About OMICS Group

OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

OMICS International Conferences

OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Intentional medication errors: Off label use?

Angela van der Salm, Director PV

Disclaimer

The views and opinions expressed in the following Power Point slides are those of the individual presenter.

Topics

- Risk management planning
- Medication errors
- Off label use
- Data capture challenges
- Signal detection
- Conclusion

Risk Management Planning

- New EU pharmacovigilance legislation in 2012:
  - Introduction of the **PRAC,** to provide recommendations for regulatory action on safety issues arising due to errors associated with the use of medicines authorised in the EU. This includes all aspects of risk management and **monitoring the effectiveness of specific measures to prevent or minimise the risk of medication errors,** as contained in the risk-management plan (RMP) for a medicine (specific EU requirement).
  - Accordingly, each periodic safety update report (PSUR) assessed by the PRAC contains data on any medication errors that occurred with a medicine during the reporting period regardless of whether it is associated with adverse reaction(s).
  - This information feeds into the continuous evaluation of the benefits and risks of each medicinal product medicinal product.

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

Risk Management Planning

- New EU pharmacovigilance legislation in 2012:
  - Art 23 (2) of DIR 2001/83/EC requires the MAH to report to the competent authorities "any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned ", including "data on the use of the medicinal product where such use is **outside the terms of the marketing authorisation**"
  - Per GVP Module V, post-marketing updates to the safety specification should include information on EU off-label use (including use in non-authorised paediatric age categories; again: specific EU requirement).

Medication errors

- The EU regulatory description of a medication error is (not defined as such in GVP Definitions, but covered in GVP Module V on 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.

- Broadly 4 categories:

  1. wrong medication;
  2. wrong dose (including strength, form, concentration, amount);
  3. wrong route of administration;
  4. wrong patient

http://www.ema.europa.eu/ema/index.jspcurl=pages/regulation/document_listing/document_listing_000345.jsp

Medication errors

- Risk management planning for medication errors should be proactive and begin early in development
- MAHs should consider the various sources of medication error and the likely impact on the benefit-risk balance (pre-and post-authorisation)
- The following aspects may be relevant:

Concentration / strength	Pharmaceutical form
Labeling	Instructions for use
Composition	Route of administration
Use in a different population / indication	Appearance (of device or packaging)

Medication errors

- Current/Ongoing initiatives:
  - 30 May 2013 EMA/CHMP/277591/2013 - Committee for Medicinal Products for Human Use (CHMP)

    Position paper on potential medication errors in the context of benefit-risk balance and risk minimisation measures

  - Draft EMA/762563/2014 - Pharmacovigilance Risk Assessment Committee (PRAC)

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

  - Draft EMA/606103/2014 - Pharmacovigilance Risk Assessment Committee (PRAC)

    Good practice guide on risk minimisation and prevention of medication errors, and Draft EMA/686009/2014

    Risk minimisation strategy for high strength and fixed combination insulin products, addendum to the good practice guide on risk minimisation and prevention of medication errors

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

Draft good practice guide –routine risk minimisation for high strength & fixed combination insulin products

- Medication errors due to mix-up between long-acting (basal) and short-acting (bolus) insulins, including by visually impaired or colour blind patients

Dr Julie Beynon (MHRA), DIA EMA RMP information day dd 30-Jun-15

Draft good practice guide –routine risk minimisation for high strength & fixed combination insulin products

- Medication error due to non-compliance with instructions for use –unnecessary dose recalculation

Draft good practice guide –routine risk minimisation for high strength & fixed combination insulin products

- Key safety messages for **high strength insulin products** addressing the risk of medication errors

Medication error	Healthcare professionals key safety messages	Patients key safety messages
Medication error due to mix-up between different product strengths, including by visually impaired or colour blind patients with diabetes mellitus;	• To encourage prescribers to always include the correct strength on the prescription. • Pharmacists are recommended to ask patients/carers to visually identify the strength of insulin dispensed in order to ensure patients/carers are able to read the dose counter of the pen device. • Healthcare professional awareness of the need to prescribe the insulin dose in units and the dose frequency for <PRODUCT NAME>.	• <PRODUCT NAME> is now available in two [or more] strengths; • Key features and differences of the design of the packages and pre-filled pen devices; • Always check the insulin label before each injection to avoid accidental mix-ups between the [2] different strengths of <PRODUCT NAME>;

Off label use

- Off label use relates to situations where the medicinal product is **intentionally** used for a medical purpose **not in accordance with the authorised product information**. This is particularly relevant where a medicinal product has an **indication restricted** to a subset of the population within a disease area, or there are situations where the medicinal product must not be given for safety reasons. The potential for use in other disease areas should also be considered where this is likely.

- EU-wide signal detection activities should include with a higher-than-regular frequency any product considered to have an identified or potential risk that could impact significantly on the benefit-risk balance or have implications for public health. This may include risks associated with significant misuse, abuse or off label use (GVP Module IX).

