European Pharmacovigilance Overview of 3 years of operation

Thoughts from Health Care Professionals

Kirsten Myhr, MScPharm, MPH, specialist in hospital pharmacy
PRAC alternate for health care professionals

Key achievements

- Scientific advisory body (PRAC), scientific advisory groups (SAG) etc.
- High competence amongst members of PRAC
- Evaluations of important safety signals
- Dialogue with other regulatory agencies
- Network of pharmacoepidemiology centres (EnCEPP)
- Eudravigilance and signal generation
- Procedure for public hearings (draft)
- Directive on medication errors (draft)
- Document on medicine shortages

Challenges in Pharmacovigilance

- EU one entity?
  - country differences in healthcare systems, perceptions
  - who prescribes, where administered, OTC status, obsolete medicines, reimbursement
- More transparency, but in practice major hurdles, cf. requests and ombudsman cases
- EMA focus on CAPs, many with little or no benefit to patients, and prices that many MSs cannot afford
- Focus on product and brand names, the current legal framework protecting products severely hampers harmonisation of active ingredients and of therapeutically equivalent substances, though “old”, off-patent products are still frequently used and rightly so
- PSURs for all NAPs evaluated in PRAC - time consuming and frustrating when assessed based on old evaluations of effect
- Lengthy processes often ending in only minor changes to safety profiles
- Post-authorisation safety studies - independence and transparency
- Company-owned registries per product not disease
  - same patients in different registries
  - lack of transparency and access to registers

Challenges in communication between regulatory authorities and practising health care professionals

- Electronic access in primary and secondary care still poor in many (most?) MSs
- Regulation regarded by HCPs as a barrier to clinical practice
- RAs often small with few qualified staff, product-oriented
- Marketing practices by MAHs confuse messages on safety by focussing on effect
- HCPs approached by MAHs insisting to talk about educational material "because it is required by EMA". Multiple forms of material for same / similar substance
- DHPC letters not read, particularly if envelopes have company logo.
- EMA evaluations of safety signals perceived as too long and message not always clear
- Confusion when advice differs btw EMA and FDA or is not issued simultaneously (e.g. metoclopramide*)
- SmPCs (EPARs), if read at all, are too long, and how to communicate any changes? Doctors don't read SmPCs/EPARs for every new patient (examples in background slides**)
- Inconsistencies in SmPCs/EPARs between MAHs
- Lack of transparency

ADR-reporting mandatory, but what is practice?

- How are reports coded? (symptoms vs diagnosis etc.)
- PRAC and signals – too much time spent on poor signals?
- ADR-reporting by industry vs by HCPs and patients
  - No feedback to prescriber from industry, no independent causality assessment
  - Follow-up of reports of missing information: a hassle to HCPs, confidentiality issues
- Prescribed by GP, but ADR report by hospital
  - limited info on medication history
- Black triangle by product
  - if different products with same API, not all have black triangle(!)
- Medication errors and off-label use as ADRs poorly understood/accepted
- Under reporting of misuse, abuse

Communicating safety issues

- How is the SmPC/EPAR perceived?
  - EPARs all presentations in one – must all text be repeated in full for each?
  - EPAR translated from US, different medicines used e.g. in preventing/treating ADRs
  - ADRs, Interactions, Cautions, Contraindications in SmPC and PIL (= EPAR)
  - Handling cytotoxics, MABs etc.
  - Pregnancy and breastfeeding
  - (see examples in background slides***)
- As guiding documents for guidelines, actions needed by individual countries
- SmPCs/EPARs legal documents? So perceived by HCPs
- PILs so unreadable that HCP will have to explain + found at the end of EPAR (example in background slides****)

Areas of improvement and priorities for future work

- Priorities in PRAC work
- Transparency
- Communication – content and dissemination of messages to meet public demands
- Improve communication between EMA, FDA, Canada etc. to (try to) harmonise safety messages
- SmPCs (EPARs), PILs
- Harmonisation of NAPs by APIs (active ingredients)
- Access to medicines for vulnerable groups
- Support to more public registries
- Facilitating reporting by HCPs and patients directly

