World Health Organization

WHO Pharmaceuticals NEWSLETTER

2017

No.3

WHO Vision for Medicines Safety
No country left behind: worldwide pharmacovigilance for safer medicines, safer patients

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Safety and Vigilance: Medicines,

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This Newsletter is also available at:
http://www.who.int/medicines

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from the WHO global database of individual case safety reports, VigiBase.

This newsletter includes two feature articles: Pilot Mobile 'APP' for reporting suspected adverse drug reactions launched in Burkina Faso and Zambia, and, Introducing a New Member in the WHO Programme for International Drug Monitoring (WHO PIDM): Paraguay.

Contents

Suggested citation. WHO Pharmaceuticals Newsletter No.3, 2017: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Printed in Switzerland

Table of Contents

Regulatory Matters

Safety of Medicines

Signal

Table of Contents

Feature

Bevacizumab

Potential risk of non-mandibular osteonecrosis in adult cancer patients

Canada. Health Canada recommends that the product safety information for bevacizumab (Avastin®) is updated to include information on the potential risk of non-mandibular osteonecrosis in adult cancer patients.

Bevacizumab, when used alone, is used for the treatment of glioblastoma. It can also be used with other chemotherapy medicines to treat cancers of the large bowel, lung, female reproductive system and the lining of the abdominal cavity.

Health Canada initiated a review of the risk of non-mandibular osteonecrosis in adult cancer patients treated with bevacizumab following the publication of two reports in the literature.

At the time of the review, Health Canada had received one report of non-mandibular osteonecrosis related to bevacizumab use. There was insufficient information to conclude that the use of bevacizumab alone had caused this condition in this report.

Health Canada also looked at information on 67 international reports of non-mandibular osteonecrosis related to the use of bevacizumab, including the two cases that triggered the safety review. In 26 of these reports, a link between bevacizumab and non-mandibular osteonecrosis could not be ruled out. In the remaining 41 reports, there were either not enough information to establish a link, or there were confounding factors such as the presence of other bone conditions or treatments known to cause bone damage.

After reviewing available data, it was determined that there is not enough information to establish a definitive link between the use of bevacizumab and non-mandibular osteonecrosis in adult cancer patients. However, Health Canada has decided to recommend updating the product safety information of bevacizumab to include information on the potential risk.

Reference:
Summary Safety Review, Health Canada, 5 April 2017 (*www.hc-sc.gc.ca*)

Canagliflozin

Increased risk of leg and foot amputations

USA. The US Food and Drug Administration (FDA) has requested that the product label for canagliflozin (Invokana® and Invokamet®) is updated to include the risk of leg and foot amputations.

Canagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor and is used with diet and exercise to lower blood sugar in adults with type-2 diabetes.

Final results from two clinical trials - the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type-2 Diabetes Mellitus) - showed that leg and foot amputations occurred twice as often in patients treated with canagliflozin compared to patients treated with placebo.

Reference:
Drug Safety Communication, US FDA, 16 May 2017
(www.fda.gov)

(See WHO Pharmaceuticals Newsletters No.2, 2017: Risk of lower limb amputation in Malaysia and Potential risk of toe amputation with SGLT inhibitors in the EU and No.3, 2016: Risk of leg and foot amputations: under investigation in the USA)

Caspofungin

Risk of Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson syndrome

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for caspofungin (Cancidas®) has been updated to include the risk of Toxic Epidermal Necrolysis (TEN) and oculomucocutaneous syndrome (Stevens-Johnson syndrome) as clinically significant adverse reactions.

Caspofungin is indicated for febrile neutropenia suspected to be caused by a fungal infection, and for the treatment of fungal infections due to *Candida* or *Aspergillus*.

The update followed reports of TEN and/or oculomucocutaneous syndrome in patients treated with caspofungin both in Japan and overseas, and following revision of the company core datasheet (CCDS) and package inserts in the United States and Europe.

Reference:
Revision of Precautions, MHLW/PMDA, 20 April 2017
(www.pmda.go.jp/english/)

Clopidogrel

Potential risk of spinal haematoma, cholecystitis and haematemesis

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has announced that the label for clopidogrel has been revised to include spinal haematoma, cholecystitis and haematemesis as adverse reactions.

Clopidogrel is a platelet aggregation inhibitor and is indicated for the reduction of the rate of cardiovascular death, myocardial infarction,

and stroke in patients with acute coronary syndrome.

At the time of review, the Korea institute of Drug safety and Risk Management (KIDS) had received three domestic reports of spinal haematoma, nine domestic and eight international reports of cholecystitis, and six domestic and 24 international reports of haematemesis with clopidogrel through Korea Adverse Event Reporting System (KAERS) from 1989 to 2015. Reports for clopidogrel and spinal haematoma/cholecystitis/ haematemesis were identified to be statistically significant compared to all the other reports from other drugs.

