



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2014
EMA/PRAC/65788/2014
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 3-6 February 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 February 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 (17-20 February 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.



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. Amiodarone - Carcinogenicity

Substance (invented name)	Amiodarone (Cordarone®)
Authorisation procedure	Non-centralised
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	6 February 2014

Recommendation

Based on the data provided by the MAH, no causal association between the use of amiodarone and the occurrence of malignant disease (especially thyroid, lung and skin cancer) can be established.

However, the available pre-clinical data and their low relevance for man should be reflected in section 5.3 of the Summaries of Product Characteristics (SmPCs) of amiodarone containing products as follows:

In a 2-years carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinical relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour induction. In the mouse, carcinomas were not observed, but a dose-dependent thyroid follicular hyperplasia was seen. These effects on the thyroid in rats and mice are most likely due to effects of amiodarone on the synthesis and/or release of thyroid gland hormones. The relevance of these findings to man is low.

The MAHs of amiodarone containing products should submit a variation to the NCAs within two months.

1.2. Basiliximab - Cardiovascular instability resulting in fatal outcome following off-label use in heart transplantation

Substance (invented name)	Basiliximab (Simulect) EMEA/H/C/000207
Authorisation procedure	Centralised
PRAC rapporteur(s)	Brigitte Keller-Stanislawski (DE)
Date of adoption	6 February 2014

Recommendation

Having considered the available evidence from six clinical trials with basiliximab in off-label heart transplantation, the MAH is requested to submit within 2 months a proposal of active communication and a variation application to EMA to update of the SmPC, in order to inform cardiac surgeons of the

lack of favourable efficacy and safety data in the available clinical trials conducted in off-label heart transplantation. The Risk Management Plan (RMP) should also be updated accordingly with those data.

With regards to cardiac events which occurred within a short timeframe after Simulect administration, the MAH is requested to carefully follow-up and analyse in subsequent Periodic Safety Update Reports (PSURs) individual case safety reports of cardiac arrest/failure following a close temporal relationship with Simulect. A specific questionnaire should be provided to ensure consistent data collection.

Case reports of non-cardiac acute respiratory distress syndrome on the first post-operative day in patients undergoing renal transplantation have been published by Massart A. et al¹. The MAH should discuss this article in the next PSUR.

1.3. Interferon beta 1a; interferon beta 1b - Thrombotic microangiopathy (TMA)

Substance (invented name)	Interferon beta-1a: Avonex (EMA/H/C/000102), Rebif (EMA/H/C/000136); Interferon beta-1b: Betaferon (EMA/H/C/000081), Extavia (EMA/H/C/000933)
Authorisation procedure	Centralised procedure
PRAC rapporteur(s)	Julie Williams (UK for Betaferon/Extavia), Dolores Montero (ES for Avonex), Qun-Ying Yue (SE for Rebif)
Date of adoption	6 February 2014

Recommendation

The PRAC considered the information already available in the product information of Rebif and the information from the case reports, including literature and concluded that a causal association of Thrombotic Microangiopathy (TMA) with interferon beta products as a class cannot be ruled out. Therefore, the PRAC recommended that TMA should be categorised as an important identified risk and included in RMP. TMA in terms of Thrombotic Thrombocytopenic Purpura (TTP) or Haemolytic Uraemic Syndrome (HUS) should also be kept under close monitoring in future PSURs for interferon beta products. Furthermore, the MAHs for Betaferon, Extavia, Rebif and Avonex should submit a variation to EMA within 2 months to amend the product information, including a proposal for a Direct Healthcare Professional Communication (DHPC), and submit updated RMPs as appropriate. The following text should be a class labelling:

Product information

Betaferon/Extavia/Avonex/Rebif

SmPC, Section 4.4: Special warnings and precautions for use

Thrombotic microangiopathy (TMA)

- **Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS) have been reported including fatal cases with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting**

¹ Massart A et al: Does basiliximab induction trigger life-threatening ARDS and shock in young patients after kidney transplantation? Clin. Nephrol. 2013 Oct 16.

treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed prompt treatment with plasma exchange is required and immediate discontinuation of [product name] is recommended.

