World Health Organization

WHO Pharmaceuticals NEWSLETTER

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

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

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

Safety and Vigilance: Medicines,

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

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

This newsletter also includes updates on Smart Safety Surveillance (3S) activities in India and Thailand.

Contents

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Clozapine

Risk of intestinal ulcer and intestinal perforation

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for clozapine (Clozaril®) should be revised to include intestinal ulcer and intestinal perforation as adverse drug reactions.

Clozapine is indicated to treat resistant schizophrenia.

Four cases of intestinal perforation have been reported in Japan in patients treated with clozapine.

The MHLW and PMDA have concluded that revision of the package insert was necessary based on the results of their investigation of the currently available evidence and in consultation with expert advisors.

Reference:
Revision of Precautions, MHLW/PMDA, 19 March 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.4, 2018: Gastrointestinal effects in Australia)

Denosumab

Risk of hypercalcaemia and multiple vertebral fractures

Japan. MHLW and PMDA have announced that the package insert for denosumab (Ranmark Subcutaneous Injection®) should be revised to include hypercalcaemia and multiple vertebral fractures following discontinuation of denosumab treatment, as adverse drug reactions.

Denosumab is indicated for bone lesions associated with multiple myeloma or bone metastasis of solid carcinoma and bone giant cell tumour.

Cases of hypercalcaemia after discontinuation of denosumab treatment have been reported overseas.

In a clinical study, there were cases of multiple vertebral fractures in the patient group taking denosumab compared to no cases in the placebo group.

One case involving hypercalcaemia after discontinuation of denosumab treatment has been reported in Japan during the previous three fiscal years. No cases involving multiple vertebral fractures after discontinuation of denosumab treatment have been reported.

Reference:
Revision of Precautions, MHLW/PMDA, 19 March 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.4, 2018: Risk of multiple vertebral fractures in Japan; No.3, 2016: Contraindicated in patients with unhealed lesions from dental or oral surgery in Australia; No.4, 2015: Risk of Osteonecrosis of the jaw and hypocalcaemia in Egypt; No.5, 2014: Association with the risk of atypical femoral fractures in Canada; No.4, 2012: Risk of severe symptomatic hypocalcemia, including fatal cases in Canada; No.4, 2012: Osteonecrosis of the Jaw (ONJ) in New Zealand)

Direct-acting antivirals for chronic hepatitis C

Risk of hypoglycaemia

Ireland. The Health Products Regulatory Authority (HPRA) is updating the Summary of Product Characteristics (SmPC) and Package Leaflets (PL) for direct-acting antivirals for chronic hepatitis C to include hypoglycaemia in patients with diabetes, particularly upon treatment initiation.

Direct-acting antivirals for chronic hepatitis C include daclatasvir (Daklinza®), sofosbuvir/velpatasvir (Epclusa®), and dasabuvir (Exviera®).

Rapid reduction in hepatitis C viral load during initial treatment with direct-acting antiviral therapy for hepatitis C may improve metabolism in patients with diabetes, and this could result in symptomatic hypoglycaemia.

Diabetic patients commencing treatment with direct-acting antivirals should be advised of the risk of hypoglycaemia in association with treatment. Also, patients with diabetes should be closely monitored for changes in blood glucose levels, particularly in the first three months of treatment.

Reference:
Drug Safety Newsletter, HPRA, April 2019 *(www.hpra.ie)*

(See WHO Pharmaceuticals Newsletter No.1, 2019: Risk of hypoglycaemia in patients with diabetes in UK)

Dulaglutide (genetical recombination)

Risk of severe diarrhoea and vomiting

Japan. MHLW and PMDA have announced that the package insert for dulaglutide (Trulicity Subcutaneous Injection®) should be revised to include severe diarrhoea and vomiting as adverse drug reactions.

Dulaglutide is indicated for treatment of type-2 diabetes mellitus.

A total of seven cases involving severe gastrointestinal disorders have been reported in Japan during the previous three fiscal years. Of the seven cases, a causal relationship to the product could not be excluded in three cases.

