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®.

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### Safety of Medicines

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### 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:**

(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:
(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.
**Regulatory Matters**

**Reference:**

**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 issue on the medicines monitoring scheme to obtain further information on these possible effects.

DAAs 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 by the US FDA on systemic fluoroquinolone drugs. The Health Canada safety review focussed on serious known side effects, specifically tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders. The side effects of tendonitis, 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:**

(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 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 tendonitis, 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:**

(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)
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 arrhythmia, or hypertension).

Several reports have noted that anaphylaxis is more likely to be fatal in patients with underlying coronary heart disease compared with those without.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 7:1, February 2017 (www.gov.uk/mhra)

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 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 (136 events in 158 cases), zolpidem tartrate (129 events in 126 cases), clonazepam (121 events in 118 cases), and ethyl lofazepate (74 events in 64 cases). These are all benzodiazepine (BZ) receptor agonists. Reports of dependence-related events were limited for barbiturates (BA) and non-BA drugs, and even the most frequently reported pentobarbital calcium had only 17 events in 15 cases.

Based on the safety information obtained and reviews and guidelines on

(CDSO) 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 urticaria, pruritus associated with skin disease (eczema, dermatitis, cutaneous pruritus), anxiety, tension and depressed mood. It is also used as an anaesthetic premedication and for prophylaxis of pre- or post-operative nausea/vomiting.

Cases of acute generalized exanthematous pustulosis have been reported in patients treated with hydroxyzine in Japan and overseas.

Reference:
Revision of Precautions, MHLW/PMDA, 14 February 2017 (www.pmda.go.jp/english/)
Dependence and Withdrawal

Symptoms in Japan, the PMDA has determined that the revisions of the package insert were necessary.

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

Idelalisib

Risk of serious infections

Canada. Health Canada has updated the safety information of idelalisib (Zydelig®) to include information on the risk of serious infections associated with its use.

Idelalisib is used for treatment of 2 types of blood cancers: relapsed chronic lymphocytic leukaemia and follicular lymphoma.

Health Canada reviewed the risk of serious infections with idelalisib because of the increased rates of serious infection on the clinical trial reports (sometimes leading to death) amongst those treated with idelalisib, compared to those who were not.

In March 2016, Health Canada reported that clinical trials involving idelalisib, in Canada and internationally, were being stopped due to serious side effects. In May 2016, Health Canada reported that serious side effects seen in clinical trials included infections with Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV). These clinical trials were testing new uses of idelalisib: earlier treatment and different drug combinations than authorized in Canada.

At the time of the review, Health Canada had received a total of 23 reports of death associated with idelalisib use (six from clinical trials and 17 from after being on the market) in Canada. In these reports, there was one death reported with a PJP infection, and none with CMV infection. These reports did not provide strong evidence that idelalisib alone was the cause of death, since the disease itself or other patient risk factors may also be associated with these infections. These cases all occurred in patients with other risk factors for PJP.

A search of the scientific literature found cases describing serious infections in patients treated with idelalisib.

Health Canada’s review of the available information concluded that there was a risk of serious infections, which may lead to death, associated with idelalisib use.

Reference:
Summary Safety Review, Health Canada, 3 March 2017 (www hc-sc.gc.ca)
(See WHO Pharmaceuticals Newsletters No.1, 2017 and No.5, No.4, No.3 and No.2 in 2016 for related information)

Iodine-containing contrast agents

Possible risk of hypothyroidism in infants: added to the medicines monitoring scheme

New Zealand. The Medsafe has highlighted a possible risk of hypothyroidism in infants exposed to iodine-containing contrast agents (ICAs) and has placed this safety concern on the medicines monitoring scheme to obtain further information on this possible adverse reaction.

ICAs are medicines used to enhance the ability of blood vessels and organs to be seen on medical imaging such as computed tomography (CT) scans. ICAs can be administered intravascularly (intravenously or intra-arterially) or enterally.

This follows an US FDA review of ten cases of hypothyroidism in infants exposed to ICAs - six in full term infants with major cardiac abnormalities and four in premature infants. In these reports hypothyroidism was diagnosed 7 to 30 days after receiving an ICA. Improvement was documented in eight cases – four of which required treatment with thyroxine.

No reports of hypothyroidism associated with ICAs have been reported to the Centre for Adverse Reactions Monitoring (CARM) in New Zealand.