Off label use

- Post-marketing updates to the safety specification in the RMP should include information on EU off-label use (including use in non-authorised paediatric age categories)
  - Information from drug utilisation studies (or other observational studies where indication is a variable) should be provided where available. This includes drug utilisation studies which were requested by NCAs for purposes other than risk management.
  - When off label use is a safety concern or a concern has been raised by NCAs regarding off label use, MAHs should attempt to quantify such use along with a description of the methods used to arrive at these figures.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

Off label use - Example

Basiliximab – SIMULECT (CAP)

Cardiovascular instability resulting in fatal outcome in association with off-label use in cardiac transplantation

- Basiliximab: monoclonal antibody authorised in the prophylaxis of acute kidney transplant rejection in de novo renal transplantation.
- Signal of cardiovascular instability triggered by 3 fatal cases following off-label use in heart transplantation, identified by the Swedish Medicines Agency.
- Search in EudraVigilance: cases of cardiac failure and cardiac arrest in temporal association with basiliximab when used within its authorised indication.
- PRAC agreed the signal needed further investigation.

Georgy Genov, EMA, DIA EuroMeeting 2014

Off label use - Example

Basiliximab – SIMULECT (CAP)

Cardiovascular instability resulting in fatal outcome in association with off-label use in cardiac transplantation

- Feb 2013 PRAC: MAH requested to perform a cumulative analysis of all cases describing thromboembolic events, rhythm disorders (e.g. arrhythmia, bradycardia), or cardiac failure/insufficiency.
- May 2013 PRAC: MAH requested to submit an additional analysis with regard to cardiac events which occurred within 48 h after basiliximab administration and a refined analysis of safety and efficacy in heart transplantation from all clinical trials.
- Feb 2014 PRAC: MAH requested to submit within 2 months
  - proposal of active communication
  - variation application to update the SPC
- in order to inform cardiac surgeons of the lack of favourable efficacy and safety data in the available clinical trials conducted in off-label heart transplantation.

Georgy Genov, EMA, DIA EuroMeeting 2014

Off label use - Example

Basiliximab – SIMULECT (CAP)

Cardiovascular instability resulting in fatal outcome in association with off-label use in cardiac transplantation

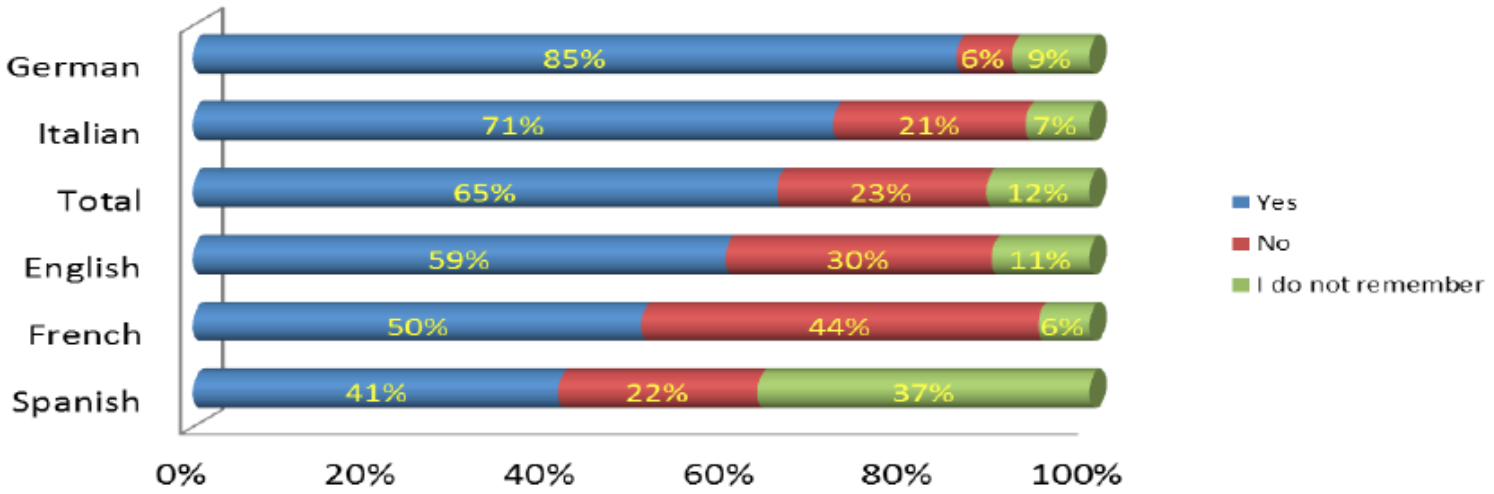
- Result: new warning added in SmPC section 4.4

  Use in heart transplantation

  The efficacy and safety of Simulect for the prophylaxis of acute rejection in recipients of solid organ allografts other than renal have not been demonstrated. In several small clinical trials in heart transplant recipients, serious cardiac adverse events such as cardiac arrest (2.2%), atrial flutter (1.9%) and palpitations (1.4%) have been reported more frequently with Simulect than with other induction agents.
- DHPC requested by CHMP to remind cardiac surgeons and physicians in EU heart transplant centres that Simulect is indicated only for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation.

