



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 7-10 October 2013

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 October 2013.

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 (21-24 October 2013) 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.

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. Boceprevir; indinavir; quetiapine - Drug interaction between protease inhibitors and quetiapine

Substance (invented name)	Boceprevir (Victrelis) – EMEA/H/C/002332 Indinavir (Crixivan) - EMEA/H/C/000128
Authorisation procedure	Centralised
PRAC rapporteur(s)	France
Date of adoption	10 October 2013

Recommendation

Based on a case of possible interaction between lopinavir/ritonavir and quetiapine resulting in deep coma, in view of the potential seriousness of an interaction between quetiapine and strong inhibitors of cytochrome P450 (CYP) 3A4 such as HIV and HCV protease inhibitors, and because co-administration of protease inhibitors is already contra-indicated in the Summaries of Product Characteristics (SmPCs) of quetiapine-containing products, the PRAC, having considered the responses from the MAH of Crixivan and Victrelis, maintains its recommendation to update the product information of all protease inhibitors with a contra-indication to use quetiapine concomitantly. Consequently, the MAH of Crixivan and Victrelis should submit to EMA, within 1 month, variations to update their product information as follows:

Summary of Product Characteristics

4.3. Contraindications

*[In the already existing list of contraindicated medicines highly dependent on CYP3A / CYP3A4 for clearance]
quetiapine [...] (see section 4.5)*

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

Antipsychotics		
Quetiapine	Due to CYP3A inhibition by [Crixivan/Victrelis], concentrations of quetiapine are expected to increase.	Concomitant administration of [Crixivan/Victrelis] and quetiapine is contra-indicated as it may increase quetiapine-related toxicity. Increased plasma concentrations of quetiapine may lead to coma.

Package Leaflet

2. Before you take [Crixivan/Victrelis] – Do not take [Crixivan/Victrelis] with any of the following medicines:

- Quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder)

1.2. Doxycycline – Photo-onycholysis

Substance (invented name)	Doxycycline
Authorisation procedure	Non-centralised
PRAC rapporteur(s)	UK
Date of adoption	10 October 2013

Recommendation

The PRAC considered the information already available in the product information of some doxycycline-containing products in the EU and the information from the case reports and recommended that for products where photo-onycholysis is not already included in section 4.8:

MAHs should submit within 2 months a variation to the NCAs concerned to add photo-onycholysis as an adverse reaction to section 4.8. of the SmPC, in the System Organ Class "Skin and subcutaneous tissue disorders", and accordingly to section 4 of the package leaflet.

1.3. Efavirenz; emtricitabine, efavirenz, tenofovir - Interaction with Ginkgo biloba

Substance (invented name)	Efavirenz (Sustiva - EMEA/H/C/000249, Stocrin - EMEA/H/C/000250) Efavirenz / emtricitabine / tenofovir disoproxil (Atripla - EMEA/H/C/000797)
Authorisation procedure	Centralised
PRAC rapporteur(s)	Portugal
Date of adoption	10 October 2013

Recommendation

Based on two published cases suggesting an interaction between efavirenz and Ginkgo biloba extracts with a negative impact on efavirenz and/or on viral load and having reviewed the MAHs' response, the PRAC still considers that a deleterious pharmacokinetic interaction between efavirenz and Ginkgo biloba extracts is plausible and should be reflected in the product information of efavirenz-containing medicinal products. However, the PRAC acknowledges that the current level of evidence and the expected magnitude of the risk do not warrant a contra-indication at this stage.

- The MAHs of efavirenz-containing medicinal products should submit to EMA, within 1 month, variations to update their product information as shown below.

Summary of Product Characteristics

4.4 Special warnings and precautions for use

Concomitant use of Ginkgo biloba extracts is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz exposure may be increased when given with medicinal products (for example ritonavir) or food (for example, grapefruit juice) which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations such as Ginkgo biloba extracts which induce these enzymes may give rise to decreased plasma concentrations of efavirenz; concomitant use of Ginkgo biloba extracts is not recommended (see section 4.4).

Package Leaflet

2. What you need to know before you take [efavirenz/Atripla]

[Efavirenz/Atripla] may interact with other medicines, including herbal medicines such as Ginkgo biloba extracts. As a result, the amounts of [Efavirenz/Atripla] or other medicines in your blood may be affected. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels. It is important to tell your doctor or your pharmacist if you are taking any of the following:

(...)

