25 April 2014
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Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 7-10 April 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 7-10 April 2014 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][1] reference numbers).

PRAC recommendations to provide additional data 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 April 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. Adalimumab - Missed dose due to malfunction of the pre-filled pen device

Substance (invented name)	Adalimumab (Humira) - EMEA/H/C/000481
Authorisation procedure	Centralised
EPITT No	17701
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	10 April 2014

Recommendation

Having considered the evidence from the cumulative review, the total complaint rate, the actions undertaken by the MAH to minimise the latter, the existence of a procedure to replace malfunctioning devices and the lack of evidence of significant clinical risks associated with the complaints, as well as the importance to raise patients' awareness on the significance of the yellow indicator of the pre-filled pen, the MAH for Humira (adalimumab) should submit to the EMA a variation within 2 months to update the package leaflet with the addition of the below sentence (new wording underlined):

Package Leaflet:

Section 3: How to use Humira, under the title 'Giving the Injection':

6. You will see a yellow indicator move into the window during the injection. The injection is complete when the yellow indicator stops moving. The yellow indicator is part of the plunger, and thus, if it is not shown at all in the window, the plunger has not advanced, and no injection of the drug has taken place.

The MAH should provide with this submission details concerning the procedure for replacement of a device that has failed to deliver the drug and clarification as to how this information is communicated to patients and prescribers. More specific details regarding the procedure for collecting malfunctioning pens for analysis (e.g. addressed envelopes and information to health care givers) should be given.

The MAH should address in the next PSUR (Data Lock Point: 31 December 2016) complaints due to device malfunction from the EU, including provision of complaint rates per number of devices sold over time.

1.2. Clindamycin – Drug interaction with warfarin leading to international normalised ratio (INR) increased

Substance (invented name)	Clindamycin
Authorisation procedure	Non-centralised
EPITT No	17700
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	10 April 2014

Recommendation

Following the assessment of the cumulative review submitted by the MAH, the PRAC agreed that the presented information is suggestive of a causal relationship between the administration of clindamycin and an increase in INR in patients maintained on vitamin K antagonists such as warfarin, acenocoumarol and fluindione. This includes three published literature reports in addition to spontaneous data. Two potential mechanisms have been proposed, with an effect on gut flora synthesis and absorption of vitamin K likely to have a greater impact than any pharmacokinetic interaction with metabolism of R-warfarin. Therefore, the PRAC recommended that the MAHs of the products containing clindamycin should submit a variation within 2 months to the NCA to update the Product Information (PI) and include the following information below (new wording underlined):

Changes to the Product Information

Summary of Product Characteristics:

Section 4.5 - Interaction with other medicinal products and other forms of interaction:

Vitamin K antagonists

Increased coagulation tests (PT/INR) and/or bleeding, have been reported in patients treated with clindamycin in combination with a vitamin K antagonist (e.g. warfarin, acenocoumarol and fluindione). Coagulation tests, therefore, should be frequently monitored in patients treated with vitamin K antagonists.

Package Leaflet:

Section 2: Before you take Clindamycin – Taking other medicines.

Warfarin or similar medicines – used to thin the blood. You may be more likely to have a bleed. Your doctor may need to take regular blood tests to check how well your blood can clot.

1.3. Fentanyl patches – Accidental exposure

Substance (invented name)	Fentanyl
Authorisation procedure	Non-centralised
EPITT No	17778
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	10 April 2014

Recommendation

Following the assessment of the cumulative review performed by MAH, the PRAC endorsed the MAH's proposal to circulate a Direct Healthcare Professional Communication (DHPC) to highlight to Healthcare Professionals (HCPs) the risk of accidental exposure leading to fatal outcomes especially in children. The initial draft should be submitted to the Reference Member State (RMS) within 2 weeks and should include measures to minimize the risk, provide clear instruction on how to inform the patient (including: always provide package leaflet) and reinforce the need for proper and safe disposal of the patches. In addition to the DHPC the PRAC also suggested educational material as an additional tool to further minimise the risk of accidental exposure to patients. The MAH – Johnson and Johnson Pharmaceutical – should submit within one month: proposals for educational material, proposals on how to improve patch visibility and timelines for implementation.

