

EURORDIS-SCOPE Pharmacovigilance training

An introduction to Pharmacovigilance

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22nd March 2017



Contents



- A look back at the history of pharmacovigilance (PV)
- Signal management
- Risk Management Plans
- Early access to medicines
- A look ahead to the future

What is PV?

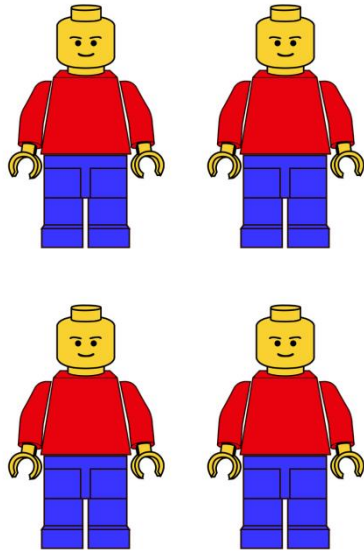


*“Pharmacovigilance is defined as the science and activities relating to the **detection, assessment, understanding and prevention of adverse effects or any other drug-related problem**”*

Why do we need PV?



Clinical trials



Real world use

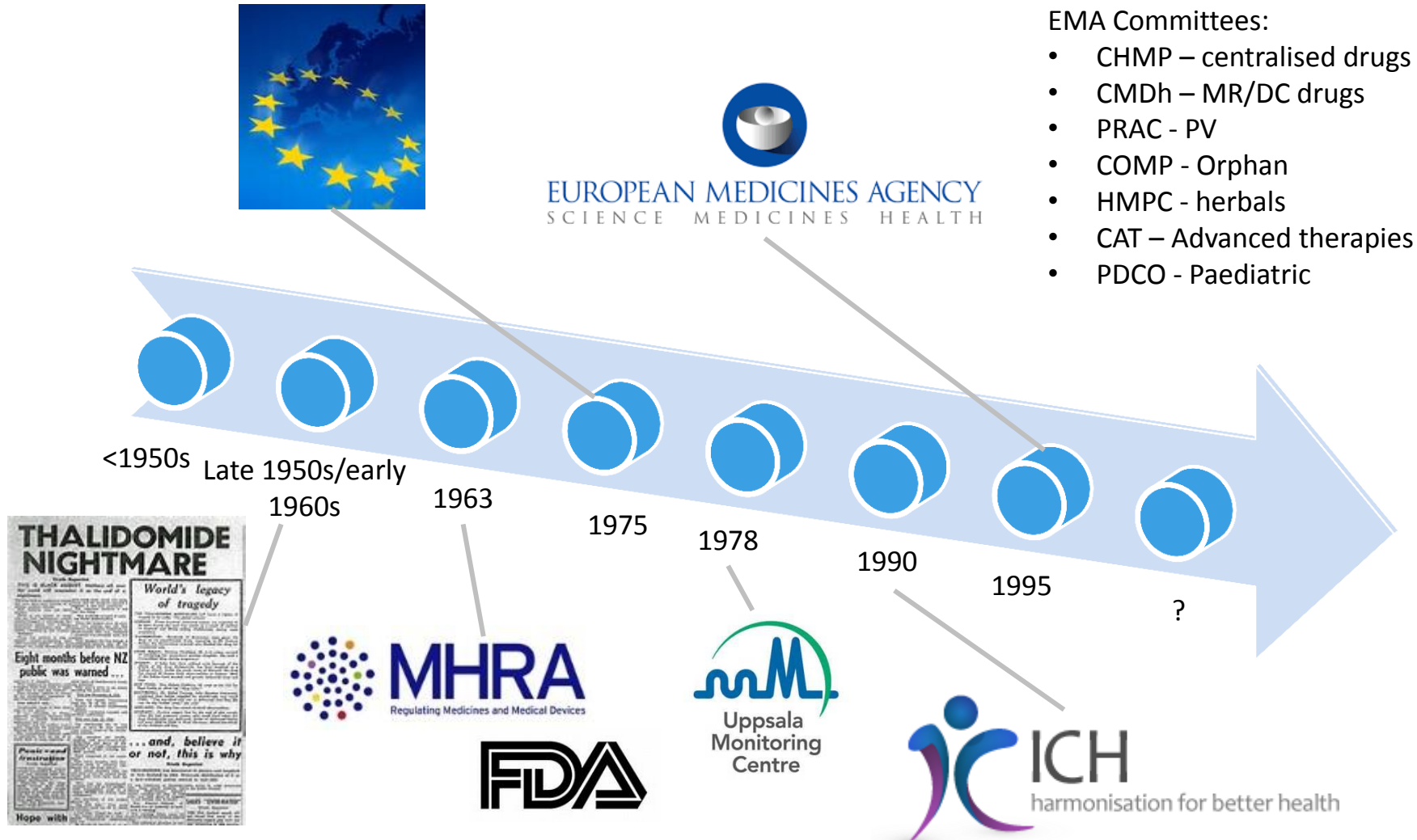


Why do we need PV?

- **Thalidomide:**
- Late 1950s -1961 prescribed to pregnant women as a cure for morning sickness
- >10 000 babies born with birth defects worldwide
- Tests on pregnant animals were not a legal requirement



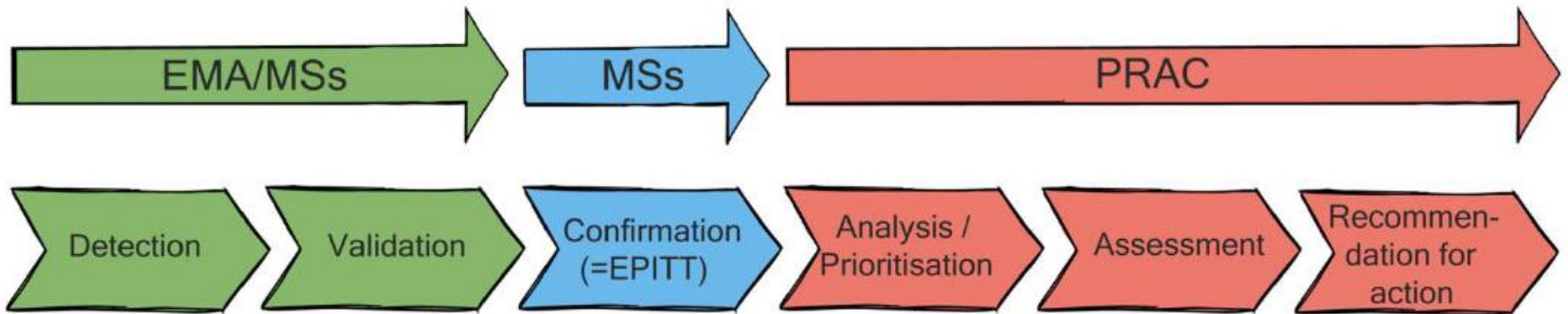
A look back



EMA Committees:

- CHMP – centralised drugs
- CMDh – MR/DC drugs
- PRAC - PV
- COMP - Orphan
- HMPC - herbals
- CAT – Advanced therapies
- PDCO - Paediatric