This recommendation announced by MFDS was based on signal analysis evaluation process in KIDS using adverse event reports.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, April 2017

Codeine and tramadol

Restriction of use in children and advice against use in breastfeeding women

USA. The US FDA has changed the labels of prescription medicines containing codeine and tramadol to inform of the restriction of use in children and recommend against the use of codeine and tramadol medicines in breastfeeding mothers due to risk of serious adverse reactions in breastfed infants. These adverse reactions include excess sleepiness, difficulty breastfeeding or serious breathing problems that could result in death.

Codeine and tramadol are approved to treat pain, and codeine is also approved to treat cough.

The FDA reviewed adverse event reports submitted to the FDA from January 1969 to May 2015 and identified 64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years. Nine cases of serious breathing problems, including three deaths, with the use of tramadol in children younger than 18 years from January 1969 to March 2016 were also identified. The majority of serious adverse effects with both codeine and tramadol occurred in children younger than 12 years, and some cases occurred after a single dose of the medicine.

In a review of the medical literature the FDA found numerous cases of excess sleepiness and serious breathing problems in breastfed infants, including one death. A review of the available medical literature for data regarding tramadol use during breastfeeding did not reveal any cases of adverse events. However, tramadol and its active form are also present in breast milk, and tramadol has the same risks associated with ultra-rapid metabolism as codeine.

Reference:
Drug Safety Communication, US FDA, 20 April 2017 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletters No.2 and No.1, 2017, No.6 and No.1 in 2016, No.6, No.5, No.4 and No.3 in 2015, No.5 and No.4 in 2013, and No.5 in 2012 for related information)

Denosumab

Risk of multiple vertebral fractures

Japan. The MHLW and the PMDA have announced that the package insert for denosumab (Pralia®) has been updated to include the risk of multiple vertebral fractures as a clinically significant adverse reaction. The MHLW/PMDA have also advised transitioning to an alternative antiresorptive medicine if treatment with denosumab is discontinued, to prevent multiple vertebral fractures that can occur due to a temporary increase in bone resorption.

Denosumab is indicated for osteoporosis.

Off-treatment follow-up results of overseas clinical studies showed a higher incidence of multiple new vertebral fractures in patients who discontinued denosumab compared with those who discontinued placebo which led to the revision of the company core data sheet (CCDS). In addition, overseas pre-market clinical studies showed a temporary increase in bone resorption after discontinuation of denosumab treatment. The time to onset of the multiple new vertebral fractures after discontinuation of denosumab treatment found in the studies was consistent with the time to onset of the temporary increase in bone resorption. Based on these findings, the MHLW/PMDA concluded that updating the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 20 April 2017 *(www.pmda.go.jp/english/)*

Dipeptidylpeptidase-4 (DPP-4) inhibitors

Risk of arthralgia

Canada. Health Canada has updated the product safety information for all dipeptidylpeptidase-4 (DPP-4) inhibitors to include information on the risk of arthralgia (severe joint pain).

DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin and sitagliptin) are used to treat type-2 diabetes in adults. They are used along with an appropriate diet and exercise to control blood sugar. In some cases, they are used with another anti-diabetic drug.

Health Canada reviewed the potential risk of arthralgia with

the use of DPP-4 inhibitors following the identification of reports of adverse effects in the published literature and in the US FDA Adverse Event Reporting System (FAERS) database.

At the time of the review, Health Canada received 10 Canadian reports of severe joint pain and 20 international reports from the manufacturers associated with the use of a DPP-4 inhibitor (saxagliptin, sitagliptin or linagliptin).

Of all the reports, 17 noted that the patient developed joint pain within the first 30 days of taking the DPP-4 inhibitor. The majority of patients either improved or recovered from their joint pain after the treatment was stopped.

Some of the cases have also reported medical conditions that may have contributed to the joint pain including gout, pre-existing rheumatoid arthritis, Crohn's disease and obesity.

Health Canada's review of the available information concluded there is a potential link between the use of DPP-4 inhibitors and the development of severe joint pain.

Reference:
Summary Safety Review, Health Canada, 27 April 2017 *(www.hc-sc.gc.ca)*

(See WHO Pharmaceuticals Newsletters No.6, 2015: Risk of severe joint pain in Egypt and No.5, 2015: DPP-4 inhibitors for Type 2 diabetes may cause severe joint pain in the USA)

Factor VIII medicines

No clear evidence to suggest a difference in inhibitor development between plasma-derived and recombinant products

EU. The European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the prescribing information of factor VIII medicines should be updated to reflect the conclusion that there is no clear and consistent evidence of a difference in inhibitor development between classes of factor VIII medicines.

