MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

Adverse reactions from medication errors.- Regulatory experience in EU

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Before July 2012

After July 2012

PhVWP of CHMP

Advise on safety issues:

- At request of CHMP
- At request of MS

PRAC

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

PRAC: Integration of activities

- **Priorisation and assessment of signals**
  - Inc signals consequence of reported medication errors
- **RMP assessment**
  - ID of potential for medication errors
  - Risk minimisation activities
  - Impact assessment of additional risk minimisation activities, i.e.
    - ADR frequency
    - Specific surveys
- **PSUR assessment**
  - Data collected on medication errors

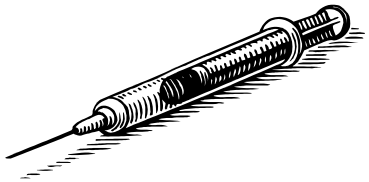
Retrospective review of (potential) safety issues consequence of medication errors in PhVWP/PRAC

Rotavirus vaccine

Confusion on route of administration or target

Bortezomib

Methysergide



Fosphenytoin

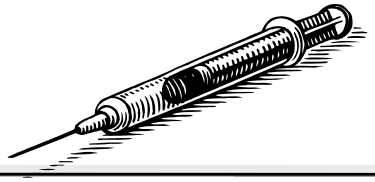
Non “standard posologies”

Colchicine

Metrotrexate

Same product , different posologies for different indications

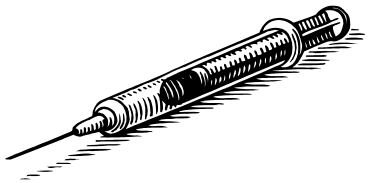
Marketing of new strengths, pharmaceutical forms, formulations, devices for the active substance



- Sodium oxibate
- Topotecan
- Memantine
- Advagraf/prograf
- Pramipexole
- Olanzapine
- Levetiracetam
- Eptacog alpha

Disproportion

total volume-volume for injection



Revatio

Romiplostin

Perfalgan in children

Tocilizumab

Romiplostin

Complexity in infusion preparation/method of administration

Mecasermin

Dexametasone intravitreal implant

Regulatory actions most commonly taken

- **Clarify product information, i.e.**
  - SmPC/PIL
  - Outer package
- **DHPC**
- **Additional risk minimisation activities:**

  Educational material

Example in EU: Nplate® educational material

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES

The Member States must ensure that all conditions with regard to the safe and effective use of the medicinal products described below are implemented:

The MAH shall agree the details of an educational programme with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing, all physicians are provided with a healthcare professional information pack containing the following:

- Educational material
- Summary of Product Characteristics (SPC) and Package Leaflet and Labelling

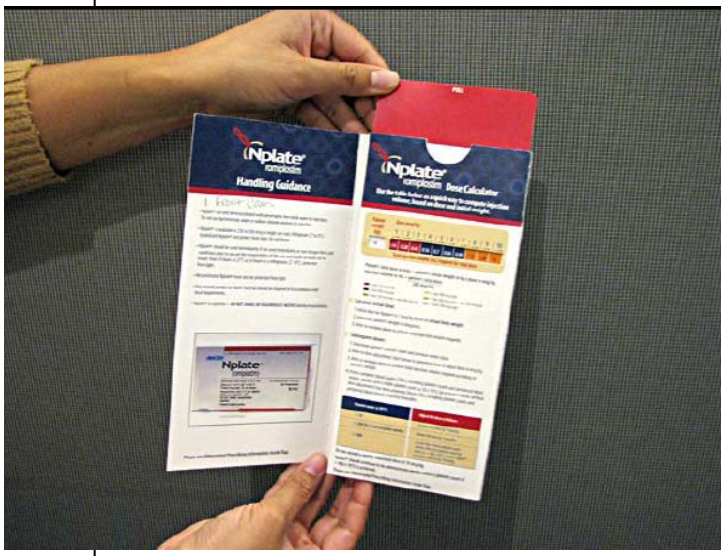
Key elements to be included in the educational material

- Posology
- Obligations of the health care professional in relation to the prescribing of romiplostim and the need to provide comprehensive advice on risk-benefit to patients.
- The documents will discuss the following identified and potential risks:
  - The incidence in clinical trials and likelihood of reoccurrence of thrombocytopenia after cessation of treatment. Advice on management of patients upon cessation of romiplostim.
  - Background information on reticulin in the bone marrow. Background rates of reticulin in the bone marrow in ITP patients and the observed incidence and potential mechanism of action of reticulin deposition in response to romiplostim. Warning that, whilst no data exists, an outcome of reticulin deposition in response to romiplostim may be bone marrow fibrosis. Advice on when further investigations and a bone marrow biopsy might be appropriate.

