21 January 2014
EMA/PRAC/720475/2013/Rev. 1[1]
Pharmacovigilance Risk Assessment Committee

PRAC signal recommendations requesting an update of the product information

Adopted between September 2012 and July 2013

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) requesting an update of the product information for the period September 2012 - July 2013. The text in this document is extracted from the PRAC meeting minutes which are published on the EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf

PRAC recommendations for 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, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting and corresponding variations have been or 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.

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MAHs are expected to submit the variation according to the timeline specified in the PRAC recommendation. The specified timeline is usually calculated from either the date of direct communication by a regulatory authority or the date of publication of the PRAC recommendation, whichever comes first. For the purpose of this document, the date of publication is the date of publication of the PRAC meeting minutes.

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.

Table of Contents

1. Adalimumab – Dermatomyositis

Substance (invented name)	Adalimumab (Humira) - EMEA/H/C/000481
Authorisation procedure	Centralised
PRAC meeting date	26-29 November 2012
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of publication of the meeting minutes	10 January 2013

Summary of Recommendation(s)

The MAH for Humira (adalimimab) should submit within 60 days a variation to update the product information as regards as dermatomyositis, including the worsening of symptoms of dermatomyositis.

Substance (invented name)	Adalimumab (Humira) - EMEA/H/C/000481
Authorisation procedure	Centralised
PRAC meeting date	13-16 May 2013
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of publication of the meeting minutes	13 June 2013

Summary of Recommendation(s)

The MAHs for Humira (adalimumab) should be requested to submit a variation to the EMA to update the product information in relation to 'worsening of symptoms of dermatomyositis', within 60 days. (SmPC section 4.8:"worsening of symptoms of dermatomyositis"; frequency: unknown)

2. Agomelatine – Angioedema

Substance (invented name)	Agomelatine (Valdoxan) - EMEA/H/C/000915
Authorisation procedure	Centralised
PRAC meeting date	26-29 November 2012
PRAC rapporteur(s)	Qun-Ying Yue (SE)
Date of publication of the meeting minutes	10 January 2013

Summary of recommendation(s)

The MAH for Valdoxan/Thymanax (agomelatine) should submit within 60 days a cumulative review of the signal, including an analysis of all case reports of angioedema (narrow SMQs) and related terms, and a proposal for amending the product information.

A type II variation was suggested as an appropriate regulatory procedure to address the signal.

3. Atazanavir – Angioedema

Substance (invented name)	Atazanavir sulphate (Reyataz) - EMEA/H/C/000494
Authorisation procedure	Centralised
PRAC meeting date	26-29 November 2012
PRAC rapporteur(s)	Isabelle Robine (FR)
Date of publication of the meeting minutes	10 January 2013

Summary of recommendation(s)

The MAH for Reyataz (atazanavir) should submit within 60 days a cumulative review consisting of an analysis of all case reports of angioedema (narrow SMQs) and related terms and anaphylactic reaction (narrow SMQs), and a proposal for updating the product information.

A type II variation was suggested as an appropriate regulatory procedure to address the signal.

4. Bevacizumab – Anaphylactic shock

Substance (invented name)	Bevacizumab (Avastin) – EMEA/H/C/000582
Authorisation procedure	Centralised
PRAC meeting date	13-16 May 2013
PRAC rapporteur(s)	Doris Stenver (DK)
Date of publication of the meeting minutes	13 June 2013

Summary of recommendation(s)

The MAH for Avastin (bevacizumab) should submit to the EMA, within 30 days, a variation for an update of the product information which reflects the most recent information identified in Eudravigilance. Furthermore the MAH should provide information regarding the status for development of an assay aiming at diagnosing anaphylaxis due to IgE hypersensitivity.

A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

5. Cinacalcet - Fatal case with severe hypocalcaemia in a pediatric clinical study

Substance (invented name)	Cinacalcet (Mimpara) - EMEA/H/C/000570
Authorisation procedure	Centralised
PRAC meeting date	4-7 March 2013
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of publication of the meeting minutes	11 April 2013

Summary of recommendation(s)

No further regulatory action is currently recommended further to the dissemination of the DHPC.

Further PRAC recommendations could be provided before finalisation of the assessment of the variation submitted by the MAH at CHMP level, as applicable.

