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

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

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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 Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

Contents

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Regulatory Matters

Safety of Medicines

Signal

Aflibercept

Risk of osteonecrosis of the jaw

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has announced that the package insert of aflibercept (Zaltrap®) will be updated to include the new information related to the risk of osteonecrosis of the jaw (ONJ). In addition, in agreement with the NPRA, the product registration holder of aflibercept has issued a Direct Health-care Professional Communication (DHPC) letter on this matter.

Aflibercept (Zaltrap®) is indicated for combination with irinotecan/5-fluorouracil/folinic acid for chemotherapy for metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.

The NPRA has received five ADR reports related to this product in Malaysia. The reported adverse events include impaired healing, skin hyperpigmentation, back ache and hypertensive crisis, but no ONJ case report associated with aflibercept has been received to date.

There have been eight post-marketing cases of ONJ in patients treated with aflibercept reported worldwide. These patients also had other known risk factors for ONJ, namely concomitant bisphosphonate therapy, invasive dental procedures, or infection.

Reference:
REAKSI Drug Safety News, NPRA, No. 33, January 2017

Aluminium potassium sulfate hydrate/tannic acid

Risk of rectovaginal fistula

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for aluminium potassium sulfate hydrate/tannic acid (Zione®) has been updated to include the risk of rectovaginal fistula as a clinically significant adverse reaction and as a precaution.

Aluminium potassium sulfate hydrate/tannic acid is indicated for prolapsed internal haemorrhoids.

Two cases associated with rectovaginal fistula have been reported in Japan. Of these, a causal relationship could not be excluded in one case. In addition, rectovaginal fistula may occur in association with the administration procedure.

Reference:
Revision of Precautions, MHLW/PMDA, 21 March 2017 *(www.pmda.go.jp/english/)*

Aripiprazole

Risk of impulse control disorders

Australia. The Therapeutic Goods Administration (TGA) has updated the precautions and adverse effects sections of the product information documents for aripiprazole (Avilify® and others) to include additional information about impulse control disorders.

Aripiprazole is used for the treatment of schizophrenia and treatment of manic or mixed episodes associated with bipolar I disorder in adults as monotherapy and in combination with lithium or valproate.

Cases of obsessive-compulsive disorder, eating disorder and impulse-control problems, including gambling and hyper-sexuality, have been reported in patients being treated with aripiprazole.

The updated precautions section of the product information warns that patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges reported were increased sexual urges, compulsive spending, binge or compulsive eating and other impulsive and compulsive behaviours.

The TGA stated that impulse-control symptoms can be associated with the underlying disorder, however, in some cases urges were reported to have stopped when the dose was reduced or the medication was discontinued.

Reference:
Medicines Safety Update, TGA, Vol. 8, No. 1, February 2017 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.3, 2016: Risk of impulse-control problems in the US and No.6, 2015: Risk of certain impulse control behaviours in Canada)

Canagliflozin

Risk of lower limb amputation

Malaysia. The NPRA has updated the local package insert of canagliflozin (Invokana®) to include the risk of lower limb amputation. In addition, the product registration holder of canagliflozin has issued a DHPC letter on this safety issue in agreement with the NPRA.

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor that is used for the management of Type II Diabetes mellitus.

Canagliflozin was registered in Malaysia in 2016. At the time of this publication, the NPRA had not received any ADR reports related to this product.

Reference:
MADRAC Newsletter, NPRA, Volume 21, December 2016

(See page 12 potential risk of toe amputation with SGLT2 inhibitors in EU)

Chlorhexidine gluconate

Rare but serious allergic reactions

USA. The US Food and Drug Administration (FDA) has warned that rare but serious allergic reactions have been reported with products containing chlorhexidine gluconate. Although rare, the number of reports of serious allergic reactions to these products have increased over the last several years. As a result, the FDA has requested the manufacturers of over-the-counter (OTC) antiseptic products containing chlorhexidine gluconate to add a warning about this risk to the drug facts labels.

Chlorhexidine gluconate is mainly available in OTC products to clean and prepare the skin before surgery and before injections in order to help reduce bacteria that potentially can cause skin infections. These products are available as solutions, washes, sponges. Chlorhexidine gluconate is also available as a mouthwash to treat gingivitis and as an oral chip to treat periodontal disease.

