EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 3-6 March 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 3-6 March 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 (17-20 March 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. Goserelin - Long duration flushing and hyperhidrosis

Substance (invented name)	Goserelin (Zoladex)
Authorisation procedure	Non-centralised
EPITT No	17698
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	6 March 2014

Recommendation

The PRAC considered the available data from post-marketing reports and the published literature. Whilst the limitations of the post-marketing data were noted it was agreed that there were a small number of cases of hot flushes and/or hyperhidrosis which prolonged after stopping goserelin that are not explained by comorbidities/concomitant treatments or the patient's age. Moreover, there is a biological plausibility for this effect and the published literature supports that goserelin can have effects on the hypothalamic-pituitary-gonadal axis that may persist after stopping treatment. In men, LH and testosterone levels have been shown to remain markedly suppressed at the end of the recommended dosing interval and that this suppression can persist for several months beyond goserelin's expected duration of pharmacological effect

Based on the data, there is sufficient evidence to conclude that in some patients goserelin can cause flushing and hyperhidrosis that persists after cessation of treatment and beyond the drug's expected duration of effect on the hypothalamic-pituitary-gonadal axis.

The PRAC agreed that the MAH of Goserelin should submit a variation to the NCAs to update the product information to reflect this information, within two months:

Section 4.8 of the SmPC (Summary of Product Characteristics)

The footnote to the table which lists adverse reactions should be amended as follows:

"b These are pharmacological effects which seldom require withdrawal of therapy. **Hyperhidrosis and hot flushes may continue after stopping Zoladex.**"

Section 4 (Possible Side effects) of the PL (Package Leaflet)

The PL should be amended as indicated below:

Hot flushes and sweating. **Occasionally these side effects may continue for some time (possibly months) after stopping Zoladex.**

1.2. Tenofovir disoproxil fumarate – Acute kidney injury caused by co-administration with non-steroidal anti-inflammatory drugs (NSAIDs)

Substance (invented name)	Tenofovir disoproxil fumarate (Viread, EMEA/H/C/000419); Efavirenz / emtricitabine / tenofovir disoproxil fumarate (Atripla, EMEA/H/C/000797); Emtricitabine / rilpivirine hydrochloride / tenofovir disoproxil fumarate (Eviplera, EMEA/H/C/002312); Elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate (Stribild, EMEA/H/C/002574); Emtricitabine / tenofovir disoproxil fumarate (Truvada, EMEA/H/C/000594)
Authorisation procedure	Centralised
EPITT No	17777
PRAC rapporteur	Isabelle Robine (FR)
Date of adoption	6 March 2014

Recommendation

Available data from spontaneous cases and the literature suggest that the co-administration of non-steroidal anti-inflammatory drugs (NSAIDs) (in particular high dose or multiple NSAIDs) with tenofovir may expose patients to a higher risk of renal injury, especially if they present additional risk factors for renal impairment. Therefore the PRAC considers that a specific warning should be included in the product information of tenofovir-containing products. As there is currently insufficient evidence to support a pharmacokinetic interaction, consideration should be given to the conduct of a drug-drug interaction study. Consequently, the PRAC recommends the following:

The MAH of tenofovir-containing medicinal products should submit a variation within 1 month to the EMA to update the product information as described below:

SmPC
4.4. Special warnings and precautions for use
Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction. If tenofovir disoproxil fumarate is co-administered with an NSAID, renal function should be monitored adequately.

PL
2. What you need to know before you take [Viread]
Other medicines and [Viread] (…) It is very important to tell your doctor if you are taking other medicines that may damage your kidneys. These include:
- aminoglycosides, pentamidine or vancomycin (for bacterial infection),
- amphotericin B (for fungal infection),
- foscarnet, ganciclovir, or cidofovir (for viral infection),
- interleukin-2 (to treat cancer),
- adefovir dipivoxil (for HBV),
- tacrolimus (for suppression of the immune system),
- non-steroidal anti-inflammatory drugs (NSAIDs, to relieve bone or muscle pains)

The MAH should discuss in the next PSUR for Viread (DLP: 31/03/2014), the feasibility and value of performing a pharmacokinetic drug-drug interaction study involving tenofovir and individual NSAIDs to assess the effect of NSAIDs on tenofovir clearance.

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
Bupropion	Pancytopenia (17727)	Sabine Straus (NL)	Additional data requested (submission by 10/05/2014)	GlaxoSmithKline
Cefepime	Convulsions (17859)	Margarida Guimarães (PT)	Additional data requested (submission by 10/05/2014)	Bristol-Myers Squibb
Quetiapine	Suicidality in major depressive disorder (MDD) patients (17709)	Sabine Straus (NL)	Additional data requested (submission by 10/05/2014)	AstraZeneca
Regorafenib	Hypersensitivity, drug reaction with eosinophilia and systemic symptoms (DRESS) (17813)	Sabine Straus (NL)	Assess in the next PSUR (submission by 04/06/2014)	Bayer Pharma AG
Tacrolimus; febuxostat	Potential drug-drug interaction between systemic tacrolimus and febuxostat (17809)	Almath Spooner (IE)	Additional data requested (submission by 10/05/2014)	Astellas Pharma Europe B.V.; Menarini International Operations Luxembourg S.A.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Cefepime	Drug reaction with eosinophilia and systemic symptoms (DRESS) (17866)	N/A	Routine pharmacovigilance	MAHs of cefepime-containing products
Testosterone	New publications suggesting the risk of cardiovascular events (17877)	Maia Uusküla (EE)	Under consideration	MAHs of testosterone-containing products