World Health Organization

WHO Pharmaceuticals NEWSLETTER

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Prepared in collaboration with the WHO Collaborating Centre for International Drug Monitoring, Uppsala Sweden

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 "drug information officers" 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:

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This Newsletter is also available on our Internet website:
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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

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Safety of Medicines

Signal

Afatinib maleate

Risk of acute pancreatitis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for afatinib maleate (Giotrif®) has been updated to include the risk of acute pancreatitis as a clinically significant adverse reaction.

Afatinib is used to treat unresectable or recurrent epidermal growth factor receptor (EGFR) mutation-positive non-small-cell-lung cancer.

A total of four cases of acute pancreatitis have been reported with the use of afatinib in Japan. Of these, a causal relationship could not be excluded in two cases. Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Precautions to the package insert have been revised to include:
Acute pancreatitis: Acute pancreatitis may occur. Patients should be carefully monitored. If abnormalities, such as abdominal pain and increased serum amylase are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Aripiprazole

Risk of impulse-control problems

USA. The US Food and Drug Administration (FDA) has issued a safety warning to patients and doctors about new impulse-control problems and use of aripiprazole.

Aripiprazole is used to treat mental disorders such as schizophrenia, bipolar disorder, Tourette's disorder, and irritability associated with autistic disorder.

Pathological gambling is already listed as an adverse effect. However, the FDA is now aware of other compulsive behaviours which have been reported with aripiprazole use such as: eating, shopping and sexual actions.

A review of the FDA Adverse Event Reporting System (FAERS) and the literature identified 184 cases of impulse-control problems reported with use of aripiprazole. In the majority of cases there were not prior histories of compulsive behaviours and the uncontrollable urges stopped once doses were reduced or medication discontinued. As a result, new warning labels about all compulsive behaviours to the drug labels and patient medication guides for aripiprazole products will be added.

(See WHO Pharmaceuticals Newsletters No.6, 2015: Risk of certain impulse control behaviours in Canada)

Reference:
Drug Safety Communication, US FDA, 3 May 2016 (*www.fda.gov*)

Celecoxib

Risk of serious heart and stroke adverse effects

Canada. Health Canada has announced that the prescribing information for celecoxib will be updated to include warnings of an increased risk of serious heart and stroke related adverse effects in doses greater than 200mg per day.

Celecoxib is used for relief of symptoms of osteoarthritis, adult rheumatoid arthritis, and ankylosing spondylitis. It is also indicated for the short-term management of moderate to severe acute pain, for example, following dental extraction.

The regulatory action follows results of a review of scientific and medical literature conducted by Health Canada. Health Canada concluded that there is an increased risk of serious heart and stroke related adverse effects linked with use of celecoxib at doses greater than 200 mg per day and the risk may be higher in patients taking the drug for over 18 months. At the time of the review, Health Canada received 39 cases of death due to heart and stroke related adverse effects reported with use of celecoxib.

Health Canada has determined that the overall benefits of celecoxib continue to outweigh the risks, when used as recommended. There is currently an ongoing trial being carried out to study the relative cardiovascular safety profile of different doses of celecoxib, ibuprofen and naproxen.

Reference:
Summary Safety Review, Health Canada, 11 April 2016 (*www.hc-sc.gc.ca*)

Chlorhexidine antiseptic non-prescription topical products

Serious allergic reactions

Canada. Health Canada has conducted a safety review which shows that topical chlorhexidine may cause serious allergic anaphylactic reactions when used in the mouth, on open wounds, or

immediately before or during surgery.

Chlorhexidine topical products are available without a prescription at concentrations of 2-4% in various formulations such as creams, liquids, gels and sprays. They are used as a topical antiseptic to reduce the risk of bacterial infection.

Symptoms of a serious allergic reaction, including anaphylaxis, may include itchy hives with swelling of the face, eyes, lips, mouth or throat; difficulty breathing; throat tightness or hoarseness; and fainting. An anaphylactic reaction is a serious and potentially life-threatening hypersensitivity reaction.

The review was triggered by published cases of serious allergic reactions linked to the use of topical chlorhexidine. At the time of the review, Health Canada had received 53 reports of serious allergic reactions with use of non-prescription topical chlorhexidine products, of which three were anaphylactic reactions.

Health Canada's Antiseptic Skin Cleansers monograph already requires that the labelling for non-prescription topical chlorhexidine products include a warning statement to minimize the risk of allergic reactions. Health Canada will work to update the product information with these new findings.

Reference:
Summary Safety Review, Health Canada, 13 May 2016 (*www.hc-sc.gc.ca*)

Denosumab

Contraindicated in patients with unhealed lesions from dental or oral surgery

Australia. The Therapeutic Goods Administration (TGA) has announced that the Australian Product Information for denosumab (Xgeva®) will be updated to include that denosumab is contraindicated in patients with unhealed lesions from dental or oral surgery due to increased risk of osteonecrosis of the jaw.

The lower strength preparations of denosumab (Prolia®) are used to treat osteoporosis in postmenopausal women, and osteopaenia in men who are receiving androgen deprivation therapy for non-metastatic prostate cancer. The higher strength preparation (Xgeva®) is used for the prevention of skeletal/related events in adults with bone metastases from solid tumours.

Osteonecrosis of the jaw is a known adverse event associated with denosumab. The product information for denosumab includes this adverse effect. Following the TGA review, and similar regulatory actions in the United Kingdom, the TGA has worked with the sponsor of denosumab brand to add the contradiction to the Australian product information.

(See WHO Pharmaceuticals Newsletters No.4, 2015: further measures to minimise risk of osteonecrosis of the jaw in the United Kingdom)

Reference:
Medicines Safety Update, TGA, 2 April 2016 (*www.tga.gov.au*)

Edoxaban tosilate hydrate

Risk of hepatic function disorder, jaundice

Japan. The MHLW and the PMDA have announced that the package insert for edoxaban tosilate hydrate (Lixiana®) will be updated to include risk of hepatic function disorder, jaundice as clinically significant adverse reactions.

Edoxaban tosilate hydrate is used to reduce the risk of: ischemic stroke and systemic embolism in patients with non-valvular arterial fibrillation; and venous thromboembolism in patients undergoing certain lower limb orthopaedic procedures (e.g. total knee and/or hip replacement, hip fracture surgery). It is also used to treat and prevent relapse of venous thromboembolism.

A total of five cases associated with hepatic function disorder and jaundice have been reported in Japan, of which a causal relationship to the product could not be ruled out. Following an investigation of available evidence and advice from experts the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Erlotinib

Restricted to patients with epidermal growth factor receptor (EGFR) mutations

Australia. The TGA has announced that the indication for erlotinib (Tarceva®) will be restricted to patients with epidermal growth factor receptor (EGFR) mutations when used for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not progressed on first-line chemotherapy.

Erlotinib is used to treat certain types of NSCLC and can also be used in combination with gemcitabine for the treatment of pancreatic cancer.

A study found that overall survival was not superior in patients randomised to receive

maintenance erlotinib followed by chemotherapy upon progression, compared to patients randomised to receive maintenance placebo followed by erlotinib upon progression. Hence, there is no demonstrable benefit of first-line maintenance treatment versus second-line treatment with erlotinib for patients whose tumours do not harbour an epidermal growth factor receptor-activating mutation. Consequently, the indication for this medicine has been updated.

Reference:
Medicines Safety Update, TGA, 2 April 2016 (*www.tga.gov.au*)

Febuxostat

Risk of heart failure

Canada. Health Canada has requested manufacturers of febuxostat to revise the prescribing information to include a statement regarding the potential increased risk factors of heart failure in patients with pre-existing cardiovascular disease and/or risk factors.

Febuxostat (Uloric®) is used to treat gout. As of March 2015, there were 32 cases of heart failure suspected to be linked to use of febuxostat reported in the WHO global database of Individual Case Safety Reports, VigiBase®. This triggered Health Canada to conduct a safety review. The indication for which febuxostat is used, hyperuricaemia is linked to an increased risk of cardiovascular disease, and is a possible confounding factor when investigating heart failure as a potential adverse drug reaction, however this does not rule out the potential association of febuxostat and onset or worsening heart failure.

Reference:
Summary Safety Review, Health Canada, 1 April 2016 (*www.hc-sc.gc.ca*)

Fexofenadine hydrochloride/ pseudoephedrine hydrochloride combination

Risk of acute generalised exanthematous pustulosis

Japan. The MHLW and the PMDA have announced that the package insert for fexofenadine hydrochloride/ pseudoephedrine hydrochloride combination preparation (Dellegra®) will be updated to include acute generalised exanthematous pustulosis as clinically significant adverse reactions.

This preparation is used to treat allergic rhinitis. Cases of acute generalised exanthematous pustulosis have been reported with use of the fexofenadine/ pseudoephedrine preparation in Japan and other countries. The core datasheet prepared by the marketing authorization has been updated. Following an investigation of available evidence and advice from experts the MHLW/PMDA concluded that revision of the package insert was necessary.

The following text will be added to the package insert:

Acute generalised exanthematous pustulosis: Acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored. If symptoms, such as pyrexia, erythema and many small pustules are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Fluoroquinolone antibacterial drugs

Restricting use

USA. The US FDA has issued advice based on the benefit-harm assessment for the use of fluoroquinolone antibacterials and in certain types of infections.

A FDA safety review has shown that systemic use of fluoroquinolones is associated with serious adverse effects which involve tendons, muscles, joints, nerves and central nervous system. These adverse effects outweigh the benefits of fluoroquinolone when used for acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections.

The FDA recommends that fluoroquinolones should be reserved for those with no alternative treatment options.

The drug labels and medication guides for all fluoroquinolone antibacterial medication will be updated to reflect this new safety information.

Reference:
Drug Safety Communication, US FDA, 12 May 2016 (*www.fda.gov*)

Gabapentin

Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for gabapentin tablets and syrup will be updated to include anaphylaxis as a clinically significant adverse reaction.

Gabapentin is used in Japan for: the treatment of partial seizures in patients with

epilepsy for whom other antiepileptic medications are not sufficiently effective (in combination with other antiepileptic medication); and for moderate to severe restless legs syndrome.