Medicines for vulnerable groups

- Children
  - Lacking medicines / relevant studies of medicines for important paediatric disorders
  - Paediatric preparations delayed in EMA because NAPs needing to be harmonised are not given priority? (morphine mixture since 2009?)
  - Confusion in labelling, e.g. mg/ml vs mg/5 ml on mixtures
  - Drug shortage and safety

- Pregnancy and breastfeeding
  - harmonisation of wording
    - Antihistamines, locally administered medicines for asthma and allergy (see example in background slide***)
    - Injectables, orals vs topical vs inhalation of same substance

- The elderly
  - Few relevant clinical trials, extrapolation of data = b/r profile lacking
  - Polypharmacy – studies needed

Background slides

Examples taken from questions and ADR-reports received at a regional medicines information and pharmacovigilance centre

* Metoclopramide - restriction of use

Metoclopramide is, amongst others, for nausea and vomiting, stimulating bowel movements acontractions. FDA issued a warning that the risk of dystonic reactions increases with increased duration of use. They recommended a maximum duration of 30 days. The assessment of risk was on the European level done in CMDh as metoclopramide products all had nationally approved MAs.

Ref. 20 December 2013 EMA 13239/2014 Corr.1

This resulted in a conclusion of a maximum duration of use of 5 days in nausea and vomiting. Use in pregnancy for nausea and vomiting was not amongst the indications listed, may be because no product in any member state had that as approved indication. But metoclopramide is regarded as the safest antiemetic in pregnancy and the conclusion left us with less safe alternatives. Pregnant women may need longer treatment than 5 days. The different conclusions by FDA and EMA is difficult to understand by HCPs and patients.

** SmPC – can you find what you want?

This example is the SmPC/EPAR of Herceptin (trastuzumab) and is chosen just because I recently was confronted by HPs intending to administer the subcutaneous injection but struggled to find information, especially on handling and administration.

The full SmPC is 136 pages and consists of 3 different formulations, powder for infusion, vial for injection and solution for injection in administration system. On the slides, 1 for each formulation, more info is given. Obviously not easy to find important information for doctors and nurses who administer the medicine.

SmPC/EPAR for Herceptin (trastuzumab): 3 presentations, 136 pages, here summarised on 3 slides

1. NAME OF THE MEDICINAL PRODUCT

Herceptin 150 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures.

The reconstituted Herceptin solution contains 21 mg/mL of trastuzumab.

For a full list of excipients, (see section 6.1).

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Powder for infusion

Pg 30: 6.6 on reconstitution

6.6 Special precautions for disposal and other handling

Appropriate aseptic technique should be used. Each vial of Herceptin is reconstituted with 7.2 mL of water for injections (not supplied). Use of other reconstitution solvents should be avoided. This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overage of 4 % ensures that the labelled dose of 150 mg can be withdrawn from each vial.

Herceptin should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of Herceptin that can be withdrawn from the vial.

The reconstituted solution should not be frozen.

Instructions for reconstitution:
1) Using a sterile syringe, slowly inject 7.2 mL of water for injections in the vial containing the lyophilised Herceptin, directing the stream into the lyophilised cake.
2) Swirl the vial gently to aid reconstitution. DO NOT SHAKE!

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Herceptin results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Determine the volume of the solution required:

- based on a loading dose of 4 mg trastuzumab/kg body weight, or a subsequent weekly dose of 2 mg trastuzumab/kg body weight:

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (4 mg/kg for loading or 2 mg/kg for maintenance)}}{\text{21 (mg/mL, concentration of reconstituted solution)}}$$

- based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3-weekly dose of 6 mg trastuzumab/kg body weight:

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (8 mg/kg for loading or 6 mg/kg for maintenance)}}{\text{21 (mg/mL, concentration of reconstituted solution)}}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9 % sodium chloride solution. Do not use with glucose-containing solutions (see section 6.2). The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for 24 hours (do not store above 30°C).