ICAs are known to increase the risk of hyperthyroidism, particularly in those with a history of thyroid disease. Most New Zealand data sheets include advice regarding this risk. Observational studies have demonstrated that adults and children exposed to ICAs are at increased risk of developing hypothyroidism. However, studies in infants and neonates are limited.

Medsafe has considered the overall benefit-risk balance for ICAs remains positive, therefore Medsafe has not recommended to change the use of these products in infants.

Reference:
Safety Information, Medsafe, 2 March 2017 (www.medsafe.govt.nz)
(See WHO Pharmaceuticals Newsletter No.6, 2015: Rare cases of underactive thyroid in infants in the US)

Itraconazole

Risk of acute generalized exanthematous pustulosis

India: The PvPI-IPC has recommended that the CDSCO revise the drug safety label of itraconazole to include acute generalized exanthematous pustulosis as a potential adverse drug reaction.

Itraconazole is used for systemic infections of aspergillosis and candidosis, cryptococcosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis,
Lamotrigine

New information on drugs to be used in combination

Japan. The MHLW and the PMDA have announced that the package insert for lamotrigine (Lamictal®) has been updated to include perampanel and lacosamide as drugs that do not affect glucuronidation of lamotrigine.

Lamotrigine is as an antiepileptic, as monotherapy or as concomitant therapy with other antiepileptics.

Perampanel and lacosamide, both antiepileptics, have been approved in Japan. In the overseas clinical trial data for perampanel and lacosamide, it has been reported that these drugs had no effect on the pharmacokinetics of lamotrigine.

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

Low-molecular-weight heparins

Potential risk of bleeding in or around the spinal cord (spinal/epidural hematoma)

Canada. Health Canada has updated the Canadian safety information of low-molecular-weight heparins (LMWH; Fragmin®, Fraxiparine®, Innohep® and Lovenox®) to include information on the recommended length of time between LMWH injection and spinal/epidural anaesthesia or spinal puncture. This length of time can vary, but should be determined by the prescriber in accordance with recommendations in the Canadian safety information.

LMWH are prescription drugs which are authorized to treat or prevent blood clots.

Health Canada has reviewed information related to the known rare risk of bleeding in or around the spinal cord (spinal/epidural haematoma) in patients receiving LMWH to prevent blood clots while undergoing spinal/epidural anaesthesia or spinal puncture. The review was initiated because of an update by the US FDA to the safety information for LMWH related to this risk.

At the time of the review, Health Canada had received two Canadian cases of bleeding in or around the spinal cord in patients receiving LMWH and undergoing spinal/epidural anaesthesia or spinal puncture. In these two reports, there was not enough information to determine what may have played a role in the bleeding that occurred.

This safety review looked at 153 international reports of bleeding in or around the spinal cord in patients receiving LMWH while undergoing spinal/epidural anaesthesia or spinal puncture. In these 153 reports, it was found that a short length of time between LWMH use and the spinal procedure may have increased the risk of bleeding.

Health Canada’s review concluded that the risk of bleeding may increase if the spinal procedure is carried out soon after injection of LWMH.

Reference:
Summary Safety Review, Health Canada, 8 February 2017 (www.hc-sc.gc.ca) (See WHO Pharmaceuticals Newsletter No.6, 2013: Recommendations to decrease risk of spinal column bleeding and paralysis in the US)
**Menthol containing OTC topical pain relievers**

**Risk of serious skin burns**

**Canada.** Health Canada has updated the labelling standard for OTC topical pain relievers containing menthol alone or in combination, to inform about this risk.

OTC topical pain relievers are applied on the skin to relieve pain in muscles or joints. These products, which may contain menthol, methyl salicylate or capsaicin, either alone or in combination, relieve pain by slightly irritating the skin surface. This irritation reduces the feeling of pain in the underlying joints and muscles.

Health Canada has carried out a follow-up safety review, following the safety review in 2013 and based on the additional safety information gathered by Health Canada or obtained by certain manufactures on these products.

At the time of the review, Health Canada had received a total of 29 reports of serious skin burns related to the use of OTC topical pain relievers containing menthol, methyl salicylate or capsaicin in Canada. The products were used as directed in 28 reports; in some reports, other factors may have played a role in the development of burns. In the remaining reports, the product was not used as directed. Of these 29 reports, there were seven reports involving products containing only menthol, two reports involving products containing only methyl salicylate, and one report involving a product containing only capsaicin. There were 19 reports involving products containing multiple ingredients, and most of these contained menthol and methyl salicylate together.