The PRAC agreed on the multifaceted nature of the risk and on the need to have a stepwise approach. The MAH should assess in the PSUR the effectiveness of the above risk minimisation measures evaluating spontaneous cases and the reporting rate. Based on the outcome of the evaluation, further measures might be warranted.

The PRAC recommended that Johnson and Johnson Pharmaceutical should submit within 1 month to the NCAs a variation or article 61.3 notification - as appropriate - to implement the strengthened wording in their Product Information (PI) as described below. The MAHs of generic products containing fentanyl TTS should update their PI in line with that of the reference product.

Summary of Product Characteristics (SmPC)

Section 4.4: Special warnings and precautions for use:

Accidental Exposure by Patch Transfer

Accidental transfer of a fentanyl patch to the skin of a non-patch wearer (particularly a child), while sharing a bed or being in close physical contact with a patch wearer, may result in an opioid overdose for the non-patch wearer. Patients should be advised that if accidental patch transfer occurs, the transferred patch must be removed immediately from the skin of the non-patch wearer. (see section 4.9 Overdose)

Use in Children

[…]

To guard against accidental ingestion by children, use caution when choosing the application site for [invented name] (see Section 6.6, Instructions for use/handling) and monitor adhesion of the patch closely."

Section 6.6: Instructions for use / handling

[…]

Used patches should be folded so that the adhesive side of the patch adheres to itself and then they should be safely discarded. Unused patches should be returned to the (hospital) pharmacy.

In line with the SmPC the wording in the PL should be, as follows

Package Leaflet (PL)

Section 2: Warning and precaution

[Product name] is a medicinal product that could be life threatening to children. This is also the case with used transdermal patches. Bear in mind that the design of this medicinal product could be tempting to a child which in some cases may lead to a fatal outcome. [Product name] can have life-threatening side effects in persons that are not using prescribed opioid medicines on a regular basis.

Patch sticking to another person

The patch should be used only on the skin of the person for whom it was ordered by the doctor. Cases have been reported where a patch was accidentally stuck to a family member while in close physical contact or sharing the same bed as the patch wearer. A patch sticking to another person (particularly a child) may result in an overdose. In case the patch sticks to the skin of another person, take the patch off immediately and seek medical attention.

Section 5: How to store

Keep unused and used [product name] patches out of children's reach.

Handling the patch

Used patches should be folded so that the adhesive side of the patch adheres to itself and then they should be safely discarded. Accidental exposure to used and unused patches particularly in children may lead to a fatal outcome. Unused patches should be returned to the (hospital) pharmacy.

1.4. Levonorgestrel-releasing intrauterine device (IUD) – Risk of uterine perforation, final study results of EURAS-IUD study

Substance (invented name)	Levonorgestrel
Authorisation procedure	Non-centralised
EPITT No	2706
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	10 April 2014

Recommendation (see also section 2)

To reflect the final results of the EURAS IUD study, the product information for Mirena should be updated. Furthermore, the MAH (Bayer Healthcare Pharmaceuticals) should submit additional data and information. This should be done within a worksharing variation to be submitted within two months. The requested additional data and information should be submitted to the appointed RMS (SE) for the worksharing variation within that variation.

The product information should be updated with regard to the following points:

- Information on the perforation rate should be updated based on the incidence observed in the study.
- Information on breastfeeding and post-partum status as risk factors should be updated.
- Information on possible delayed diagnosis of perforations should be included.
- The need for thorough follow-up of the correct IUD position as clinically indicated (e.g. in women with risk factors) according to diagnostic standard should be emphasized. Further on, information to consider limitations of physical examination for detection of partial perforation should be included.
- Information on the possible need of an operative procedure to remove the IUD in case of perforation should be included in the PI.
- A recommendation should be included to educate patients on possible signs of uterine perforation (severe low abdominal pain, loss of threads, etc.).