Signal management



Signal Detection

Drug-ADR combination that is a possible drug safety issue

Signal Detection- NCA

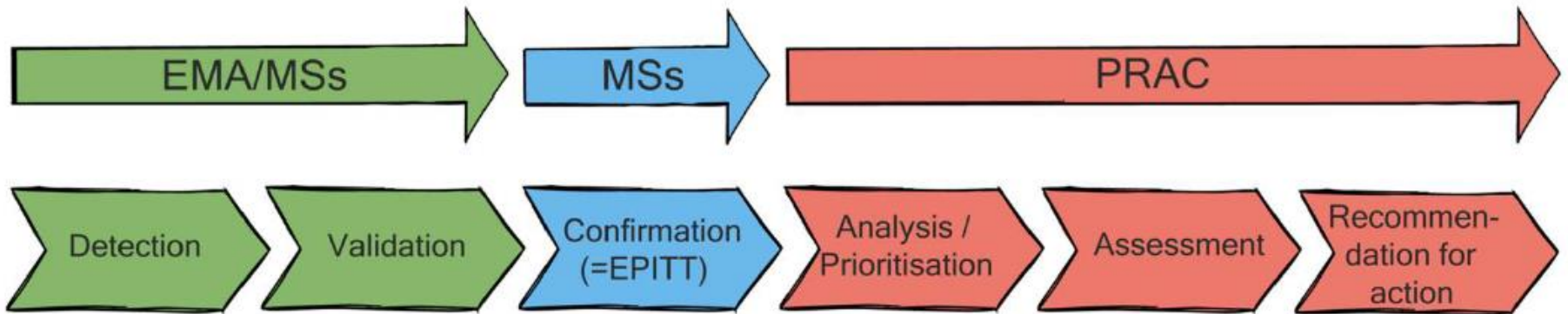


- UK MHRA case study

- Weekly review
- Algorithm applied to prioritise reports
- Established vs Black Triangle/Additional monitoring
- Discussed at multi-disciplinary meeting
- Further review discussed at a management meeting



Signal management



Regulatory action options

- Update product information
 - Listed side effects
 - Restrict use – Contraindications, reduce dose
 - Risk management
- Drug withdrawal, rarely

How we can communicate

Bulletins

Websites

GOV.UK Home > Drug Safety Update

Apremilast (Otezla): risk of suicidal thoughts and behaviour

From: Medicines and Healthcare products Regulatory Agency
Therapeutic area: Dermatology, Psychiatry, and Rheumatology

There is an increased risk that some patients may experience psychiatric symptoms with apremilast, including depression and suicidal thoughts. Stop treatment if patients have new psychiatric symptoms or if existing symptoms worsen.

Advice for healthcare professionals:

- apremilast is associated with an increased risk of psychiatric symptoms, including depression, suicidal thoughts, and suicidal behaviours
- suicidal thoughts and behaviour, including completed suicide, have been reported in patients with or without a history of depression
- carefully assess the benefits and risks of starting/continuing treatment in patients with a history of psychiatric symptoms, or in those who are taking medicines likely to cause psychiatric symptoms
- stop treatment if patients experience new psychiatric symptoms or if existing symptoms get worse
- advise patients to inform a healthcare professional if they notice changes in their mood

HPRA An tUdaráis Rialála Táirgí Sláinte Health Products Regulatory Authority

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ABOUT US MEDICINES VETERINARY MEDICAL DEVICES BLOOD, TISSUES, ORGANS COSMETICS CONTROLLED SUBSTANCES

Medicines > Safety Notices

> Our Role Recall of Batches of Viridal Duo Powder and Solvent for Solution for Injection to Patient Level in Ireland

> Medicines Information

thebmj Research > Education > News & Views > Campaigns

Research

Safety of pertussis vaccination in pregnant women in UK: observational study

BMJ 2014 ; 349 doi: <https://doi.org/10.1136/bmj.g4219> (Published 11 July 2014)

Cite this as: *BMJ* 2014;349:g4219

ANSM @ansm · Jan 9

Risques associés à l'usage de l'anticoagulation AVK-HBPM : une publication sur les résultats d'une étude de l'ANSM ow.ly/IO57307PoAU

28 15

Social Media

Medical Journals

theguardian

home > UK > society law scotland wales northern ireland all

Obesity

Anti-obesity drug Reductil banned across Europe

Sibutramine blamed for increasing patients' chances of suffering a heart attack or stroke

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This article is 7 years old

Denis Campbell, health correspondent
Friday 22 January 2010 00:39 GMT

One of the country's most commonly prescribed anti-obesity drugs has been banned across Europe after it was blamed for increasing patients' chances of suffering a heart attack or a stroke.

The European Medicines Agency (EMA) ordered doctors across the continent to stop prescribing sibutramine and told pharmacists not to dispense the drug, which is marketed in the UK as Reductil.

