3 October 2013
EMA/PRAC/550442/2013
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 2-5 September 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 2-5 September 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 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 (16-19 September 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. Brentuximab vedotin –Pulmonary toxicity

Substance (invented name)	Brentuximab vedotin (Adcetris, H/C/002455)
Authorisation procedure	Centralised
Signal	PTs Pneumonitis, interstitial lung disease, pulmonary alveolar haemorrhage, pulmonary toxicity
PRAC rapporteur(s)	Netherlands
Date of adoption	19 August 2013 (written procedure)

Recommendation

1. Based on the assessment of the cumulative review, the MAH is requested to include the risk of pulmonary toxicity as an important potential risk in the risk management plan (RMP), by 17 Oct 2013; and to propose adequate pharmacovigilance activities to investigate this risk. More data is needed to evaluate the risk of pulmonary toxicity in patients with poorer conditions such as hepatic and renal impaired patients. Evaluation of the risk of pulmonary toxicity in these subpopulations should be included in the investigation plan proposed for the risk of pulmonary toxicity.
2. The MAH should submit a variation to EMA by 6 Sep 2013 in order to include pulmonary toxicity as warning in the summary of products characteristics (SmPC) of brentuximab vedotin.
3. The possible effect of previous treatment with bleomycin in occurrence of pulmonary toxicity events should remain under close monitoring.

1.2. Hydroxychloroquine & Chloroquine – Hypoglycaemia

Substance (invented name)	Hydroxychloroquine & Chloroquine (PLAQUENIL & associated brand names)
Authorisation procedure	Nationally Authorised Product
Signal	Metabolism and nutrition disorders (SOC); Glucose metabolism disorders (incl diabetes mellitus) (HLGT); Hypoglycaemic conditions NEC (HLT); Hypoglycaemia (PT)
PRAC rapporteur(s)	Denmark
Date of adoption	5 September 2013

Recommendation

In light of the information provided in EudraVigilance and in the literature, and considering the MAH for Plaquenil will submit a national variation in Ireland to update sections 4.4 and 4.8 of the SmPC and the patient information leaflet (PIL)/labelling to include information on the risk of hypoglycaemia, the MAHs for hydroxychloroquine or chloroquine containing products should submit a variation to the national competent authorities (NCAs) concerned, within 60 days, to include in the SmPC and PIL the following:

1. HYDROXYCHLOROQUINE

Section 4.4 of the SmPC:

Hydroxychloroquine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications. Patients treated with hydroxychloroquine should be warned about the risk of hypoglycaemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycaemia during treatment with hydroxychloroquine should have their blood glucose level checked and treatment reviewed as necessary.

Section 4.8 of the SmPC:

Under the SOC 'Metabolism and nutrition disorders':

Adverse Event: '*Hypoglycaemia' (see section 4.4).* Frequency: unknown.

PIL:

Hydroxychloroquine can cause lowering of the blood glucose level. Please ask your doctor to inform you of signs and symptoms of low blood glucose levels. A check of the blood glucose level may be necessary

PIL – Side Effects section:

Side effects with frequency unknown:

Lowering of the blood glucose level

2. CHLOROQUINE

Section 4.4 of the SmPC:

Chloroquine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications. Patients treated with chloroquine should be warned about the risk of hypoglycaemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycaemia during treatment with chloroquine should have their blood glucose level checked and treatment reviewed as necessary.

Section 4.8 of the SmPC:

Under the SOC 'Metabolism and nutrition disorders':

Adverse Event: 'Hypoglycaemia' (see section 4.4). Frequency: unknown.

PIL

Chloroquine can cause lowering of the blood glucose level. Please ask your doctor to inform you of signs and symptoms of low blood glucose levels. A check of the blood glucose level may be necessary

PIL – Side Effects section:

Side effects with frequency unknown:

Lowering of the blood glucose level

1.3. Nicardipine - Acute pulmonary oedema in off-label use during pregnancy

Substance (invented name)	Nicardipine (Loxen and associated names)
Authorisation procedure	Nationally Authorised Product
Signal	Nicardipine and acute pulmonary oedema during off-label use in pregnancy (as tocolytic)
PRAC rapporteur(s)	Italy
Date of adoption	5 September 2013

Recommendation

Considering the available evidence, the PRAC recommended that the MAH should update the product information of nicardipine containing medicinal products. A statement for both oral and parenteral formulations should be implemented (in sections 4.6 and 4.8 of the product information) in order to highlight the risk of acute pulmonary oedema when nicardipine is used in pregnancy as a tocolytic, especially in cases of multiple pregnancies and/or concomitant use of beta-2 agonists. In addition, taking into account the results presented by the MAH and considering that pulmonary oedema is reported in CCDS, this adverse reaction should also be added to section 4.8 of summary of products characteristics (SmPC). The MAHs should submit a variation within 60 days to the national competent authorities (NCAs) concerned.

Nicardipine SmPC proposed text modification. <u>The following changes to be applied to both oral and injective formulations</u>.

SmPC section	Proposed text
4.6 Fertility, pregnancy and lactation	**Pregnancy** …… Acute pulmonary oedema has been observed when nicardipine has been used as tocolytic during pregnancy (see section 4.8), especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists.
4.8 Undesiderable effects	Respiratory, thoracic and mediastinal disorders Frequency: unknown Pulmonary oedema* *cases have been also reported when used as tocolytic during pregnancy (see section 4.6)

The patient leaflet should be ***updated*** accordingly.

2. Recommendations for submission of additional data

INN	Signal	PRAC Rapporteur	Action for MAH	MAH
Denosumab	Vasculitis	Sweden	Additional data requested (submission in the next PSUR)	Amgen Limited
Dexmedetomidine	Infantile apnoeic attack	UK	Additional data requested (submission by 09/11/2013)	Orion Pharma
Interferon beta 1a, interferon beta 1b	Thrombotic microangiopathy (TMA)	UK	Additional data requested (submission by 09/11/2013)	Bayer Pharma AG (Betaferon), Merck Serono Europe Limited (Rebif), Novartis Europharm Ltd (Extavia)
Triamcinolone acetonide	Postmenopausal haemorrhage	UK	Additional data requested (submission by 09/11/2013)	Bristol Myers Squibb
Ustekinumab	Dermatitis exfoliative	UK	Additional data requested (submission by 09/11/2013)	Janssen Research & Development, LLC
Vemurafenib	Renal failure	Sweden	Additional data requested (submission in the next PSUR)	F. Hoffmann-La Roche AG

3. Other recommendations

INN	Signal	Action for MAH	MAH
Fingolimod	Spontaneous abortion and blighted ovum	Monitor in PSUR	Novartis Europharm Ltd