Factor VIII products replace the missing factor VIII in patients with haemophilia. Human plasma-derived factor VIII medicines are extracted from blood plasma. Recombinant factor VIII is produced from DNA technology. The body may develop inhibitors as a reaction to these medicines, particularly in patients starting treatment for the first time.

The review was started following a study which concluded that inhibitors develop more frequently in patients receiving recombinant factor VIII medicines than in those receiving plasma-derived factor VIII medicines.

The review included relevant studies which differed in their design, patient populations and findings, and the PRAC concluded that they did not provide clear evidence of a difference in the risk of inhibitor development between the two classes of factor VIII medicines.

In addition, due to the different characteristics of individual products within the two classes, the PRAC considered that evaluation of the risk of inhibitor development should be at the product level instead of at the class level. The risk for each individual product will continue to be assessed as more evidence becomes available.

Reference:
News and press release, EMA, 5 May 2017 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletter No.3, 2013: Review on the benefits and risks in previously untreated patients with haemophilia A with Kogenate® and Helixate® started in the EU)

General anaesthetic and sedation drugs

Potential risk of effects on development of children's brains

USA. The US FDA has announced that the labels for general anaesthetic and sedation medicines will be updated to include information on potential effects on brain development in children younger than three years. The updated label changes include:

- A new warning stating that exposure to anaesthetic and sedation medicines for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than three years.
- Additional information describing results of animal studies in pregnancy and the young. Exposure to general anaesthetic and sedative medicines for more than three hours can cause widespread loss of nerve cells in the developing brain, resulting in long-term negative effects on the animal's behaviour or learning in young animals.

Anaesthetic and sedative medicines are necessary for infants, children and pregnant women who require surgery or other painful and stressful procedures. In addition, untreated pain can be harmful to children and their developing nervous systems.

Reference:
Drug Safety Communication, US FDA, 27 April 2017 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletter No.1, 2017: Potential risk of effects on development of children's brains in the USA)

Ingenol mebutate

1. Risk of hypersensitivity reactions, herpes zoster and eye injury

Australia. The Therapeutic Goods Administration (TGA) has updated the Product Information for ingenol mebutate (Picato gel®) to add warnings of hypersensitivity reactions, herpes zoster and ophthalmic injury as precautions and adverse effects.

Ingenol mebutate is indicated in actinic keratosis.

The TGA investigated safety concerns relating to ingenol mebutate following reports of severe allergic reactions, herpes zoster, ophthalmic injury and local skin reactions in the United States. Some of these cases were associated with the medicine not being used in accordance with its directions for use.

The TGA investigation found that the risk of local skin reactions was well-communicated in the Product Information. However, the Product Information did not address the potential adverse events of hypersensitivity/anaphylaxis, herpes zoster reactivation or, ophthalmic injury.

Reference:
Medicines Safety Update, TGA, Vol. 8, No. 2, April-May 2017 *(www.tga.gov.au)*

Ingenol mebutate is indicated for the cutaneous treatment of nonkeratotic, non-hypertrophic actinic keratosis in adults, and is available for topical use in different strengths.

There have been reports of keratoacanthoma occurring within the area treated with ingenol mebutate, with a time to onset ranging from weeks to months.

The HPRA has advised health-care professionals to counsel patients to be vigilant for new skin lesions developing within the area treated with ingenol, and to immediately consult their doctor should any occur.

Reference:
Drug Safety Newsletter, HPRA, March 2017

Interferon alfa and interferon beta

Risk of pulmonary arterial hypertension (PAH)

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has issued instructions to update the package inserts for interferon alpha and interferon beta containing products to include the potential risk of pulmonary arterial hypertension (PAH).

Interferons are a group of glycoproteins that have immunoregulatory, antiviral and antineoplastic functions. Indications include treatment

For interferon beta, a total of 73 ADR reports with 137 adverse events were received by NPRA between 2002 to January 2016. Two reports were associated with the SOC Respiratory, Thoracic and Mediastinal Disorders, namely difficulty in breathing and sneezing.

Whilst there were no reports specifically on PAH, two cases reported patients experiencing symptoms of PAH namely, chest pain (with use of peginterferon alfa-2a) as well as oedema and abdominal distension (with interferon beta-1b).

Reference:
Reaksi Drug Safety News, NPRA, No. 34, March 2017

(See WHO Pharmaceuticals Newsletter No.6, 2016: Risk of pulmonary arterial hypertension in Canada)

Iodinated contrast medium

Potential risk of hypothyroidism

Canada. Health Canada has updated the product safety information for all iodinated contrast medium (ICM) products to include information on potential risk of hypothyroidism in certain patients (mostly infants). In addition, Health Canada will publish a Health Product Risk Communication to inform health-care professionals about