The FDA has identified 52 cases of anaphylaxis, a severe form of allergic reaction, with the use of chlorhexidine gluconate products applied to the skin. Between January 1969 and early June 2015, the FDA received 43 reported cases worldwide. More than half of these 43 cases were reported after 2010, and after the FDA's public health notice in 1998. These include only reports submitted to FDA, so there are likely additional cases about which we are unaware. The serious allergic reaction cases reported outcomes that required emergency department visits or hospitalizations to receive treatments. These allergic reactions resulted in two deaths. Eight additional cases of anaphylaxis were published in the medical literature between 1971 and 2015 and one case was identified in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) database between 2004 and 2013.

Reference:
Drug Safety Communication, US FDA, 2 February 2017 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletter No.3, 2016: Serious allergic reactions in Canada)

Codeine

Risk of respiratory depression

Malaysia. The NPRA has reviewed the risk of respiratory depression with codeine and has issued a directive to update the local package inserts of codeine-containing products with this safety issue.

Codeine-containing medicines are used to treat pain and reduce cough.

Since the year 2000, the NPRA has received 16 ADR reports with 32 adverse events suspected to be related to codeine in Malaysia. Three reports were associated with breathing problems, namely shortness of breath (2) and breathing difficulty (1).

Reference:
MADRAC Newsletter, NPRA, Volume 21, December 2016

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

Dienogest/ethinylestradiol containing products

Use should be limited to women who choose oral contraception

EU. The European Medicines Agency (EMA) has recommended that medicines containing a combination of dienogest 2 mg and ethinylestradiol 0.03 mg (Valette® and others) can continue to be used to treat moderate acne when suitable treatments, applied to the skin or antibiotics taken by mouth, did not work. However, these medicines should only be used for the treatment of acne in women who also choose oral contraception. The prescribing information for these medicines will be updated in line with these recommendations.

Medicines containing dienogest 2 mg and ethinylestradiol 0.03 mg are used as oral contraceptives and for the treatment of moderate acne.

Having evaluated the existing data on the effectiveness of the combination in the treatment of acne, EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that there is sufficient evidence to support its use in moderate acne. Regarding the risk of side effects, the CHMP considered that the available data do not raise any new safety concern. The known risk of venous thromboembolism (VTE or blood clots in veins), which can occur with all combined hormonal contraceptives, is considered low. However, the data on the risk with dienogest/ethinylestradiol are not sufficient to accurately estimate in comparison with other contraceptives and further data are still awaited.

Considering the observed benefits of dienogest/ethinylestradiol in the treatment of acne, the potential risk of VTE and the nature of the disease, the CHMP concluded that this combination should only be used after certain other treatments have failed, and only when oral contraception is chosen. The CHMP also recommended that women should be assessed by their doctor 3 to 6 months after starting treatment and periodically thereafter to review the need for continuation of treatment.

Reference:
Press release, EMA, 27 January 2017 *(www.ema.europa.eu)*

Direct-acting antivirals

Possible effects on blood glucose control when used in patients with type 2 diabetes: added to the medicine monitoring scheme

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) has highlighted possible effects of direct-acting antivirals on blood glucose control when used in patients with type 2 diabetes exposed to direct-acting antivirals (DAAs) and has placed this issues on the medicines monitoring scheme to obtain further information on these possible effects.

DAA regimens such as ombitasvir/paritaprevir/ ritonavir co-packaged with dasabuvir (Viekira Pak®) are used for the treatment of chronic hepatitis C infection.

Medsafe has been recently alerted to a case of type 2 diabetic patient who started hepatitis C treatment with Viekira Pak®. Eight weeks after starting treatment, the patient's blood glucose control improved (HbA1c almost halved).

There are case reports in the scientific literature which describe improvement of diabetes with hepatitis C treatment. Patients experienced reduced insulin resistance and improved blood glucose control. However, the available information on the association between hepatitis C treatment and effects on blood glucose control in patients with type 2 diabetes is not definitive. There may be differences in effect depending on which hepatitis C virus genotype the patient is infected with, which treatment they undergo and interactions with other factors such as weight. In addition, there are some case reports with increases in blood glucose levels.

Medsafe has considered that the overall benefit-risk balance for DAAs remains positive.

Reference:
Safety Information, Medsafe, 13 March 2017 (*www.medsafe.govt.nz/*)

Fluoroquinolones

Potential risk of persistent and disabling side effects

Canada. Health Canada has recommended updating the safety information for all fluoroquinolone products to include information about the risk of persistent and disabling side effects including tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders.

Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin) are antibiotics which are authorized to treat many types of bacterial infections including urinary tract and respiratory infections.