The review of the safety information provided by manufacturers identified over 100 additional international reports of serious burns linked to the use of topical pain relievers. The majority of these cases contained menthol, alone or in combination with methyl salicylate. There were no cases of serious burns linked to the use of topical muscle and joint pain relievers containing methyl salicylate or capsaicin alone.

In the medical literature, there is only one case of serious skin burns linked to the use of a topical pain reliever product containing menthol and methyl salicylate; however, the product was used inappropriately.

Health Canada’s current review has established a link between the use of topical pain relievers containing menthol and the risk of rare but serious skin burns; however, there was not enough information to draw the same conclusions for the products containing methyl salicylate or capsaicin alone.

**Reference:**


(See WHO Pharmaceuticals Newsletter No.5, 2012: Rare cases of serious burns with Over-The-Counter Topical Muscle and Joint Pain Relievers in the US)

**Olanzapine**

**Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**

**Malaysia.** The NPRA has reviewed the risk of Eosinophilia and Systemic Symptoms (DRESS) with olanzapine and issued a directive to update the local package inserts of olanzapine-containing products with this safety issue.

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

Since the year 2000, the NPRA has received 283 ADR reports with 488 adverse events suspected to be related to olanzapine in Malaysia. There were four reports (0.8%) involving severe cutaneous adverse reactions (SCARs), namely erythema multiforme (3) and DRESS (1).

**Reference:**

MADRAC Newsletter, NPRA, Volume 21, December 2016

(See WHO Pharmaceuticals Newsletter No.3, 2016: Risk of serious skin reactions in the US)

**SGLT2 inhibitors**

**Potential risk of toe amputation**

**EU.** The EMA has informed about a potential increased risk of lower limb amputation in patients taking the sodium-glucose co-transporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin and empagliflozin used for type 2 diabetes. The EMA has also recommended to include a warning of the potential increased risk of toe amputation in the prescribing information for these medicines.

Canagliflozin, dapagliflozin and empagliflozin are type 2 diabetes mellitus medicines of the class SGLT2 inhibitors.

The review of SGLT2 inhibitors was prompted by an increase in lower limb amputations (mostly affecting the toes) in patients taking canagliflozin in two clinical trials (CANAgliflozin cardioVascular Assessment Study: CANVAS and CANVAS-R). The studies, which are still ongoing, involved patients at high risk of heart problems and compared canagliflozin with placebo.

As of September 2016, the incidence of lower limb amputation in the CANVAS study was 7 in 1000 patient-years with canagliflozin 100 mg daily and 5 in 1000 patient-years with canagliflozin 300 mg daily, compared with 3 in 1000 patient-years with placebo. (One patient-year is equivalent to 1 patient taking the medicine for 1 year.) The study enrolled around 4300 patients.
As of September 2016, the incidence of lower limb amputation in the CANVAS-R study was 8 in 1000 patient-years with canagliflozin and 4 in 1000 patient-years with placebo. The study enrolled over 5800 patients.

The incidences of lower limb amputation given above for both CANVAS and CANVAS-R are based on interim data, and final incidence rates will depend on analysis of the final study datasets.

All patients with diabetes (especially those with poorly controlled diabetes and problems with the heart and blood vessels) are at higher risk of infection and ulcers (sores) which can lead to amputations. The mechanism by which canagliflozin may increase the risk of amputation is still unclear.

An increase in lower limb amputations has not been seen in studies with other medicines in the same class, dapagliflozin and empagliflozin. However, data available to date are limited and the risk may also apply to these other medicines.

Further data are expected from ongoing studies with canagliflozin, dapagliflozin and empagliflozin.

(See page 5 risk of lower limb amputation with canagliflozin in Malaysia)

### Tramadol-containing products

#### Risk of serious respiratory depression in children and adolescents

Canada. Health Canada has updated the product information for tramadol-containing products to further manage the risk of serious breathing problems. Health Canada has also reminded that tramadol is not recommended for use in patients under 18 years of age.

Tramadol is an opioid prescription drug to treat moderate to moderately severe pain in adults.

Health Canada has carried out safety review on tramadol, after a safety review of codeine and the risk of serious breathing problems in children.

At the time of the review, Health Canada had not received any reports of serious breathing problems related to the use of tramadol in children and adolescents in Canada.

This safety review found one international report of respiratory depression in the published literature, linked to the use of tramadol in a 5-year old child. The child was an ultra-rapid metabolizer and this may have played a role.

