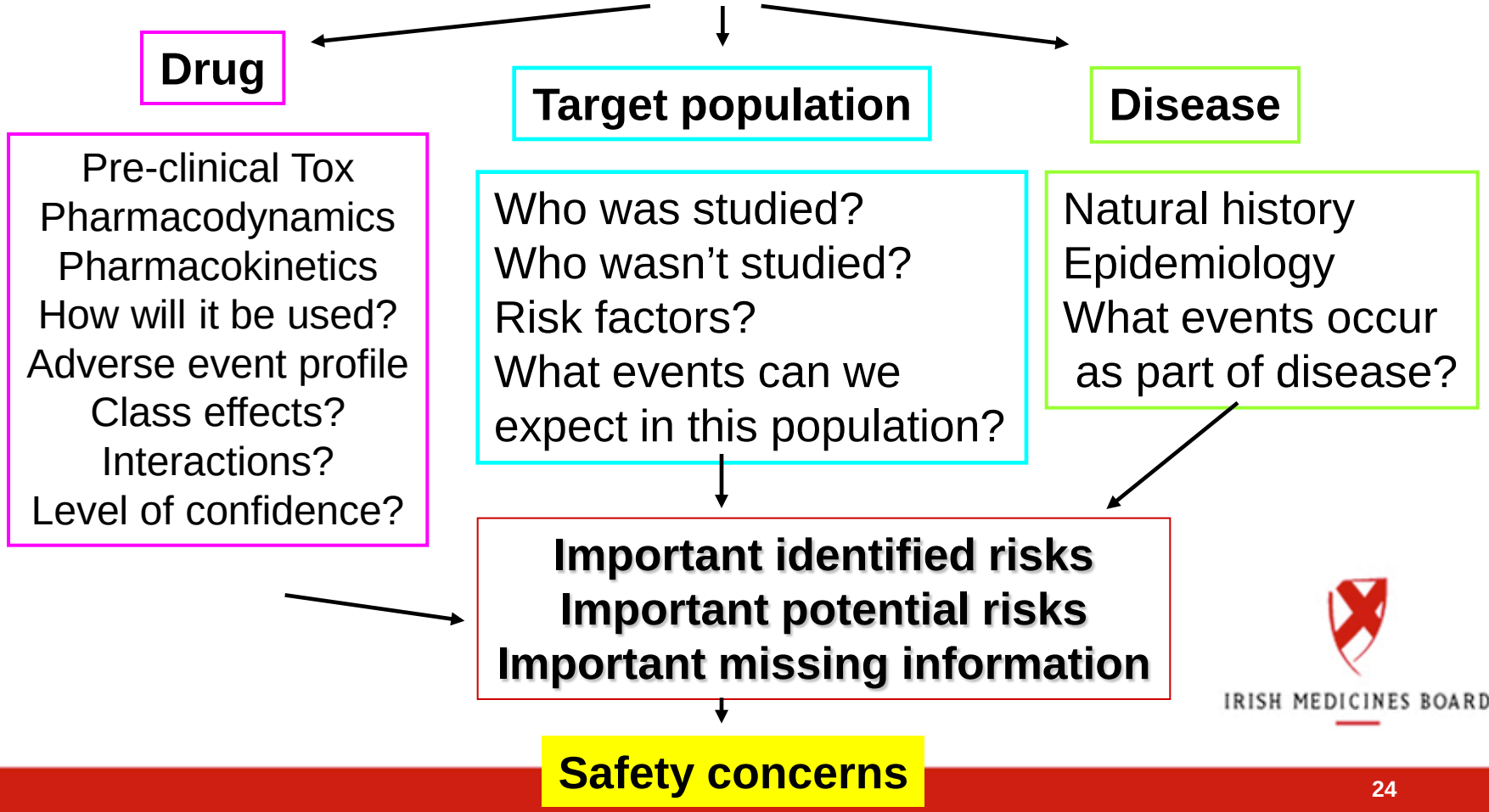
Safety specification

Identify: **what is known**
what is not known (‘known unknowns’)



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Preventable harms

V.B.8.6.1. RMP module SVI section "Potential for harm from overdose"

Special attention should be given to medicinal products where there is an increased risk of harm from overdose, whether intentional or accidental. Examples include medicinal products where there is a narrow therapeutic mar
risk of intentional overd
has occurred during cl

V.B.8.6.4. RMP module SVI section "Potential for medication errors"

For the purposes of the RMP, medication error refers to any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer. Medication errors are an important cause of morbidity and mortality and many could be prevented or mitigated. They fall broadly into 4 categories:

V.B.8.6.3. RMP module SVI section "Potential for misuse for illegal purposes"

The potential for misuse for illegal purposes should be considered. Misuse, as defined in GVP Module VI, refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information. Misuse for illegal purposes has the additional connotation of an intention of misusing the medicinal product to cause an effect in another person.

