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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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 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 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