Many studies suggest that differences in how the liver works could affect the risk of side effects experienced by patients using tramadol. These studies help to confirm that ultra-rapid metabolizer patients may be more at risk of developing respiratory depression with the use of tramadol.

(See WHO Pharmaceuticals Newsletters No.6, 2015: Risk of slowed or difficult breathing in children in the US and No.5, 2015: Tramadol oral drops not for children under the age of 12 years in Australia)

### Vemurafenib

#### Risk of acute kidney injury

Japan. The MHLW and the PMDA have announced that the package insert for vemurafenib (Zelboraf®) has been updated to include the risk of acute kidney injury as a clinically significant adverse reaction. In addition, the company core datasheet (CCDS) has also been updated.

Vemurafenib is indicated for BRAF mutation-positive radically unresectable malignant melanoma.

A total of two cases associated with acute kidney injury have been reported in Japan. A causal relationship could not be excluded in both cases.

Reference: Revision of Precautions, MHLW/PMDA, 14 February 2017 (www.pmda.go.jp/english/)

### Warfarin

#### Risk of calciphylaxis

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

Warfarin is an oral anticoagulant which acts by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X.

Since the year 2000, the NPRA has received 341 warfarin-related ADR reports with a total of 563 adverse events in Malaysia. Most of the adverse events were reported as skin and subcutaneous tissue disorders (111 cases, 19.7%), nervous system disorders (92 cases, 16.3%) and gastrointestinal system disorders (63 cases, 11.2%). At present, no reports of calciphylaxis have been received locally. One report described a female patient who developed pain and skin necrosis after taking warfarin, however it was not confirmed whether this was calciphylaxis or warfarin-induced skin necrosis (WISN), as no skin biopsy was done.

Reference: MADRAC Newsletter, NPRA, Volume 21, December 2016
(See WHO Pharmaceuticals Newsletter No.4, 2016: Reports of calciphylaxis in the US)
**Andrographis paniculata**

Potential risk for allergic reactions

New Zealand. The Medsafe has reminded that products containing andrographis have the potential to cause serious allergic reactions.

Andrographis paniculata is a herb included in some natural health products. These products are used by consumers to support a healthy immune system, support recovery from the common cold and help with symptoms of the cold.

In New Zealand, a number of cases have been identified by CARM which reported allergic reaction in consumers taking andrographis-containing products. The reported reactions include dyspnoea, flushing, urticaria and anaphylaxis.

Similar reports have been noted internationally. Between December 2002 and April 2014, the TGA in Australia received 43 reports of anaphylaxis and 78 reports of other allergic-type reactions associated with products that contain andrographis.

WHO Global ICSR database, VigiBase® contains 198 reports related to andrographis. Of these reports, 147 reports involved hypersensitivity reactions such as urticaria, pruritus, anaphylactic reactions, eyelid oedema, face oedema and angioedema. These reports were submitted by countries participating in the WHO Programme for International Drug Monitoring (P IDM).

**Reference:**
Safety Information, Medsafe, 24 March 2017 (www.medsafe.govt.nz)

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**Bevacizumab used with colorectal stents**

Potential increased risk of bowel rupture: not enough evidence

Canada. Health Canada has issued an article to raise awareness of potential increased risk of bowel rupture with the use of bevacizumab (Avastin®) and a colorectal stent at the same time.

Bevacizumab is used as part of the treatment, along with a specific type of chemotherapy, for certain cancers including those in the bowel. It is available as a solution for injection. Colorectal stents are part of a group of devices and are licensed for treatment of intestinal strictures.

At the time of the review, Health Canada received six reports of bowel rupture related to the use of colorectal stents and 83 reports of bowel rupture related to the use of bevacizumab in Canada. Only three of these reports mentioned that the two products were used together.

A number of published studies including a recent Canadian study reported an increased risk of bowel rupture in patients treated with colorectal stents and bevacizumab-based chemotherapy, as compared to patients receiving colorectal stents and chemotherapy without bevacizumab for the treatment of bowel cancer. It was difficult to make conclusions about the extent of the increased risk because of other factors that could also have played a role in the bowel rupture, including the type of cancer itself and how much the cancer had grown or developed.

Health Canada’s review concluded that there is limited evidence at this time to suggest an increased risk of bowel rupture when colorectal stents and bevacizumab are used together to treat colon cancer patients.

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**Bisphophonates**

Potential risk of osteonecrosis beyond the area of the jawbone: not enough evidence

Canada. Health Canada has reviewed the potential risk of osteonecrosis related with bisphosphonate use. The review was made due to the product information updates in Europe that warn about the risk of severe bone damage in the outer part of the ear canal.