3.9.2 Medication Errors

This subsection should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient. Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product. A medication error may arise at any stage in the medication use process, and may involve patients, consumers, or healthcare professionals.

This information may be received by the MAH via spontaneous reporting systems, medical information queries, customer complaints, screening of digital media, patient support programmes, or other available information sources.

Signals or risks identified from any information source and/or category of reports should be presented and evaluated in the relevant section of the PBRER.

Risk characterisation as a success factor for effective risk minimisation

'Is it preventable?' or 'identify risk factors and monitoring strategies to mitigate risk?'?

- **Patient characteristics relevant to risk (e.g., age, pregnancy/lactation, disease, disease severity, hepatic/renal impairment, relevant co-morbidity, polymorphism),**
- **Dose, route of administration;**
- **Duration of treatment, risk period;**
- **Predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker;**
- **Reversibility;**

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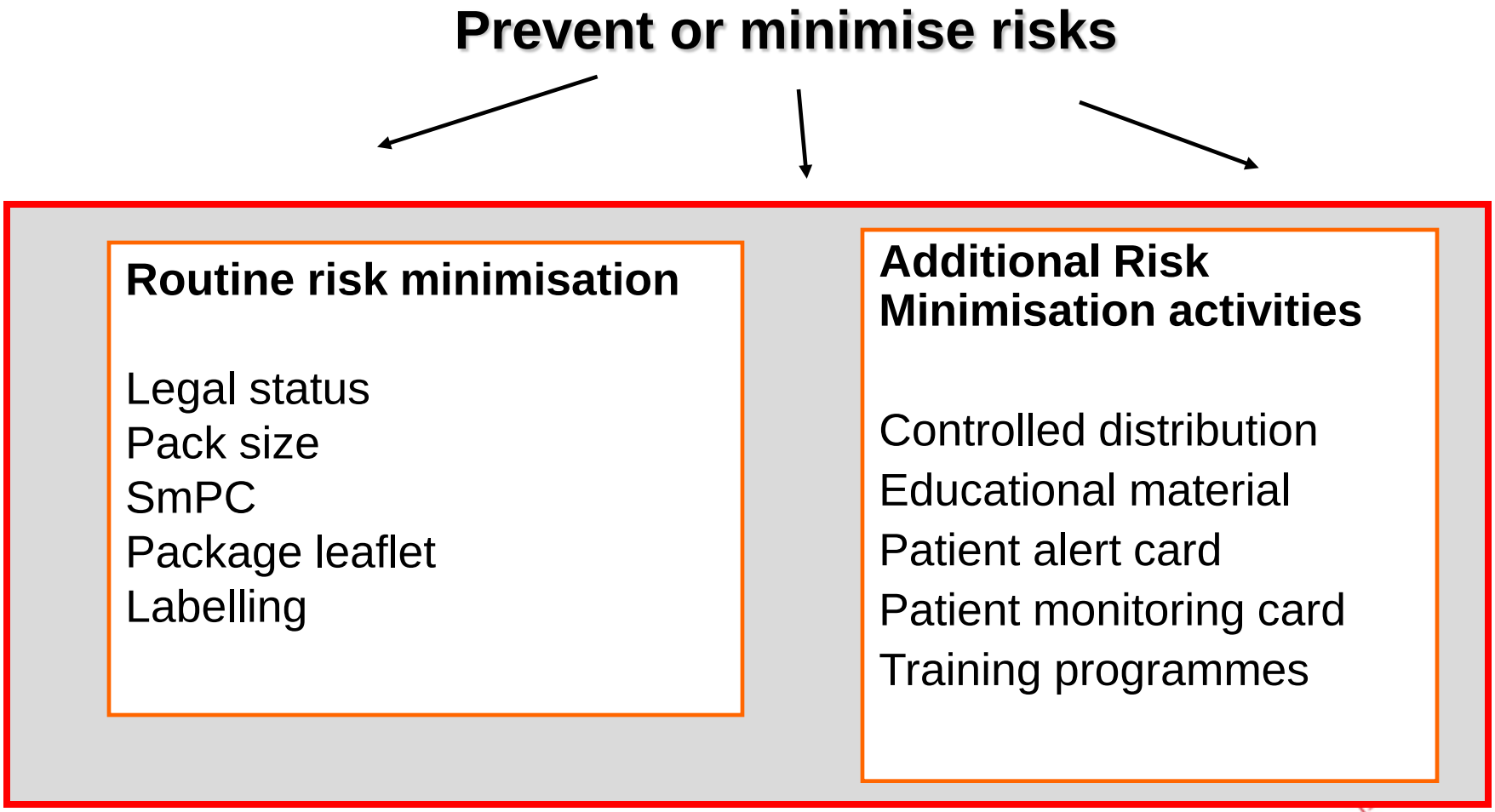
Risk Minimisation Plan