Reference:
Revision of Precautions, MHLW/PMDA, 19 March 2019 *(www.pmda.go.jp/english/)*

Elvitegravir boosted with cobicistat

Risk of treatment failure and maternal-to-child transmission of HIV-1

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for products containing elvitegravir boosted with cobicistat (Genvoya®, Stribild®) is being updated to warn against use during pregnancy.

Elvitegravir is an integrase inhibitor used to treat HIV-1. Cobicistat is a pharmacokinetic enhancer used to increase elvitegravir levels.

Pharmacokinetic data indicate that exposure of elvitegravir in preparations boosted with cobicistat, is lower during the second and third trimesters of pregnancy than during the postpartum period. Low elvitegravir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child, and therefore elvitegravir and cobicistat combinations should not be used during pregnancy.

Reference:
Drug Safety Update, MHRA, 16 April 2019 *(www.gov.uk/mhra)*

Fluoroquinolone antibiotics

Risk of musculoskeletal and nervous systems damage

United Kingdom. The MHRA has announced that new restrictions for the indication of fluoroquinolones are being introduced to reduce the risk of disabling, long-lasting or potentially irreversible adverse reactions affecting the musculoskeletal and nervous systems.

Fluoroquinolone antibiotics available in the UK include: ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin. Fluoroquinolone antibiotics are indicated for serious, life-threatening bacterial infections.

The restrictions follow an EU wide safety review. Fluoroquinolones can very rarely cause long-lasting, disabling, and potentially irreversible adverse effects, sometimes affecting multiple systems, organ classes, and senses. The first signs of these adverse reactions include: tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy and central nervous system effects.

Health-care professionals should not prescribe fluoroquinolones for non-severe or self-limiting infections, or non-bacterial conditions. Health-care professionals should prescribe with special caution for people older than 60 years and for those with renal impairment or solid-organ transplants, because they are at a higher risk of tendon injury. Also, use of corticosteroids with a fluoroquinolone should be avoided, since co-administration could exacerbate fluoroquinolone-induced tendinitis and tendon rupture.

Reference:
Drug Safety Update, MHRA, 21 March 2019 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.1, 2019: Risk of tendon damage and neuropathies in Ireland; No.6, 2018: Risk of long-lasting and disabling effects in Europe; No.2, 2017: Potential risk of persistent and disabling side effects in Canada; No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in USA)

Hydrochlorothiazide

Risk of non-melanoma skin cancer

New Zealand. Medsafe has announced it is working with sponsors of hydrochlorothiazide-containing products to update the product information to include information about the risk of non-melanoma skin cancer.

Hydrochlorothiazide is used in combination with cilazapril, quinapril, losartan or amiloride, to treat high blood pressure and build-up of excess fluid in the body (oedema).

While the mechanism is unknown, hydrochlorothiazide has skin photosensitizing effects. Patients who are at higher risk of developing non-melanoma skin cancer (e.g. personal or family history of skin cancer) should take protective measures in any case. Also, health-care professionals should encourage patients taking a hydrochlorothiazide preparation to check their skin and lips regularly and report any changes or new skin lesions or moles.

Reference:
Safety Communications, Medsafe, 15 April 2019 *(www.medsafe.govt.nz/)*

(See WHO Pharmaceuticals Newsletter No.2, 2019: Potential risk of non-melanoma skin cancer (NMSC) in Canada and Singapore; No.1, 2019: Risk of non-melanoma skin cancer in Egypt; No.6, 2018: Risk of non-melanoma skin cancer in UK)

Influenza HA vaccine

Risk of acute generalised exanthematous pustulosis

Japan. MHLW and PMDA have announced that the package inserts for influenza HA vaccines (Influenza HA Vaccine KMB® and other preparations) should be revised to include acute generalised

exanthematous pustulosis as an adverse drug reaction.

Influenza HA vaccine is indicated for prophylaxis of influenza.

One case associated with acute generalised exanthematous pustulosis has been reported in Japan during the previous three fiscal years. A causal relationship with the product could not be excluded for this case.

Reference:
Revision of Precautions, MHLW/PMDA, 9 May 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.6, 2018: Possible risk of lichen planus or lichenoid drug eruption in New Zealand)

Irinotecan

Risk of serious and fatal thromboembolic events

United Kingdom. The MHRA has updated the Summary of Product Characteristics (SPC) for irinotecan (Onivyde®) to include warnings of the risk of thromboembolic events.