Bisphophonates (alendronate (Fosamax® and Fosavance®), risedronate (Actone®), etidronate (Didrone® and Didrocal®), pamidronate, zoledronate (Zometa® and Aclasta®) and clodronate (Clasteon® and Bonefos®)) are prescription drugs which are used for the treatment of bone-related diseases such as: osteoporosis; Paget’s disease of bone; bone metastases; hypercalcaemia of malignancy; and a particular type of blood cell cancer known as multiple myeloma.

At the time of the review, Health Canada received 15 reports of severe bone damage related to the use of those bisphosphonates that do not have a warning about osteonecrosis in Canada. Among these reports, none were related to severe bone damage of the external ear canal. Out of the 15 reports, seven were excluded from the safety review because the bone damage was established before the patient took the bisphosphonate product. For the remaining eight reports, a link between osteonecrosis and

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Health Canada will continue to monitor safety information involving colorectal stents and bevacizumab.

**Reference:**
the use of the bisphosphonate could not be established. This was either due to lack of information, the existence of other health conditions such as previous bone fracture or the patient being exposed to cortisone.

This safety review found 11 patient reports in the scientific literature on the use of bisphosphonates that do not have a warning about severe bone damage. Severe bone damage to the external ear canal was noted in five reports. In the remaining 6 reports, severe damage to other bones was noted. Overall, the review of these 11 cases could not conclude whether bisphosphonate use played a role in the severe bone damage because of other factors such as the patient having other diseases (e.g., diabetes) or receiving other treatments (e.g., cancer treatments).

Health Canada’s review of the available information did not establish a link between the use of the following bisphosphonates [risedronate, etidronate and clodronate] and the risk of severe bone damage of the external ear canal or other parts of the body other than the jaw. The review also did not establish a link between the use of [alendronate and clodronate] and the risk of severe bone damage (in areas other than the outer ear canal and the jaw).

Health Canada will continue to monitor safety information involving bisphosphonates.

Reference:

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Certain anti-neoplastic, immunosuppressant or immunomodulatory medications

Potential risk of progressive multifocal leukoencephalopathy (PML)

Australia. The TGA has provided advice on the potential risk of progressive multifocal leukoencephalopathy (PML) for health care professionals who prescribe anti-neoplastic, immunosuppressant or immunomodulatory medications as follows:

- Prescribers of anti-neoplastic, immunosuppressant or immunomodulatory medications should be aware of PML as a potential adverse event.
- Prescribers should consider PML in any immunosuppressed patient presenting with new onset focal neurological deficits.
- Prescribers should be aware that in Multiple Sclerosis (MS) patients, PML can sometimes be confused with an MS relapse, which has the potential to delay PML diagnosis and treatment.
- Prescribers should monitor patients being treated with medicines known to be associated with PML for any new focal neurological signs or symptoms.
- Prescribers should consider testing for anti-John Cunningham Virus (JCV) antibodies in patients prior to starting medicines that have been associated with PML or during treatment if antibody status is not known.
- If a prescriber suspects PML, immunosuppressive medications should be withheld and appropriate investigations ordered (gadolinium-enhanced MRI and cerebrospinal fluid analysis for JC viral DNA are recommended).

PML can be a complication in those who are exposed to antineoplastic or immunosuppressive therapies such as fludarabine (Fludara®), cyclophosphamide (Endoxan®), azathioprine (Imuran®), mycophenolate mofetil (Cellcept® and Myfortic®), tacrolimus (Prograf®), everolimus (Certican®), sirolimus (Rapamune®) and cyclosporine (Neoral®); and monoclonal antibodies including natalizumab (Tysabri®), rituximab (Mabthera®), alemtuzumab (Mabcampath®), vedolizumab (Entyvio®), brentuximab vedotin (Adcetris®) and Ofatumumab (Azerra®) as well as in those with HIV/AIDS, haematological malignancies (for example, lymphoproliferative disorders) and organ or haemopoietic stem cell transplantation.

More recently, PML was reported in patients receiving immunomodulatory therapy, namely fingolimod (Gilenya®) or dimethyl fumarate (Tecfidera®) for the treatment of MS.

As of 16 November 2016, the TGA’s Database of Adverse Event Notifications (DAEN) includes 30 reports of PML. It should be noted that not all of these reports document confirmed cases.