The watchdog's Committee for Medicinal Products for Human Use (CHMP) acted after a study of 9,800 patients said the risks of sibutramine outweighed its minimal benefits.

About 86,000 people took the drug last year. It is prescribed alongside lifestyle changes for patients who are classed as clinically obese, because they have a Body Mass Index of at least 30, and also in profoundly overweight people who also have a condition such as type 2 diabetes or abnormal levels of fat in their blood.

Press releases

Others:

- Direct Healthcare Professional Communication
- Product information

Diclofenac and cardiovascular risk



30 May 2013 Last updated at 00:40

2.8K Share

Common painkillers 'pose heart risk'

By James Gallagher

Health and science reporter, BBC News

Two common painkillers, ibuprofen and diclofenac, can slightly increase the risk of heart problems if taken in high doses for a long time, data suggests.

People with severe arthritis often take the drugs, which also calm inflammation, to go about daily life.

The researchers said some patients would deem the risk acceptable, but they should be given the choice.

A study, **published in the Lancet**, showed the drugs posed greater risks for smokers and the overweight.

The risks have been reported before, but a team of researchers University of Oxford analysed the issue in unprecedented detail to help patients make an informed choice.



PHARMACOEPIDEMOLOGY AND DRUG SAFETY 2014

Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3594

COMMENTARY

The European Medicines Agency's use of prioritised independent research for best evidence in regulatory action on diclofenac[†]

Peter Arlett^{1*}, Sinan B. Sarac², Andrew Thomson³, Claire Davies³, Tania Teixeira¹, Kevin V. Blake¹ and Doris Stenver²

- Review of diclofenac and cardiovascular risk identified serious cardiac events, in particular for high and long doses
- Led to SmPC contraindications, warnings and precautions
- Reclassified from pharmacy to prescription
- Communicated in PI, press, publication etc

Risk Management Plans



There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.

(Donald Rumsfeld)

izquotes.com

Risk Management Plans



PASS/PAES studies

- Can be voluntary or imposed as a condition of MA approval
- Can be clinical trials or a non-interventional study

Post-Authorisation Safety Study (PASS)

- Enhance safety knowledge
- E.g. real world data in special populations

Post-Authorisation Efficacy Studies (PAESs)

- Every day use efficacy
- Few to date

Non-interventional study details published on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website:

http://www.encepp.eu/encepp_studies/indexRegister.shtml

Clinical trials: <https://www.clinicaltrialsregister.eu/>

Risk Management Plans



Risk Management Plans

- Applications for **all** new MA (including generics)
 - New active substance
 - Biologics/Biosimilars
 - New indications – including extension to a different population
 - New route of administration/formulation
- Significant change to an existing marketing authorisation
- Reclassification application (e.g. POM to Pharmacy-only)
- Emerging safety issues, affecting the risk-benefit balance

European Medicines Agency publishes first summary of a risk-management plan for a medicine

News

11/03/2014

European Medicines Agency publishes first summary of a risk-management plan for a medicine

Initiative increases transparency and public access to relevant information on medicines

RMP guidance: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp

Search RMP or EPAR: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

Orphan drugs: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp&mid=WC0b01ac058001d12b

Thalidomide – Multiple Myeloma

- Reintroduction of a withdrawn drug
- Pregnancy Prevention Plan
- Restricted population
- Controlled distribution
- Package of educational & training tools



NEW first-line licence for THALIDOMIDE PHARMION™

Thalidomide Pharmion™, used in combination with melphalan plus prednisone (MPT), is indicated as first-line treatment for patients with untreated Multiple Myeloma:

- ≥ 65 years³
- Ineligible for high-dose chemotherapy³

Thalidomide Pharmion is prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme.

