Access to safe medicines
Where is the link with the European Medicines Agency?

3rd EFIM Day – 17 March 2017 - Brussels

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The request

- Access to new medicines among internists in Europe
  - How to balance access and cost-effectiveness (particularly in light of new premium-priced biologicals)?
  - How to set priorities?

- Medication errors
  - How to cope with rising frequency

My response

- Where the regulatory and clinical contexts come together
- What the Agency does and doesn’t do
- Tools supporting early access
- Regulators’ contribution to medicines affordability
- Risk minimisation
Where do the regulatory and clinical contexts come together?
What do we do?

- Facilitate development and access to medicines
- Evaluate applications for marketing authorisation
- Monitor the safety of medicines across their life cycle
- Provide information on human and veterinary medicines to healthcare professionals and patients
Achieving EMA’s mission

**Foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public health in the European Union**

**Evidenced-based decisions**

Regulatory decision-making is based on assessment of:

- Valid scientific evidence generated by marketing authorisation applicants/holders
- Data and information available from alternative sources
  - academic studies, public authority studies (including by regulators);
  - use of data-sources on real-life use of medicines; clinical guidelines;
  - reports in EudraVigilance and in the scientific literature

**Feasible and proportionate decisions**

- Incorporate clinical expertise and practical experience
- Address patient needs in real life (including values and preferences)
- Consider implementation in local healthcare contexts
Foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public health in the European Union

Interaction with various stakeholders including healthcare professionals’, patients’ and consumers’ organisations, academia and industry associations

Thousands of experts serve in the Agency’s scientific committees, working parties and scientific assessment teams

Methods to collect patients’ and healthcare professionals’ input through direct consultation
The European medicines regulatory network

~ 50 national regulatory authorities  European Commission  European Medicines Agency
Does it work in clinical TRIALS?

Does it work in clinical PRACTICE?

Does it contribute to more efficient use of resources?

Efficacy

Effectiveness

Efficiency

Benefit/Risk
- EMA

HTA assessment
- National → HTAN

Health systems
- National

HCPs
Interaction with healthcare professionals

Different roles of healthcare professionals all along the medicine’s life-cycle, in the context of the patient’s journey

Bring on board different fields of clinical expertise and practitioners in Europe, active within the broad spectrum of health care, including primary care
Support the Agency in order to access the best possible independent expertise and obtain information on the current use of medicines in real clinical practice.

Contribute to a more efficient and targeted communication to healthcare professionals, to support their role in the safe and rational use of medicines.

Enhance healthcare professional organisations’ understanding of the role of the EU medicines Regulatory Network.

Network of European healthcare professional organisations.
How are medicines approved?

Different authorisation routes: one set of common rules

Centralised procedure (via EMA)

National procedures (via NCAs)
Which medicines are approved through the centralised procedure?

- Human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune, and other immune dysfunctions, and viral diseases
- Medicines derived from biotechnology processes, such as genetic engineering
- Advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines
- Officially designated ‘orphan medicines’ (medicines used for rare human diseases)
What is the benefit of the centralised procedure for EU citizens?

- Medicines are authorised for all EU citizens at the same time
- Centralised safety monitoring
- Product information available in all EU languages at the same time
An intricate regulatory environment

Supporting research and innovation of medicines

| Innovation task force (H&V) |
| Paediatric investigation plan (PIP) (H) |
| Scientific advice (H&V) |
| Qualification of novel methodologies (H) |
| Advanced therapy medicinal product classification (H) |
| Regulatory and administrative assistance for small- and medium-sized enterprises (H&V) |
| Orphan designation (including protocol assistance, fee reductions, market exclusivity) (H) |
What we do not do

• Evaluate the initial marketing authorisation application of all medicines in the EU
• Evaluate applications for the authorisation of clinical trials
• Carry out research or develop medicines
• Take decisions on the price or availability of medicines
• Develop treatment guidelines
• Develop laws concerning medicines
• Issue marketing authorisations
Access to medicines

According to the authors, there are five main ways European regulators can help:

• Enable the rapid approval of generics and biosimilars, as this facilitates competition and drives down prices;

• Work to ensure ‘me-too’ products (medicines comparable to already approved options) continue to come on the market at reasonable speed, again to drive down prices through increased competition;
INITIAL-EVALUATION APPLICATIONS BY TYPE OF APPLICATION (2011-2015)

<table>
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<tr>
<th>Year</th>
<th>Non-orphan medicinal products</th>
<th>Orphan medicinal products</th>
<th>Similar biological products</th>
<th>Generics, hybrid and abridged, well-established use, informed-consent and PUMA applications</th>
<th>Scientific opinions for non-EU markets (Article 58 applications)</th>
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Access to medicines

- Encourage companies to conduct clinical trials that both satisfy the needs of regulators (i.e. demonstrate quality, safety and efficacy of the medicine) as well as the health-technology-assessment bodies (i.e. support the demonstration of the value once the medicine is authorised, to guide payers in their reimbursement decisions);
Access to medicines

- Facilitate the collection of other data that are important for payers by taking their needs into account when asking companies to conduct post-approval studies. This could for example help payers when considering outcome-focused deals that tie the price of a medicine to the result for patients;
Access to medicines

• Support higher efficiency of research and development in the area of medicines: by fostering a better model for the development of medicines, it is expected that companies would potentially be able to reduce the price of their medicines. This could also mean reflecting on new approaches to medicines’ development, such as the adaptive pathways approach that is being explored by EMA.
Early access tools: Overview

**PRIME**
- Major public health interest, unmet medical need.
- Dedicated and reinforced support.
- Enable accelerated assessment.
- Better use of existing regulatory & procedural tools.

