25 February 2016
EMA/PRAC/87046/2016
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 8-11 February 2016

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 8-11 February 2016 (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 (22-25 February 2016) 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 timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

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[2]

1.1. Bcr-abl tyrosine kinase inhibitors: imatinib; dasatinib; nilotinib; bosutinib; ponatinib – Hepatitis B virus (HBV) reactivation

Authorisation procedure	Centralised
EPITT No	18405
PRAC rapporteur(s)	Dolores Montero Corominas (ES)
Date of adoption	11 February 2016

Recommendation

Having considered the available evidence, the PRAC has agreed that the MAH(s) of Bcr-Abl tyrosine kinases, namely imatinib, dasatinib, nilotinib, bosutinib and ponatinib-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined).

In addition, the MAH should distribute a direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the CHMP.

(Applicable to imatinib, dasatinib and nilotinib)

Summary of Product Characteristics

4.4 Special warnings and precautions for use

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with (BRANDNAME DRUG). Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with BRANDNAME DRUG should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

4.8 Undesirable effects

Table 1 Tabulated summary of adverse reactions

Infections and infestations

Frequency 'not known': Hepatitis B reactivation

[2] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

Description of selected adverse reactions:

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

Package Leaflet

2. What you need to know before you take BRANDNAME DRUG

Talk to your doctor, pharmacist or nurse before taking BRANDNAME DRUG

- if you have ever had or might now have a hepatitis B infection. This is because BRANDNAME DRUG could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.

4. Possible side effects

- Recurrence (reactivation) of Hepatitis B infection when you have had hepatitis B in the past (a liver infection).

(Applicable to bosutinib and ponatinib)

Summary of Product Characteristics

4.4 Special warnings and precautions for use

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with (BRANDNAME DRUG). Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with BRANDNAME DRUG should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

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Description of selected adverse reactions:

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

Package Leaflet

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Talk to your doctor, pharmacist or nurse before taking BRANDNAME DRUG

- if you have ever had or might now have a hepatitis B infection. This is because BRANDNAME DRUG could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.

4. Possible side effects

- Recurrence (reactivation) of Hepatitis B infection when you have had hepatitis B in the past (a liver infection).

1.2. Levodopa/carbidopa (intestinal gel) – Intussusception

Authorisation procedure	Non centralised
EPITT No	18424
PRAC rapporteur(s)	Qun-Ying Yue (SE)
Date of adoption	11 February 2016

Recommendation

Having considered the available evidence and the known association of carbidopa/levodopa (intestinal gel) with intussusception, the PRAC has agreed that the MAH of Duodopa (AbbVie) should submit a variation within 2 months, to amend the product information as described below (new text underlined / text to be removed ~~strikethrough~~):

Summary of Product Characteristics:

4.4 Special warnings and precautions for use

Reported complications in the clinical studies, and seen post-marketing, include bezoar, ileus, implant site erosion/ulcer, intestinal haemorrhage, intestinal ischaemia, intestinal obstruction, intestinal perforation, intussusception, pancreatitis, peritonitis, pneumoperitoneum and post-operative wound infection. Intussusception has also been reported post marketing. Bezoars are retained concretions of ~~undigested food~~ indigestible material (such as vegetable or fruit non-digestible fibers) in the intestinal tract. Most bezoars reside in the stomach but bezoars may be encountered elsewhere in the intestinal tract. A bezoar around the tip of the jejunal tube may function as a lead point for intestinal obstruction or the formation of intussusception. Abdominal pain may be a symptom of the above listed complications. Some events may result in serious outcomes, such as surgery and/or death. Patients should be advised to notify their physician if they experience any of the symptoms associated with the above events.

4.8 Undesirable effects

Table 1. Adverse Reaction Data Derived From Clinical Trials and Postmarketing Experience

Uncommon (> 1/1,000 to < 1/100)

Device- and Procedure-Related Adverse Reactions

Gastrointestinal disorders

Intussusception

Package Leaflet:

4. Possible side effects

Side effects from the pump or tube

Uncommon: may affect up to 1 in 100 people

- Inflamed colon (colitis).
- Inflamed pancreas (pancreatitis).
- The tube goes through the wall of the large intestine.
- Blockage (obstruction), bleeding or ulcer in the gut.
- Sliding of one part of the gut into an adjacent part of the gut (intussusception)
- Food getting stuck around the tube causing it to block.
- Pocket of infection (abscess) – this could happen after the tube is placed in your stomach

1.3. Mitotane – Sex hormone disturbances and development of ovarian macrocysts

Authorisation procedure	Centralised
EPITT No	18301
PRAC rapporteur(s)	Dolores Montero Corominas (ES)
Date of adoption	11 February 2016

Recommendation

Having considered the proposal from the MAH of Lysodren (Laboratoire HRA Pharma) to update the product information, the PRAC recommended that the MAH should submit a variation within 60 days to update the product information as follows (new text underlined):

Summary of Product Characteristics

4.4 Special warnings and precautions for use

Premenopausal women: Ovarian macrocysts have been observed with higher incidence in this population. Isolated cases of complicated cysts have been reported (adnexal torsion and haemorrhagic cyst rupture). Improvement after mitotane discontinuation has been observed. Women should be urged to seek medical advice if they experience gynecological symptoms such as bleeding and/or pelvic pain.

4.8 Undesirable effects

SOC: Investigations (frequency not known):

- Blood androstenedione decreased (in females)
- Blood testosterone decreased (in females)
- Sex hormone binding globulin increased
- Blood free testosterone decreased (in males)

SOC: Reproductive system and breast disorders (frequency not known):

- Ovarian macrocysts

Premenopausal women: non-malignant ovarian macrocysts (with symptoms such as pelvic pain, bleeding) have been described.

Package Leaflet

2. What you need to know before you take Lysodren

Warnings and precautions

You should tell your doctor if any of the following applies to you:

- If you have gynaecological problems such as bleeding and/or pelvic pain.

4. Possible side effects

Frequency not known

- Ovarian macrocysts (with symptoms such as pelvic pain, bleeding)
- Decreased androstenedione (precursor of sex hormones) in blood tests in females
- Decreased testosterone (sex hormone) in blood tests in females
- Sex hormone binding globulin (a protein which binds sex hormones) increased in blood tests
- Decreased free testosterone (sex hormone) in blood tests in males

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Rivaroxaban	Spontaneous spinal haematoma (18606)	Qun-Ying Yue (SE)	Assess in the next PSUR (submission by 24/11/2016)	Bayer Pharma AG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Autoimmune haemolytic anaemia (AIHA) and haemolytic anaemia (HA) (18447)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	AbbVie Ltd
Alogliptin; linagliptin	Arthralgia (18489)	Menno van der Elst (NL)	Update RMP and monitor in PSUR	Takeda Pharma A/S; Boehringer Ingelheim International GmbH
Peginterferon alfa-2a	Acquired haemophilia (18476)	Qun-Ying Yue (SE)	Monitor in PSUR	Roche Registration Limited
Sofosbuvir	Hepatitis B virus (HBV) reactivation (18607)	Rafe Suvarna (UK)	Under consideration	Gilead Sciences International Ltd
Ustekinumab	Pemphigoid (18469)	Julie Williams (UK)	Routine pharmacovigilance	Janssen-Cilag International N.V.