---------- etc

  - The incidence of medication errors in clinical trials. Provision of dosing calculator to simplify the calculation of the correct dose and guide in correct reconstitution and administration.

Annex II.B in EPAR of NPLATE® in the Website (www.ema.europa.eu)



"Provision of dosing calculator to simplify the calculation of the correct dose and guide in correct reconstitution and administration"

Example in EU: Nplate® educational material

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

agencia española medicamento productos sanita

Nplate® (romi
Please refer to
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(e.g. corticoste
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- Nplate® can only be reconsti
  Do not use bacteriostatic wat
- Nplate® is available in 250 c
  and protect from light. Do n
- Nplate® should be used imm
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  from light.
- Reconstituted Nplate® must
- Any unused product or wast
  local requirements.
- Nplate® is a protein—DO N

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Any unused
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Nplate® Single-Use Vial
250 µg
500 µg

Storage of

Chemical an
for 24 hours

From a micr
used immed
of the user a
refrigerator

Use the table b
volume,

Patient weight (kg)	Dose (µ
	1 µg/kg
	Total i

Patient's total dose in
Injection volume in m

= One 250-µg vial
= One 500-µg vial
= One 250-µg vial + one

Calculate initial dose:

1. Initial dose for Nplate®
2. Determine patient's wei
3. Refer to window above

Subsequent doses:

1. Determine patient's plat
2. Refer to dose adjustmer
3. Refer to window above
   patient's weight.
4. Platelet counts should b
   for at least 4 weeks with
   should be assessed mon

Platelet count (x
< 50
> 200 for 2 conse
> 400

Directions for dose reconstitut

- Nplate® is a highly potent peptide administere
  is supplied as a powder for reconstitution with s
- Nplate® is available in two vial sizes that provid
  reconstituted. Because of the holdup in the vial
  of Nplate® is less than the reconstituted amoun
  — Nplate® 250 micrograms powder for solut
  reconstituted with 0.72 mL sterile water fo
  volume of 0.5 mL. An additional overfill is
  250 µg of romiplostim can be delivered.
  — Nplate® 500 micrograms powder for solut
  reconstituted with 1.2 mL sterile water for
  volume of 1.0 mL. An additional overfill is
  500 µg of romiplostim can be delivered.
- Smaller amounts of Nplate® may be required fo
  whom low weekly doses are appropriate, as wel
- Administer Nplate® as a weekly subcutaneous i
  based on platelet count response.
- Injection volume may be very small. Use a syrin

PULL

40	0.08	0.16	0.24	0.32	0.4	0.48	0.56	0.64	0.72	0.8
45	0.09	0.18	0.27	0.36	0.45	0.54	0.63	0.72	0.81	0.9
50	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
55	0.11	0.22	0.33	0.44	0.55	0.66	0.77	0.88	0.99	1.1
60	0.12	0.24	0.36	0.48	0.6	0.72	0.84	0.96	1.08	1.2
65	0.13	0.26	0.39	0.52	0.65	0.78	0.91	1.04	1.17	1.3
70	0.14	0.28	0.42	0.56	0.7	0.84	0.98	1.12	1.26	1.4
75	0.15	0.3	0.45	0.6	0.75	0.9	1.05	1.2	1.35	1.5
80	0.16	0.32	0.48	0.64	0.8	0.96	1.12	1.28	1.44	1.6
85	0.17	0.34	0.51	0.68	0.85	1.02	1.19	1.36	1.53	1.7
90	0.18	0.36	0.54	0.72	0.9	1.08	1.26	1.44	1.62	1.8

Conclusions

- New presentations during product lifecycle and complexity in preparations: the most frequent cause of errors: The simplest the best
- Interaction with patient safety organisations (in hospital network for message dissemination)
- PRAC may facilitate identification and follow-up

Thank you for the attention!!