6. Cinacalcet - QT prolongation / ventricular arrhythmias

Substance (invented name)	Cinacalcet (Mimpara) - EMEA/H/C/000570
Authorisation procedure	Centralised
PRAC meeting date	3-5 September 2012
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of publication of the meeting minutes	5 October 2012

Summary of recommendation(s)

The MAH should be requested to respond to an agreed list of questions within 30 days.

Having regard to the urgency of the matter, a type II variation should be submitted as a regulatory procedure to address the signal. A 30 day-assessment timetable was supported.

The PRAC will provide advice to the CHMP regarding the assessment of such Type II variation.

Post-meeting note: following the meeting, the MAH requested a 1-month extension of the timeline to submit the requested variation in order to allow for inclusion of additional data from the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) study, since study data were likely to allow better evaluation of the signal. The PRAC agreed to this extension request.

7. Clopidogrel - Acquired haemophilia A

Substance (invented name)	Clopidogrel (Plavix) - EMEA/H/C/000174 / (Iscover) - EMEA/H/C/000175
Authorisation procedure	Centralised / Non-centralised
PRAC meeting date	4-7 March 2013
PRAC rapporteur(s)	Margarida Guimaraes (PT)
Date of publication of the meeting minutes	11 April 2013

Summary of recommendation(s)

The MAH for Plavix/Iscover (clopidogrel) should submit to the EMA, within 30 days, a cumulative review of the cases of acquired haemophilia associated with clopidogrel, and a proposal for amending the product information as well as a proposal for a Direct Healthcare Professional Communication (DHPC) and a communication plan.

A 30-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

8. Clopidogrel - Cross-reactivity between clopidogrel and ticlopidine among patients with previous allergic and/or haematologic reactions to one of these products

Substance (invented name)	Clopidogrel (Plavix) - EMEA/H/C/000174 / (Iscover) - EMEA/H/C/000175 and ticlopidine (Ticlid)
Authorisation procedure	Centralised / Non-centralised
PRAC meeting date	4-7 March 2013
PRAC rapporteur(s)	Margarida Guimaraes (PT)
Date of publication of the meeting minutes	11 April 2013

Summary of recommendation(s)

The MAHs for Plavix/Iscover (clopidogrel) should be requested to submit to the EMA within 30 days a variation to update the product information to include the information on cross-reactivity between thienopyridines.

Section 4.4 of the Summary of Product Characteristics (SmPC): "Thienopyridines (clopidogrel, prasugrel and ticlopidine) may cause mild to severe allergic reactions such as: rash, angioedema, thrombocytopenia and neutropenia. Observational studies and post-marketing surveillance data highlighted the possibility of occurrence of a cross reactivity between thienopyridines. Patients who develop an allergic reaction (e.g. haematological or cutaneous reaction) to clopidogrel may have an increased risk of developing the same or another allergic reaction to another drug of the same pharmacological class, ticlopidine or prasugrel. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised (see section 4.8).

9. Clopidogrel - Eosinophilic pneumonia

Substance (invented name)	Clopidogrel (Plavix) - EMEA/H/C/000174 / (Iscover) - EMEA/H/C/000175
Authorisation procedure	Centralised
PRAC meeting date	7-10 January 2013
PRAC rapporteur(s)	Maria Alexandra Pego (PT)
Date of publication of the meeting minutes	7 February 2013

Summary of recommendation(s)

The MAHs for the reference, centrally authorised clopidogrel-containing medicines should be requested to submit to the EMA within 60 days a variation to update the product information to include "eosinophilic pneumonia - very rare" (Section 4.8 of the Summary of Product Characteristics) as an undesirable effect.

The MAHs of generics products should then be requested to submit to the EMA or to the national competent authorities of the MSs, as applicable, a variation to align their product information to that of the originator.

10. Docetaxel - Serious and fatal drug interactions involving CYP3A4 (grapefruit juice and dronedarone)

Substance (invented name)	Docetaxel (Taxotere) - EMEA/H/C/000073 / (Docetaxel Winthrop) - EMEA/H/C/000808 Dronedarone (Multaq) - EMEA/H/C/001043
Authorisation procedure	Centralised/Non-centralised
PRAC meeting date	8-11 April 2013
PRAC rapporteur(s)	Isabelle Robine (FR)
Date of publication of the meeting minutes	16 May 2013

Summary of recommendation(s)

The MAHs for the reference, centrally authorised docetaxel containing medicines (Taxotere and Docetaxel Winthrop) should be requested to submit to the EMA within 60 days a variation to update the product information with regard to this signal.