Georgy Genov, EMA, DIA EuroMeeting 2014

Off label use – patient's view



	Yes	No	I do not remember
German	69	5	7
Italian	20	6	2
English	38	19	7
French	26	23	3
Spanish	11	6	10
TOTAL	164	59	29

Rob Camp, EuroRDis Survey results, DIA EuroMeeting 2014

Data capture Challenges

- There is **no legal requirement to record reports** on medication errors or off-label use in the MAH safety database for the collection of Individual Case Safety Reports (ICSRs).

- There is **no legal requirement to submit ICSRs** of medication errors or off-label use if not linked to a suspected adverse reaction

- However, the information **should be collected** for the fulfillment of the pharmacovigilance tasks. In this aspect, appropriate recording mechanisms should be in place to ensure that these reports are considered in signal management activities and included in the RMPs and in the PSURs (as necessary).

http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/03/WC500184248.pdf

Data capture Challenges

- Case study 1:

  Consumer reports taking drug X for inflammation. The label only states fever and pain.

  Code as off label use? Or as misuse? Or as medication error?

- Case study 2:

  Consumer reports taking drug X for inflammation as prescribed by his physician. The label only states fever and pain.

  Code as off label use? Is this misuse?

- Case study 3:

  Consumer reports taking drug Z already for 2 months. The label states that the drug should not be taken longer than for 10 days without consulting a physician.

  Code as off label use? Or as Inappropriate duration of drug administration?

Data capture Challenges

Concept	Intentional?	By Whom?	Therapeutic Use?	Additional Sections in this Document
Misuse	Yes	Patient/consumer	Yes*	3.16.1
Abuse	Yes	Patient/consumer	No	3.16.2
Addiction	Yes	Patient/consumer	No	3.16.3
Medication error	No	Patient/consumer **or** healthcare provider	Yes	3.15
Off label use	Yes	Healthcare provider	Yes	3.27

Signal detection

- Drug X is indicated for:
  - Choriocarcinoma and similar trophoblastic diseases
  - (Non-Hodgkin's) Lymphoma
  - (Acute lymphocytic) Leukaemia
  - Treatment and prevention of leukemic meningitis
  - Osteogenic sarcoma
  - Metastatic or recurrent head and neck cancer
  - Advanced cancers of urinary bladder
  - Advanced mycosis fungoïdes (skin carcinoma)
  - Active rheumatoid arthritis in adult patients,
  - Polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate,
  - Severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy, and severe psoriatic arthritis in adult patients.
  - Mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.

Signal detection

- **MAH A has Drug X indicated** for:
  - Choriocarcinoma and similar trophoblastic diseases
  - (Non-Hodgkin's) Lymphoma
  - (Acute lymphocytic) Leukaemia
  - Treatment and prevention of leukemic meningitis
  - Osteogenic sarcoma
  - Metastatic or recurrent head and neck cancer
  - Advanced cancers of urinary bladder
  - Advanced mycosis fungoïdes (skin carcinoma)
  - **Active rheumatoid arthritis in adult patients,**
  - **Polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate,**
  - **Severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy, and severe psoriatic arthritis in adult patients.**
  - Mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.

Signal detection

- MAHs would consider a certain report differently depending on their own label, therefore the same report on a certain ADRs may be reported as associated with off-label use.
- Particular issue for literature publications!
- How to conduct signal detection for off label use in larger databases, if for MAH A, several indications are considered off label that are “in-label” for other MAHs?
- MAHs need to have a policy in place on how to code certain adverse events (make use of MedDRA Points to Consider documentation)!

Conclusion

- At the time of obtaining the MA, the safety data collected defines the label and intended use.
- Post-marketing, health care providers or consumers may not use your product according to the label: medication error or off-label use (/misuse)
- From the reported information, it may not always be easy to distinguish between the unintentional medication error from the intentional off-label/misuse, so what is the specific issue? (if any…).
- Code reports according to company policy (create one for consistency).
- Managing product usage outside of routine pharmacovigilance activities, requires adequate knowledge and solid data => Joint effort for MAH and Regulators

Questions?

Let us meet again..

We welcome you all to our future conferences of OMICS International

5th International Conference & Exhibition on Pharmacovigilance & Clinical Trials

On

September 19 - 21, 2016 at Vienna, **Austria**

http://pharmacovigilance.pharmaceuticalconferences.com/