25 September 2014
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Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 8-11 September 2014

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 8-11 September 2014 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][1] reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (22-25 September 2014) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available guidance. Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

[1] The relevant EPITT reference number should be used in any communication related to a signal.

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The established procedures and timelines for submission of variation applications pertaining to generic medicinal products are to be followed.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the Questions and Answers on signal management.

1. Recommendations for update of the product information

1.1. Androgen deprivation therapy – QT interval prolongation due to long-term use

Substance (invented name)	Abiraterone (Zytiga, EMEA/H/C/002321), Degarelix (Firmagon, EMEA/H/C/000986), other androgen deprivation therapy
Authorisation procedure	Centralised and Non-centralised
EPITT No	13886
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	11 September 2014

Recommendation

Having considered the available evidence, including the case reports from EudraVigilance and the literature papers, suggesting a potential association between the use of medicinal products used for androgen deprivation therapy and QT interval prolongation, as a consequence of low testosterone levels, the PRAC agreed that the MAHs of androgen deprivation therapy (see list below) should submit a variation within 2 months to the EMA and NCA(s) to amend the Product Information (PI) as described below (new text underlined).

Summary of Product Characteristics

Section 4.4:

Androgen deprivation therapy may prolong the QT interval.

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating [PRODUCT NAME].

Section 4.5:

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of [PRODUCT NAME] with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

Section 4.8:

Frequency unknown/rare/uncommon*: QT prolongation (see sections 4.4 and 4.5)

*frequency as derived from clinical trials/safety studies, if no data is available frequency should be labelled as “unknown”.

Package leaflet

Section 2. What you need to know before you use [PRODUCT NAME]

Warnings and precautions
Please tell your doctor if you have any of the following:
Any heart or blood vessel conditions, including heart rhythm problems (arrhythmia), or are being treated with medicines for these conditions. The risk of heart rhythm problems may be increased when using [PRODUCT NAME].

Other medicines and [PRODUCT NAME]
[PRODUCT NAME] might interfere with some medicines used to treat heart rhythm problems (e.g. quinidine, procainamide, amiodarone and sotalol) or might increase the risk of heart rhythm problems when used with some other drugs(e.g. methadone (used for pain relief and part of drug addiction detoxification), moxifloxacin (an antibiotic), antipsychotics used for serious mental illnesses).

Section 4. Possible side effects
Uncommon/rare/not known*: changes in ECG (QT prolongation)

List of Androgen Deprivation Therapy products

- Products with the ATC codes L02AE Gonadotropin releasing hormone analogues, L02BX Other hormone antagonists and related agents and L02BB Anti-androgens, namely:
    - Buserelin;
    - Leuprorelin;
    - Goserelin;
    - Triptorelin;
    - Histrelin;
    - Abarelix;
    - Degarelix;
    - Abiraterone;
    - Flutamide;
    - Nilutamide;
    - Bicalutamide;
- Products which are not yet listed in the WHO ATC DDD codes:
    - Enzalutamide

1.2. Chlorhexidine cutaneous solutions – Chemical injury including burns when used in skin disinfection in premature infants

Substance (invented name)	Chlorhexidine gluconate containing products - cutaneous solutions
Authorisation procedure	Non-centralised
EPITT No	18000
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	11 September 2014

Recommendation

The PRAC reviewed the data submitted by the MAHs (Ecolab Ltd, Mölnlycke Health Care and CareFusion UK), and the advice provided by the Paediatric Committee (PDCO).

Having considered the evidence from spontaneous reporting, published literature, as well as the potential seriousness of the chemical injuries associated with the use of chlorhexidine solutions for skin disinfection in premature infants, the PRAC recommended that the MAHs for all chlorhexidine containing cutaneous solutions should submit to the NCAs a variation within 2 months to amend the Summary of Product Characteristics (SmPC), Package Leaflet (PL) and the product labelling as described below (new text underlined):

1. Changes to the SmPC:

4.4 Special warnings and precautions for use

The use of chlorhexidine solutions, both alcohol based and aqueous, for skin antisepsis prior to invasive procedures has been associated with chemical burns in neonates. Based on available case reports and the published literature, this risk appears to be higher in preterm infants, especially those born before 32 weeks of gestation and within the first 2 weeks of life.