SmPC, Section 4.8: Undesirable effects

"Blood and lymphatic system disorders"

Rare: Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome

Package leaflet (PL), Section 2: What you need to know before you use [product name]

Warnings and precautions

- **Cases of formation of blood clots in the small blood vessels may occur during your treatment, from several weeks of treatment up to several years after starting [product name]. Your doctor may want to monitor your blood pressure, blood (platelet count) and the function of your kidney.**

PL, Section 4: Possible side effects

Rare:

- **Formation of blood clots in the small blood vessels as occurs in thrombotic thrombocytopenic purpura / Haemolytic uremic syndrome: a disorder that may present with increased bruising, bleeding, decreased platelets, anaemia, hypertension, extreme weakness, and renal disorders.**

Risk Management Plan

Betaferon/Extavia/Rebif

- Important Identified Risks

Identified Risk: **Thrombotic microangiopathy (TMA)**

List of Questions:

Rebif

The PRAC agreed that the MAH of Rebif should address a list of questions concerning the potential for a formulation-related increased risk with new versus old formulation and the responses should be submitted together with a variation.

1.4. Mefloquine - Possibly permanent neurologic (vestibular) side effects

Substance (invented name)	Mefloquine-containing medicinal products: mefloquine (Lariam, Mephaquin), mefloquine/artesunate (Falcitrim)
Authorisation procedure	'Non-centralised': NAPs
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	6 February 2014

Recommendation

Having considered the MAH's response the PRAC concluded that MAHs for mefloquine-containing medicinal products should submit a variation to the NCAs within 2 months to amend the product label as follows:

SmPC, section 4.4: Special warnings and precautions for use

[...]

~~Due to the long half-life of mefloquine,~~ Adverse reactions may **also** occur and persist up to ~~several months~~ after discontinuation of the drug.

In a small number of patients it has been reported that **neuropsychiatric reactions (e.g. depression, dizziness or vertigo and loss of balance) may persist** ~~continued~~ for months **or longer, even** after discontinuation of the drug.

[...]

SmPC, section 4.8: Undesirable effects

a) Summary of safety profile

At the doses given for acute malaria, adverse reactions to mefloquine may not be distinguishable from symptoms of the disease itself. In chemoprophylaxis, the safety profile of mefloquine is characterised by a predominance of neuropsychiatric adverse reactions. ~~Due to the long half-life of mefloquine,~~ Adverse reactions may **also** occur ~~or persist up to several weeks~~ after discontinuation of the drug. ~~Of~~ ~~†~~ The most common adverse reactions to mefloquine chemoprophylaxis, **are** nausea, vomiting and dizziness. **Nausea and vomiting** are generally mild and may decrease with prolonged use, in spite of increasing plasma drug levels. **In a small number of patients it has been reported that neuropsychiatric reactions (e.g. depression, dizziness or vertigo and loss of balance) may persist for months or longer, even after discontinuation of the drug.**

PL

The package leaflet should be updated accordingly.

1.5. Paracetamol - Drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP)

Substance (invented name)	Paracetamol
Authorisation procedure	Non-centralised
PRAC rapporteur(s)	Veerle Verlinden (BE)
Date of adoption	6 February 2014

Recommendation

The PRAC considered all scientific evidence including the safety data from the RegiSCAR registry and recommended that the MAHs of single- and multi-ingredient paracetamol-containing products for any route of administration should submit to the NCAs an update of the SmPC and the PL at the next routine opportunity as follows:

SmPC

Addition of the following information in section 4.8:

Very rare cases of serious skin reactions have been reported.

PL

Addition of the following information in section 4:

Very rare cases of serious skin reactions have been reported.

When a product already contains information on skin reactions, this information should be updated by this wording.

1.6. Ustekinumab - Dermatitis exfoliative

Substance (invented name)	Ustekinumab (Stelara) – EMEA/H/C/000958
Authorisation procedure	Centralised
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	6 February 2014

Recommendation

Having considered the available evidence from the initial signal detection analysis and from the clinical and post-marketing data submitted by the MAH, and in view of the seriousness of the reaction of exfoliative dermatitis, which can be life-threatening, the PRAC agreed that the MAH for ustekinumab should submit within 2 months a variation application to update the SmPC and the package leaflet with the risk of exfoliative dermatitis and skin exfoliation according to the wording detailed hereafter.