Measuring effectiveness of risk minimisation.

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Preventable Adverse (Drug) Reactions – some scenarios

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Methotrexate and cases of unintentional overdose due to medication error

pharmacy practice | medication safety

Medication Safety Briefing

The Irish Medication Safety Network is a community of pharmacists and other specialists working in medication safety in the acute sector. The group first met prior to the HPAI conference in April 2006 as the HPAI Medication Safety Special Interest Group and is now meeting regularly. The primary aim of the group is to improve patient safety through collaboration and shared learning and action. The group has also sent representatives to the International Medication Safety Network meetings in Salamanca 2006 and Dublin 2007.

In the first of a new series on medication safety issues for the IPJ, Clara Kirke, Drug Safety Co-ordinator at the Adelaide & Meath Hospital, Dublin incorporating the National Children's Hospital Tallaght, looks at methotrexate.

Methotrexate

Methotrexate is an antimetabolite which is currently primarily used in the treatment of rheumatoid arthritis, psoriasis and Crohn's disease. Methotrexate can result in serious patient harm when errors are made in its use, and care must be taken when prescribing, dispensing and administering it. It is crucial that the patient's dose is taken once weekly only.

Case 1

'Methotrexate as directed' prescribed for a patient. Community pharmacy dispensed a box of 28 methotrexate 2.5mg tablets. Patient unsure of dosing, took one tablet on most days for

Dispensing in the community

- Ensure that the label specifies the dose and that it should be taken once weekly. Clarify with the patient what day of the week they usually take their methotrexate and include this on the label.
- Never label methotrexate "As directed"
- If the prescription is unclear or states any frequency other than once weekly, it must be queried. Do not accept assurances that the dose is once daily – this will never be correct.
- Consider keeping and dispensing one strength only of methotrexate (2.5mg) to minimise the chance of patient confusion over the dose they should take.
- Enter an alert to the computer system that methotrexate should be once weekly only
- Consider putting a reminder re. once weekly dosing at the methotrexate storage area.

the doctor was aware that they were taking methotrexate. Patients should be told to inform any doctor, dentist or pharmacist dealing with them that they are on methotrexate

Toxicity

Methotrexate can cause a number of serious adverse reactions, including myelosuppression (blood disorders), liver and pulmonary toxicity, which may occur suddenly and late in treatment. The first signs of myelosuppression may be sore throat, bruising, mouth ulcers or infections. Nausea, vomiting, abdominal discomfort or dark urine may be signs of liver toxicity. Respiratory effects such as shortness of breath, cough or fever could indicate pneumonitis.

Milder effects of mucositis and gastro-

Tús Áite do Shábháilteacht Othar
Patient Safety First

Safe Treatment with Oral Methotrexate

– A Shared Responsibility Demanding a Shared Solution?