Remove any soaked materials, drapes or gowns before proceeding with the intervention. Do not use excessive quantities and do not allow the solution to pool in skin folds or under the patient or drip on sheets or other material in direct contact with the patient. Where occlusive dressings are to be applied to areas previously exposed to [insert product name], care must be taken to ensure no excess product is present prior to application of the dressing.

Section 4.8 (undesirable effects):

Chemical burns in neonates (frequency unknown)

2. Changes to the PL (to be included in the section providing information necessary before using the chlorhexidine product):

Use with care in newborn babies, especially those born prematurely. <Product name> may cause chemical skin burns.

Where tear-off portion exist in leaflets, this information should include the following wording:

Use with care in neonates, especially those born before 32 weeks of gestation and within the first 2 weeks of life. <Product name> may cause chemical skin burns.

Do not use excessive quantities and do not allow the solution to pool in skin folds or under the patient or drip on sheets or other material in direct contact with the patient.

3. Wording proposed for product labelling of all chlorhexidine products, including those not regulated as medicines:

Use with care in newborn babies, especially those born prematurely. <Product name> may cause chemical skin burns.

The PRAC considered that communication of this important safety issue to relevant hospital physicians, nursing staff and pharmacists responsible for neonatal/ paediatric intensive care units would be important and may be best delivered by means of a communication issued by NCAs . The following key elements were agreed, which could be highlighted in such communications:

- Risk of severe chemical injuries when using alcohol-based or water-based chlorhexidine solutions on preterm infants
- The risk appears to be higher in preterm infants, especially those born before 32 weeks of gestation and within the first 2 weeks of life
- The minimum amount of chlorhexidine solution required should be used and the solution should not be allowed to pool in skin folds or under the patients. Any excess solution and any soaked materials, drapes, or gowns from the skin should be removed
- Patients should be observed closely to detect and manage cutaneous side effects at an early stage.

Finally, the PRAC agreed that MAHs of chlorhexidine cutaneous solutions should strengthen their pharmacovigilance activities in terms of closely monitoring cutaneous adverse events in neonates through signal detection and literature monitoring.

1.3. Imatinib – Decreased estimated glomerular filtration rate

Substance (invented name)	Imatinib (Glivec), EMEA/H/C/000406
Authorisation procedure	Centralised
EPITT No	17946
PRAC rapporteur(s)	Dolores Montero Corominas (ES)
Date of adoption	11 September 2014

Recommendation

Having assessed the data provided by the MAH, the PRAC considered the safety review performed by the MAH does not allow ruling out a role of imatinib in declining renal function. The PRAC recommended that MAH for Glivec (innovator of imatinib) should submit a variation within 2 months to the EMA, to amend the PI as described below (new text underlined).

Following the update of the reference product, the MAH(s) of generic/hybrid products containing imatinib should update their product information in line with that of the reference product.

Summary of Product Characteristics:

Section 4.4

Long-term treatment with imatinib may result in a clinically significant decline in renal function. It is important that renal function (including glomerular filtration rate) is tested prior to treatment initiation and monthly during therapy with imatinib, with particular attention to those patients exhibiting internal and external risk factors for renal dysfunction, including concomitant use of GFR affecting medicinal products such as diuretics, ACE inhibitors, angiotensin receptor blockers and non-steroidal anti-inflammatory drugs (NSAIDs)

Section 4.8

Frequency 'not known' [unless the MAH can provide a more precise estimate]: Renal failure chronic

Package leaflet

Section 4. Possible side effects.

Not known [unless the MAH can provide a more precise estimate].

Renal failure chronic

Additionally, the MAH should submit in the next PSUR (DLP 10 May 2015) a response to a request for supplementary information list of questions.

1.4. Leuprorelin – Medication error - wrong technique in drug usage process

Substance (invented name)	Leuprorelin (Eligard)
Authorisation procedure	Non-centralised
EPITT No	17753
PRAC rapporteur(s)	Carmela Macchiarulo (IT)
Date of adoption	17 September 2014

Recommendation

Having considered EudraVigilance data, post-marketing reports and studies by Astellas, the MAH of Eligard, as well as literature, the PRAC has agreed that the MAH of Eligard (leuprorelin) should submit a variation within 1 month to the NCA to amend the product label as described below (new text underlined). The new SmPC should be disseminated together with the direct healthcare professional communication (DHPC).