Summary of product characteristics (SmPC) - section 4.4 should be updated to contain a warning: 'Grapefruit (fruit or juice) consumption should be avoided (see section 4.5)'.

Section 4.5, two warnings should be added as follows: 'In case of grapefruit consumption as fruit or juice, the occurrence of docetaxel side-effects may increase, as a result of increased intestinal bioavailability. Therefore, as long as docetaxel is given, grapefruit should be avoided (see section 4.4)'.

'In case of combination with dronedarone or with CYP3A4 inhibitors (boosted PIs with ritonavir, azole antifungals and some macrolides) the occurrence of docetaxel side-effects may increase, as a result of reduced metabolism. A close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during the treatment with dronedarone or the CYP3A4 inhibitor'.

The package leaflet should be updated accordingly in section 2 - What you need to know before you take Taxotere/Docetaxel Winthrop - Taxotere/Docetaxel Winthrop with food and drink: 'Grapefruit (fruit or juice) consumption should be avoided while taking Taxotere/Docetaxel Winthrop. It can interfere with the usual effect of your medicine'.

The MAHs of generics products should subsequently align their product information to that of the originator in accordance with current procedures.

No mention of dronedarone needs to be specifically reported in the product information since general advice to avoid concomitant use with substances that inhibit or are metabolised by cytochrome P450-3A4 is already provided.

11. Duloxetine - Interaction with linezolid leading to serotonin syndrome

Substance (invented name)	Duloxetine (Ariclaim, Cymbalta, Xeristar, Yentreve), EMEA/H/C/552, EMEA/H/C/572, EMEA/H/C/573, EMEA/H/C/545
Authorisation procedure	Centralised
PRAC meeting date	13-16 May 2013
PRAC rapporteur(s)	Dolores Montero Corominas (ES)
Date of publication of the meeting minutes	13 June 2013

Summary of recommendation(s)

The MAH for centrally authorised duloxetine medicines should submit to the EMA, within 60 days, a proposal for amending the product information regarding interaction with linezolid possibly leading to serotonin syndrome, in the framework of a variation.

SmPC section 4.4 Special warnings and precautions for use.

~~Use with antidepressants~~
~~Caution should be exercised when using <name> in combination with antidepressants. In particular the combination with selective reversible MAOIs is not recommended.~~

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with duloxetine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs , tricyclic antidepressants or triptans), with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.5).
Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular

aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If concomitant treatment with duloxetine and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

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

Monoamine oxidase inhibitors (MAOIs).

12. Efavirenz - Interaction with *Ginkgo biloba*

Substance (invented name)	Efavirenz (Sustiva) - EMEA/H/C/000249 / (Stocrin) - EMEA/H/C/000250
Authorisation procedure	Centralised
PRAC meeting date	13-16 May 2013
PRAC rapporteur	Margarida Guimarães (PT)
Date of publication of the meeting minutes	13 June 2013

Summary of recommendation(s)

The MAH for efavirenz-containing medicinal products (Stocrin/Sustiva, Atripla) should submit to the EMA, within 60 days, a variation to update the product information relating the interaction of efavirenz with Ginkgo biloba.

SmPC: section 4.3 Contraindications

Herbal preparations containing St. John's wort (Hypericum perforatum) or Ginkgo biloba must not be used while taking efavirenz due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

St. John's wort (Hypericum perforatum): co-administration of efavirenz and St. John's wort or herbal preparations containing St. John's wort is contraindicated. Plasma levels of efavirenz can be reduced by concomitant use of St. John's wort due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John's wort and the dose of efavirenz may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).Ginkgo biloba extracts: co-administration

of efavirenz and Ginkgo biloba extracts is contraindicated. Plasma levels of efavirenz may be reduced by concomitant use of Ginkgo biloba extracts (see section 4.3).