Although no cases of anaphylaxis have been reported with the use of gabapentin in Japan, there have been cases reported in other countries. Following an investigation of available evidence and advice from experts the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Hepatitis C antivirals

Risk reactivation of hepatitis B virus

Japan. The MHLW and the PMDA have announced that the package insert for various hepatitis C antivirals (telaprevir, simeprevir sodium, daclatasvir, asunaprevir, vaniprevir, sofosbuvir, ledipasvir acetonate/ sofosbuvir and ombitasvir) will be updated to include precautions with use in patients currently infected or with a history of hepatitis B virus infection.

Hepatitis C antivirals are used to improve viraemia in patients with chronic hepatitis C infections. Different medications are used for specific serogroups and genotype for example sofosbuvir is used in patients with serogroup 2 (genotype 2) and asunaprevir in serogroup 1 (genotype 1).

Cases of reactivation of hepatitis B reported with simeprevir, daclatasvir, asunaprevir, sofosbuvir, and ledipasvir acetonate/sofosbuvir have occurred in Japan as well as other cases outside Japan. It is thought that the increase in hepatitis B viral load is associated with decrease in hepatitis C viral load after initiating treatment with hepatitis C direct acting antivirals. Hepatitis C direct acting antivirals, for which there were no reports of reactivation of hepatitis B virus worldwide and in Japan, may carry the same risk.

Following an investigation of available evidence and advice from experts the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 18 May 2016 (*www.pmda.go.jp/english/*)

Ibrutinib

Risk of hepatotoxicity

Australia. The TGA has announced that the product information for ibrutinib has been updated with new safety information relating to the risk of hepatotoxicity.

Ibrutinib (Imbrivica®) is used to treat certain types of blood cancers such as mantle cell lymphoma and chronic lymphocytic leukaemia (including small lymphocytic lymphoma).

There have been isolated case reports of severe hepatotoxicity in post-marketing settings for patients being treated with ibrutinib. The time to onset was variable ranging from five days to three months after starting ibrutinib.

Health-care professionals are advised to monitor liver function and therapy should be withheld if patients develop liver function abnormalities (≥that Grade 3 elevations) with or without a rise in bilirubin. Ibrutinib can be reinitiated once symptoms of hepatotoxicity decrease to Grade 1 or baseline. If toxicity reoccurs the dose should be reduced by one 140 mg capsule. A second dose reduction may also be considered if necessary, however, if toxicity continues after the second dose reduction, ibrutinib should be discontinued.

Reference:
Medicines Safety Update, TGA, 2 April 2016 (*www.tga.gov.au*)

Idelalisib

Risk of serious infection and deaths

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has issued interim treatment recommendations for idelalisib and risk of serious and fatal infections.

Idelalisib is used to treat chronic lymphocytic leukaemia and follicular lymphoma.

The recommendations were formed in light of findings from clinical trials assessing the use of idelalisib in conditions outside its currently authorized drug combinations or indicted populations (e.g. standard therapy in first-line chronic lymphocytic leukaemia and to the treatment of relapsed indolent non-Hodgkin lymphoma, small lymphocytic lymphoma).

There were an increased number of deaths in the idelalisib treatment group compared with placebo, mainly due to infections such as cytomegalovirus. Precautionary measures have been issued in a letter sent to health-care professionals.

(See WHO Pharmaceuticals Newsletters No.2, 2016: risk of a particular type of lung infection (pneumocystis jirovecii pneumonia) in the EU)

Reference:
Drug Safety Update, MHRA, Volume 9, issue 10: 10 May 2016 (*www.gov.uk/mhra*)

Ipilimumab

Risk of drug reaction with eosinophilia and systemic symptoms (DRESS)

Canada. Health Canada has announced that the prescribing information for ipilimumab (Yervoy®) has been updated to include the potential risk of eosinophilia and systemic symptoms (DRESS).

Ipilimumab is used to treat malignant melanoma. DRESS is a group of rare and serious potentially life-threatening adverse reaction to medications. Symptoms include: fever, severe skin rash, swollen face with peeling of skin over large areas of the body.

Health Canada conducted a safety review after identifying a possible risk of DRESS with ipilimumab during routine review of published case reports. At the time of the review there were three cases of DRESS in the WHO global database for Individual Case Safety Reports, VigiBase® reported with ipilimumab use. Health Canada concluded that there might be a link. Ipilimumab affects the immune system in a way that may increase the chances for DRESS to develop.

Reference:
Summary Safety Review, Health Canada, 22 April 2016 (*www.hc-sc.gc.ca*)

Levodopa containing products

Risk of angle closure glaucoma

Japan. The MHLW and the PMDA have announced that the package insert for preparations containing levodopa will be updated to include angle closure glaucoma as a clinically significant adverse reaction.

Levodopa is used for treatment and prophylaxis of symptoms associated with Parkinson's disease/Parkinson's syndrome. Such symptoms include: akinesia, muscle rigidity, tremor, impaired activities of daily living, mask-like faces, gait disturbance, language disorder, abnormal posture, pulsion, oily face, dysgraphia, psychiatric symptom and ptyalism.

There have been two cases of angle closure glaucoma reported with the use of levodopa/benserazide hydrochloride combination in Japan for which a causal relationship to the product could not be ruled out. Following an investigation of available evidence and advice from experts the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Metformin

Warnings for certain patients with reduced kidney function

USA. The US FDA has requested that the recommendations for use in product labels for metformin-containing medicines are changed to expand its use in patients with mild or moderately impaired kidney function.

Metformin is used to lower blood glucose levels in patients with type-2 diabetes alongside diet and exercise. It is available as a single product or in combination with other medicines used to treat diabetes. Diabetes can lead to kidney damage, hence current labelling strongly recommends against use of metformin in patients with renal impairment due to risks of developing lactic acidosis (build-up of lactic acid in the blood).

The request follows a review of studies published in the medical literature which concluded that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function.

Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2 and initiation of metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended. Further treatment recommendations based on the eGFR are provided in the product label.

Reference:
Drug Safety Communication, US FDA, 8 April 2016 (*www.fda.gov*)

Moviprep® combination oral solution

Risk of loss of consciousness

Japan. The MHLW and the PMDA have announced that the package insert for Moviprep® combination oral solution (sodium chloride/potassium chloride/sodium sulfate anhydrous/macrogol 4000/ ascorbic acid/sodium L-ascorbate) will be updated to include syncope and loss of consciousness in the clinically significant adverse reaction section.

Moviprep® combination is used as a pretreatment prior to colonoscopy or large intestine surgery, to eliminate intestinal contents.

There have been nine cases of syncope or loss of consciousness reported with the use of Moviprep®, for which a causal relationship could not be eliminated in six of the cases (in Japan). Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

The following will be added to the package insert:

Syncope and loss of consciousness:
Syncope and loss of consciousness may occur, and there have been reports of cases associated with decreased blood pressure. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures should be adopted. For home use, patients should be instructed with references to "important precautions" section.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Olanzapine

Risk of serious skin reactions

USA. The FDA has announced that the drug labels for olanzapine containing products will be updated to include an additional warning describing Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Olanzapine is used to treat mental health disorders such as schizophrenia and bipolar disorder.

DRESS is a severe condition that usually starts as a rash and spreads to all parts of the body. Symptoms include fever, swollen lymph glands and swelling in the face.

To date there have been 23 cases of DRESS reported with olanzapine in the FDA adverse event reporting system.

The FDA recommends that health-care professionals stop treatment with olanzapine immediately if DRESS is suspected and they should inform patients of the signs and symptoms of severe skin reactions, instructing them to seek medical care immediately, should they occur.

Reference:
Drug Safety Communication, US FDA, 10 May 2016 (*www.fda.gov*)

Oseltamivir phosphate

Risk of ischaemic colitis

Japan. The MHLW and the PMDA have announced that the package insert for oseltamivir phosphate (Tamiflu®) capsule and syrup preparations will be updated to include ischaemic colitis as a clinically significant adverse reaction.

Oseltamivir is used for treatment and prophylaxis of infections with type A and B influenza virus.

A total of four cases of ischaemic colitis have been reported with use of oseltamivir in Japan, of which the causality in one case could not be ruled out. Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Peramivir hydrate

Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for peramivir hydrate preparations for infusion (Rapiacta®) will be updated to include shock and anaphylaxis as clinically significant adverse reactions.

Peramivir hydrate is used for treatment of infections with type A and B influenza virus. In Japan there have been a total of 17 cases of anaphylaxis reported with use of peramivir, of which the causal relationship of eight cases (one fatal) could not be ruled out. Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

The following text will be added as a precaution in the package insert:
Shock and anaphylaxis may occur. During the administration, patients should be carefully monitored under the conditions where emergency treatment is available. Shock and anaphylaxis may occur even after discontinuation of administrations, and therefore, caution should be exercised.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Pomalidomide

Risk of hepatitis B reactivation

The United Kingdom. The MHRA has issued advice to health-care professionals recommending the establishment of patients' hepatitis B status before initiating treatment with pomalidomide.

Pomalidomide (Imnovid®) combined with dexamethasone is indicated for adults with relapsed and refractory multiple myeloma who have received at least two previous treatment regimens, including lenalidomide and bortezomib, and who have shown disease progression on the last therapy.

A review by EU medicines regulators of clinical studies and cases of suspected adverse drug reactions reported by health-care professionals and in the literature has concluded that pomalidomide can cause hepatitis B reactivation. The review assessed cases worldwide up to 7 August 2015, and identified five patients who developed hepatitis B reactivation while receiving treatment with pomalidomide.

'Dear doctor' letters have been issued to health-care professionals.

(See WHO Pharmaceuticals Newsletters No.5, 2015: risk of hepatic function disorder and jaundice in Japan)

Reference:
Drug Safety Update, MHRA, Volume 9, issue 10: 10 May 2016 (*www.gov.uk/mhra*)

Proton pump inhibitors

Risk of *Clostridium difficile* infection

Canada. Health Canada has concluded that the evidence to suggest an association between the use of proton pump inhibitors and *Clostridium difficile* infection is limited.

Proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole and dexlansoprazole) are used to reduce stomach treatment of heartburn and stomach/intestinal ulcers.

Symptom of *Clostridium difficile* infection range from mild diarrhoea to life-threatening multi-organ failure, especially in elderly patients with other pre-existing conditions.