Tim Delaney, B.Sc.(Pharm.), M.Sc. Mgmt (O.B.), FPSI
Programme Lead - Medication Safety
Quality & Patient Safety Directorate,
Health Service Executive

Audit form

National Community Pharmacy Audit of Methotrexate 2011

	Correct	Incorrect
1. What is the name of the dispensing software installed on your dispensary system? ○ Cliniscript ○ McLernon ○ Other	○	●
2. Is there a WRITTEN Methotrexate Safe Supply Protocol in place in your pharmacy? ○ Yes ○ No ○ Don't know	○	●
3. Are you aware of the PSI Safe Practice on the Supply of Methotrexate 2008 guidelines? ○ Yes ○ No		

Risk of unintentional overdose - methotrexate

IRISH MEDICINES BOARD
Drug Safety NEWSLETTER
47TH EDITION

Oral Methotrexate – Risk of unintentional overdose due to medication errors

Oral methotrexate is indicated in the treatment of active rheumatoid arthritis, adult psoriasis and in a number of oncological indications, with differing dosage regimens for the respective indications (see section 4.2 of the Summary of Product Characteristics (SPC) available on www.imb.ie).

For rheumatology and dermatology indications, methotrexate should be administered as a once weekly dose only. The patient and/or carers should be informed of the risks associated with overdose and the need to adhere to once weekly dosing. For these indications, it is also suggested that the day of intake should be specified on the prescription and dispensing label.

Medication errors resulting in inadvertent overdose due to erroneous daily intake of the weekly dose have been reported in Ireland and elsewhere. The IMB has also received reports of strength confusion resulting in error between the 10 mg and 2.5 mg tablets. The IMB would like to remind healthcare professionals of the need for vigilance when prescribing, dispensing, administering and counselling patients and/or carers in relation to methotrexate, particularly following initiation of treatment, a change in the dose, or a change in the tablet strength usually taken.

In the context of experience across the EU in relation to this issue, the PhVWP of the EMA recently reviewed this issue to consider possible additional, regulatory actions to further minimise the risk of medication error with oral

- Cases of overdose, sometimes fatal, due to erroneous daily intake instead of weekly intake have been reported. In these cases, symptoms commonly reported are haematological and gastrointestinal reactions.
- Healthcare professionals should ensure that the patient and/or their carer understands the prescribed therapy, including the dose and frequency, with any treatment changes highlighted. Great care should be taken to give and repeat clear instructions on dosage.
- Patients and/or carers should also be informed of the potential risk of serious adverse reactions in the case of overdose and of the signs and symptoms of toxicity.
- Any adverse drug reactions suspected to be related to a medication error with methotrexate should be notified to the IMB in the usual way.

Key message

Methotrexate for oral use in rheumatology and dermatology indications should be taken once a week only.
Patients and/or carers should be informed of the risk of overdose due to erroneous daily intake of the weekly dose.
Healthcare professionals should also be aware of the risk of error due to strength confusion.

Miconazole oral gel (Daktarin oral gel) – Interaction with warfarin

Risk of unintentional overdose-methotrexate

PSI
THE PHARMACEUTICAL SOCIETY OF IRELAND
Cumann Cógaiseoirí na hÉireann
THE PHARMACY REGULATOR