Package Leaflet

2. What you need to know before you take <efavirenz>

Do not take <efavirenz>

(….)

if you are currently taking any of the following medicines:

astemizole or terfenadine (used to treat allergy symptoms)

bepridil (used to treat heart disease)

cisapride (used to treat heartburn)

ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and

methylergonovine) (used to treat migraine and cluster headaches)

midazolam or triazolam (used to help you sleep)

pimozide (used to treat certain mental conditions)

St. John's wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety)

Ginkgo biloba extracts (a herbal remedy)

If you are taking any of these medicines, tell your doctor immediately. Taking these medicines

with <efavirenz> could create the potential for serious and/or life-threatening side-effects or stop <efavirenz> from working properly.

(…)

Other medicines and <efavirenz>

You must not take <efavirenz> with certain medicines. These are listed under Do not take <efavirenz>, at the start of Section 2. They include some common medicines and a herbal remedies (St. John’s wort and Ginkgo biloba extracts) which can cause serious interactions.

13. Erlotinib - Palmar-plantar erythrodysaesthesia syndrome (PPES)

Substance (invented name)	Erlotinib (Tarceva) - EMEA/H/C/000618
Authorisation procedure	Centralised
PRAC meeting date	1-3 October 2012
PRAC rapporteur(s)	Doris Stenver (DK)
Date of publication of the meeting minutes	31 October 2012

Summary of recommendation(s)

The MAH for Tarceva (erlotinib) should submit a type II variation in order to update the product information to address the signal. A 60-day timetable was supported for this variation, which will lead to a further PRAC recommendation.

14. Etanercept – Dermatomyositis

Substance (invented name)	Etanercept (Enbrel) - EMEA/H/C/000262
Authorisation procedure	Centralised
PRAC meeting date	10 - 13 June 2013
PRAC rapporteur(s)	Julie Williams (UK)
Date of publication of the meeting minutes	11 July 2013

Summary of recommendation(s)

The MAHs for Enbrel (etanercept) should be requested to submit a variation to the EMA to update the product information as regards as 'worsening of symptoms of dermatomyositis', within 60 days.

15. Exenatide / Liraglutide - Gastrointestinal stenosis and obstruction

Substance (invented name)	Exenatide (Byetta) - EMEA/H/C/000698 / (Bydureon) - EMEA/H/C/002020 Liraglutide (Victoza) - EMEA/H/C/001026
Authorisation procedure	Centralised
PRAC meeting date	7-10 January 2013
PRAC rapporteur(s)	Qun-Ying Yue (SE) Menno Van der Elst (NL)
Date of publication of the meeting minutes	7 February 2013

Summary of recommendation(s)

The MAH for the centrally authorised products containing exenatide and liraglutide should be requested to submit to the EMA within 60 days a variation proposing appropriate amendments to the RMP and product information.

Substance (invented name)	Exenatide (Byetta) - EMEA/H/C/000698 / (Bydureon) - EMEA/H/C/002020) Liraglutide (Victoza) - EMEA/H/C/001026
Authorisation procedure	Centralised
PRAC meeting date	10-13 June 2013
PRAC rapporteur(s)	Qun-Ying Yue (SE) Menno van der Elst (NL)
Date of publication of the meeting minutes	11 July 2013

Summary of recommendation(s)

The MAHs for the centrally authorised exenatide (Bydureon, Byetta) and liraglutide (Victoza) containing medicines should be requested to submit to the EMA within 60 days a variation to update the product information to include “intestinal obstruction” (Section 4.8 of the Summary of Product Characteristics) as an undesirable effect.

16. Filgrastim, Pegfilgrastim - Systemic capillary leak syndrome (SCLS) and cytokine release syndrome (CRS)

Substance (invented name)	Filgrastim (Neupogen) – MRP product Filgrastim (Biograstim) – EMEA/H/C/000826 Filgrastim (Filgrastim Hexal) - EMEA/H/C/000918 Filgrastim (Nivestim) - EMEA/H/C/001142 Filgrastim (Ratiograstim) - EMEA/H/C/000825 Filgrastim (Tevagrastim) - EMEA/H/C/000827 Filgrastim (Zarzio) - EMEA/H/C/000917 Pegfilgrastim (Neulasta) - EMEA/H/C/000420
Authorisation procedure	Centralised / Non-centralised
PRAC meeting date	4-7 March 2013
PRAC rapporteur(s)	Julie Williams (UK) (Rapp) Kirsti Villikka (FI) (Co-Rapp)
Date of publication of the meeting minutes	11 April 2013

Summary of recommendation(s)

The MAH for the reference filgrastim and pegfilgrastim-containing medicines Neupogen (filgrastim) and Neulasta (pegfilgrastim) should submit within 30 days (to the NCAs and to the EMA as appropriate), a proposal for amending the product information, including a DHPC and a communication plan.