Thalidomide – Leprosy (Brazil)



- Second highest prevalence of Leprosy in the world (after India)
- 100 cases of birth defects in last 6 years
- Government and clinicians keen to continue use



Sodium valproate & neurodevelopmental disorders



- Indicated for epilepsy and bipolar disorder
- Risk of congenital malformations
- Management
 - Communication materials
 - Label warning on packs regarding risks in pregnancy
 - Cards and checklists



Valproate Dashboard to monitor impact in UK



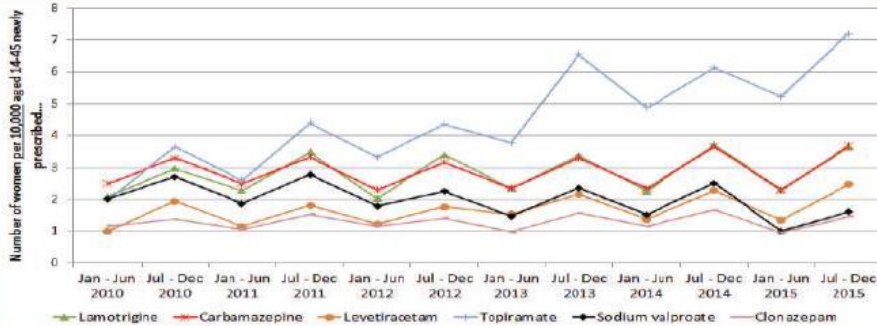
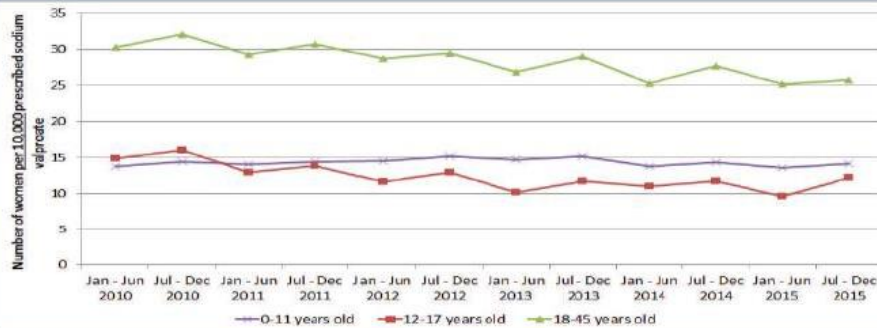
Supporting the safe use of sodium valproate

Aims/objectives:

- That sodium valproate is only provided to women who may become pregnant when there is no safe and effective alternative
- That all women who need valproate fully understand the risks associated with pregnancy

Prescribing by GPs *

Target - To reduce use in women aged 14-45 by ~80%



In July—December 2015 for every 10,000 women aged 14-45* at least...

- 15** were prescribed sodium valproate and had epilepsy
- 4** were prescribed valproate and had bipolar disorder
- 4** were prescribed valproate and had migraines

5/10,000 pregnancies
Rate of exposure to sodium valproate in pregnancy in 2015 *

Patient awareness †

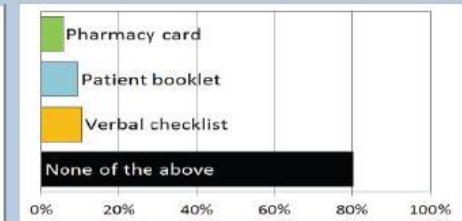
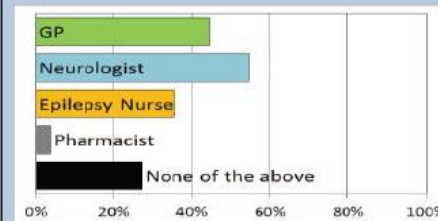
Target - 100% awareness & communication

Of 620 epileptic women aged 16-50 currently taking valproate...

80% are aware of any effects on development and/or physical health of a child born to a woman taking sodium valproate

Have ever discussed pregnancy and sodium valproate with a....