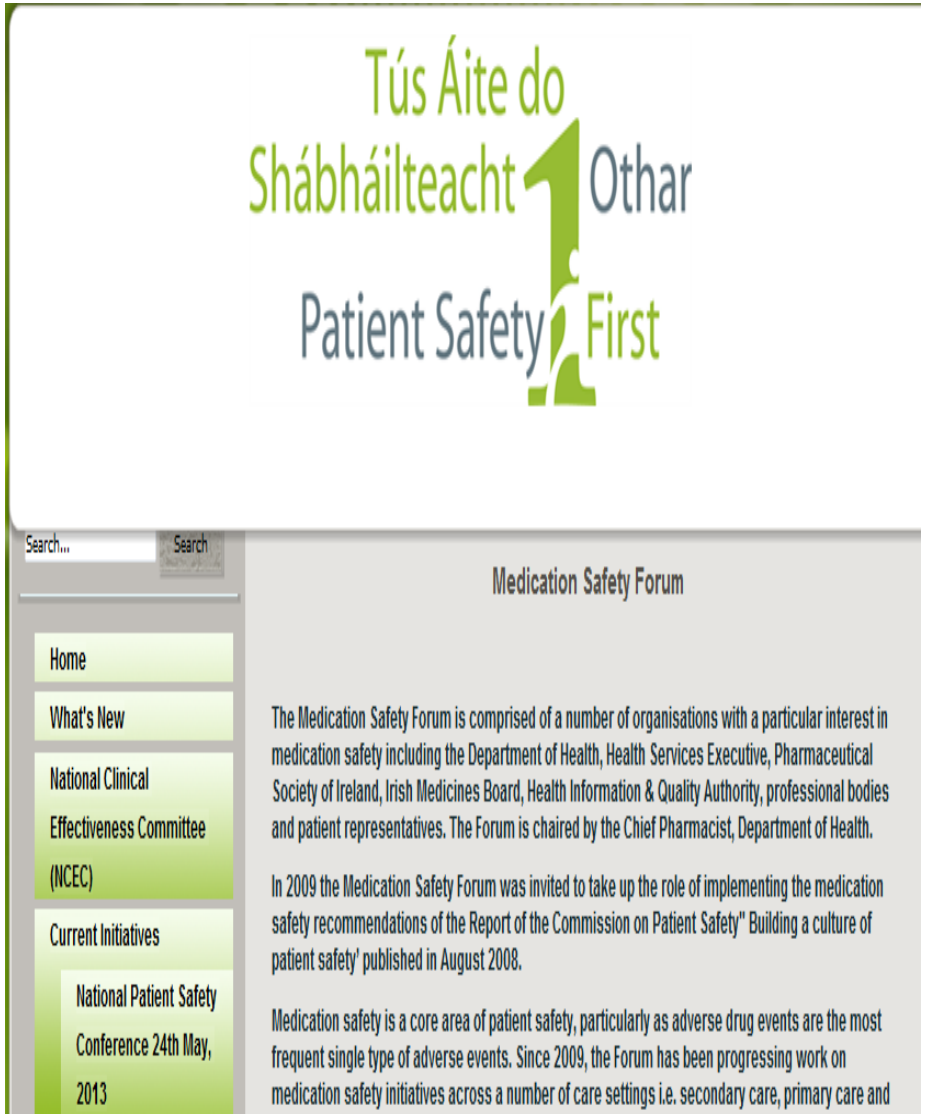
Guidance for Pharmacists on Safe Supply of Oral Methotrexate

1. Introduction

Methotrexate is a potent immunosuppressant used in the treatment of active rheumatoid arthritis in adults, severe recalcitrant psoriasis and some oncological indications.
Oral methotrexate for rheumatological and dermatological indications is administered on a once-weekly basis.
Incorrect dispensing, prescribing and use of methotrexate can result in significant patient morbidity and mortality, due to severe adverse effects which can occur abruptly. Such cases have been reported in Ireland and elsewhere and are of concern to all individuals involved in the supply of methotrexate.
These cases have primarily related to overdosage with oral methotrexate, where errors occurred in the prescribing, dispensing or use of the drug, most commonly where the drug was taken daily rather than weekly. Other cases of patient harm have resulted from confusion between the different strengths of oral methotrexate tablets; cases of deliberate overdosage have also been reported.
Errors in dosing may, in some cases, have been compounded by a lack of monitoring for recognised side-effects and symptoms of toxicity. (See signs of methotrexate toxicity detailed below)
Pharmacists play a critical role in ensuring the safe use of methotrexate, through their participation in the educating, counselling and monitoring of patients.

National Medication Safety Forum - Dialogue

- Commission on Patient Safety and Quality Assurance (CPSQA) established in January 2007, by the Health Ministry.
- CPSQA report ‘Building a Culture of Patient Safety’ published in July 2008.
- Medication Safety Forum established by Department of Health and Health Information Quality Authority as mutil-agency/stakeholder group to explore medication safety issues and report recommendations.



EU perspective

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

10 January 2012, revised on 22 March 2012
EMA/CHMP/PhVWP/973945/2011 Rev. 1[1]
Patient Health Protection

Monthly report **Issue number: 1112**

Pharmacovigilance Working Party (PhVWP)
December 2011 plenary meeting

Methotrexate – Risk of overdose due to erroneous daily intake of the weekly dose in rheumatologic and dermatologic indications

Product information for methotrexate for oral use in rheumatologic and dermatologic indications should emphasise that it should be taken once a week and patients should be informed of the risk of overdose due to erroneous daily intake of the intended weekly dose. Key elements for risk minimisation should be consistently reflected in product information across the EU to minimise the risk of inadvertent overdose.