Section 4.8 of the SmPC (Undesirable effects) as a post-marketing life-threatening ADR in cancer patients and healthy donors.

Section 4.4 of the SmPC (Special warnings and precautions for use) ‘Capillary leak syndrome is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who

develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care'.

Additionally, the section 4 of the PIL (Possible side effects) should be updated to contain an appropriate description of symptoms indicative of CLS which may need medical attention.

The same MAH is also requested to submit an updated Risk Management Plan within 90 days to include the important identified risk of "capillary leak syndrome" and the potential risk of "cytokine release syndrome" and proposed pharmacovigilance activities, as appropriate. Follow-up to the remaining biosimilar products will be in accordance to current procedures.

17. Fingolimod - Haemophagocytic syndrome

Substance (invented name)	Fingolimod (Gilenya) - EMEA/H/C/002202
Authorisation procedure	Centralised
PRAC meeting date	8-11 April 2013
PRAC rapporteur(s)	Evelyne Falip (FR)
Date of publication of the meeting minutes	16 May 2013

Summary of recommendation(s)

The MAHs for Gilenya (fingolimod) should be requested to submit to the EMA within 60 days a variation to provide some further clarification on the signal, including a proposal for an update of the product information with regards to haemophagocytic syndrome (Section 4.8 of the SmPC: information about the occurrence of two fatal cases of HPS) as well as a proposal for a DHPC and communication plan.

18. Infliximab - Dermatomyositis

Substance (invented name)	Infliximab (Remicade) - EMEA/H/C/000240
Authorisation procedure	Centralised
PRAC meeting date	26-29 November 2012
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of publication of the meeting minutes	10 January 2013

Summary of recommendation(s)

The MAH for infliximab (Remicade) should submit within 60 days a variation to update the product information in relation to dermatomyositis, including worsening of symptoms of dermatomyositis.

19. Lopinavir / ritonavir, quetiapine - Major sedation due to drug interaction between lopinavir / ritonavir and quetiapine

Substance (invented name)	Lopinavir/ritonavir (Kaletra) - EMEA/H/C/000368 / (Aluvia) - EMEA/H/W/000764
Authorisation procedure	Centralised
PRAC meeting date	8-11 July 2013
PRAC rapporteur	Isabelle Robine (FR)
Date of publication of the meeting minutes	5 September 2013

Summary of recommendation(s)

The MAH for Kaletra (lopinavir / ritonavir) should submit to the EMA, within 30 days, a variation with a proposal for amending the product information to include a contraindication for the concomitant use of quetiapine.

SmPC Section 4.3. Contraindications: Concomitant medicinal product levels increased – Antipsychotics; Quetiapine: increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contra-indicated (see section 4.5).

Section 4.5 Interaction with other medicinal products and other forms of interaction:Antipsychotics; Quetiapine; Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase; Concomitant administration of Kaletra and quetiapine is contra-indicated as it may increase quetiapine-related toxicity.

The MAHs of all other protease inhibitor-containing medicinal products (ATC code J05AE) should also introduce a contraindication in the product information for these medicines, by appropriate procedures, within 30 days.

Post-meeting note: similar wordings applicable to the SmPCs of other protease inhibitor-containing medicinal products were adopted by PRAC and CHMP via written procedure on 14 August 2013.

20. Mirtazapine – Pancreatitis

Substance (invented name)	Mirtazapine (Remeron) – innovator product
Authorisation procedure	Non-centralised
PRAC meeting date	8-11 April 2013
PRAC rapporteur(s)	Sabine Straus (NL)
Date of publication of the meeting minutes	16 May 2013

Summary of recommendation(s)

The MAHs for the reference, nationally authorised mirtazapine–containing medicine should be requested to submit to the National Competent Authorities (NCAs) of the MSs within 60 days a variation to update the product information to include “pancreatitis” (Section 4.8 of the Summary of Product Characteristics - under the SOC Gastrointestinal disorders - frequency “rare”) as an undesirable effect with the frequency “rare” (as observed in clinical trials).