**Accelerated Assessment**
- Major public health interest, unmet medical need.
- Reduce assessment time to 150 days.

**Adaptive Pathways**
- Scientific concept of development and data generation.
- Iterative development with use of real-life data.
- Engagement with other healthcare-decision makers.

**Conditional MA**
- Unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in emergency situations.
- Early approval of a medicine on the basis of less complete clinical data.

**Parallel advice**

Other...Compassionate Use, MA under EC etc.
Early access to medicines that address specific public health needs

Accelerated assessments

Seven medicines received a recommendation for marketing authorisation following an accelerated assessment. This mechanism is reserved for medicines that have the potential to address unmet medical needs. It allows for faster assessment of eligible medicines by EMA’s scientific committees (within up to 150 days rather than up to 210 days).

**Cancer**

- **Darzalex**
  for patients with multiple myeloma

- **Kisplyx**
  for patients with advanced renal cell carcinoma

- **Cabometxyx**
  for patients with advanced renal cell carcinoma

- **Empliciti**
  for patients with multiple myeloma

- **Lartruvo**
  for patients with soft tissue sarcoma

**Haematology/ Haemostaseology**

- **Coagadex**
  for patients with factor X deficiency

**Infections**

- **Epclusa**
  for patients with chronic hepatitis C virus infection

*In: Human medicines highlights 2016*
Conditional marketing authorisations

Eight medicines received a recommendation for a conditional marketing authorisation, one of the possibilities in the EU to give patients early access to new medicines. This tool allows for the early approval of a medicine on the basis of less complete clinical data than normally required if the medicine addresses an urgent unmet medical need. These medicines are subject to specific post-authorisation obligations for medicines developers that aim to obtain complete data on the medicine.

**Cancer**

- **Alecensa**
  for patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer

- **Darzalex**
  for patients with multiple myeloma

- **Ninlaro**
  for patients with multiple myeloma

- **Lartruvo**
  for patients with soft tissue sarcoma

- **Venclyxto**
  for patients with chronic lymphocytic leukaemia

**Vaccine**

- **Pandemic influenza vaccine H5N1**
  MedImmune
  to protect children (12 months to 18 years) against influenza during a flu pandemic

**Haematology/Haemostaseology**

- **Zalmoxis**
  an advanced therapy medicine for patients receiving a haploidentical haematopoietic stem cell transplant (HSCT)

**Hepatology**

- **Ocaliva**
  for patients with primary biliary cholangitis
PRIME scheme - Goal & Scope

To foster the development of medicines with major public health interest.

Reinforce scientific and regulatory advice
- Foster and facilitate early interaction
- Raise awareness of requirements earlier in development

Optimise development for robust data generation
- Focus efficient development
- Promote generation of robust and high quality data

Enable accelerated assessment
- Facilitated by knowledge gained throughout development
- Feedback of relevant SA aspects to CHMP
Justification for eligibility to PRIME

For products under development yet to be placed on the EU market

**Unmet medical need**

- Epidemiological data about the disease
- Description of available diagnostic, prevention and treatment options/standard of care (SOC), their effect and how medical need is not fulfilled

**Potential to significantly address the unmet medical need**

- Description of observed and predicted effects, clinical relevance, added value and impact
- If applicable, expected improvement over existing treatments

**Data required at different stages of development**
How do we monitor the safety of medicines already on the market?

Clinical studies
  - Medical literature

Safety reports from patients and healthcare professionals

Patient registries
  - Regulatory bodies outside the EU

Data inputs that may lead to safety concerns

EMA/PRAC assessment

PRAC recommendation
  - Maintain
  - Change
  - Suspend
  - Revoke

Final decision by Member States or European Commission

Communication to the network

Various/potential data inputs received that might lead to safety concerns
Safe use of Keppra

• Measures for use of correct dosing syringe to avoid medication errors
• Keppra (levetiracetam) to treat epilepsy in adults and children.
• In children dose depends on the child’s bodyweight and age
• Cases of accidental overdose have been reported with levetiracetam oral solution; the majority of cases occurred in children aged between 6 months and 11 years.
• Most of the cases occurred when the medicine was used with a wrong dosing syringe or wrong dose measurement
• only the syringe provided with the package should be used to measure the dose of Keppra
• different medicine’s cartons and labels coloured differently and clearly indicate the volume of the bottle, the volume of the dosing syringe, and the age range of the child that the medicine should be used for
Recommendations to minimise ketogenic risk with SGLT2 inhibitors for diabetes

• Recommendations to minimise the risk of diabetic ketoacidosis in patients taking SGLT2 inhibitors

• A number of these cases have been atypical, with patients not having blood sugar levels as high as expected

• Recommendations to update the product information of SGLT2 inhibitors to list diabetic ketoacidosis as a rare adverse reaction (affecting up to 1 in 1,000 patients).