Health Canada started a safety review following a review done by the US FDA on systemic fluoroquinolone drugs. The Health Canada safety review focussed on serious known side effects that included: tendonitis/tendinopathy, peripheral neuropathy, worsening of myasthenia gravis, hypersensitivity and serious skin reactions, mental disorders, depression and suicide/self-injury, convulsions, cardiovascular disorders, phototoxicity and vision disorders.

At the time of the review, Health Canada identified 115 reports of persistent and disabling side effects associated with the use of fluoroquinolones. In 78 of these reports, a probable (29 reports) or possible (49 reports) causal link could be made between the use of fluoroquinolones and persistent disability. In the remaining cases, there was either not enough information available or it was unlikely that the reports of persistent disability were related to the use of fluoroquinolones.

Most of the side effects that were reported in the 115 reports and linked to persistent disability included tendonitis/ tendinopathy, peripheral neuropathy and central nervous system disorders. The side effects of tendinopathy, peripheral neuropathy and central nervous system disorders are included in the current safety information. However, the possibility of persistent duration of these events was not included in the safety information for all fluoroquinolone products.

There was little information in the scientific and medical literature on persistent and disabling nature of side effects reported with fluoroquinolone use.

Health Canada's review concluded that some of the known side effects, specifically tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders, already linked to the use of fluoroquinolones, may be persistent and/or disabling.

Reference:
Summary Safety Review, Health Canada, 23 January 2017 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in the US and No.3, 2016: Restricting use in the US)

Furosemide

Risk of dermatitis lichenoid

India: The Pharmacovigilance Program of India-Indian Pharmacopoeia Commission (PvPI-IPC) has recommended that the Central Drugs Standard Control Organisation

(CDSCO) revise the drug safety label of furosemide to include dermatitis lichenoid as potential adverse drug reaction.

Furosemide is a diuretic used to treat oedema and mild to moderate hypertension.

Between 2011 and November 2016, the PvPI received four furosemide-dermatitis lichenoid ICSRs. The cases were reviewed by the Signal Review Panel (SRP)-PvPI-IPC and it was concluded that there was a strong causal relationship between furosemide and dermatitis lichenoid in these cases. The PvPI-IPC has reminded health-care professionals that dermatitis lichenoid is a potential adverse drug reaction with furosemide use.

Reference:
Based on the communication from IPC, NCC-PvPI, India (*www.ipc.gov.in*)

Hydroxyzine

Risk of acute generalized exanthematous pustulosis

Japan. The MHLW and the PMDA have announced that the package inserts for hydroxyzine (Atarax® and others) have been updated to include the risk of acute generalized exanthematous pustulosis as a clinically significant adverse reaction.

Hydroxyzine is indicated for

Hyoscine butylbromide

Risk of serious adverse effects in patients with underlying cardiac disease

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated prescribing information for hyoscine butylbromide (Buscopan®) to help to minimise the risk of serious adverse reactions in patients with cardiac disease.

Hyoscine butylbromide, given intravenously or intramuscularly, is indicated in acute muscular spasm, as in renal or biliary colic; in radiology for differential diagnosis of obstruction and to reduce spasm and pain in pyelography; and in other diagnostic procedures where spasm may be a problem (e.g., gastroduodenal endoscopy).

The MHRA has received nine reports of patients who died after receiving hyoscine butylbromide injection (including a report from a coroner). In most of these cases, the fatal adverse reaction was reported as acute myocardial infarction or cardiac arrest. Hyoscine butylbromide injection can cause adverse effects including tachycardia, hypotension, and anaphylaxis. These effects can be more serious in patients with underlying cardiac disease (e.g., heart failure, coronary heart disease, cardiac

Hypnotics/sedatives, anxiolytics and antiepileptics with drug dependence or withdrawal symptoms

Risk of dependence

Japan. The MHLW and the PMDA have announced that the package inserts for hypnotics/sedatives, anxiolytics and antiepileptics with dependence, drug dependence or withdrawal symptoms have been updated to underline the risk of dependence such as developing physical dependence with long-term use even within an approved dose range.

These medicines are used for the treatment of insomnia, anxiety, tension, depression, sleep disorder and others. They are also used as an anaesthetic premedication.

The package inserts for hypnotics/sedatives, anxiolytics, and antiepileptics include "dependence," "drug dependence," or "withdrawal symptoms" (excluding transplacental) as ADRs in the precautions section. PMDA, upon request from the MHLW, investigated whether there was a need to revise the package inserts.

Of the drugs subject to investigation, dependence related events were reported with etizolam (720 events in 695 cases), alprazolam (179 events in 171 cases), triazolam