The safety review was initially conducted in 2012, and revisited following the emergence of new information in the scientific literature. The literature reports of *Clostridium difficile* infection and/or recurrence in those exposed to a proton pump inhibitor, included patients with other known risk factors that could have contributed to the development of the infection.

At the time of this review, Health Canada had received a total of eight additional reports of *Clostridium difficile* infection in patients who were using proton pump inhibitors following the two received in 2012. There were a total of 233 reports of *Clostridium difficile* infection in patients who were using proton pump inhibitors in the WHO global database of Individual Case Safety Reports (ICSRs), VigiBase®.

The prescribing information for proton pump inhibitors will be updated to provide more information on various risk factors and to remind health-care professionals and patients to use the lowest dose of proton pump inhibitor for the shortest duration appropriate to the condition being treated.

Reference:
Summary Safety Review, Health Canada, 6 May 2016 (*www.hc-sc.gc.ca*)

Rivaroxaban

Risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced that the package insert for rivaroxaban (Xarelto®) will be updated to include risk of thrombocytopenia as a clinically significant adverse reaction.

Rivaroxaban is used to reduce the risk of ischemic stroke and systemic embolism in patients with nonvalvular arterial fibrillation and to treat and prevent the relapse of deep vein thrombosis and pulmonary thromboembolism.

A total of 15 cases of thrombocytopenia reported with the rivaroxaban originate from Japan. The causal relationship to rivaroxaban could not be ruled out in seven of these cases. Other cases have been reported in countries other than Japan. Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Saxagliptin and alogliptin containing products

Risk of heart failure

USA. The US FDA has requested that a new safety warning is added to the product labels of saxagliptin- and alogliptin-containing products to advise on the risk of heart failure.

Saxagliptin and alogliptin are used to lower blood glucose levels in combination with diet and exercise in patients with type 2 diabetes.

The warning was issued following the evaluation of two clinical trials conducted in patients with heart disease, and discussions at the FDA Endocrinologic and Metabolic Drugs Advisory Committee meeting in April 2015. The trials showed a higher number of hospitalization in patients who were exposed to saxagliptin- or alogliptin-containing medicines compared to patients who took placebo.

The recommendations advise health-care professionals to consider discontinuing saxagliptin- and alogliptin-containing products in patients who develop heart failure and monitor their diabetes control. If a patient's blood sugar level is not well-controlled with their current treatment, other diabetes medicines may be required.

(See WHO Pharmaceuticals Newsletters No.2, 2014: Saxagliptin review heart failure risk in USA)

Reference:
Drug Safety Communication, US FDA, 4 April 2016 (*www.fda.gov*)

Trabectedin

Risk of cardiac dysfunction

Japan. The MHLW and the PMDA have announced that the package insert for trabectedin (Yondelis®) will be updated to include cardiac dysfunction as a clinically significant adverse reaction. In addition precautions on administration in patients with previous anthracycline exposure or those with cardiac dysfunction will be added.

Trabectedin is used for treatment of soft tissue sarcoma. The precautions follow results of a phase III clinical trial, which showed that patients treated for soft tissue sarcoma with prior exposure to anthracyclines had a higher incidence rate of cardiac dysfunction in the trabectedin group than in the control group.

Trabectedin is often administered to patients who have received prior anthracyclines, which have cardiotoxicity, or those with cardiac dysfunction. More careful administration is required in these patients.

The Company core datasheet (CCDS) and label in the United States have also been updated following results of this trial.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Vildagliptin and sitagliptin phosphate hydrate

Risk of pemphigoid

Japan. The MHLW and the PMDA have announced that the package inserts for vildagliptin (Equam and Equmet combination®) and sitagliptin phosphate hydrate (Glactiv® and Januvia®) preparations will be updated to include risk of pemphigoid as a clinically significant adverse reaction.

Vildagliptin and sitagliptin phosphate hydrate are used to treat type 2 diabetes mellitus, and if necessary and judged appropriate, vildagliptin is combined with metformin for this indication.

A total of 28 cases associated with pemphigoid have been reported with use of vildagliptin and seven with use of sitagliptin in Japan. Of these a causal relationship to vildagliptin and sitagliptin could not be ruled out in eight and seven cases respectively.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Precautions to the package insert have been revised to include:
Pemphigoid: Pemphigoid may occur. If blister, erosion or other signs and symptoms are observed, patients should be referred to a dermatologist and appropriate measures such as discontinuation of administration should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 21 April 2016 (*www.pmda.go.jp/english/*)

Aflibercept

Risk of systemic adverse effects: insufficient evidences

Canada. Health Canada has announced the result of a safety review which shows that there is insufficient evidence to conclude the association of systemic adverse effects with use of aflibercept (Eylea®).

Aflibercept is administered via intravitreal injection and is used to treat vision impairment caused by diseases of the retina (e.g. diabetic macular oedema).

The review was conducted to investigate the risk of systemic adverse effects (in areas of the body outside the eye) associated with aflibercept, following results of three scientific studies.

The studies observed that aflibercept is removed from the body's blood stream slower than alternative products which could possibly lead to systemic toxicity. At the time of the review, Health Canada received four reports of systemic side effects related to bleeding. These reports either involved cases of bleeding at the injection site (haemorrhage into the eye) or did not contain enough information to assess causality.

Health Canada concluded that there was not enough evidence to support that aflibercept is associated with greater risk of systemic adverse effects. The potential for experiencing systemic adverse effects is already mentioned in the Canadian product information for aflibercept.

Reference:
Summary Safety Review, Health Canada, 10 May 2016 (*www.hc-sc.gc.ca*)

Anticholinergic Drugs

Possible cognitive problems in the elderly

Saudi Arabia. The Saudi Food and Drug Authority (SFDA) has notified health-care professionals that certain anticholinergic drugs might be associated with cognitive impairment and an increased risk of memory loss, known as dementia, in elderly patients.

Anticholinergic drugs are widely used for treatment of various clinical conditions including vomiting, gastrointestinal spasms, bladder problems, Parkinson's disease, and depression.

In 2015, the SFDA reviewed all available evidence on the association between anticholinergic drugs and cognitive impairment in older adults. The SFDA concluded that there is a potential risk of cognitive impairment and dementia with long-term use of anticholinergic drugs and the general awareness about this risk is low.

The SFDA has advised health-care professionals to consider the lowest effective dose of anticholinergic drugs with regular monitoring for signs of confusion or dementia in elderly patients particularly when prescribing any of these drugs for a long-term use.

Reference:
Saudi Vigilance, Saudi Food and Drug Authority, 24 May 2016

Brintellix® (vortioxetine)

Brand name change to avoid confusion with Brilinta® (ticagelor)

USA. The US FDA has approved the brand name change for Brintellix® (vortioxetine) to prevent confusion with Brilinta® (ticagrelor).

Vortioxetine is used to treat depression whereas ticagrelor is a blood-thinning agent.

There have been continuous reports of prescribing and dispensing errors between these two products. The brand name Brintellix® will be changed to Trintellix® and there is expected to be a lag time associated with manufacturing bottles that contain the new brand name. The FDA has made recommendations on how to reduce risk of name confusion during the transition period.

(See WHO Pharmaceuticals Newsletters No.5, 2015: Brintellix® (vortioxetine) and Brilinta® (ticagrelor), Similar drug names leading to potential medication error in USA)

Reference:
Drug Safety Communication, US FDA, 2 May 2016 (*www.fda.gov*)

Canagliflozin

Risk of leg and foot amputations: under investigation

USA. The US FDA has issued a safety alert informing the public of investigations into the potential risk in leg and foot amputations with use of canagliflozin (Invokana® and Invokamet®).

Canagliflozin is used in combination with diet and exercise to lower blood sugar in adults with type 2 diabetes. It is available in an individual preparation and as a combination with metformin.

An increased risk of leg and foot amputations was identified in the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial.

This risk has not been observed in a second similar trial, the CANVAS-R.

Health-care professionals are advised to follow recommendations in the canagliflozin drug labels, and to monitor patients for signs and symptoms such as any new pain or tenderness, sores or ulcers, or infections in their legs or feet.

The FDA continues to evaluate this safety issue and will update the public when more information is obtained.

Reference:
Drug Safety Communication, US FDA, 18 May 2016 (*www.fda.gov*)

Fluconazole

Risk of miscarriage in pregnancy: under investigation

USA. The US FDA is investigating results from a Danish study which suggests that there is an increased risk of miscarriage with the use of oral fluconazole (Diflucan®) during pregnancy.

Oral fluconazole is used to treat yeast infections of the vaginal area, mouth and oesophagus.

It is also used to treat C*ryptococcal* meningitis and is often used prophylactically in immunocompromised patients.

The FDA advises cautious prescribing of oral fluconazole in pregnancy, until the FDA reviews this study and other available data.

Reference:
Drug Safety Communication, US FDA, 26 April 2016 (*www.fda.gov*)

Pertuzumab

Risk of Stevens-Johnson Syndrome: limited evidence

Canada. Health Canada has concluded that the evidence to support a link between the use of pertuzumab (Perjeta®) and the risk of Stevens-Johnson Syndrome is limited.

Pertuzumab is used in combination with other treatments to treat patients with breast cancer that has spread to other parts of the body.

During routine review of information received from the manufacturer, Health Canada identified a possible risk of Stevens-Johnson Syndrome which triggered Health Canada to conduct a safety review.

At the time of the review there were no reports of Stevens-Johnson Syndrome linked to use of pertuzumab that originated from Canada. In addition, there were no reports identified in the literature. The reports received from the manufacturer were limited by missing information and presence of other contributing factors. The Canadian prescribing information already includes information regarding Stevens-Johnson Syndrome in one or two other medications that are used in combination with pertuzumab. Health Canada has asked the manufacturer to continue monitoring for this risk worldwide.