The RMP for ustekinumab should be updated by the MAH accordingly to reflect the changes of the SmPC regarding the risk of erythrodermic psoriasis which should be classified as an important identified risk.

In the next PSUR the MAH should discuss the feasibility of using data from a new or existing epidemiological study to investigate

- The occurrence of skin exfoliation, exfoliative dermatitis and erythrodermic psoriasis in patients with plaque psoriasis, and
- The effect of ustekinumab exposure on these outcomes.

A targeted communication to inform dermatologists of the risk of exfoliative dermatitis and skin exfoliation in the form of DHPC² should be submitted by the MAH. This communication should include information on the nature and strength of the evidence for ustekinumab-induced skin exfoliation and exfoliative dermatitis.

Change to the product information

SmPC

4.4 Special warnings and precautions for use

Serious skin reactions

In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms similar to exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis.

4.8 Undesirable effects

Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation Rare: Exfoliative dermatitis (see section 4.4)
--	--

PL

Look out for serious side effects

Some patients may have serious side effects that may need urgent treatment

Allergic reactions – these may need urgent treatment, so contact your doctor or get emergency medical help straight away if you notice any of these signs.

[...]

Infections – these may need urgent treatment, so contact your doctor straight away if you notice any of these signs.

[...]

Shedding of skin - redness and shedding of skin over a large area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should contact your doctor straight away if you notice any of these signs.

² See Guideline on good pharmacovigilance practices, Annex II – Templates: Direct Healthcare Professional Communication (DHPC) ([EMA/36988/2013](https://www.ema.europa.eu/en/medicines/human/EPAR/ustekinumab/ustekinumab.htm)).

Other side effects

Common side effects (may affect up to 1 in 10 people):

- Diarrhoea
- Nausea
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Tooth infections
- Redness and pain where the injection is given.

Uncommon side effects (may affect up to 1 in 100 people):

- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis).
- **Peeling of the skin**

Rare side effects (may affect up to 1 in 1000 people):

- **Redness and shedding of skin over a large area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis).**

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
Cetuximab	Increased fatal adverse events in patients with advanced solid tumours – publication from clinical trials	Ulla Wändel Liminga (SE)	Comment in the ongoing PSUR on the scientific literature related to the signal and provide additional data on the use of the product	Merck KGaA
Enzalutamide	Myalgia	Dolores Montero Corominas (ES)	Additional data requested (submission by 12/04/2014)	Astellas Pharma Europe B.V.
Lansoprazole	Haemolytic anaemia	Kirsti Villikka (FI)	Additional data requested (submission by 12/04/2014)	Takeda
Mycophenolate mofetil	Bronchiectasis and Hypogammaglobulinaemia (Publication from <i>Boddana P et al.</i> ; Clinical Transplantation 2011)	Julie Williams (UK)	Additional data requested (submission by 12/04/2014)	Roche Registration Ltd
Panitumumab	Increased fatal adverse events in patients with advanced solid tumours – publication from clinical trials	Julie Williams (UK)	Comment in the PSUR on the scientific literature related to the signal and provide additional data on the use of the product	Amgen Europe B.V.
Vildagliptin; Vildagliptin, metformin	Interstitial lung disease	Qun-Ying Yue (SE)	Additional data requested (submission by 12/04/2014)	Novartis Europharm Ltd

3. Other recommendations

INN	Signal	PRAC Rapporteur	Action for MAH	MAH
Etanercept	Glioblastoma and other brain neoplasms	Julie Williams (UK)	The available evidence does not support a causal association; the PRAC recommended routine review through the PSURs.	Pfizer Limited
Paracetamol	Drug exposure in pregnancy – publication by <i>Brandlistuen et al.</i> ; <i>Int. J. Epidemiol.</i> , 2013	Veerle Verlinden (BE)	No action for MAH	Not applicable