24 January 2014
EMA/PRAC/25732/2014
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 6-9 January 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 6-9 January 2014.

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 (20-23 January 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.

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8668
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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. Orlistat - Pharmacokinetic drug interaction (at absorption) with highly active antiretroviral therapy (HAART) leading to loss of HAART efficacy

Substance (invented name)	Orlistat - alli (EMEA/H/C/000854), Xenical (EMEA/H/C/000154)
Authorisation procedure	Centralised and non-centralised
PRAC rapporteur(s)	Isabelle Robine (FR)
Date of adoption	9 January 2014

Recommendation

The PRAC considered the evidence from literature reports and the cumulative reviews provided by the MAHs regarding the possibility of an interaction and agreed that taking into account the risk of reduced efficacy of HAART with subsequent risk of emergence of resistance, the Marketing Authorisation Holders of orlistat-containing products should submit a variation of the product information within 2 months as follows:

Proposed changes to the SmPC and PIL for Alli:

Summary of Product Characteristics

Section 4.4 Special warnings and precautions for use

Antiretrovirals for HIV

Patients should consult a physician before taking alli concomitantly with antiretroviral medications. Orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV (see section 4.5).

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

Antiretrovirals for HIV

Based on reports from literature and post-marketing experience orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV (see section 4.4).

Package Leaflet

Other medicines and Alli

Talk to your doctor before taking Alli if you are taking

Medicines to treat HIV. It is important that you consult your doctor before taking Alli if you are receiving treatment for HIV.

Labelling (outer carton sleeve) – Instructions on use:

Talk to your doctor before taking alli

…

If you are taking medicines for HIV.

Proposed changes to the SmPC and PIL for Xenical

Summary of Product Characteristics

Section 4.4 Special warnings and precautions for use

Antiretrovirals for HIV

Orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV (see section 4.5).

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

There are some case reports of reduced efficacy of antiretroviral HIV medicines, antidepressants and antipsychotics coincidental to the initiation of orlistat treatment in previously well controlled patients. Therefore orlistat treatment should only be initiated after careful consideration of the possible impact in these patients.

Package Leaflet

Other medicines and Xenical
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. This is important as using more than one medicine at the same time can strengthen or weaken the effects of the medicines.

Xenical may modify the activity of
…
- Medicines to treat HIV.

1.2. Triamcinolone acetonide (suspension for injection) - Postmenopausal haemorrhage

Substance (invented name)	Triamcinolone acetonide (suspension for injection)
Authorisation procedure	Non-centralised
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	9 January 2014

Recommendation

Postmenopausal haemorhage is not mentioned in the SmPC, however menstrual irregularities are stated. Based on the evidence provided the PRAC has concluded that it is appropriate to update the product information for intraarticular/intramuscular triamcinolone.

It is recommended that the MAH updates section 4.4 and 4.8 of the SmPC to include appropriate wording regarding the risk vaginal haemorrhage (see next paragraph). Section 4 of the PIL should be updated to state that postmenopausal women may also experience vaginal bleeding. It is also recommended that the MAH submits a variation to calculate the frequencies of all their adverse events within section 4.8 in line with the SmPC guideline. The variation should be submitted within 2 months.

Section 4.4 special warnings and Precautions for use. The current warning shall be amended as follows: "Menstrual irregularities may occur **and in postmenopausal women vaginal bleeding has been observed.** ~~,and t~~This possibility should be mentioned to female patients **but should not deter appropriate investigations as indicated**."

Section 4.8 Undesirable effects. The current warning shall be amended as follows: "Endocrine: menstrual irregularities**,** ~~and~~ amenorrhoea **and postmenopausal vaginal bleeding**"

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	PRAC Rapporteur	Action for MAH	MAH
Abatacept	Angioedema	Kirsti Villikka (FI)	Assess in the next PSUR (submission by 03 March 2014)	Bristol-Myers Squibb Pharma EEIG
Dexmedetomidine	Infantile apnoeic attack	Julie Williams (UK)	Additional data requested (submission by 08 March 2014)	Orion Corporation
Duloxetine	Vasculitis	Dolores Montero Corominas (ES)	Assess in the next PSUR (submission by 01 November 2014)	Eli Lilly Nederland B.V.
Fluticasone fuorate	Oral and upper respiratory fungal infection	Adam Przybylkowski (PL)	Additional data requested (submission by 08 March 2014)	Glaxo Group Ltd
Leuprorelin	Medication errors (wrong technique in drug usage process)	Carmela Macchiarulo (IT)	Additional data requested (submission by 08 March 2014)	Astellas
Tenofovir disoproxil fumarate; Diclofenac	Acute kidney injury caused by co-administration of tenofovir disoproxil fumarate and diclofenac - publication from Bickel M et al, HIV Medicine 2013	Isabelle Robine (FR)	Additional data requested (submission by 03 February 2014)	Gilead Sciences International Ltd

3. Other recommendations

INN	Signal	PRAC Rapporteur	Action for MAH	MAH
Pazopanib	Retinal detachment and retinal tear	Doris Stenver (DK)	To be determined in the context of the on-going PSUR assessment	Glaxo Group Ltd
Tapentadol	Suicidal ideation	Martin Huber (DE)	Update of the Risk Management Plan	Grünenthal