Reference:
Summary Safety Review, Health Canada, 4 April 2016 (*www.hc-sc.gc.ca*)

A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from individual case safety reports (ICSRs) available in VigiBase®, the WHO international database of suspected adverse drug reactions. The database contains over 13 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase® is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase® data is performed in accordance with UMC's current routine signal detection process.
More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 29). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC's vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information, visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

Dabigatran and thromboembolism: analysis of case histories for risk factors

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Summary

The combination of dabigatran and the WHO-ART preferred term thromboembolism stands out disproportionately in VigiBase®, the WHO global database of ICSRs. As of 1 October 2015, a widened search identified 734 ICSRs for dabigatran under the High Level Term (HLT) thromboembolism, and 1,193 under the HLT thrombosis. These terms included both venous and arterial events. Dabigatran is a direct thrombin inhibitor, the pivotal protease of the coagulation cascade, and is indicated for the prevention of thromboembolic events both in patients with non-valvular atrial fibrillation (NVAF) and after major orthopaedic surgery. From clinical trials of efficacy these events are not unexpected. In addition, there are five published case reports in which patients unexpectedly developed atrial thrombosis on dabigatran therapy, and one more published report described dabigatran failure in preventing deep vein thrombosis. Reports in VigiBase® were therefore assessed to determine the circumstances in which dabigatran became ineffective in clinical practice and whether there were modifiable risk factors. Because of the large number of reports a decision was made to examine a sample of reports that were the most informative from four groups of reports:

(1) reports with the indication prevention of venous thromboembolism (VTE) and adverse drug reaction (ADR) terms (a) arterial thrombosis or embolism and (b) venous thrombosis or embolism and

(2) reports with the indication NVAF and ADR terms (a) and(b) as for group (1).

A high proportion of patients had known risk factors for thrombosis in addition to the indications for dabigatran. Information in the reports also suggested that inappropriately low dose, concomitant use of pro-thrombotic agents or use of proton pump inhibitors may contribute. Dabigatran plasma concentration monitoring may be appropriate in a subgroup of patients.

Introduction

Dabigatran is a direct thrombin inhibitor. Thrombin is the pivotal protease of the coagulation cascade by enabling transformation of fibrinogen to fibrin, and therefore inhibition of thrombin prevents development of thrombosis and increases the risk of bleeding. The anti-coagulation effect is in direct correlation to the plasma concentration of dabigatran. The mean half-life is 8.8 hours. Renal excretion is the dominant elimination pathway; consequently, half-life is prolonged with decreased renal function. Dabigatran is taken as the prodrug dabigatran etexilate which is an efflux pump P-glycoprotein substrate. Thus, dabigatran plasma levels were elevated when given following known P-glycoprotein inhibitors such as amiodarone and verapamil, and reduced with inducers such as rifampicin. A number of proton pump inhibitors interact with P-glycoprotein, and in one study the mean area under the curve for dabigatran was reduced by 30% with pantoprazole. Unlike the

vitamin K antagonists, repeated monitoring for anticoagulant effect is considered unnecessary for dabigatran. Dabigatran is approved for prevention of stroke and systemic embolism in adult patients with NVAF and additional risk factors for stroke; prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement surgery; and more recently, treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism. Dose adjustment is required in patients above the age of 75 or 80 years according to the indication, patients with reduced kidney function, and other patients who are at increased risk of bleeding. The recommended daily doses of dabigatran for NVAF are 300 mg and, for older patients and patients with creatinine clearance 30 to 50 ml/min, 220 mg daily in two divided doses. For prevention of VTE after major orthopaedic surgery the corresponding recommended daily doses are 220 mg and 150 mg. Medical knowledge and adherence to treatment are needed for successful use of these drugs in clinical practice. The most commonly (>15%) reported adverse reactions are gastritis-like symptoms and bleeding.[1-4]

Thrombosis, venous or arterial, is the formation of a blood clot (thrombus) in a blood vessel or the heart. The thrombus, if detached, travels through the bloodstream and may occlude a vessel distant from the original site. This phenomenon is referred to as thromboembolism. The most common form of thromboembolism is venous thromboembolism when a blood clot that forms in a deep vein migrates to another location e.g., a deep vein thrombus in the leg may break off and cause a pulmonary embolus. The risk of thrombosis is influenced by both genetic and environmental factors. Trauma (particularly after surgery or parturition), immobility, cardiac and vascular disorders, obesity, coagulation disorders, age over 65 years, sepsis, medical conditions such as malignancy, and medications such as hormonal therapy, are predisposing causes of venous thrombosis. Likewise atherosclerosis is the major risk factor for arterial thrombosis.[5,6]

Clinical trial data for dabigatran have provided a rate for lack of efficacy.[7-12] Subsequently, case reports of thromboembolic events have been published where the authors have expressed concern and have discussed various hypotheses about why these events occurred.[13-17] Our study of case reports in VigiBase® was undertaken to ascertain whether investigation of a larger number of reports than those published would help identify circumstances and modifiable risk factors for thromboembolism occurring during dabigatran treatment in clinical practice.

Literature and Labelling

The product literature does not refer to thromboembolism as an adverse reaction as dabigatran is indicated for preventing such events.[1]

In the RE-MODEL trial (knee replacement), dabigatran treatment was for 6-10 days, while in the RE-NOVATE trial (hip replacement) it was for 28-35 days; respectively, 2,076 and 3,494 patients were treated. The rate of symptomatic pulmonary embolism during treatment was low, both with the 220 mg daily dose (0.0% for knee replacements, 0.4% for hip), and the 150 mg daily dose (0.1% for knee replacement and 0.1% for hip). The rate of symptomatic deep vein thrombosis was 0.1% for knee replacement and 0.5% for hip surgery within the 220 mg group; whereas recorded rates were 0.4% and 0.8% within the 150 mg daily dose group respectively. Similarly, the rate of symptomatic VTE during the three-month RE-NOVATE II study period was low (0.3%) and comparable with that reported in RE-NOVATE.[7-9]

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study for patients with NVAF at moderate to high risk of stroke and systemic embolism. The primary objective in this study was to determine if dabigatran etexilate was non-inferior to warfarin in reducing the occurrence of the composite endpoint stroke and systemic embolism. The incidence of ischaemic or unspecified stroke was 2.64% at the 220 mg and 1.83% at the 300 mg dabigatran daily dose. Half of the study patients continued into the RELY-ABLE two-year follow-up study. Pulmonary embolism was reported with a very low frequency of 0.12 to 0.15% per year in the RELY trial, and this is consistent with the rate in the RELY-ABLE trial. In addition, symptomatic "deep vein thrombosis" was regarded as a safety outcome in the RELY-ABLE trial and occurred with a frequency of 2/2914 (0.07%) in the dabigatran 220 mg daily group compared to 6/2937 (0.20%) in the 300 mg daily group.[10,11]

In the 2008 European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) Assessment Report, the event "deep vein thrombosis" is described among the most frequent adverse events in the pivotal studies of venous thromboembolism prevention after knee and hip total replacement with a frequency of 9.3% and 6.4% for dabigatran 150 mg and 220 mg daily respectively. In addition, deep vein thrombosis was reported among the most common reasons for discontinuation due to adverse events.[12]

Shah et al. described left atrial thrombus formation with consequent cerebrovascular accident in a 60-year-old man on dabigatran therapy. This patient had a past medical history of hypertension, coronary artery disease, chronic atrial fibrillation, and stroke. They speculated that lack of patient adherence may have decreased the bioavailability and effectiveness of dabigatran.[13]

Sharma et al. described two cases of dabigatran failure leading to left atrial thrombosis. One patient suffered a stroke due to cardiac embolism ten weeks after dabigatran therapy was started. This patient had a history of congestive heart failure. The other patient had a concomitant active lung cancer. They speculated that the "downstream" single-point blockade of the coagulation cascade (at the level of thrombin) may incite a compensatory increase in the "upstream" coagulation factor levels. At the same time they suggested that the absence of routine monitoring could prevent diagnosis of subtherapeutic drug levels.[14]

There are two more cases in the literature describing atrial thrombosis[15,16]: in these cases we consider the risk may have been increased by the presence of valvular atrial fibrillation in one and the concomitant use of lansoprazole in the other.

Finally, one case report described dabigatran failure in preventing recurrent deep vein thrombosis in an 80-year old patient. This patient had a history of paroxysmal atrial fibrillation ten years prior and several risk factors: intensive parachuting career, venous insufficiency, three past events of DVT, insertion of an inferior vena cava filter (18 years prior), mild obesity and the presence of a pacemaker.[17]

Reports in VigiBase®

As of 1 October 2015 there were 1,826 reports for dabigatran in VigiBase®, the WHO international database of suspected adverse drug reactions, with the WHO-ART High Level Terms (HLT) thrombosis (1,193 reports) and thromboembolism (734); a total of 101 reports overlap both HLTs. The HLT thrombosis includes the following preferred terms (PTs): deep vein thrombosis (531 reports), thrombosis (609) and arterial thrombosis (74). The HLT thromboembolism includes the PTs thromboembolism (715) and embolism (20). The reports were submitted worldwide but half of them came from the United States.

In order to understand why thrombosis had developed in these patients we decided to systematically investigate venous and arterial thrombotic and/or embolic events separately, in correlation with dabigatran therapeutic indications. The aim was to see if there was a range of risk factors some of which may be modifiable. Case reports were first selected on the indication. Two indications were chosen according to the product information of the drug: (1) non-valvular atrial fibrillation (NVAF), and (2) prevention of venous thromboembolism (VTE) after major orthopaedic surgery.

There were thus four groups of reports:

1a. Indication - Prevention of VTE
ADR terms - arterial thrombosis or embolism

1b. Indication - Prevention of VTE
ADR terms - venous thrombosis or embolism

2a. Indication - NVAF
ADR terms - arterial thrombosis or embolism

2b. Indication - NVAF
ADR terms - venous thrombosis or embolism

Reports in VigiBase® are of variable quality and completeness. Some contain narrative and some do not. A measure of completeness of reports has been developed by Uppsala Monitoring Centre.[18] Because of the large number of reports of thromboembolism associated with dabigatran it was decided to select reports from each of the four groups listed that were likely to be the most informative, based on their vigiGrade completeness score[18] (ranging from 0.8 to 1.0) and presence of a narrative. Exclusions were suspected duplicates, and reports which on closer inspection did not fit the indication criteria or where it was not clear if the suspected ADR was arterial or venous.

1a. Venous thromboembolism prevention after orthopaedic surgery and WHO-ART PTs arterial thrombosis or embolism

Only five case reports were identified with indications and ADR terms that fitted the criteria out of the 23 reports found in VigiBase®. Patients were all aged over 59 years and were predominantly male. Only one case provided information regarding duration of dabigatran use to reaction onset (time to onset), which was negative and thus discarded. One patient had an unspecified coagulopathy and one antiphospholipid syndrome. One report mentioned that the patient had not been taking dabigatran for one week.

