25 November 2013
EMA/PRAC/693228/2013
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 4-7 November 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 4-7 November 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 (18-21 November 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.

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1. Recommendations for update of the product information

1.1. Leflunomide - Drug reaction with eosinophilia and systemic symptoms (DRESS)

Substance (invented name)	Leflunomide (Arava, EMEA/H/C/000235, and all generics)
Authorisation procedure	Centralised and Non-centralised
PRAC rapporteur(s)	Sabine Straus
Date of adoption	7 November 2013

Recommendation

In light of the data available in EudraVigilance (EV) and in the literature, and considering the known association of leflunomide with severe skin reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme listed in the Summary of Product Characteristics [SmPC], severe skin reactions listed as an identified risk in the Risk Management Plan [RMP]), the PRAC recommended that the MAH for Arava (leflunomide) should submit a variation within 2 months to the EMA, to amend the product label as described below. The MAHs of generic products containing leflunomide should update their product information in line with that of the reference product.

Summary of Product Characteristics:

Section 4.4 - Special warnings and precautions for use:

Skin Reactions

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Very rare cases of Stevens Johnson syndrome or toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported in patients treated with leflunomide. As soon as skin and/or mucosal reactions are observed which raise the suspicion of such severe reactions, Arava and any other possibly associated treatment must be discontinued, and a leflunomide washout procedure initiated immediately. A complete washout is essential in such cases. In such cases re-exposure to leflunomide is contra-indicated (see section 4.3).

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Section 4.8 – Undesirable effects:

Skin and subcutaneous tissue disorders

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Common: increased hair loss, eczema, rash (including maculopapular rash), pruritus, dry skin

Uncommon: urticaria

Very rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme

Not known: cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis, *DRESS*

Package Leaflet:

Section 2: What you need to know before you take Arava

Warnings and precautions

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Arava can occasionally cause some problems with your blood, liver, lungs, or nerves in your arms or legs. It may also cause some serious allergic reactions (including Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), or increase the chance of a severe infection. For more information on these, please read section 4 (Possible side effects).

DRESS appears initially as flu-like symptoms and a rash on the face then an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.

Section 4: Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop taking Arava:

- if you experience weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic reaction,

- if you develop a skin rash or ulcers in your mouth, as these may indicate severe, sometimes life-threatening reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, DRESS), see section 2.

Very rare side effects (may affect up to 1 in 10,000 people)

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- severe sometimes life-threatening reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, DRESS).

1.2. Lenograstim - (Systemic) capillary leak syndrome (CLS)

Substance (invented name)	Lenograstim (Granocyte)
Authorisation procedure	Non-centralised
PRAC rapporteur(s)	Isabelle Robine
Date of adoption	7 November 2013

Recommendation

Having considered the available evidence from case reports provided in the MAH review and the scientific literature and given the seriousness and potentially life-threatening nature of systemic capillary leak syndrome, the PRAC recommended that the MAH of lenograstim should submit a variation within 1 month to the NCA concerned to amend the product information as follows:

Addition of capillary leak syndrome in section 4.8 of the SmPC (Undesirable effects) as a post-marketing life-threatening Adverse Drug Reaction (ADR): 'Capillary Leak syndrome, which can be life-threatening if treatment is delayed, has been reported <include frequency here> in the post-marketing setting following administration of granulocyte-colony-stimulating factors, mostly in cancer patients undergoing chemotherapy (see section 4.4)'.

In the table of adverse reactions in section 4.8:

Vascular disorders – *(Frequency to be determined)* - Capillary leak syndrome*

** There have been post-marketing reports of life-threatening capillary leak syndrome (see section 4.4).*

Advice on clinical management of symptoms should be provided in section 4.4 of the SmPC (Special warnings and precautions for use) as follows: Capillary leak syndrome has been reported after G-CSF administration and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Lenograstim should be discontinued if patients develop symptoms of capillary leak syndrome and appropriate symptomatic treatment, which may include a need for intensive care, should be given (see section 4.8).