The MAHs of generics products should subsequently be requested to align their product information with that of the originator in accordance with current procedures.

21. Nicardipine – Thrombocytopenia

Substance (invented name)	Nicardipine (Austria: Karden; Belgium: Rydene; France: Loxen; Germany: Antagonil; Ireland: Cardene; Italy: Bionicard; Cardioten; Cardip; Cordipina; Cordisol; Farnic; Lisanirc; Neucor; Nicant; Nicapress; Nicardal; Nicardium; Nicarpin; Nicaven; Nimicor; Niven; Perdipina; Ranvil; Vasodin; Vasonorm; Netherlands: Cardene; Portugal: Nerdipina; Spain: Dagan; Flusemide; Lecibral; Lincil; Lucenfal; Nerdipina; Vasonase; Vatrasin; United Kingdom: Cardene)
Authorisation procedure	Non-centralised
PRAC meeting date	26-29 November 2012
PRAC rapporteur(s)	Carmela Macchiarulo (IT)
Date of publication of the meeting minutes	10 January 2013

Summary of recommendation(s)

The MAHs for nicardipine-containing medicines should submit within 60 days a variation to update the product information by adding ‘thrombocytopenia’ (Section 4.8 of the Summary of Product Characteristics) in the products information of medicines marketed in EU MS where this information is not mentioned.

The MAHs for nicardipine-containing medicinal products are requested to monitor the haematological disorders possibly associated with the use of nicardipine in the next PSURs.

22. Pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) – Narcolepsy

Substance (invented name)	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a) (Pandemrix) - EMEA/H/C/000832
Authorisation procedure	Centralised
PRAC meeting date	29-31 October 2012
PRAC rapporteur(s)	Julie Williams (UK)
Date of publication of the meeting minutes	29 November 2012

The PRAC discussed the available data and recommended a revision of the wording included the product information regarding the "very rare risk of narcolepsy", to reflect the totality of the epidemiological evidence in children and adolescents under 20 years of age. The PRAC was informed of the final data from a French study which raised a signal for the adult population. The Vaccine Adverse Event Surveillance & Communication (VAESCO) study contains the French data and thus reported the same signal. The PRAC was also informed that additional data from ongoing studies are expected in the next few months and agreed that further discussions on whether there is a need to amend the product information regarding narcolepsy in adults should await evaluation of these new data.[2]

Summary of recommendation(s)

The MAH for Pandemrix should submit a type II variation in order to update the product information.

A 60-day timetable for this variation was agreed; an additional PRAC recommendation will be provided if requested by the CHMP.

Substance (invented name)	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a) (Pandemrix) - EMEA/H/C/000832
Authorisation procedure	Centralised
PRAC meeting date	10-13 June 2013
PRAC rapporteur(s)	Julie Williams (UK)
Date of publication of the meeting minutes	11 July 2013

Since the product information currently reported that the increase in risk of narcolepsy has not been found in adults (older than 20 years), the PRAC considered this statement is no longer appropriate and should be removed.[1]

[2] This text is extracted from the PRAC meeting minutes and provided in this document for the sake of clarity. For further details please refer to the relevant PRAC meeting minutes published on the EMA website.

Summary of recommendation(s)

The MAH for Pandemrix, should be requested to submit to the EMA within 60 days a variation to update the product information to reflect these new findings, including a review of the current totality of evidence on the risk of narcolepsy with Pandemrix in children, adolescents and older age groups, in the context of the benefits of the vaccine in these respective age groups.

23. Roxithromycin - Hearing disorders

Substance (invented name)	Roxithromycin
Authorisation procedure	Non-centralised
PRAC meeting date	4-7 February 2013
PRAC rapporteur(s)	Carmela Macchiarulo (IT)
Date of publication of the meeting minutes	7 March 2013

Summary of recommendation(s)

The MAHs for roxithromycin-containing medicines should be requested to submit within 60 days a variation to update the product information as regards the risk of hearing disorders (SOC – Ear and vestibular disorders – section 4.8 of the SmPC and PL: ear and vestibular disorders: deafness transitory, hypoacusis, vertigo and tinnitus) to the NCAs of the MSs.