Summary of Product Characteristics:

Section 4.4 - Special warnings and precautions for use

Lack of clinical efficacy may occur due to incorrect reconstitution of the product (see section 4.2).

The MAH should also submit to the NCA, within 1 month, a room temperature storage variation to allow storage of the product at room temperature for up to 1 month. Additionally, they should submit within 6 months, a variation to modify the device so that it will be impossible to remove the blue plunger rod without removing the grey stopper.

Finally, the PRAC recommended the following actions to be submitted within 1 month:

1) The MAH should submit the proposed poster in English language with the following revisions: The poster should be simplified, showing only the critical steps during reconstitution, leaving out the other parts of the product information.

2) The MAH should clarify why in the proposed DHPC it is stated “PRODUCT AT ROOM TEMPERATURE: Timely removal from the fridge (approximately 30 minutes prior to reconstitution)”, considering that the French SmPC as well as the authorized Italian SmPC don’t indicate the time of removal from the fridge. A proper justification of this statement should be submitted with the DHPC proposal.

3) The MAH should submit a proposal for the dissemination of the DHPC and the poster, based on the health care professionals involved in the administration of Eligard (with accurate ratios of different HCPs per country) and submit a respective communication plan. After adoption by the PRAC the correct set of the HCPs to be reached by these additional RMMs should be agreed at national level.

4) The MAH should submit the final results of the pilot survey to evaluate the effectiveness of the DHPC.

5) The contents of the effectiveness study protocol are partially endorsed. Timelines for the conduct of the study should be submitted. In addition, the MAH should assess the effectiveness of the risk minimisation by means of a comparison of the reporting rate of medication error cases and lack of efficacy cases before and after the DHPC. An accordingly updated study protocol should be submitted.

6) The MAH's response does not address the PRAC request to make a proposal for a new presentation of Eligard with fewer and easier handling steps nor does the MAH provide a justification against it. The MAH should submit a timetable for the reformulation of the product. In the absence of a proposal from the MAH for a new presentation, the marketing authorisation of the current presentations may be reconsidered.

2. Recommendations for submission of supplementary information

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a **causal relationship** between the medicine and the reported adverse event.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Latanoprost	Increased number of eye disorders after change of formulation (18068)	Julie Williams (UK)	Supplementary information requested (submission by 08/11/2014)	Pfizer
Lithium (carbonate, citrate, sulfate, acetate and gluconate)	Solid renal tumours (18090)	Martin Huber (DE)	Supplementary information requested (submission by 08/11/2014)	Sanofi-Aventis, GlaxoSmithKline
Natalizumab	Neonatal haematological abnormalities (thrombocytopenia /anaemia) (18067)	Brigitte Keller-Stanislawski (DE)	Assess in the next PSUR (submission by 16/10/2014)	Biogen Idec Ltd
Paliperidone	Accidental exposure of children to oral formulation (18069)	Qun-Ying Yue (SE)	Supplementary information requested (submission by 08/11/2014)	Janssen-Cilag International N.V.
Paroxetine	Aggression (18089)	Sabine Straus (NL)	Supplementary information requested (submission by 08/11/2014)	GlaxoSmithKline
Temozolomide	Dehydration leading to renal failure (18064)	Martin Huber (DE)	Assess in the next PSUR (submission by 10/10/2014)	Merck Sharp & Dohme Limited
Teriparatide	Non-uraemic calciphylaxis (18056)	Julie Williams (UK)	Supplementary information requested (submission by 08/11/2014)	Eli Lilly Nederland B.V.
Thiotepa	Pulmonary arterial hypertension (18046)	Arnaud Batz (FR)	Supplementary information requested (submission by 08/11/2014)	Adienne S.r.l. S.U.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Cefepime	Convulsions (17859)	Margarida Guimarães (PT)	Routine pharmacovigilance	Bristol-Myers Squibb
Interferon alfa-2a, interferon alfa-2b, interferon beta-1a, interferon beta-1b, Peginterferon alfa-2a, Peginterferon alfa-2b	Pulmonary arterial hypertension (18059)	Qun-Ying Yue (SE)	No action at this stage	Not applicable
Sodium containing effervescent, dispersible and soluble medicines	Cardiovascular events (17931)	Julie Williams (UK)	No action at this stage	Not applicable