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

Herceptin is for single-use only, as the product contains no preservatives. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

No incompatibilities between Herceptin and polyvinylchloride, polyethylene or polypropylene bags have been observed.

1. NAME OF THE MEDICINAL PRODUCT

Herceptin 600 mg solution for injection in vial

Pg 31: Vial for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 5 mL contains 600 mg of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures.

For the full list of excipients, see section 6.1.

Not obvious that it is for subcutaneous injection

3. PHARMACEUTICAL FORM

Solution for injection

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed. Herceptin subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulation and vice versa, using the three-weekly (q3w) dosing regimen, was investigated in study MO22982 (see section 4.8).

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not Kadcyla (trastuzumab emtansine).

6.2 Incompatibilities

Herceptin subcutaneous formulation is a ready to use solution which should not be mixed or diluted with other products.

Page 56

6.6 Special precautions for disposal and other handling

Herceptin should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Herceptin is for single-use only.

As Herceptin does not contain any antimicrobial-preservative, from a microbiological point of view, the medicine should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. After transfer of the solution to the syringe, it is recommended to replace the transfer needle by a syringe closing cap to avoid drying of the solution in the needle and not compromise the quality of the medicinal product. The hypodermic injection needle must be attached to the syringe immediately prior to administration followed by volume adjustment to 5 mL.

Pg 42: This para on not confusing different formulations is not added to the powder for infusion SmPC

1. NAME OF THE MEDICINAL PRODUCT

Herceptin 600 mg solution for injection in administration system

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One administration system contains 600 mg/5 mL of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures.

For the full list of excipients, see section 6.1.

Pg 59: solution for injection in administration system. Not obvious that it is for subcutaneous injection

3. PHARMACEUTICAL FORM

Solution for injection

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed. Herceptin subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Method of administration

Page 60-61

The Herceptin 600 mg solution for injection in administration system is ready to use and is for single use only. The 600 mg dose should be administered as a subcutaneous injection every three weeks. The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. The injection site may need to be shaved to facilitate the fixing and removal of the adhesive pad of the administration system.

During the treatment course with Herceptin subcutaneous formulation in administration system, other medicinal products for subcutaneous administration should preferably be injected at different sites. Patients should be observed for six hours after the first injection and for two hours after subsequent injections for signs or symptoms of administration-related reactions (see sections 4.4 and 4.8).

For instructions on use and handling of Herceptin subcutaneous formulation, refer to section 6.6 of the SmPC, and section 7 of the package leaflet.

6.6 Special precautions for disposal and other handling

Page 85: 6.6

Herceptin should be inspected visually to ensure there is no particulate matter or discolouration prior to administration. Presence of small air bubbles is acceptable. The product should not be used if it has been dropped, or if it is visibly damaged. The administration system should not be allowed to come into contact with water.

The administration system is for single-use only.

Once removed from the refrigerator, the administration system must be stored for 1 hour at room temperature and not above 30 °C to allow the medicine to warm up to room temperature. The administration system should not be exposed to direct sunlight or warmed up in any other way (e.g. heat source exposure), as this can degrade the medicine.

** SmPCs (EPARs) and interactions

The next slide shows 4.5 Interactions section in the EPAR for Betmiga (mirabegron) – a medicine which is only for symptomatic relief of urinary incontinence problems. Target group is obviously the elderly most of whom will be on other medicines as well.

The information on interactions is so extensive that you wonder if the prescribing doctor will read it all. It means that a risk to the target group is there. The long section starts with whether mirabegron will be affected by other medicines. Then starts the information on how it might affect other medicines. Included in that latter group is an important medicine, metoprolol. And also digoxin. The rest of the other medicines so far listed as being affected includes e.g. an antipsychotic, thioridazine, that was banned for at least 20 years ago. That can lead one to suspect that most data were collected long time ago.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data

Mirabegron is transported and metabolised through multiple pathways. Mirabegron is a substrate for cytochrome P450 (CYP) 3A4, CYP2D6, butyrylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron inhibited P-gp-mediated drug transport at high concentrations.