24. Roxithromycin - Rhabdomyolysis secondary to interaction with statins

Substance (invented name)	Roxithromycin
Authorisation procedure	Non-centralised
PRAC meeting date	4-7 February 2013
PRAC rapporteur(s)	Carmela Macchiarulo (IT)
Date of publication of the meeting minutes	7 March 2013

Summary of recommendation(s)

The MAHs for roxithromycin-containing medicines should be requested to submit to the NCAs of the MSs within 60 days a variation to update the product information as regards risk of rhabdomyolysis secondary to interaction with statins.

Section 4.5 of the SmPC: Interaction with other medicinal products and other forms of interaction:

HMG-CoA Reductase Inhibitors

When roxithromycin and an HMGCoA reductase inhibitor (statin) are combined, there is a potential risk of muscle related adverse events, such as rhabdomyolysis due to a possible increase of the statin exposure.

Caution should be exercised when a statin is combined with roxithromycin and patients should be monitored for signs and symptoms of myopathy.

25. Sugammadex - Respiratory symptoms unrelated to hypersensitivity reaction

Substance (invented name)	Sugammadex (Bridion) - EMEA/H/C/000885
Authorisation procedure	Centralised
PRAC meeting date	4-7 February 2013
PRAC rapporteur(s)	Kirsti Villikka (FI)
Date of publication of the meeting minutes	7 March 2013

Summary of recommendation(s)

The MAH for Bridion (sugammadex) should be requested to update the product information as regards information available on bronchospasm and respiratory events. The paragraph 'Drug hypersensitivity' in section 4.8 of the SmPC should be amended to include 'bronchospasm' and 'obstructive events'. The paragraph 'Pulmonary patients' in section 4.8 should be updated with further clinical and post-marketing data. Current information: "one clinical trial …in two patients" should be expanded.

Relevant changes should be reflected in the Risk Management Plan. Such changes should be considered in the framework of the ongoing procedure for the renewal of the marketing authorisation submitted to the EMA - see 9.2.3.

The MAH should closely monitor pulmonary obstructive events and submit to the EMA a cumulative review of new data since November 2012 in the next PSUR.

26. Tamsulosin - Dry mouth syndrome

Substance (invented name)	Tamsulosin (OMNIC, OMNIC OCAS)
Authorisation procedure	Non-centralised
PRAC meeting date	8 July – 11 July 2013
PRAC rapporteur(s)	Sabine Straus (NL)
Date of publication of the meeting minutes	5 September 2013

Summary of recommendation(s)

The MAH(s) for tamsulosin-containing medicines should submit to the NCA of the MS, within 60 days, a variation for amending the product information to include 'dry mouth' (SmPCs section 4.8: SOC Gastrointestinal Disorders 'Dry Mouth'; frequency: 'unknown').

27. Temozolomide - Hepatic Failure

Substance (invented name)	Temozolomide (Temodal) - EMEA/H/C/000229
Authorisation procedure	Centralised
PRAC meeting date	4-7 March 2013
PRAC rapporteur(s)	Martin Huber (DE)
Date of publication of the meeting minutes	11 April 2013

Summary of recommendation(s)

The MAH for Temodal (temozolomide) should be requested to submit to the EMA, within 60 days, a variation proposing appropriate amendments to the product information, including a proposal for a communication plan and provision of supplementary information as requested by the PRAC.

The MAHs should also be requested to submit an updated Risk Management Plan within the next regulatory procedure to reclassify the 'important potential risk' of 'hepatobiliary disorders' to an 'important identified risk' and include information on 'severe liver injuries' including those with fatal outcome.

28. Ticagrelor - Food interaction with grapefruit juice

Substance (invented name)	Ticagrelor (Brilique) - EMEA/H/C/001241 / (Possia) - EMEA/H/C/002303
Authorisation procedure	Centralised
PRAC meeting date	4-7 February 2013
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of publication of the meeting minutes	7 March 2013

Summary of recommendation(s)

The MAH for Brilique/Possia (ticagrelor) should be requested to submit to the EMA, within 60 days, a variation including a proposal for amending the product information (Section 4.5 of the SmPC and 1 - Taking Brilique/Possia with food and drink - in the PL) in order to address the signal.