- Ginkgo biloba extracts (a herbal remedy)

- The MAHs should continue to monitor this interaction and discuss it in the next PSUR.
- Formal advice from the Agency's Committee on Herbal Medicinal Products (HMPC) will be sought on this interaction.

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
Aflibercept	Blindness	France	Assess in the next PSUR	Bayer Pharma AG
Agomelatine	QT prolongation	Sweden	Assess in the next PSUR	Laboratoires Servier
Amiodarone	Carcinogenicity	Netherlands	Additional data requested (submission by 06/12/2013)	Sanofi
Azithromycin	Potentially fatal heart events	Finland	Additional data requested (submission by 31/01/2014)	Pfizer

INN	Signal	PRAC Rapporteur	Action for MAH	MAH
Cabazitaxel	Medication error potentially leading to inappropriate dose	France	Additional data (submission by 16/11/2013) and Dear Healthcare Professional Communication requested	Sanofi Aventis
Cefuroxime for intracameral use	Eye inflammation and macular oedema	Sweden	Assess in the next PSUR	Laboratoires THEA
Clarithromycin	Cardiovascular events	Ireland	Assess in the next PSUR	Abbott
Etanercept	Glioblastoma and other brain neoplasms	UK	Additional data requested (submission by 06/12/2013)	Pfizer
Exenatide; liraglutide	Cholecystitis and cholelithiasis	Sweden, Netherlands	Assess in the next PSUR	Exenatide: AstraZeneca AB Liraglutide: Novo Nordisk A/S
Gabapentin	Hypoglycaemia	Germany	Assess in the next PSUR	Pfizer
Mefloquine	Possibly permanent neurologic (vestibular) side effects	Germany	Additional data requested (submission by 06/12/2013)	Roche
Orlistat	Pharmacokinetic drug interaction (at absorption) with highly active antiretroviral therapy (HAART) leading to loss of HAART efficacy	France	Additional data requested - answers to List of Questions (submission by 22/11/2013)*	GlaxoSmithKline
Quetiapine	Suicidality in major depressive disorder (MDD) patients	Netherlands	Additional data requested (submission by 31/12/2013)	AstraZeneca
Tapentadol	Suicidal ideation	Germany	Additional data requested (submission by 09/11/2013)	Grünenthal

* The PRAC assessed the evidence from literature reports and the cumulative reviews provided by the MAHs regarding the possibility of an interaction at its October 2013 meeting. The PRAC concurred with the MAH proposal and agreed that in view of the critical importance of adequate therapeutic management of HIV infection and taking into account the OTC status of orlistat, the risk of reduced efficacy of antiretroviral treatment and the subsequent risk of emergence of viral resistance, the concomitant use of orlistat with HAART should be contraindicated. Following the PRAC recommendation for a contraindication, the CHMP agreed to further investigate the possible mechanism for this interaction in collaboration with the PRAC and the MAH before providing an opinion. Further PRAC recommendation on this issue can be expected in January 2014.

3. Other recommendations

INN	Signal	PRAC Rapporteur	Action for MAH	MAH
Adalimumab; infliximab	Glioblastoma and other brain neoplasms	Sweden	The available evidence does not support a causal association; the PRAC recommended routine review through the PSURs.	Adalimumab: AbbVie Ltd Infliximab: Janssen Biologics B.V.
Fondaparinux	Heparin-induced thrombocytopenia	Sweden	The available evidence does not support causal association and the currently approved product information covers the issue in a sufficient manner; no further regulatory action required.	
Human papillomavirus vaccine [type 6, 11, 16, 18] (recombinant, absorbed)	Postural orthostatic tachycardia syndrome (POTS)	Sweden	The available evidence does not support a causal association; the PRAC recommended routine review through the PSURs.	Sanofi Pasteur
Human papillomavirus vaccine [type 6, 11, 16, 18] (recombinant, absorbed)	Primary, premature ovarian failure	Sweden	The available evidence does not support a causal association; the PRAC recommended routine review through the PSURs.	Sanofi Pasteur

INN	Signal	PRAC Rapporteur	Action for MAH	MAH
Human papillomavirus vaccine [type 16, 18] (recombinant, adjuvanted, adsorbed)	Primary, premature ovarian failure	Belgium	The available evidence does not support a causal association; the PRAC recommended routine review through the PSURs.	GlaxoSmithKline Biologicals S.A.
Pandemic H1N1 and seasonal trivalent influenza vaccines	Review of latest evidence for Guillain-Barré syndrome (GBS)	UK	There is no new, specific and conclusive evidence relating to an association between any H1N1 vaccine and GBS; no further regulatory action required.	