1b. Venous thromboembolism prevention after orthopaedic surgery and venous thrombosis or embolism

There were 331 reports in this group. After removal of suspected duplicates, the 31 best reports were selected, according to their completeness score and the presence of a narrative. After removal of reports outside of the inclusion criteria 22 reports were fully assessed.

These 22 reports, all from health care professionals save three from observational post-authorization studies, involved 14 females and 8 males. The age range was 46 to 85 years, median 68 years. Time to onset (recorded for 21 patients) ranged from 14 hours to 9 months. Seventeen patients experienced the reaction within the first 18 days, whereas for the other four patients the times to onset were one month (two patients), two months and nine months. Dabigatran daily dose (recorded for 20 patients) was consistent with the recommended daily dose for all except five patients. Two were taking greater than the

recommended dose and three less. In one case the patient started dabigatran therapy with one dose of 110 mg after total hip replacement according to treatment indication in the product information. The advice to then proceed with 110 mg twice daily does not appear to have been followed and she experienced a deep vein thrombosis 14 hours after the post-operative dose. This patient was described as being at a higher risk of bleeding which may have influenced the dose regime prescribed. Another patient who took less than the recommended dose had factor V deficiency and this may have affected the prescribing decision. All these 22 patients experienced a deep vein thrombosis. Four reports described pulmonary embolism subsequent to the deep vein thrombosis. Fifteen reports included the WHO-ART PT "medicine ineffective".

Recorded administration and onset dates indicated that seventeen patients definitely experienced deep vein thrombosis under dabigatran treatment and one just after discontinuing dabigatran earlier than recommended. For three patients the anticoagulant therapy was prolonged beyond the recommended period.

Potential contributory or alternative explanations were explored. Three patients, mentioned above, were taking less than the recommended dose and two of these were also taking a proton pump inhibitor. Four other patients were also taking proton pump inhibitors. In one report, rabeprazole, which was started two days after the commencement of dabigatran, was taken for three days and then stopped, with deep vein thrombosis occurring two days later. One patient was taking the pro-thrombotic agent tranexamic acid which was co-suspect but may have been given for bleeding; the patient who discontinued dabigatran early was also taking the pro-thrombotic drug exemestane and had breast cancer. In one case the patient's medical history included congestive cardiac failure and hypertension; this patient had not been wearing anti-embolism stockings. For three patients the venous thromboembolism was more unexpected since one had factor V deficiency and two were taking greater than recommended doses.

Dabigatran was withdrawn in all cases except for one. Generally, the thrombotic event was treated with alternative anticoagulants such as warfarin or heparins.

2a. Non valvular atrial fibrillation and arterial thrombosis

There were 77 cases in VigiBase® for this indication/ reaction combination. Fifteen reports were left to be discussed after applying the report quality and exclusion criteria.
These 15 reports, all from health-care professionals, involved eight females and seven males. The age range was 46 to 83 years, median 66 years. Time to onset was stated in all cases except for one, and ranged from one day to three years. Nine patients experienced the reaction within the first two months, whereas for the other five patients the time to onset was reported as three months, six months, two years (two patients), and three years. Dabigatran daily dose was recorded for all patients and was consistent with the recommended daily doses stated in the product information in all but two patients. All patients experienced arterial thrombotic events under dabigatran therapy save two for whom clear administration and onset dates were not provided and one where thrombosis occurred on discontinuation. In this case a withdrawal syndrome was suggested.

Intracardiac thrombus was found in three patients; one of these developed severe embolism in both legs and one an aortic thrombosis and deep vein thrombosis. Other sites were cerebral (10 patients), aortic and leg arteries. One of the eight patients with stroke had a history of recurrent cerebrovascular accident occurring first on rivaroxaban therapy, and recurring after 24 days when the patient was switched to dabigatran. However, this patient had not taken his antihypertensive therapy for several days.

Lack of efficacy was stated in 3 reports out of 15.

These patients presented with several risk factors for arterial thrombosis, such as diabetes and hypertension, as expected in many patients with atrial fibrillation (AF). In three cases the concomitant presence of dyslipidemia and hypertension was reported and in one case coronary artery disease. One patient presented with atrial septal defect. Two patients were taking dabigatran 150 mg daily which is lower than the recommended dose. In one of these the thrombosis occurred on stopping dabigatran.

2b. Non valvular atrial fibrillation and venous thromboembolism

This category represents less expected events, since arterial events are expected if there is lack of dabigatran efficacy in preventing embolization from atrial fibrillation. There were 401 reports in VigiBase® regarding this indication/reaction combination. In addition a separate search for cases with AF as indication and the preferred term "embolism" highlighted another 473 cases. Thirty-seven case reports remained to be studied after applying report quality and exclusion criteria.

These 37 reports, all from health-care professionals, involved 23 females and 14 males. The age range was 40 to 88 years, median 79 years. Time to onset was stated for 28 patients and ranged from one day to three years. Nineteen patients experienced the reaction within the first four months, whereas for the other patients the

time to onset ranged from five months to three years. One patient who developed pulmonary embolism had been taking alteplase and acetyl salicylic acid. Dabigatran was added and pulmonary embolism symptoms developed rapidly, perhaps too soon for dabigatran to be effective. In one case the patient, who was taking a lower than recommended dose, experienced two pulmonary embolic events six days apart before discontinuing dabigatran.

Eighteen patients experienced a deep vein thrombosis. One patient experienced right atrial thrombosis on dabigatran therapy that led to pulmonary embolism. Differentiation between in situ and in transit right thrombus could not be established. One patient developed a cardio-embolic occlusion of both right and left limb arteries following atrial thrombosis. It is likely that such thrombosis occurred in the left atrium and therefore would be classified as arterial thrombosis. Seventeen patients experienced a pulmonary embolism. The preferred term "medicine ineffective" was reported in three cases within this group.

Administration and onset dates indicate that 29 patients out of the 37 clearly developed the reaction on dabigatran therapy including all patients who experienced a pulmonary embolism. Fourteen patients developed deep vein thrombosis on therapy whereas one developed it four days after the drug was discontinued after eight months of therapy.

Dabigatran was discontinued in all cases except two for whom this information was not provided and two cases where the dabigatran dose was not changed.

Five patients died, and in three of these cases cardiogenic shock, cerebral haemorrhage and recurrent pulmonary embolism were respectively stated as the cause of death.

Regarding risk factors for venous thrombosis, the dabigatran daily dose was lower than recommended for five patients. Two patients were taking adjusted doses due to compromised renal function. Two other patients were taking optional lower doses as their age was between 75 and 80. One patient aged 72 years was taking the adjusted 220 mg daily dose even though the renal function was recorded as normal. Seven patients were taking a proton pump inhibitor, one with a lower and one with a higher than recommended daily dose of dabigatran. Three patients were taking a prothrombotic agent, letrozole, estradiol or cyproterone. These may represent treatments for cancer and be unavoidable. Five patients had concomitant neoplasms; however one was localized prostate cancer that was considered non-contributory. The other four had stomach cancer, cerebellar tumour, non-Hodgkin's lymphoma and one atrial myxoma recently removed. In one case a concomitant bacterial pneumonia was recorded. A pacemaker had been recently implanted in one patient for atrioventricular block. All these patients were on dabigatran therapy for NVAF and, as expected, some of them were affected by arterial hypertension, congestive heart failure and coronary artery disease. In one case, the patient experienced a cardiogenic shock that would appear to have started with a myocardial infarction that led first to pulmonary embolism, lung haemorrhage and consequently to shock. In contrast to the patients with apparent risk factors for VTE, these events were particularly unexpected in four elderly patients who were taking greater than the recommended daily dose, four patients taking concomitant antithrombotic agents and three who were taking p-glycoprotein inhibitors (amiodarone, dronedarone or verapamil), including one of those who was taking a greater than recommended daily dose of dabigatran.

Discussion

Out of the 122 most informative reports selected, the 79 reports that fitted our inclusion criteria were presented and discussed. Across all the four groups three modifiable potential risk factors for lack of dabigatran efficacy were identified. Ten patients were taking lower than recommended doses and three of these were taking concomitant proton pump inhibitors. Ten other patients were also taking proton pump inhibitors. Five patients were taking prothrombotic agents, tranexamic acid, estradiol, exemestane, cyproterone and letrozole respectively. As indicated in the introduction, there is a theoretical reason for an interaction with proton pump inhibitors leading to decreased dabigatran plasma levels but this was not found to be clinically important in one pharmacokinetic study with pantoprazole.[1] Upper gastrointestinal symptoms are common adverse reactions to dabigatran which may lead to proton pump inhibitor use. There is also a high proton pump inhibitor use prevalence in many countries so without further studies a firm conclusion cannot be drawn. Only one report had sufficient detail to show commencement of a proton pump inhibitor after dabigatran had been commenced and shortly before thrombosis occurred. However, it is possible that for patients whose dabigatran plasma levels are at the lower end of the therapeutic range or with other risk factors for VTE the interaction may be clinically important. On the other hand, an 86-year-old patient was taking a higher than recommended dose of dabigatran in the presence of rabeprazole but experienced a deep vein thrombosis anyway.

In most cases the use of the lower recommended dose was appropriate, as the patients had renal failure or were aged over 75 years. However some patients in the older age group will have adequate renal function and in these cases dabigatran

plasma level monitoring could be useful to find the appropriate dose.

Risk factors that were less modifiable were the presence of a coagulopathy in two patients and antiphospholipid syndrome in another. Patients with atrial fibrillation, in particular, had co-morbidities that could lead to or be due to atherosclerosis, such as hypertension, diabetes, dyslipidemia and coronary artery disease, and this would have increased arterial thrombotic risk. However, these patients would also have been represented in clinical trials as the co-morbidities are often closely linked with atrial fibrillation. At least three patients who developed pulmonary embolism had active cancer.