Given that cases of overdose, sometimes fatal, with methotrexate in rheumatologic and dermatologic indications due to erroneous daily instead of weekly intake have been reported in the EU, the PhVWP agreed to review how to further minimise the risk of medication errors. The PhVWP concluded that a simple message emphasising the need for adherence to once weekly intake in rheumatologic and dermatologic indications, and a consistent warning on the risk of overdose should be included in the summaries of product characteristics (SmPCs), the package leaflets (PLs) and the labelling of all

[2] The active substances included in this review were buserelin, goserelin, histrelin, leuprorelin, nafarelin and triptorelin.
[3] The active substances included in this review were atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

Intravenous Paracetamol - additional risk minimisation activities agreed at EU level.

PERFALGAN (paracetamol) 10 mg/ml solution for infusion – Risk of dosing errors in infants resulting in overdose with serious outcome

PERFALGAN (paracetamol) solution for infusion contains 10mg/ml; accidental overdosing of infants may have a serious outcome

PERFALGAN 10 mg/ml solution for infusion contains paracetamol and is indicated for the short-term treatment of moderate pain, especially following surgery, or fever in situations where intravenous administration is justified by an urgent therapeutic need or because other routes of administration are not possible.

The PhVWP noted that, as of 31 December 2009, 22 cases of paracetamol overdose had been reported worldwide in children aged 1 day to 1 year. The root-cause of this error lies in the confusion between milligrams (mg) and millilitres (ml), with children being given x ml when x mg had been prescribed, resulting in the administration of a dose 10 times higher than prescribed.

The PhVWP welcomed the fact that risk minimisation activities have been or will be initiated in Member States as appropriate. These activities may include a direct healthcare professional communication and a poster for paediatric wards in hospitals. These communication materials remind healthcare

IRISH MEDICINES BOARD

National Dissemination of recommendations

Drug Safety NEWSLETTER

June 2011 – 42nd EDITION INSERT

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Intravenous Paracetamol Solutions for Infusion – Risk of Medication Errors in Infants and Children

Bristol-Myers Squibb Pharmaceuticals

South County Business Park, Leopardstown, Dublin 18. Tel. (01) 291 3800 Fax (01) 291 3899

May 2010

IMPORTANT PHARMACOVIGILANCE INFORMATION

Serious cases of overdose reported in infants and children with PERFALGAN® 10 mg/ml, solution for infusion.

Dear Healthcare Provider,

In agreement with the Irish Medicines Board, Bristol-Myers Squibb would like to draw the attention of healthcare professionals to the risk of **accidental overdose in neonates and infants** during treatment with PERFALGAN 10mg/ml solution for infusion, (50 ml vial)[1].

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Wrong route of administration – environmental considerations - Velcade

16th January 2012

Dear Healthcare Professional,

The correct administration of VELCADE (bortezomib) is via the intravenous route.

The purpose of this communication is to remind you that the correct procedure for administering VELCADE (bortezomib) 3.5 mg powder for solution for injection is via the intravenous route and to recommend some measures to reduce the risk of incorrect administration.

This communication has been agreed with the European Medicines Agency and the Irish Medicines Board.

AUTHORISED ROUTE OF ADMINISTRATION

The **only** authorised route of administration for VELCADE is intravenous injection.
VELCADE **must not** be administered by any other route.

RECOMMENDED PRECAUTIONARY MEASURES

In order to reduce administration route errors, the following specific precautionary measures should be considered:

- When possible, use different connectors for medicinal products to be administered via the intrathecal or intravenous route.
- When possible, administer intrathecal chemotherapy at a different time to any other parenteral chemotherapy.
- Clearly label syringes with the name of medicinal product and route of administration to be used.
- Ensure procedures are in place to enforce double reading of syringe labelling before administration.
- Intravenous and intrathecal injections should be handled only by trained healthcare professionals.
- Train and inform healthcare professionals involved in administration and/or management

Additional Risk Minimisation - Condition of the MA for line extension

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

Prior to launch of Velcade 3.5mg new dual route of administration (subcutaneous and intravenous) package, in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the national competent authority.
The MAH shall ensure that, at launch of Velcade 3.5mg new dual route package and thereafter, all healthcare professionals involved in the prescribing, dispensing, handling or administration of Velcade 3.5mg are provided with educational material.