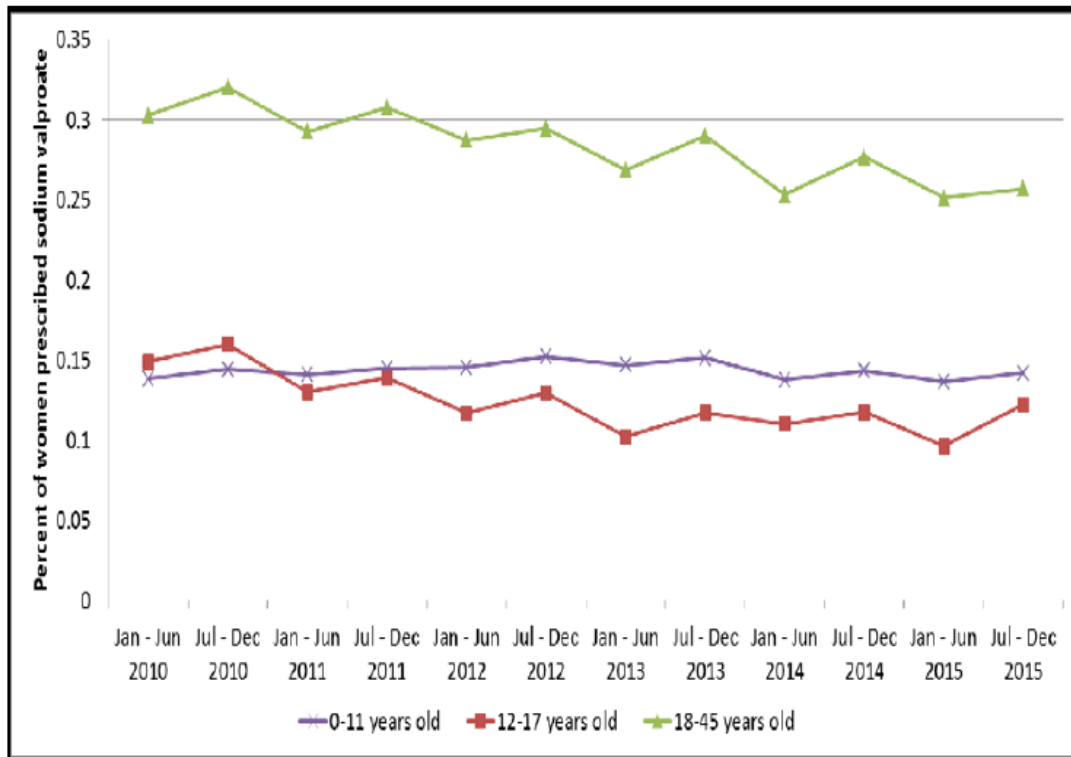
Have received the following information...



† Data from a survey conducted by Epilepsy Society, Epilepsy Action, and Young Epilepsy

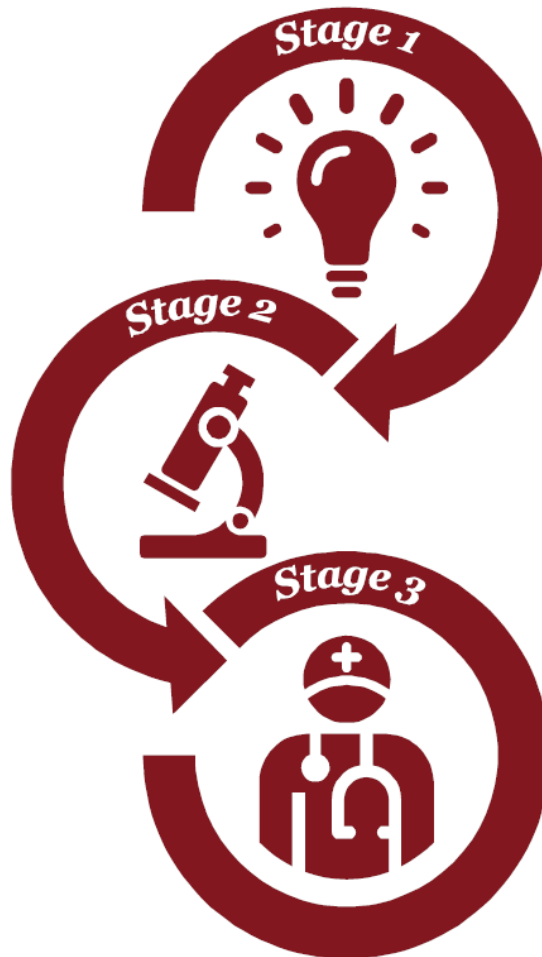
* Data from the UK Clinical Practice Research Datalink (www.cprd.com)