Irinotecan is indicated to treat metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in adults who have progressed following gemcitabine-based therapy.

A routine EU review assessed serious cases of thromboembolic events in patients receiving irinotecan. In the cumulative review from October 2015 to April 2018, 23 serious cases of thromboembolic events were identified, of which four were fatal. The reported events included pulmonary embolism, vena cava thrombosis, deep vein thrombosis, catheter site thrombosis and subclavian vein thrombosis.

The risk of thromboembolic events has been included in the product information for irinotecan since it was licensed, but due to the increased reporting frequency and the seriousness of the reported events, additional warnings were added to the SPC, highlighting the need for a thorough medical history to identify patients with multiple risk factors.

Reference:
Drug Safety Update, MHRA, 21 March 2019 *(www.gov.uk/mhra)*

Lenvatinib

Risk of interstitial lung disease

Japan. MHLW and PMDA have announced that the package insert for lenvatinib (Lenvima®) will include interstitial lung disease as an adverse drug reaction.

Lenvatinib is indicated for unresectable thyroid cancer and unresectable hepatocellular carcinoma.

Eleven cases of interstitial lung disease have been reported in Japan during the previous three fiscal years. Of these cases, a causal relationship with the product could not be excluded in four cases. Also, a total of four patient mortalities have been reported, and of the four cases a causal relationship with the product could not be excluded for one.

Reference:
Revision of Precautions, MHLW/PMDA, 9 May 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.6, 2018: Risk of pneumothorax in Japan)

Nivolumab (genetical recombination)

Risk of pituitary impairment

Japan. The MHLW and PMDA have announced that the package insert for nivolumab (Opdivo®) should be revised to include conditions related to pituitary impairment such as hypophysitis, hypopituitarism, and adrenocorticotropic hormone deficiency as adverse drug reactions.

Indications of nivolumab includes malignant melanoma, unresectable advanced or recurrent non-small cell lung cancer and relapsed or refractory classical Hodgkin lymphoma. Also, nivolumab is used for chemotherapy to treat unresectable, advanced or recurrent gastric cancer that has progressed after initial cancer chemotherapy.

A total of 76 cases involving pituitary impairment have been reported in Japan during the previous three fiscal years. Of the 76 cases, a causal relationship with the product could not be excluded for 11 cases. Also, two patient mortalities have been reported, including one case for which a causal relationship with the product could not be excluded.

MHLW and PMDA advise that patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of use should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 9 May 2019 *(www.pmda.go.jp/english/)*

Opioid pain medicines

Risk of uncontrolled pain and withdrawal symptoms following sudden discontinuation

USA. The US Food and Drug Administration (FDA) has required changes to the prescribing information for opioid pain medicines to warn of serious withdrawal symptoms, uncontrolled pain, psychological distress and suicide following sudden

discontinuation or a rapid decrease in dose.

Opioids are used to manage pain when other analgesic treatments cannot be taken or are not able to provide enough pain relief. Common opioids include codeine, fentanyl, hydrocodone, morphine and oxycodone.

Rapid discontinuation can result in uncontrolled pain or withdrawal symptoms. Patients may attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin and other substances.

Health-care professionals should not abruptly discontinue opioids in a patient who is physically dependent. When health-care professionals and their patients have agreed to taper the dose of an opioid analgesic, a variety of factors should be considered which include: the dose of the drug, the duration of treatment, the type of pain, and the physical and psychological attributes of the patient.

There are no standard opioid tapering schedules that are suitable for all patients. A patient-specific plan should be created to gradually taper the dose of the opioid and patients should be monitored and supported to prevent serious withdrawal symptoms, worsening of pain or psychological distress.

Reference:
Safety Alerts for Human Medical Products, US FDA, 9 April 2019 *(www.fda.gov)*

Quetiapine

Risk of serious skin diseases

Japan. MHLW and PMDA have announced that the package insert for quetiapine (Seroquel® and Bipresso®) should be revised to include toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme as adverse drug reactions.

Quetiapine is indicated for schizophrenia and improvement of depressive symptoms in patients with bipolar disorder.