The patients of most interest were those who developed VTE while taking dabigatran to prevent arterial embolism due to atrial fibrillation. These patients were older than those in the other groups and older age is a risk factor for VTE. A high proportion of patients who developed pulmonary embolism clearly had a number of serious co-morbidities that could have contributed. Active cancer is known to account for almost 20% of incident VTE events.[19] Pneumonia was co-reported in one case. Pulmonary embolism and pneumonia are both prevalent conditions after stroke, moreover a patient developing pneumonia is likely to be further predisposed to supervening pulmonary embolism.[20] One patient had a recently implanted pacemaker but it was not specified whether the pacemaker was intravenous, which is a VTE risk factor.[19] As expected, the rest of the patients presented with thrombotic risk factors such as arterial hypertension, congestive heart failure, myocardial infarction and coronary disease. In general however, the risk of VTE associated with congestive heart failure, independent of hospitalization, is low.[19] It is therefore possible that patients who develop pulmonary embolism while taking dabigatran for stroke prevention represent a group of predisposed individuals in whom co-morbid hypercoagulable states overcome the effect of dabigatran.

It is also known that AF is associated with a hypercoagulable state.[21-23] Noel et al. described a higher incidence of deep vein thrombosis and pulmonary embolism in stroke patients with NVAF.[21] However, atrial fibrillation is not listed as a cause of venous thromboembolism in standard texts unless there has been immobility due to stroke.[24]

Three patients developed thrombosis on stopping dabigatran; one was taking a sub-therapeutic dose. There is one published case series of thrombosis developing within one month of dabigatran withdrawal. The possibility of rebound, and therefore the question of how to stop dabigatran safely, was raised.[25] Dabigatran has a much shorter half-life than warfarin and it is possible therefore that thrombosis might be more likely to develop when doses are missed or when therapy is discontinued. There was little information on whether patients were compliant or not in the reports we extracted.

Most surprising was reports of thromboembolism in patients who were taking greater than recommended dabigatran doses, other antithrombotic agents, or interacting medicines that decrease dabigatran clearance. There is no clear explanation for these observations.

Assessment limitations

It is acknowledged that the information in VigiBase® is heterogeneous, i.e., it originates from multiple sources (different countries and types of reporters) and the amount of information given may vary from case to case. As an example, even though there were several patients apparently following treatment guidelines, little information on whether patients were compliant or not could be retrieved.

Our case series presents patients with additional risk factors to those connected with the primary indication for dabigatran and include neoplasm, concomitant prothrombotic medications, myocardial infarction and coronary artery disease. It is not possible at this stage to compare the effectiveness of dabigatran with warfarin or enoxaparin in the type of patients this case series represents.

Conclusion

The most informative reports in VigiBase® reporting venous or arterial thrombotic or embolic events in patients on dabigatran therapy were collected and analysed according to the dabigatran indication. The information in two thirds of the 79 most informative reports indicated that dabigatran was ineffective in overcoming multiple thrombosis risk factors. However, modifiable risk factors included lower than recommended doses, co-prescription of pro-thrombotic medicines and, possibly, co-prescription of proton pump inhibitors.

The 79 discussed reports were submitted from Americas, Asia and Europe, with most of them coming from Europe.

Spontaneous reporting is used for collecting information about unexpected adverse reactions once drugs are on the market. It is not used to assess drug efficacy, but can be used to detect unexpected cases of failure of therapy.[26] In the case of the topic of this study, it has been useful in highlighting risk factors for dabigatran ineffectiveness in clinical practice, including those that might be modifiable. Given the strong correlation between dabigatran plasma levels and anticoagulant effect, therapeutic drug monitoring

could provide valuable information for dose selection in patients on potentially interacting medicines, elderly patients with apparently normal renal function to ensure they receive an adequate dose, and where there are concerns about adherence.

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Response from Boehringer Ingelheim

The signal report by the WHO Uppsala Monitoring Centre (UMC) investigates disproportionality of the WHO ART preferred term thromboembolism in VigiBase®, the WHO global database of ICSRs. It concludes that this disproportionality may be caused by patients who on top of their base line thromboembolic risk have additional risk factor for thrombosis.

Thromboembolic events during dabigatran treatment have been closely monitored by the marketing authorization holder (MAH) as a topic of special interest since launch of the product. In the last Periodic Safety Update Report (PSUR) (reporting period 19 Mar 2015 to 18 Sep 2015) the MedDRA Standard MedDRA Queries (SMQ) 'Embolic and thrombotic events (narrow)' and 'Lack of efficacy/effect' identified 608 events resulting in a reporting rate of 8.4 case reports per 10,000 patient years of exposure. The findings in this report confirmed analyses of all previous reports. In total, the pharmacovigilance database of the MAH contains 8,444 post-approval case reports with MedDRA Preferred Terms from these SMQs, resulting in a reporting rate of 16.3 case reports per 10,000 patient years. In the MAH's pharmacovigilance database thromboembolic events are amongst the most commonly spontaneously reported adverse events comprising approx. 10% of all case reports.

The fact that
(i) a different dictionary was used for the analysis of the VigiBase® (WHO ART) than was used for the analysis by the MAH (MedDRA), and
(ii) the databases probably cover different populations for which thromboembolic cases have been reported, explains the minor differences found in the number of cases containing thromboembolic events, the proportion of thromboembolic events compared to other event reports for dabigatran, and the types of different thromboembolic events.

The MAH did not perform an analysis on the various types of thromboembolic events in different indications, since approx. 40 % of spontaneous reports do not provide a clear indication for use. Therefore, no reliable conclusion on the frequency of a given thromboembolic event in a certain indication is possible.

In the analysis of thromboembolism in the VigiBase® database a limited number of cases were selected for in depth analysis. The major portion of patients in the cases selected for an in depth investigation who experience a thromboembolic event have further risk factors in addition to the patients' base line risk which increase the probability of lack of effect (i.e. thromboembolic event despite anticoagulation), such as active cancer, or coagulopathies such as anti-phospholipid syndrome. Another reason mentioned in the analysis is incompliant use (not taking the drug, taken a dose lower than recommended) which is a known important factor in lack of efficacy.

Overall, the analysis performed by the Uppsala Monitoring Centre in VigiBase® is in line with the findings of the MAH seen in continuous monitoring of this important event.

In the analysis performed by the UMC concomitant intake of proton pump inhibitors is speculated to be a risk factor for thromboembolic events during anti-coagulation with dabigatran. However, an interaction of dabigatran with proton pump inhibitors leading to decreased plasma levels has been found to be minor in a pharmacokinetic interaction study of dabigatran with the proton pump inhibitor pantoprazole by the MAH. The interaction between dabigatran and pantoprazole was found not clinically relevant. The fact that many patients with thromboembolic events receive proton pump inhibitors concomitantly may simply reflect the frequent use of proton pump inhibitors. Proton pump inhibitors are frequently used in gastrointestinal disorders and are available in many countries as OTC drugs.

Dabigatran treatment is safe and efficacious when used according to dosing recommendation in the product information which is based on patient characteristics (e.g. renal impairment, age and co-medication). The assessment of individual plasma concentration does not add value for the dose selection of dabigatran etexilate and its risk-benefit assessment for the individual patient.

Dabigatran plasma levels are confounded by age and renal function. Age is by far the more relevant determinant of the risk of stroke and bleeding. Therefore there cannot be one therapeutic range for dabigatran applying to all patients.

Measurements of plasma levels are affected by several layers of variability and uncertainty (including for example an inappropriate sampling time-point and the intra-individual variability of plasma levels). In clinical practice, this is likely to lead to unreliable and potentially misleading test results. Clinical characteristics of the patient have been proven to be reliable and valid decision criteria for dose selection.

Plasma level measurements may at most guide the physician in specific clinical situations, but if used as a decision criterion for dose adoption it bears the risk of compromising the positive benefit/risk profile of dabigatran treatment.

In clinical trials, fixed dose dabigatran has been shown to be at least as safe and efficacious as monitored warfarin in different approved indications. In the opinion of the MAH the data provided in this analysis by the UMC do not provide evidence that monitoring of drug levels would further reduce the risk of thromboembolic events in patients receiving dabigatran.

In conclusion

- This signal report confirms results from routine pharmacovigilance activities performed by the MAH which are regularly reported to Health authorities
- There is no evidence that concomitant use of proton pump inhibitors has an impact on the anticoagulant effect of dabigatran
- Plasma level measurements may at most guide the physician in specific clinical situations, but if used as a decision criterion for dose adoption it bears the risk of compromising the positive benefit/risk profile of dabigatran treatment.

Febuxostat and allergic vasculitis

Dr Ian Boyd, Australia

Summary

Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting xanthine oxidase (XO). Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine being converted to xanthine and xanthine converted to uric acid. Both steps in the above transformations are catalyzed by XO. Febuxostat is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). After the elimination of one suspected duplicate there are currently (1 July 2015) seven individual case safety reports in VigiBase®, the WHO international database of suspected adverse drug reactions, of allergic vasculitis in association with febuxostat. The reports are from France, Germany, India, Japan and the United States. Febuxostat was the only drug suspected in one of the seven cases. The outcome of the allergic vasculitis was stated in all seven cases and in all cases the patients had either recovered or were recovering after the withdrawal of febuxostat.

Case reports in VigiBase® suggest that there is a possible signal for the association of febuxostat and allergic vasculitis. Although there were other drugs suspected in six of the seven reports, febuxostat appears to be the most likely explanation in four of the six reports and a possible cause in the remaining two reports, as well as in the report where it was the only suspected drug. Time to onset is consistent with a

drug induced effect. Dechallenge is very supportive of a drug association with all patients recovered or recovering on withdrawal of febuxostat although there were other suspected drugs for which a positive dechallenge was also present. In addition, there is a report in the literature in which a patient developed biopsy-confirmed cutaneous leukocytoclastic vasculitis, likely but not definitively febuxostat-related.