The educational material shall consist of the following:

- SmPC
- Reconstitution, dosing and administration booklet
- Reconstitution poster
- Dosing Slide Rule

The Reconstitution, dosing and administration booklet shall contain the following key elements:

- Velcade 3.5mg can be administered both intravenously and subcutaneously while Velcade 1mg can be administered only intravenously
- different reconstitution requirements for intravenous (IV) or subcutaneous (SC) use
- dosing instructions and examples: how to calculate the body surface area of a patient and the volume of reconstituted Velcade (both IV and SC use) required for different body surface areas (cross reference to Dosing Slide Rule)
- advice on method of administration for both IV and SC use, including the need to rotate injection sites for SC use
- storage precautions for reconstituted solution
- potential risks of administration errors including overdosing, underdosing and that inadvertent intrathecal administration has resulted in death
- to report any adverse event, or medication error, experienced with the administration of Velcade 3.5mg

OARD

Medication errors due to incorrect dosing

IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

29th EDITION

Prograf and Advagraf (Tacrolimus): Risk of serious medication errors

Prograf and Advagraf are not interchangeable and should not be substituted without careful therapeutic monitoring

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02 DEC 2008

Astellas Pharma Co., Ltd.
25 The Courtyard,
Kilcarbery Business Park,
Clondalkin,
Dublin 22.
Ireland.
Registered Office

Dear Healthcare Professional,

Astellas wishes to draw your attention to a series of cases of medication errors involving Prograf and Advagraf. Both of these medicines contain the immunosuppressant tacrolimus, but are given according to different dosing schedules.

The medication errors have resulted in patients being dosed incorrectly. This has caused serious adverse reactions, including biopsy-confirmed acute rejection of transplanted organs and toxicity due to overexposure.

It is important to note the correct use of these medicines:

- **Prograf is an immediate-release formulation that must be taken twice a day, once in the morning and once in the evening.**
- **Advagraf is a prolonged-release formulation that must be taken once a day in the morning.**

12th February 2010

Advagraf, Prograf & Modigraf ▼

Important safety reminder concerning risk of medication errors with oral tacrolimus products leading to serious adverse drug reactions

Dear Healthcare Professional,

Astellas wishes to remind you about the risk of medication errors associated with the oral tacrolimus products Prograf, Advagraf, and the recently launched new granular formulation Modigraf ▼, which must be suspended in water prior to consumption.

These immunosuppressant medicines are indicated for prevention and treatment of transplant

Advagraf/Prograf Medication Errors – Risk Management

Errors occurred at various stages of the medication use process - prescribing, dispensing and administration.

Risk Minimization Activities:

- DHPC to specialists, general practitioners and pharmacists.
- Patient organisations
- Modified product information – SPC and Package leaflet.
- Revision of labeling of the Advagraf outer-packaging – clearly states 'Once Daily'.

Pharmacovigilance Activities:

- specific targeted questionnaire to collect case information, continued review in PSURs/PBRER, addressed in the RMP.

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Incorrect use of the device for administration

ETHICON™

omrix Biopharmaceuticals Ltd.

27 August 2010

Dear Health Care Professional,

SUBJECT: *Risk of Life-Threatening Air or Gas Embolism with the Use of Spray Devices Employing Pressure Regulator to Administer the product: EVICEL™ Solutions for Sealant (Human)*

Omrix Biopharmaceuticals Ltd. and Ethicon, Inc. would like to inform you of an important safety update of the product information for the EVICEL™ Solutions for Sealant (Human) products.

Key Messages:

Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer EVICEL™. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface.

The safety update includes the following instructions for sealant application using a spray device to help prevent air or gas embolism:

- When applying EVICEL™ using a spray device, the pressure should be within the range recommended by the spray device manufacturer.

Effectiveness of risk minimisation

- What is the actionable message?
- Clarity of the messages in the product information.
- Is it sufficient to influence clinical actions?
- Limiting factor – message clarity or tools for delivery?
- How to improve accessibility of information?
- Is the risk sufficiently characterised to consider process indicators as a reasonable proxy for outcome indicators?
- Fit for purpose PV plan to inform risk minimisation and to avoid preventable harms
- What does success look like?

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Conclusions

- Effective risk minimisation is a shared goal.
- Supporting the provision of the right drug, at the right dose, at the right time, to the right patient, and with the right information and monitoring.
- Analysis and understanding of data collected is critical in defining RM strategies.
- New legislation increases focus on real world use of the medicine and preventing harms from medication errors, unintentional overdose, misuse and abuse.
- Challenges and opportunities for collaborations and synergies.
- Continuous Pharmacovigilance required to ensure risk minimisation relevant, effective and sustainable.

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