UK prevalence of prescribing sodium valproate - CPRD



- Rate of prescribing in younger females relatively consistent
- Suggestion of flattening of expected increase in prescribing in women 18-45yrs Jul-Dec 2015

Early Access to Medicines: MHRA



Promising Innovative Medicines (PIM) designation

- Submission of PIM application form
- Early dialogue between the applicant and MHRA, NICE, NHS and the devolved administrations
- Applicant informed of PIM designation via confidential letter

EAMS Scientific Opinion (SO)

- Submission of dossier with latest available data
- Interim disclosure of positive SO (where applicable) at Day 45 to NICE, NHS and the devolved administrations to facilitate NHS adoption
- Applicant informed of SO on or before Day 75 – 90

EAMS Patient Access in the NHS

- Discussion between the applicant and the NHS about managed entry for the product
- Collection of real world data
- Agreement of key considerations for transition to access post-marketing authorisation

Early Access to Medicines: MHRA



- Dupilumab is a monoclonal antibody
- Approved for severe atopic dermatitis
- Benefits: Led to reduced severity and extent of eczema lesions
- Risks: Allergic reactions, cold sore, eye inflammations and worsening asthma
- Public Assessment Report published



[Home](#)

Decision

Early access to medicines scheme (EAMS) scientific opinion: Dupilumab for treatment of dermatitis

From: [Medicines and Healthcare products Regulatory Agency](#)
Part of: [Early access to medicines scheme \(EAMS\): scientific opinions](#)
First published: 13 March 2017

EAMS scientific opinion given to Dupilumab to treat adult patients with severe atopic dermatitis, including the public assessment report.

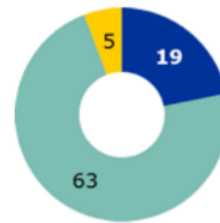
EAMS Scientific opinion: <https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-dupilumab-for-treatment-of-dermatitis>

PRIME (PRiority MEdicines): EMA



- Launched in 2016
- Mostly oncology
- 19 approved
- EMA committees assess these

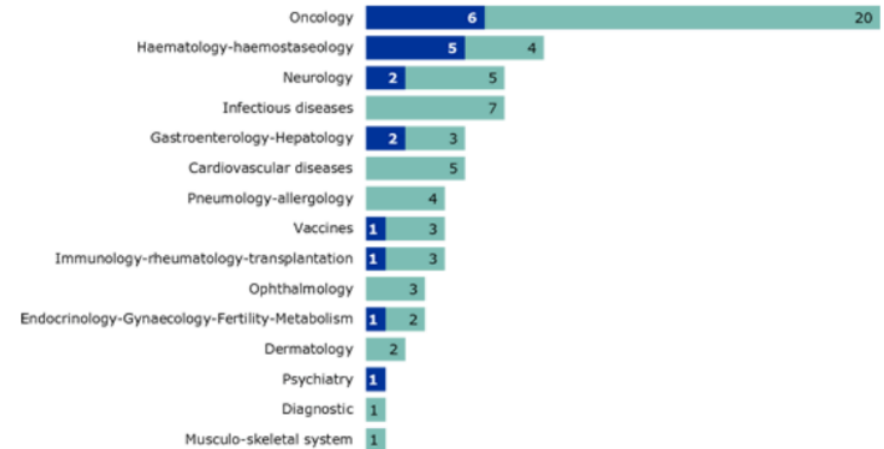
Applications and eligibility decisions



Type of applicant



Therapeutic areas



■ Granted ■ Denied ■ Out of scope*

Recommendations adopted by 23 February 2017

PRIME further information:

http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/regulation/general/general_content_000660.jsp%26mid%3DWC0b01ac058096f643

Global response



- Collaboration between academia, industry and government
- Clinical trials fast tracked in the UK (<4 days)
- Multiple Ebola vaccines in development
- One has been approved through PRIME (Zaire strain)



The Ebola outbreak in West Africa is spreading faster than efforts to control it, World Health Organization (WHO) head Margaret Chan has said.