Introduction

Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting xanthine oxidase (XO). Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine being converted to xanthine and xanthine converted to uric acid. Both steps in the above transformations are catalyzed by XO. Febuxostat is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). The most commonly reported adverse reactions in clinical trials and post-marketing experience are gout flares, liver function abnormalities, diarrhoea, nausea, headache, arthralgia, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated with systemic symptoms, have occurred in the post-marketing experience. Adverse skin reactions reported include rash (common), dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular and rash papular (uncommon) and toxic epidermal necrolysis, Stevens Johnson syndrome, angioedema, drug reaction with eosinophilia and systemic symptoms, generalized rash, erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic, rash erythematous, rash morbillifom, alopecia and hyperhidrosis (rare).[1]

Vasculitis comprises a heterogeneous group of inflammatory vascular lesions that can involve any kind of blood vessel, irrespective of its lumen or location. Vasculitis gives rise to such conditions as ischaemia or thrombosis, which may cause serious organ damage and be life-threatening. Vasculitis is a necrotizing inflammatory lesion of blood vessels, leading to their occlusion or disruption, with clinical sequelae. The clinicopathological diagnosis of vasculitis is supported by the demonstration of elevated levels of acute-phase reactants (demonstrated by, for example, erythrocyte sedimentation rate, differential blood count showing thrombocytosis and leukocytosis, and C-reactive protein), high levels of rheumatoid factors and cryoglobulins, hypocomplementaemia, antinuclear antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA) especially those ANCAs directed against proteinase 3 or myeloperoxidase.[2] Allergic vasculitis, also known as hypersensitivity vasculitis, is an acute form of this condition that is marked by inflammation or redness of the skin that occurs when contact is made with an irritating substance. It is characterized by the appearance of red spots on the skin, most commonly, palpable purpura. Palpable purpura are raised spots that are usually red in colour but may darken to a purple colour. However, there are many other types of rashes that can occur. Causes of skin inflammation include medications, infections or any other foreign object which may induce an allergic reaction.[3] Hypersensitivity vasculitis is usually represented histopathologically as leukocytoclastic vasculitis (LCV) which is a term commonly used to denote a small vessel vasculitis. Hypersensitivity vasculitis is thought to be mediated by immune complex deposition. In this form of vasculitis, circulating antigens in the body (produced by factors such as medications, infections, and neoplasms) induce antibody formation. These antibodies bind to the circulating antigen and create immune complexes, which then deposit within vessels, activating complement and inducing inflammatory mediators. Inflammatory mediators, adhesion molecules, and local factors may affect the endothelial cells and may play a role in the manifestations of this disease.[4]

It should be noted that in MedDRA, the preferred term is hypersensitivity vasculitis with allergic vasculitis and leukocytoclastic vasculitis as lower level terms. In WHO-ART vasculitis allergic is an included term along with leukocytoclastic vasculitis with vasculitis as the preferred term. The more commonly used term, allergic vasculitis, will be used throughout this article.

Reports in VigiBase®

As of 1 July 2015 there are eight individual case safety reports of allergic vasculitis in association with febuxostat in VigiBase®, the WHO international database of suspected adverse drug reactions (Table 1). After the elimination of one suspected duplicate, the reports were submitted from Germany (2 reports), the United States (2), France, India and Japan (1 report each). The patients ranged in age from 48 to 85 years but six of the patients were aged 70 years or over with a median of 75 years. There were four males and three females.

Febuxostat was the only drug suspected in one of the seven cases. There were other drugs also suspected in the remaining six cases including the combination of colchicine, tiemonium methylsulfate and Papaver somniferum (opium poppy) in one report, hydroxycarbamide, allopurinol, influenza vaccine and levofloxacin, all in one report each, and moxifloxacin,

phenprocoumon and torasemide in the remaining report. Concomitant drugs were reported in six of the seven cases and apart from the use of corticosteroids, antihypertensives and drugs for the treatment of pain in two cases each, the concomitant drugs were used to treat a variety of conditions. Febuxostat was reported to have been administered orally, as expected, in all seven cases. Dosage was reported in five cases and was 40 mg daily in three reports and 80 mg daily in the other two reports. The indication for use was stated in six reports and included gout in three reports and hyperuricaemia in three reports.

Time to onset was reported in three of the reports and ranged from the same day the drug was administered to 18 days (median 14 days).

The outcome of the allergic vasculitis was stated in all seven reports. All of these patients were reported as recovered or recovering on withdrawal of febuxostat.

Other reactions were reported in four of the seven cases. These included other skin reactions including skin exfoliation in two cases, renal and urinary disorders in two cases and a small number of other reactions.

Literature and Labelling

The product literature does not refer to allergic vasculitis although it does refer to a wide range of skin reactions and it also notes that rare serious hypersensitivity reactions to febuxostat, some of which were associated with systemic symptoms, have occurred in the post-marketing experience. In the literature, there is a report on the use of febuxostat in allopurinol-intolerant patients. Although the drug was well tolerated in 12 of 13 patients, one patient previously hospitalized with documented exfoliative erythroderma during allopurinol treatment, developed biopsy-confirmed cutaneous leukocytoclastic vasculitis, likely but not definitively febuxostat-related. In the opinion of the authors, this occurrence early in treatment mandates caution, careful dose escalation, and close monitoring when febuxostat urate-lowering therapy is considered.[5]

Discussion

Case reports in VigiBase® suggest that there is a possible signal for the association of febuxostat and vasculitis allergic. Febuxostat was the only drug suspected in one of the seven cases. There were other drugs suspected in the remaining six cases.

In Case 1, the combination of colchicine, tiemonium methylsulfate and Papaver somniferum was also suspected and although it was withdrawn with recovery (as was febuxostat), it had been used for two months longer and there is no reference to vasculitis in the product information. Also, perindopril and furosemide among concomitant drugs have references in their product information that rarely associate with vasculitis. However, they appear to have been taken long term and apparently they have not been discontinued and therefore would be unlikely causes. Febuxostat appears a more likely cause in this case.

In Case 2, hydroxycarbamide was also suspected and although it was withdrawn with recovery (as was febuxostat), it had been used for almost 12 years. In the product information for hydroxycarbamide there is no specific reference to allergic vasculitis but cutaneous vasculitis is mentioned.[6] However, in view of the long usage of hydroxycarbamide, febuxostat appears a more likely cause in this case.

In Case 3, allopurinol was also suspected and although the dates of use are unclear it appears that only febuxostat was withdrawn. In the product information for allopurinol, there is no specific reference to allergic vasculitis but there is a warning concerning hypersensitivity reactions and a reference that associated vasculitis and tissue response may be manifested in various ways.[7] However, in view of the response to withdrawal of febuxostat while allopurinol was continued, febuxostat appears a more likely cause in this case.

In Case 4, influenza vaccine was also suspected. Influenza vaccine was only used once so there is no possibility of assessing a response to withdrawal but recovery did occur on withdrawal of febuxostat. For influenza vaccine, there is no specific reference to allergic vasculitis but the product information for at least one influenza vaccine notes that vasculitis has been associated in very rare cases with transient renal involvement.[8] Again, the response to withdrawal makes febuxostat a more likely cause in this case.

In Case 6/8, levofloxacin was also suspected and the reaction occurred after five days usage (compared with 18 days for febuxostat) and resolved on withdrawal of both levofloxacin and febuxostat. In the product information for levofloxacin, there is a warning indicating the drug can cause serious, potentially fatal hypersensitivity reactions and there is a specific reference to leukocytoclastic vasculitis.[9] In this case, levofloxacin appears a more likely cause.

Finally in Case 7, there were three other suspected drugs. Torasemide had a longer time to onset (21 days compared to 14 days for febuxostat) and was continued with recovery. There is no reference to vasculitis in the product information and it appears to be an unlikely cause. Phenprocoumon appears to have been taken long term and was continued with recovery. There is no reference to vasculitis in the product information and it also appears to be

an unlikely cause. Moxifloxacin had a similar time to onset to febuxostat (10 days compared to 14 days) and along with febuxostat was withdrawn with recovery. In the product information for moxifloxacin, there is a warning concerning hypersensitivity and allergic reactions but no reference to vasculitis.[10] Both febuxostat and moxifloxacin would appear to be equally likely causes. In addition, among concomitant drugs ramipril had a time to onset of 10 days similarly to moxifloxacin. According to the product information, ramipril has been rarely associated to vasculitis. Therefore ramipril would appear to be a confounder in this case.

Time to onset was reported in only three of the reports and ranged from the same day the drug was administered to 18 days (median 14 days). This would appear consistent with a drug induced effect.

The outcome of the allergic vasculitis was stated in all seven reports. All of these patients were reported as recovered or recovering and febuxostat was withdrawn in all cases. As noted above, however, other suspected drugs were also withdrawn at the same time as febuxostat. Nevertheless, the response to dechallenge in all cases is strongly suggestive of a febuxostat related effect.

As noted above, there is one report in the literature in which febuxostat was associated with cutaneous leukocytoclastic vasculitis in which the authors suggested that febuxostat was likely related.

Conclusion

In summary, there are seven reports in VigiBase® associating allergic vasculitis with the use of febuxostat. Although there were other drugs suspected in six of the seven reports, febuxostat appears to be the most likely explanation in four of the six reports and a possible cause in the remaining two reports, as well as in the report where it was the only suspected drug. Time to onset is consistent with a drug induced effect. Dechallenge is very supportive of a drug association with all patients recovered or recovering on withdrawal of febuxostat although there were other suspected drugs for which a positive dechallenge was also present. Allergic vasculitis is not mentioned in the product information for febuxostat but it does refer to a wide range of skin reactions and it also notes that rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, have occurred in the post-marketing experience. Moreover, there is a report in the literature in which a patient developed biopsy-confirmed cutaneous leukocytoclastic vasculitis, likely but not definitively febuxostat-related.

