EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 10-13 June 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 10-13 June 2014 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][1] reference numbers).

PRAC recommendations to provide supplementary information 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 (23-26 June 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.

[1] The relevant EPITT reference number should be used in any communication related to a signal.

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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. Dexmedetomidine – Infantile apnoeic attack

Substance (invented name)	Dexmedetomidine (Dexdor), EMEA/H/C/002268
Authorisation procedure	Centralised
EPITT No	17657
PRAC rapporteur	Julie Williams (UK)
Date of adoption	13 June 2014

Recommendation

Based on the additional data submitted by the Marketing authorisation holder (MAH) of Dexdor (dexmedetomidine), the PRAC concluded that there is sufficient evidence to suggest that there is a possible causal association between respiratory depression/apnoea and dexmedetomidine. Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. The PRAC recommended that the MAH for Dexdor (dexmedetomidine) should submit a variation within 2 months to the EMA, to amend the product label as follows (new wording underlined):

Summary of Product Characteristics (SmPC):

4.4 Special warnings and precautions for use

Dexdor is intended for use in an intensive care setting and use in other environments is not recommended. All patients should have continuous cardiac monitoring during Dexdor infusion. Respiration should be monitored in non-intubated patients due to the risk of respiratory depression and in some case apnoea (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects, including sedative, anaesthetic and cardiorespiratory effects. Specific studies have confirmed ~~these~~ enhanced effects with isoflurane, propofol, alfentanil, and midazolam.

4.8 Undesirable effects

Respiratory, thoracic and mediastinal disorders

Respiratory depression, apnoea

The relevant frequency should be assigned according to current guidelines.

Package Leaflet:

Section 4. POSSIBLE SIDE EFFECTS

Frequency unknown

……..

- extreme sleepiness

- change in breathing pattern or stopping breathing

The PRAC agreed that in light of this recommended update to the SmPC the MAH of Dexdor should comment on the appropriateness of the following sentence 'Dexmedetomidine is relatively free from respiratory depressive effects.' in section 5.1 of SmPC and the supporting evidence base. The response should be submitted together with a variation.

1.2. Enzalutamide – Myalgia

Substance (invented name)	Enzalutamide (Xtandi), EMEA/H/C/002639
Authorisation procedure	Centralised
EPITT No	17792
PRAC rapporteur	Dolores Montero Corominas (ES)
Date of adoption	13 June 2014

Recommendation

In light of the examination of 33 case reports in EudraVigilance, the available scientific literature articles, and the cumulative review submitted by the MAH, the PRAC has considered the data for myalgia and related reactions. The PRAC has agreed that the MAH for Xtandi (innovator of enzalutamide) should submit a variation within 2 months to the EMA to update the SmPC as described below (new wording underlined):

Summary of Product Characteristics

Section 4.8 – Undesirable effects

Under the system organ class "Musculoskeletal and connective tissue disorders"

……..

Myalgia

Muscle spasms

Muscular weakness

Back pain

The frequency category is "not known".

The package leaflet should be updated accordingly.

In addition, the MAH should provide a cumulative review of rhabdomyolysis in the next periodic safety update report (data lock point 28-Feb-2015), using the broad SMQ rhabdomyolysis/myopathy.

1.3. Fluoroquinolones – Retinal detachment

Substance (invented name)	Fluoroquinolones for systemic use: ciprofloxacin, enoxacin, flumequine, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, rufloxacin
Authorisation procedure	Non-centralised
EPITT No	15914
PRAC rapporteur	Martin Huber (DE)
Date of adoption	13 June 2014

Recommendation

The association between fluoroquinolone intake and occurrence of retinal detachment has been investigated in several epidemiological studies using various designs and data sources. Two studies (Etminan et al. 2012, Kuo et al. 2014) have found a statistically significant increased risk. This increase was not confirmed in other published studies (Chui et al. 2014, Eftekhari et al. 2014, Fife et al. 2014, Kapoor et al. 2014, Pasternak et al. 2013) as well as in a study conducted by EMA (http://www.encepp.eu/encepp/viewResource.htm?id=6709). However, in most studies, confidence intervals were relatively wide and thus a small increase in risk cannot be excluded, especially in patients with risk factors. In addition, non-clinical data support a possible ophthalmological toxicity of fluoroquinolones and, although the number of spontaneous reports of retinal detachment with fluoroquinolones is low, some cases were at least possibly related and there may also be some underreporting. In summary, a causal relationship between fluoroquinolone intake and retinal detachment can neither be established nor firmly excluded based on the available data. Given the seriousness of retinal detachment with possible sequelae and the need for immediate intervention by an ophthalmologist in case it occurs, the PRAC considered that the product information of all fluoroquinolones for systemic use should contain a warning on vision disorders.

Consequently, when no such warning is already labelled, the MAHs of fluoroquinolone-containing medicinal products for systemic use should submit, within 3 months, a variation to the relevant NCAs to update the product information as follows:

Summary of Product Characteristics

4.4 Special warnings and precautions for use

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Package Leaflet

When taking [Product]

If your eyesight becomes impaired or if your eyes seem to be otherwise affected, consult an eye specialist immediately.

[Cross-references should be added as appropriate]

The PRAC also recommended that MAHs of fluoroquinolone-containing medicinal products for systemic use should closely monitor cases of retinal detachment through routine signal detection and literature monitoring.