In vivo data

EPAR for Betmiga (mirabegron) (60 pages) – 4.5 Interactions

CYP2D6 polymorphism

CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron (see section 5.2). Interaction of mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers.

Drug-drug interactions

The effect of co-administered medicinal products on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of other medicinal products was studied in single and multiple dose studies. Most drug-drug interactions were studied using a dose of 100 mg mirabegron given as oral controlled absorption system (OCAS) tablets. Interaction studies of mirabegron with metoprolol and with metformin used mirabegron immediate-release (IR) 160 mg.

Clinically relevant drug interactions between mirabegron and medicinal products that inhibit, induce or are a substrate for one of the CYP isozymes or transporters are not expected except for the inhibitory effect of mirabegron on the metabolism of CYP2D6 substrates.

Effect of enzyme inhibitors

Mirabegron exposure (AUC) was increased 1.8-fold in the presence of the strong inhibitor of CYP3A/P-gp ketoconazole in healthy volunteers. No dose-adjustment is needed when Betmiga is combined with inhibitors of CYP3A and/or P-gp. However, in patients with mild to moderate renal impairment (GFR 30 to 89 mL/min/1.73 m^2) or mild hepatic impairment (Child-Pugh Class A) concomitantly receiving strong CYP3A inhibitors, such as itraconazole, ketoconazole, ritonavir and clarithromycin, the recommended dose is 25 mg once daily with or without food (see section 4.2). Betmiga is not recommended in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) or patients with moderate hepatic impairment (Child-Pugh Class B) concomitantly receiving strong CYP3A inhibitors (see sections 4.2 and 4.4).

Effect of enzyme inducers

Substances that are inducers of CYP3A or P-gp decrease the plasma concentrations of mirabegron. No dose adjustment is needed for mirabegron when administered with therapeutic doses of rifampicin or other CYP3A or P-gp inducers.

Effect of mirabegron on CYP2D6 substrates

In healthy volunteers, the inhibitory potency of mirabegron towards CYP2D6 is moderate and the CYP2D6 activity recovers within 15 days after discontinuation of mirabegron. Multiple once daily dosing of mirabegron IR resulted in a 90% increase in C_{max} and a 229% increase in AUC of a single dose of metoprolol. Multiple once daily dosing of mirabegron resulted in a 79% increase in C_{max} and a 241% increase in AUC of a single dose of desipramine.

metoprolol

Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6, such as thioridazine, Type 1C antiarrhythmics (e.g., flecainide, propafenone) and tricyclic antidepressants (e.g., imipramine, desipramine). Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated.

Thioridazine, withdrawn long ago

Effect of mirabegron on transporters

Mirabegron is a weak inhibitor of P-gp. Mirabegron increased C_{max} and AUC by 29% and 27%, respectively, of the P-gp substrate digoxin in healthy volunteers. For patients who are initiating a combination of Betmiga and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. The potential for inhibition of P-gp by mirabegron should be considered when Betmiga is combined with sensitive P-gp substrates e.g. dabigatran.

Digoxin, dabigatran

Other interactions

No clinically relevant interactions have been observed when mirabegron was co-administered with therapeutic doses of solifenacin, tamsulosin, warfarin, metformin or a combined oral contraceptive medicinal product containing ethinylestradiol and levonorgestrel. Dose-adjustment is not recommended.

Increases in mirabegron exposure due to drug-drug interactions may be associated with increases in pulse rate.