She told a summit of regional leaders that failure to contain Ebola could be "catastrophic" in terms of lives lost.

But she said the virus, which has claimed 728 lives in Guinea, Liberia and Sierra Leone since February, could be stopped if well managed.

Ebola kills up to 90% of those it infects.

First British volunteer injected with trial Ebola vaccine in Oxford

If vaccine tested on Ruth Atkins and other healthy volunteers is found to work, it will be fast-tracked for use in west Africa

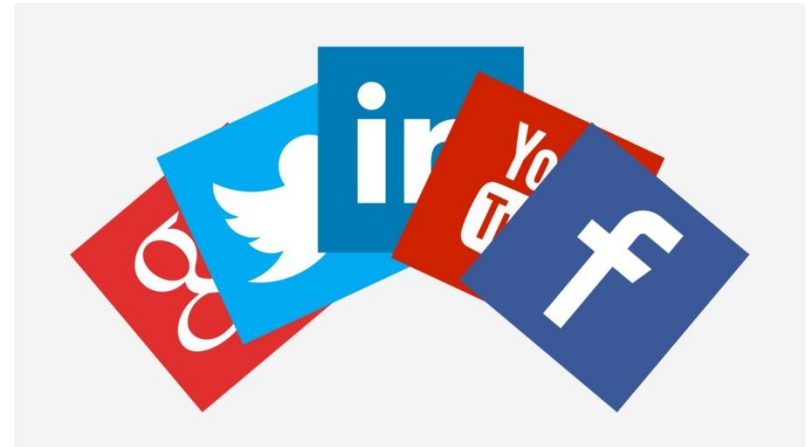


Dr Felicity Hartnell of Oxford University injects Ruth Atkins with the Ebola vaccine. Photograph: Steve Parsons/PA



A look ahead

- Fast paced
- Personalised medicines
- Social media
- Mobile apps



Questions?

Contact:

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References



Topic	URL
Advanced therapies	http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000196.jsp&mid=WC0b01ac05800292a8
Centralised product information	http://ec.europa.eu/health/documents/community-register/html/brand_full.htm
Clinical trials	https://www.clinicaltrialsregister.eu/
Dupilumab EAMS	https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-dupilumab-for-treatment-of-dermatitis
EAMS further information	https://www.gov.uk/government/statistics/early-access-to-medicines-scheme-applications-pending-refused-granted
EAMS Scientific opinion	https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-dupilumab-for-treatment-of-dermatitis
EMA database of spontaneous reports	www.adrreports.eu
Further PRAC information	http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp&mid=WC0b01ac058058cb18 http://www.encepp.eu/encepp_studies/indexRegister.shtml
Non-intervention studies	
Orphan drugs	http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp&mid=WC0b01ac058001d12b
PRAC agendas, minutes and highlights published	http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf
PRIME further information	http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/regulation/general/general_content_000660.jsp%26mid%3DWC0b01ac058096f643
RMP guidance	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp
SCOPE Methods of communication	http://www.scopejointaction.eu/assets/files/SCOPE-WP-6-Topic-1--FINAL-report.pdf
SCOPE Signal Management – Best Practice Guide	http://www.scopejointaction.eu/assets/files/WP5-Signal-Management-Best-Practice-Guide(5).pdf
SCOPE survey report: Reporting forms	http://www.scopejointaction.eu/assets/files/SCOPE-WP4-Topic-4-Survey-Report-v-0-7.pdf
Search RMP or EPAR	http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124