• The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC) PRAC recommendations were sent to the CHMP which adopted the Agency’s final opinion.

EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes

Healthcare professionals should be aware of possible atypical cases

On 25 February 2016, the European Medicines Agency (EMA) confirmed recommendations to minimise the risk of diabetic ketoacidosis in patients taking SGLT2 inhibitors (a class of type 2 diabetes medicines).

Diabetic ketoacidosis is a serious complication of diabetes caused by low insulin levels. Rare cases of this condition, including life-threatening ones, have occurred in patients taking SGLT2 inhibitors for type 2 diabetes and a number of these cases have been atypical, with patients not having blood sugar levels as high as expected.

An atypical presentation of diabetic ketoacidosis can delay diagnosis and treatment. Healthcare professionals should therefore consider the possibility of ketoacidosis in patients taking SGLT2 inhibitors who have symptoms consistent with the condition even if blood sugar levels are not high.

Following a review of the cases, EMA recommended updating the product information to list diabetic ketoacidosis as a rare adverse reaction.
Recommendations to minimise risk of PML with Tysabri

- Review of the known risk of progressive multifocal leukoencephalopathy (PML) with Tysabri (natalizumab)
- Early detection and treatment of PML when the disease is asymptomatic may improve patients’ outcomes
- Full MRI scans at least once a year / patients at higher risk of PML more frequent MRI scans (e.g. every 3 to 6 months)
- Additional measures if lesions suggestive of PML are discovered
- Recommendations are based on an initial review by PRAC; CHMP confirmed them and issued its final opinion
EMA recommends measures to ensure safe use of Keppra oral solution

Medication should only be used with dosing syringe included in the package.

Several measures have been put in place to ensure that the correct dosing syringe is used to measure Keppra oral solution, and thus avoid medication errors. Keppra (levetiracetam) is a medicine used to treat epilepsy in adults and children.

In children, the dose of Keppra depends on the child’s bodyweight and age, and the oral solution is the preferred formulation for use in children less than 6 years of age. The medicine is available as a 100 mg/ml solution in either a 150 or 200 ml size bottle, and it comes with a 1.5 or 10 ml syringe.

Cases of accidental overdose have been reported with levetiracetam oral solution; the majority of cases occurred in children aged between 6 months and 11 years. Most of the cases occurred when the medicine was used with a wrong dosing syringe (e.g., a 10 ml syringe was used instead of a 1.5 ml one, leading to a 6-fold overdose), or because of a misunderstanding of the caregivers about how to properly measure the dose. Levetiracetam overdose often has no symptoms, but it may cause sleepiness, agitation, difficulty breathing and coma.

To avoid medication errors and the risk of overdose, parents and carers are advised that only the syringe provided with the package should be used to measure the dose of Keppra. The different medicine’s cartons and labels will be coloured differently and clearly indicate the volume of the bottle, the volume of the dosing syringe, and the age range of the child that the medicine should be used for:

- 1-6 years: 6-40 ml
- 6-10 years: 4+ ml

The package leaflet will also include clearer instructions for parents and carers in order to minimise the risk of using an incorrect dose. Parents and carers are advised always to discard the syringe once the medicine’s bottle is empty.

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How is this relevant to EFIM?

Input to/participation in general EMA activities – EFIM representatives

- EMA consultations on strategic documents, policies, projects and initiatives (written or via teleconference)
  - E.g.: Publication of clinical data; European clinical trials portal and database
- EMA workshops/conferences
  - Recent examples: ATMPs, Big data, patient registries, measuring the impact of pharmacovigilance, adaptive pathways, personalised medicine.
- EMA guidelines
  Recent examples: Reflection Paper on the assessment of cardiovascular risk of medicinal products; Clinical evaluation of medicinal products used in weight control; Clinical investigation of medicinal products in the treatment of chronic heart failure
How is this relevant to EFIM?

*Input to product-specific consultations - as individual experts (subject to confidentiality)*

- Input in Scientific Advisory Groups (SAGs) and Ad-hoc expert group meetings
- Review of labelling aspects and additional risk minimisation measures including implementation
- Review of safety communications and DHPCs (including prevention of medication errors)
- Scientific Committees/Working Parties consultations (standard of care; risk minimisation measures; product information)

*EFIN permanent member of ‘EMA Working Party with healthcare professionals’ organisations’ (HCPWP)*
Search for a specific medicine

Content specially selected for healthcare professionals

Find out about latest safety communications, new approved medicines and draft guidelines open for consultation
Thank you for your attention

Further information

[Insert relevant information sources or contact details as applicable.]

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