Additionally, the section 4 of the Product Information Leaflet (PIL) (Possible side effects) should be updated as follows:

Please tell your doctor immediately if you have any of the following or combination of the following side effects:

- swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion.

These could be symptoms of a <frequency to be determined> condition called 'Capillary Leak Syndrome' which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.

With the variation, the MAH should include a proposal for a Direct Healthcare Professional Communication (DHPC) letter and a communication plan; in addition to the information specifically related to lenograstim, the DHPC should include a general statement about the risk of CLS reported with G-CSF-containing products.

The MAH should also submit a Risk Management Plan within three months to include the important identified risk of "capillary leak syndrome" and the potential risk of "cytokine release syndrome" and all other important identified and potential risks and propose pharmacovigilance activities, as appropriate.

1.3. Levetiracetam - Hyponatraemia and inappropriate antidiuretic hormone secretion (SIADH)

Substance (invented name)	Levetiracetam (Keppra, EMEA/H/C/000277, and all generics)
Authorisation procedure	Centralised and Non-centralised
PRAC rapporteur(s)	Jean-Michel Dogné
Date of adoption	07 November 2013

Recommendation

Based on the cumulative review submitted by the MAH, the PRAC agreed that the MAH for Keppra should submit within 2 months a variation application to the EMA to update the SmPC and the package leaflet according to the wording detailed as follow:

- Summary of product characteristics (SmPC): the MAH should update the tabulated list of adverse reactions of the section 4.8 of the SmPC with the PT "hyponatraemia" under the SOC "Metabolism and nutrition disorders", frequency "rare" (⩾1/10.000 to < 1/1000).

- Package leaflet: the MAH should update the section "4. Possible side effects" with the sentence "decreased blood sodium concentration", frequency "rare".

1.4. Teriparatide - Anaphylactic shock

Substance (invented name)	Teriparatide (Forsteo, EMEA/H/C/000425)
Authorisation procedure	Centralised
PRAC rapporteur(s)	Julie Williams
Date of adoption	7 November 2013

Recommendation

Having considered the available evidence from the case reports, and given the serious and potentially life-threatening nature of anaphylaxis, the PRAC recommended that the Marketing Authorisation Holders of Forsteo (Eli Lilly) should submit a variation within 2 months to the EMA to amend the product information as follows:

Addition to Summary of product characteristics, section 4.8:

Immune system disorders - anaphylaxis (*frequency to be determined*)

Package leaflet, section 4 (addition to *existing text* on allergic reactions):

Some patients may have experienced allergic reactions soon after injection, consisting of breathlessness, swelling of the face, rash and chest pain (frequency is rare). <frequency to be determined>, serious and potentially life-threatening allergic reactions including anaphylaxis can occur.

Additionally, the MAH should include anaphylaxis in the RMP as an identified risk within three months.

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
Adalimumab	Missed dose due to malfunction of the pre-filled pen device	Ulla Wändel Liminga	Additional data requested (submission by 04/01/2014)	AbbVie Ltd
Bupropion	Pancytopenia	Sabine Straus	Additional data requested (submission by 04/01/2014)	GlaxoSmithKline
Glycopyrronium bromide	Angioedema	Line Michan	Assess in next PSUR (submission by 07/12/2013)	Novartis Europharm Ltd
Goserelin	Long duration flushing and hyperhidrosis	Julie Williams	Additional data requested (submission by 04/01/2014)	Astra Zeneca
HMG-CoA Reductase Inhibitors: simvastatin	Risk of myopathy and rhabdomyolysis associated with high doses	Julie Williams	Additional data requested (submission by 04/01/2014)	Merck Sharp & Dohme Ltd

3. Other recommendations

INN	Signal	PRAC Rapporteur	Action for MAH	MAH
Bevacizumab	Anaphylactic shock	Doris Stenver	Monitor hypersensitivity reactions through routine pharmacovigilance	Roche Registration Ltd
Calcium channel blockers	Breast cancer risk	Ulla Wändel Liminga	No action for MAH	Not applicable
Paracetamol	Drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP)	Veerle Verlinden	No action for MAH	Not applicable