Table 1. Case overview of reports in VigiBase® of allergic vasculitis in association with febuxostat

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reactions (WHO-ART included terms for vasculitis and preferred terms for the rest)	Outcome
1	48/M	Colchicine/tiemonium methylsulphate/Papaver somniferum powder (S) Amoxicillin, bisoprolol, fluindione, furosemide, perindopril (all C)	Leukocytoclastic vasculitis	Recovered
2	70/M	Hydroxycarbamide (S) Amorolfine, betamethasone, clobetasol, ketoconazole, phenobarbital/ phenytoin/caffeine/sodium benzoate, phenytoin, silodosin (all C)	Allergic vasculitis*, albuminuria, haematuria	Recovering
3	85/F	Allopurinol (S) Influenza vaccine (C)	Leukocytoclastic vasculitis, dermatitis exfoliative	Recovered
4	84/F	Influenza vaccine (S) Acetylsalicylic acid, amlodipine, carvedilol, colchicine, enalapril, furosemide, gabapentin, prednisone (all C)	Leukocytoclastic vasculitis, azotaemia, hyperglycaemia, lips dry, purpura, skin exfoliation	Recovered
5	72/M	None	Vasculitis allergic	Recovered
6**	83/F	Levofloxacin (S) Citalopram, fentanyl, metoclopramide, solutions for parenteral nutrition (all C)	Allergic vasculitis*, hepatic failure	Recovered
7	75/M	Moxifloxacin, phenprocoumon, torasemide (all S) Atenolol, naloxone hydrochloride/ tilidine phosphate, ramipril (all C)	Allergic vasculitis*, hospitalisation*	Recovered
8**	83/F	Levofloxacin (S) Amino acids NOS/electrolytes NOS/carbohydrates NOS, citalopram, fentanyl, metoclopramide, solutions for parenteral nutrition (all C)	Allergic vasculitis*, hepatic failure, hospitalisation*	Recovered

NOS = Not otherwise specified
**MedDRA term*
***Cases 6 and 8 are suspected duplicates*

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Response from Teijin, Takeda and Menarini

Through routine signal detection activities and periodic analysis, the Marketing Authorization Holders (Teijin Pharma Ltd in Japan, Takeda Pharmaceuticals U.S.A., Inc. in North America, and Menarini International Operations Luxembourg S.A in Europe) have identified leukocytoclastic vasculitis as a potential signal for febuxostat since 2012 and have closely monitored it during subsequent years. Furthermore the vasculitis has been analyzed in the context of the continuous safety surveillance for risk of serious skin/ hypersensitivity reactions (as mentioned in the current EU Risk Management Plan of the product). In the signal evaluation of this signal in gout patients, the fact that uric acid per se could be an activator of the immune system, should be kept in consideration (Rheumatology 2010;49:1229-1238).

Since the market authorization of the product, 10 cases describing "vasculitis" events were collected, including a study case where the therapy used is still blinded and another case describing "Henoch-Schonlein" purpura. The reports are from Germany (2 cases), France (2 cases), USA (6 cases) and Japan (1 case) and are summarized in table 1.

Most of collected "vasculitis" reports present confounding factors, with co-morbid conditions, and other co-suspect medications. Additionally, some of these reports have insufficient information for causality assessment. Therefore current data do not allow establishing a causal relationship with febuxostat.

The issue has been further analyzed in a Safety Update Report to EU regulators (up to 20 April 2015) and as of November 2015, the conclusion of the European Authority (Pharmacovigilance Risk Assessment Committee - PRAC) has been that the signal leukocytoclastic vasculitis could be closed as a refuted signal due to small number of cases and confounding factors.

Conclusions

On the base of the available data, it is not possible to establish a causal relationship between "vasculitis" and febuxostat and the risk profile of febuxostat remains unchanged at this time. In agreement with the European Authority (PRAC), this potential signal leukocytoclastic vasculitis has been closed as a refuted signal. The MAHs will continue to monitor all relevant benefit-risk information and will take appropriate action if any new information emerges that would affect the safety profile of febuxostat.

Table 1.

Age /Sex	Febuxostat Dose	Co-Suspect drugs	Concomitant Drugs	Latency	Reactions (MedDRA PT)	Outcome	Medical history	Comment
75M	80 mg/day	Moxifloxacin, Phenprocoumon	Ramipril,Torasemide,Atenolol,ValoronN	14days	Hypersensitivity vasculitis	Resolved	Hyperuricaemia, Renal failure, Pleurisy, Pneumonia,Chronic obstructivepulmonary disease, Hypertension, Cor pulmonale, Atrialfibrillation,Coronaryartery disease	Moxifloxacin discontinued and Phenprocoum ongoing. Biopsyconfirmedallergicvasculitis.The patientreceivedsteroidtherapyandthe eventresolved. Relevantco-suspectandconcomitantdrugs.
83F	80 mg/day	Levofloxacin	Fentanyl,Citalopram, Metoclopramide,intravenous nutrition solution	18days	Hypersensitivity vasculitis,Hepatic failure	Resolved	Chronickidneydisease,Cardiac failure	Co-suspect drug discontinued. Intravenous nutrition therapy ongoing. Chronology plausibleanddechallengepositive.The patient receivedsteroidtherapyandtheevent resolved.
71M	40 mg/day	None	Simvastatin, Bunch of medications	1month	Vasculitis,Gout	Resolved	Gout,Diabetesmellitus,Alcohol use	Marketresearchcase.Thepatient developedvasculitisafterabout1monthof febuxostatstart;theeventresolvedafter dechallengeandtherapyforthevasculitis. Detailinbunchofmedicationsandaction takenwithconcomitanttherapieswere not reported.Thecaseisnotmentionedin WHO report.
44M	80 mg/day	Vancomycin, Levofloxacin, Azithromycin	Not available	30days	Vasculitis, Loss of consciousness, Unresponsive to stimuli, Respiratory failure,Encephalitis viral, Myoclonus, Pneumonia aspiration, Rhabdomyolysis, Drug eruption, Somnolence	Unknown	Gout	Thepatientsufferedfromrhabdomyolysis, encephalitisviral.Herecevedantibiotic intravenoustherapy,thereafterdevelopeda generalizedrashwithapersistentfeverand all antibioticswerediscontinued.Relevantco-suspectdrugs.Thecaseisnotincluded inWHOreport.
84F	40 mg/day	Influenza vaccine	Colchicine,Prednisone,Enalapril, Amlodipine,Carvedilol, Acetylsalicylic acid, Gabapentin,Furosemide	3days	Hypersensitivity vasculitis,Lipinjury	Resolved	Gout,Renalfailure, Hypertension,Cardiac failure congestive, Atrial fibrillation, Drug reactionwitheosinophilia andsystemic symptoms, Exfoliative rash	Literature case. The biopsy confirmed "leukocytoclastic vasculitis". Concomitant drugs wereongoingunchangedsinceatleast2-3 months.Thepatietreceivedmedroltherapy and recovered.Amongmedicalhistory "Hypersensitivesyndrome"wasmentioned.
83M	Unknown	Colchicine/ tiemonium/ opium	Not available	1week	Hypersensitivity vasculitis, Glomerulonephritis, Septic shock, Purpura, Renal failure	Resolved	Unkown	According with the reporter also other factors should have determined renal (Glomerulonephritis, Renal failure). A skin biopsy confirmed vasculitis but no renal biopsywaspossible.Thepatientexperienced alsopurpuraandsepticshock.Relevant co-suspectdrug.Thecaseisnotmentionedin WHOreport.
Unknown F	Unknown	None	Unknown	10 months	Vasculitis	Unknown	Unknown	Lackofinformationandclinicaldetails.Thecaseisnot mentionedinWHOreport
Unknown F	Unknown	None	Unknown	5days	Vasculitis	Unknown	Unknown	Lackofinformationandclinicaldetails.Thecaseisnot mentionedinWHOreport
48M	Unknown	Colchicine/ tiemonium/ opium	Perindopril,Fluindione,Furosemide, Bisoprolol, Prednisolone, Esomeprazole, Amoxicillin	Unk	Hypersensitivity vasculitis	Resolved	Congestive cardiomyopathy, Hyperthyroidism,Arthralgia,Skin ulcer (venousulcer),Transient ischaemic attack,Testicular seminoma(pure)	Timetoonsetunknown,eventonset unknown.Abiopsyofthelowerlimbsulce diagnosedforleukocytoclasticvasculitis. Relevantco-suspectdrugsandconcomitant pathologies.
61M	Blinded	None	Ibuprofen,Insulinaspart,Salbutamol, Fluticasone, Carvedilol, Clopidogrel, Glyceryl trinitrate, Insulin glargine, Montelukast, Fluticasone/Salmeterol, Fishoil,Fexofenadine,Multivitamin, Magnesium,Furosemide, Candesartan, Hydralazine, Acetylsalicylic acid, Simvastatin, Omeprazole, Isosorbide, Amlodipine,Sertraline,Ergocalciferol, Erythropoietin, Naracetamol, Oxycodone hydrochloride/Oxycodone terephthalate/paracetamol, ibuprofen, cefdiner, influenza vaccine	841 days	Vasculitis	Not resolved	Gout, Cardiac failure congestive, Hypertension, Hyperlipidaemia, Diabetes mellitus, Asthma, Osteoarthritis,Chronicsinusitis, Rhinitis allergic, Nasal septum deviation, Coronary artery disease, Sleep apnoea syndrome, Diverticulum, Renal failure, Proteinuria,Anaemia, Vertigo,Diastolic dysfunction, Erosive oesophagitis, Onychomycosis, Cardiac murmur	Clinical trial blinded case. No treatment was provided. Study drug was ongoing, The investigator assessed as not related to study drug. Relevant concurrent disease. The case isnotmentionedinWHOreport.
74M	Unknown	None	Amlodipine, Olmesartan	4days	Henoch-Schonlein purpura	Resolved	Hypertension, Hyperuricemia	Febuxostatwas discontinuedandno treatmentwas provided.Thecaseis not mentionedinWHOreport

CAVEAT DOCUMENT

Accompanying statement to data released from the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global database of Individual Case Safety Reports, VigiBase®. It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase® make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not.

Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Confidential data
According to WHO policy and UMC Guidelines, ICSRs sent from the WHO PIDM member countries to VigiBase® are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase® Data includes, but is not limited to:
- **patient identification or patient targeting**
- **identification, profiling or targeting of general practitioners or practice**

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

Any publication, in whole or in part, of information obtained from UMC must include a statement:

(i) regarding the source of the information,
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase®.

WHO Collaborating Centre for International Drug Monitoring, Box 1051, SE-751 40 Uppsala, Sweden

Third Asia Pacific Pharmacovigilance Training course in Mysuru, India

Save the date: January 16-27, 2017

Early registration is open now!

This two week course, organised by JSS University and Uppsala Monitoring Centre (UMC), provides a solid practical foundation for those working in drug safety and aims to developing pharmacovigilance knowledge and skills in the Asia Pacific region. The course draws on the 18 years of experience UMC has in providing education and training to a global network of pharmacovigilance experts and health-care professionals. The Asia Pacific course is tailored to regional needs and addresses challenges unique to this area.

In order to encourage discussion within the group, there is a limit of 30 participants on the course.

The course takes place at JSS University, in the city of Mysuru, located in the state of Karnataka, southern India.

For more information about the course, please read the course announcement from the JSS website.

To register for this course please fill the online registration form at the JSS website.

Any queries about the course should be sent to: pvtraining@jssuni.edu.in

See you in Mysuru!