1.4. Mycophenolate mofetil – Bronchiectasis and hypogammaglobulinaemia

Substance (invented name)	Mycophenolate Mofetil (CellCept and other associated names), EMEA/H/C/000082
Authorisation procedure	Centralised
EPITT No	17760
PRAC rapporteur	Rafe Suvarna (UK)
Date of adoption	13 June 2014

Recommendation

Based on the information provided and cumulative review of cases submitted by the MAH of CellCept (innovator of mycophenolate mofetil), the PRAC has agreed that the MAH of CellCept should submit a variation within 2 months to the EMA, to amend the product information to include bronchiectasis and hypogammaglobulinaemia, as described below (new text underlined). The MAHs of generic products containing mycophenolate mofetil should update their product information in line with that of the reference product.

The PRAC also agreed that a Direct Healthcare Professional Communication (DHPC) should be communicated as an additional risk minimisation measure and for the MAH of CellCept to submit the DHPC to the EMA together with the variation.

In addition, the PRAC agreed to extend the recommendation to the MAHs of products containing mycophenolic acid and their salts. Therefore the MAHs of these products should submit a variation within 2 months to their relevant NCAs to update their product information in line with that of CellCept.

Summary of Product Characteristics (SmPC) of CellCept:

Section 4.4 – Special warnings and precautions for use:

Patients treated with immunosuppressants, including CellCept, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section 4.8). Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving CellCept in combination with other immunosuppressants. In some of these cases switching CellCept to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on CellCept who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been published reports of bronchiectasis in adults and children who received CellCept in combination with other immunosuppressants. In some of these cases switching CellCept to another

immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal (see section 4.8). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Section 4.8 – Undesirable effects:

Under the section entitled 'The following undesirable effects cover adverse reactions from post-marketing experience':

……

Respiratory, thoracic and mediastinal disorders:

There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with CellCept in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults.

……..

Immune system disorders:

Hypogammaglobulinaemia has been reported in patients receiving CellCept in combination with other immunosuppressants.

The MAH should determine appropriate frequency categories for these ADRs taking into account the number of reported cases in clinical trials.

Package Leaflet of CellCept:

Section 4 - Possible side effects:

……

Other unwanted effects may include:

……

Lung problems such as:

- pneumonia, bronchitis
- shortness of breath, cough, which can be due to bronchiectasis (a condition in which the lung airways are abnormally dilated) or pulmonary fibrosis (scarring of the lung). Talk to your doctor if you develop a persistent cough or breathlessness
- fluid on the lungs or inside the chest
- sinus problems

1.5. Vildagliptin; Vildagliptin, metformin – Interstitial lung disease

Substance (invented name)	Vildagliptin (GALVUS & associated names), EMEA/H/C/000771 Vildagliptin, metformin (EUCREAS & associated names), EMEA/H/C/000807
Authorisation procedure	Centralised
EPITT No	17793
PRAC rapporteur	Qun-Ying Yue (SE)
Date of adoption	13 June 2014

Recommendation

Based on the review of data submitted to EudraVigilance and the cumulative review of safety data provided by the MAH, the PRAC concluded that a causal role of vildagliptin could not be excluded in some of the post-marketing cases considering a temporal relationship. A plausible association is at least possible; therefore the MAH of Galvus (vildagliptin) and Eucreas (vildagliptin/metformin) should submit a variation to the EMA, within 2 months, to amend section 4.8 of the SmPC with Interstitial Lung Disease in the SOC "Respiratory, thoracic and mediastinal disorders" with the frequency category "unknown". The package leaflet should be changed accordingly. The MAHs of other products containing vildagliptin should update their product information in line with that of the reference product.

1.6. Vildagliptin; Vildagliptin, metformin – Rhabdomyolysis

Substance (invented name)	Vildagliptin (GALVUS & associated names), EMEA/H/C/000771 Vildagliptin, metformin (EUCREAS & associated names), EMEA/H/C/000807
Authorisation procedure	Centralised
EPITT No	17959
PRAC rapporteur	Qun-Ying Yue (SE)
Date of adoption	13 June 2014

Recommendation

Based on the 8 supporting cases of rhabdomyolysis and 12 cases of myalgia found in EudraVigilance, and also taking into consideration findings in phase I dose-ranging study and non-clinical findings in the monkey toxicology studies the PRAC has agreed that the MAH for Galvus (innovator of vildagliptin) and Eucreas (innovator of vildagliptin/metformin) should submit a variation to the EMA within 2 months to include in the SOC Musculoskeletal, connective tissue and bone disorders 'rhabdomyolysis' in section 4.8 of the SmPCs of Galvus/Eucreas. The relevant frequency should be assigned according to current guidelines. The package leaflets should be updated accordingly. The MAH(s) of other products containing vildagliptin should update their product information in line with that of the reference product.

Within the variation submission, a cumulative review of the broad SMQ rhabdomyolysis/myopathy broad level, based on clinical trials, literature and post marketing experiences should be performed to further characterise the association, identify patients at risk and dose related information with and without the statins. Based on this review proposal to update SmPCs section 4.4 should be made.

2. Recommendations for submission of supplementary information

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 (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Chlorhexidine	Chemical injury including burns when used in skin disinfection in premature infants (18000)	Julie Williams (UK)	Supplementary information requested (submission by 12/07/2014)	Medlock, Ecolab Ltd, CareFusion UK, Regent Medical Overseas Ltd, Engelhard Arzneimittel GmbH
Ipilimumab	Posterior reversible encephalopathy syndrome (17955)	Sabine Straus (NL)	Assess in the next PSUR (submission by 03/12/2014)	Bristol-Myers Squibb Pharma EEIG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Lansoprazole	Haemolytic anaemia (17805)	Kirsti Villikka (FI)	No further action at this stage	Not applicable