29. Tiotropium bromide - Anaphylactic reaction

Substance (invented name)	Tiotropium bromide
Authorisation procedure	Non-Centralised
PRAC meeting date	10 - 13 June 2013
PRAC rapporteur(s)	Sabine Straus (NL)
Date of publication of the meeting minutes	11 July 2013

Summary of recommendation(s)

The MAHs for tiotropium should be requested to submit to the NCAs of the MSs within 60 days a variation to update the product information to include “anaphylactic reaction” (Section 4.8 of the Summary of Product Characteristics) as an undesirable effect.

30. Tolvaptan – Dehydration

Substance (invented name)	Tolvaptan (Samsca) - EMEA/H/C/000980
Authorisation procedure	Centralised
PRAC meeting date	29-31 October 2012
PRAC rapporteur(s)	Julie Williams (UK)
Date of publication of the meeting minutes	29 November 2012

Summary of recommendation(s)

The MAH for Samsca (tolvaptan) should submit a review of the possible interaction between tolvaptan and ACE-inhibitors or ARBs and risk of renal dysfunction, including a proposal for updating the product information.

A 60 day-timetable was supported to assess the results of this review, which will lead to a further PRAC recommendation.

31. Tolvaptan - Serious liver injury associated with high dose tolvaptan in patients with polycystic kidney disease

Substance (invented name)	Tolvaptan (Samsca) - EMEA/H/C/000980
Authorisation procedure	Centralised
PRAC meeting date	4-7 February 2013
PRAC rapporteur(s)	Julie Williams (UK)
Date of publication of the meeting minutes	7 March 2013

Summary of recommendation(s)

The MAH for Samsca (tolvaptan) should be requested to submit to the EMA within 30 days, in the framework of a variation, further data and a cumulative review of the signal, together with a proposal for amending the product information as well as a proposal for a DHPC and communication plan.

32. Tramadol – Hypoglycaemia

Substance (invented name)	Tramadol and tramadol-containing medicinal products
Authorisation procedure	Non-centralised
PRAC meeting date	10-13 June 2013
PRAC rapporteur(s)	Evelyne Falip (FR)
Date of publication of the meeting minutes	11 July 2013

Summary of recommendation(s)

The MAHs for the reference, nationally authorised tramadol containing medicines should be requested to submit to the NCA of the MSs within 60 days a variation to update the product information to include “hypoglycaemia” (Section 4.8 of the Summary of Product Characteristics) as an undesirable effect.

The MAHs of generic products should then be requested to submit to the national competent authorities of the MSs, as applicable, a variation to align their product information to that of the originator.

33. Trazodone - Postural hypotension and somnolence at high starting dose

Substance (invented name)	Trazodone
Authorisation procedure	Non-centralised
PRAC meeting date	13-16 May 2013
PRAC rapporteur(s)	Jolanta Gulbinovic (LT)
Date of publication of the meeting minutes	13 June 2013

Summary of recommendation(s)

The MAHs for the nationally authorised trazodone-containing medicines should be requested to submit to the NCAs of the MSs, within 60 days, a variation to update the product information to include warnings regarding the potential for orthostatic hypotension, somnolence and other anticholinergic effects in elderly patients particularly with concomitant medication use, concomitant diseases and drug interactions.

SmPC, suggested additional wording are in italics and underlined.

Section 4.2. Add cross-reference to Section 4.4.

"For very elderly or frail patients, the recommended initial dose is reduced to 100 mg a day administered in divided doses or as a single night time dose ***(See Section 4.4)***. This may be incrementally increased as described under Adults, under supervision, according to tolerance and efficacy"

Section 4.4 – Suggest separate paragraph for elderly patients.

"Elderly patients ***~~are more often more sensitive to antidepressants, in particular~~ may more often experience ~~to~~*** orthostatic hypotension, ***somnolence***, and other anticholinergic effects ***of trazodone***. ***Careful consideration should be given to the potential for additive effects with concomitant medication use such as with other psychotropics or antihypertensives or in the presence of risk factors such as comorbid disease, which may exacerbate these reactions. It is recommended that the patient/carer is informed of the potential for these reactions and monitored closely for such effects following initiation of therapy, prior to and following upward dose titration***.";

Relevant sections of patient leaflet should be updated accordingly.