One case of TEN, one case of oculomucocutaneous syndrome, and one case of erythema multiforme have been reported in Japan during the previous three fiscal years, respectively. Of these three cases no patient mortalities have been reported.

Reference:
Revision of Precautions, MHLW/PMDA, 19 March 2019 *(www.pmda.go.jp/english/)*

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Risk of necrotising fasciitis of the perineum (Fournier's gangrene)

1. Singapore. The Health Sciences Authority (HSA) has announced that the package inserts for sodium-glucose co-transporter 2 (SGLT2) inhibitors are being updated to warn about the risk of necrotising fasciitis of the perineum (Fournier's gangrene).

SGLT2 inhibitors are oral glucose-lowering agents that increase the renal excretion of glucose through the inhibition of SGLT2-mediated renal glucose reabsorption. Three SGLT2 inhibitors have been registered in Singapore. They are canagliflozin (Invokana®), dapagliflozin (Forxiga® and Xigduo XR®), and empagliflozin (Jardiance® and Glyxambi®).

The HSA has not received any local reports of Fournier's gangrene associated with SGLT2 inhibitors.

Health-care professionals are encouraged to take into consideration this risk when prescribing a SGLT2 inhibitor and to consider the possibility of Fournier's gangrene in SGLT2 inhibitor-treated patients who present with pain, tenderness, erythema or swelling in the genital or perineal area.

Reference:
Product Safety Alerts, HSA, 9 May 2019 (*http://www.hsa.gov.sg/*)

2. Japan. MHLW and PMDA have announced that the package inserts for products containing SGLT2 inhibitors should be revised to include necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) as an adverse drug reaction.

One case of Fournier's gangrene has been reported in Japan during the previous three fiscal years. A causal relationship to the product could not be excluded in this case.

A disproportionality analysis using the WHO global database of Individual Case Safety Reports (ICSRs), VigiBase® shows a higher number of adverse reaction of Fournier's gangrene or necrotising fasciitis reported for multiple SGLT2 inhibitors than would be expected in the entire database. In addition, data from other antidiabetic drugs have not shown such a trend.

Although the mechanism of Fournier's gangrene with SGLT2 inhibitors has not been elucidated, the pharmacological effect of SGLT2 inhibitors cannot be excluded.

Reference:
Revision of Precautions, MHLW/PMDA, 9 May 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.2, 2019: Risk of Fournier's gangrene in UK; No.5, 2018: Risk of serious infection of the genital area in USA)

Sorbitol, fructose (excipient)

Hereditary fructose intolerance

Japan. MHLW and PMDA have announced that the package inserts for intravenous injection products containing sorbitol or fructose as excipients should be revised to include warnings for careful administration in patients with hereditary fructose intolerance.

Sorbitol and fructose are used in various medicines as excipients. Also, fructose is a metabolite from sorbitol in the body.

Although the package inserts for intravenous injection products containing sorbitol or fructose as active ingredients already specify a contradiction in those at risk of hereditary fructose intolerance, other products containing sorbitol and fructose as excipients will also include these warnings.

This follows the decision of the European Medicines Agency (EMA) to contraindicate the use of intravenous injection products containing sorbitol or fructose as excipients in patients with hereditary fructose intolerance.

As the products investigated contain sorbitol or fructose as excipients and not as an active ingredient, it is difficult to obtain information on adverse reactions and patient

fumarate (Takecab®, Vonosap® and Vonopion®) should be revised to include toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme as adverse drug reactions.

Vonoprazan is indicated for gastric ulcer, duodenal ulcer and reflux esophagitis, and for adjunct therapy in *Helicobacter pylori* eradication.

Seven cases involving TEN have been reported with vonoprazan use in Japan during the previous three fiscal years, and of the seven cases one reported a fatality. Twenty-two cases involving oculomucocutaneous syndrome have been reported in Japan during the previous three fiscal years, but no mortality has been reported. Seventy-five cases of erythema multiforme have been reported in Japan during the previous three fiscal years, but no mortality has been reported.

Reference:

Revision of Precautions, MHLW/PMDA, 19 March 2019 *(www.pmda.go.jp/english/)*