Indication: Symptomatic treatment of incontinence

*** Medicines in pregnancy and breastfeeding

Women are denied lifesaving medicines or medicines that could control their disease during pregnancy because of the MAHs wish to not recommend medicines use. And even if the disease itself, uncontrolled is a risk to the baby. Years ago a regulatory authority proposed a standard text for medicines to control allergies and asthma but the proposal was not accepted by the MAHs. The example of Aerius (desloratadine) in the next slide is now used for new medicines. It is an improvement, but the last sentence could still be regarded as a warning against use. Even use of locally administered medicines by inhalation and eyedrops, suffer from being regarded as carrying the same risk as oral or parenteral formulations.

May be the grading system used by designated centres, by Australia, US and Canada is better, with explanation of what the codes mean. To leave this to the companies, however, is a problem as they regard the SmPc as a legal document and thus fear suits.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformative nor foeto/ neonatal toxicity of desloratadine. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Aerius during pregnancy.

As a precautionary measure, it is preferable to avoid the use of Aerius during pregnancy

Desloratadine has been identified in breastfed newborns/infants of treated women. The effect of desloratadine on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Aerius therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Antihistamines and pregnancy

**** Information on side effects in Package Insert Leaflet

This example from a PIL happens to be Herceptin (trastuzumab) as well, as when I continued to scroll down the EPAR, I came across this not patient-friendly example.

The PIL contains this very long list of side effects – not at all understandable for anyone. It seems to be a list of all reported ADRs during clinical trials regardless of terminology used. Meaning that e.g. pain has been recorded in many different forms and frequencies and that is also the case with e.g. lung and breathing problems and infections. At the very end is listed reports of foetal effects.

Very common side effects of Herceptin: may affect more than 1 in 10 people:

- infections
- diarrhoea
- constipation
- heartburn (dyspepsia)
- weakness
- skin rashes
- chest pain
- abdominal pain
- joint pain
- low counts of red blood cells and white blood cells (which help fight infection) sometimes with fever
- muscle pain
- conjunctivitis
- watery eyes
- nose bleeds
- runny nose
- hair loss
- tremor
- hot flush
- dizziness
- nail disorders
- weight loss
- loss of appetite
- inability to sleep (insomnia)

- altered taste
- low platelet count
- numbness or tingling of the fingers and toes
- redness, swelling or sores in your mouth and/or throat
- pain, swelling, redness or tingling of hands and/or feet
- breathlessness
- headache
- cough
- vomiting
- nausea

Package leaflet for Herceptin
To inform, scare or confuse the patient?

Common side effects of Herceptin: may affect up to 1 in 10 people:

- allergic reactions
- throat infections
- bladder and skin infections
- shingles
- inflammation of the breast
- inflammation of the pancreas or liver
- kidney disorders
- increased muscle tone or tension (hypertonia)
- pain in the arms and/or legs
- itchy rash
- sleepiness (somnolence)
- bruising
- haemorrhoids
- itchiness

- dry mouth and skin
- dry eyes
- sweating
- feeling weak and unwell
- anxiety
- depression
- abnormal thinking
- asthma
- infection of lungs
- lung disorders
- back pain
- neck pain
- bone pain
- acne
- leg cramps

Uncommon side effects of Herceptin: may affect up to 1 in 100 people

- deafness
- bumpy rash
- blood infection

Rare side effects of Herceptin: may affect up to 1 in 1000 people :

- weakness
- jaundice
- inflammation or scarring of the lungs

Other side effects that have been reported with Herceptin use: frequency cannot be estimated from the available data:

- abnormal or impaired blood clotting
- anaphylactic reactions
- high potassium levels
- swelling of the brain
- swelling or bleeding at the back of the eyes
- shock
- swelling of the lining of the heart
- slow heart rate

- abnormal heart rhythm
- respiratory distress
- respiratory failure
- acute accumulation of fluid in the lungs
- acute narrowing of the airways
- abnormally low oxygen levels in the blood
- difficulty in breathing when lying flat
- liver damage/failure
- swelling of the face, lips and throat
- kidney failure
- abnormally low levels of fluid around baby in womb
- failure of lungs to develop in the womb
- abnormal kidney development in the womb