1.5. Simvastatin – Risk of myopathy and rhabdomyolysis associated with high doses

Substance (invented name)	Simvastatin (Zocor and associated brand names)
Authorisation procedure	Non-centralised
EPITT No	13849
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	10 April 2014

Recommendation

The genetic polymorphism SLCO1B1*5 increases the risk of myopathy, due to increased plasma levels of simvastatin. SLCO1B1*5 occurs in ~15-18% of Europeans and was found in about 45% of myopathy cases seen with simvastatin in the SEARCH trial, and accounted for 50-60% of myopathy cases seen in the SEARCH and HPS clinical trials. Screening for SLCO1B1*5 is not established in routine clinical practice but may be conducted in some specialist centres.

Given the increased risk of myopathy that occurs with carriers of the SLCO1B1 gene c.521T>C allele, it is appropriate to include information on this genetic subpopulation in the simvastatin SmPC as a risk factor for myopathy and also highlight the importance of considering the impact of the SLCO1B1 genotype, and in particular the presence of the C allele, as part of an individual risk-benefit assessment prior to prescribing 80 mg simvastatin where the genotyping is available or the patient's genotype is already known.

The MAHs for simvastatin-containing products should submit a variation within two months to the relevant NCAs to include the following text in the SmPC (new text underlined):

Section 4.4 Special warnings and precautions for use

Reduced function of transport proteins

Reduced function of hepatic OATP transport proteins can increase the systemic exposure of simvastatin and increase the risk of myopathy and rhabdomyolysis. Reduced function can occur as the result of inhibition by interacting medicines (eg ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.

Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1 % in general, without genetic testing. Based on the results of the SEARCH trial, homozygote C allele carriers (also called CC) treated with 80 mg have a 15% risk of myopathy within one year, while the risk in heterozygote C allele carriers (CT) is 1.5%. The corresponding risk is 0.3% in patients having the most common genotype (TT) (See section 5.2). Where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses avoided in those found to carry the CC genotype. However, absence of this gene upon genotyping does not exclude that myopathy can still occur.

Section 5.2 Pharmacokinetic properties

Elimination

Simvastatin is taken up actively into the hepatocytes by the transporter OATP1B1.

Special populations

Carriers of the SLCO1B1 gene c.521T>C allele have lower OATP1B1 activity. The mean exposure (AUC) of the main active metabolite, simvastatin acid is 120% in heterozygote carriers (CT) of the C allele and 221% in homozygote (CC) carriers relative to that of patients who have the most common genotype (TT). The C allele has a frequency of 18% in the European population. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of simvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4).

2. Recommendations for submission of additional data

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
Aripiprazole	Diplopia (17913)	Margarida Guimarães (PT)	Additional data requested (submission by 12/07/2014)	Otsuka Pharmaceutical Europe Ltd
Imatinib	Decreased estimated glomerular filtration rate (eGFR) (17946)	Dolores Montero Corominas (ES)	Additional data requested (submission by 12/07/2014)	Novartis Europharm Ltd

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Complex regional pain syndrome (CRPS) linked to the process of vaccination (17644)	Jean-Michel Dogné (BE)	The available evidence does not support a causal association; the PRAC recommended review through the PSURs.	GlaxoSmithKline Biologicals
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Complex regional pain syndrome (CRPS) linked to the process of vaccination (17645)	Qun-Ying Yue (SE)	The available evidence does not support a causal association; the PRAC recommended review through the PSURs.	Sanofi Pasteur MSD, SNC
Sodium containing formulations of effervescent, dispersible and soluble medicines	Cardiovascular events (17931)	Julie Williams (UK)	No action at this stage	Not applicable