In many of these reports, patients were also receiving chemotherapy and/or had concomitant or previous use of other immunosuppressive/immunomodulatory medicines or had underlying immunosuppressive conditions. Some of the reports involved patients on treatment for MS.

The majority of reports were associated with use of monoclonal antibodies, in particular natalizumab and rituximab. There were 16 reports associated with rituximab and in 12 of these reports it was the sole suspected medication. There were 10 reports associated with natalizumab and in seven of these it was the sole suspected medication. In addition there were smaller numbers of reports that co-suspected multiple medications known to cause
imunosuppression or to have previously been associated with PML; fludarabine (4), fingolimod (2), alemtuzumab (1), leflunomide (1), azathioprine (1), mycophenolic acid (1) and tacrolimus (1).

Reference:

Eluxadoline

Increased risk of serious pancreatitis in patients without a gallbladder

USA. The US FDA has warned that eluxadoline (Viberzi®) should not be used in patients who do not have a gallbladder. The FDA is working with the manufacturer of eluxadoline to address these safety concerns.

Eluxadoline is a prescription medicine used to treat irritable bowel syndrome in adults when the main symptom is diarrhoea (IBS-D).

From May 2015, when eluxadoline was first approved, through February 2017, the FDA received reports of 120 serious cases of pancreatitis or death in the FDA Adverse Event Reporting System (FAERS) database. Seventy-six of these cases resulted in hospitalization, of which two patients died. Some cases of serious pancreatitis or death also reported spincter of Oddi spasm (n=6) or abdominal pain (n=16).

Among the 84 cases that reported a time to onset of the adverse event, serious cases of pancreatitis or death occurred after one or two doses of eluxadoline (n=48). Notably, the patient who experienced pancreatitis died within 3 days after taking the initial eluxadoline dose. Serious cases of pancreatitis also occurred subsequently with prolonged use (n=36).

Among the 68 cases that reported gallbladder status, 56 cases of pancreatitis or death occurred in patients who do not have a gallbladder. The majority of patients (n=44/56) received the currently recommended dosage of eluxadoline (75 mg) for patients who do not have a gallbladder. Of the 56 cases in patients who do not have a gallbladder, 21 reported that the patient did not abuse alcohol and 35 did not report the patient’s alcohol use status.

Reference:

Rivaroxaban, dabigatran and apixaban

Possible risk of hair loss (alopecia): no link was shown

New Zealand. The Medsafe has updated its original communication on possible risk of hair loss (alopecia) with rivaroxaban, dabigatran and apixaban.

These medicines are used in a variety of conditions including:
• Prevention of stroke and systemic embolism.
• Prevention of venous thromboembolism (VTE).
• Treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE).
• Prevention of recurrent DVT and/or PE.

Medsafe has stated that during the medicines monitoring period (30 May 2016 to 31 December 2016), no further cases of alopecia were reported to the Centre for Adverse Reactions Monitoring (CARM). The safety concern has been investigated and no link between rivaroxaban, dabigatran and apixaban and hair loss was demonstrated.

Medsafe has concluded that the balance of the benefits and risks of harm for rivaroxaban, dabigatran and apixaban remains positive and no further action is required at this time.

Reference: Safety Information, Medsafe, 7 February 2017 (www.medsafe.govt.nz)

(See WHO Pharmaceuticals Newsletter No.4, 2016: Possible risk of hair loss (alopecia) in New Zealand)

Vemurafenib

Risk of radiation injury

Australia. The TGA has advised the health-care professionals that there have been overseas reports of radiation recall and radiation sensitization in patients treated with radiation before, during or after taking vemurafenib (Zelboraf®).

Vemurafenib is indicated for the treatment of unresectable stage IIIIC or stage IV metastatic melanoma positive for a BRAF V600 mutation.

Most of the reported cases were cutaneous in nature, but some cases involving visceral organs had fatal outcomes.

As of 17 August 2016, the TGA had received no Australian reports of radiation injury associated with vemurafenib treatment.


(See WHO Pharmaceuticals Newsletters No.4, 2016: Risk of potentiation of radiation toxicity in Singapore and No.6, 2015: Risk of potentiation of radiation toxicity in the United Kingdom)

Zostavax® (live, attenuated varicella-zoster virus vaccine)

Should not use in patients with compromised immune function

Australia. The TGA has warned that live, attenuated
varicella-zoster virus vaccine (Zostavax®) should not be used in people who are immunocompromised, as this is associated with a risk of mild to serious complications (including death) from infection with the vaccine virus.

Zostavax® is used for:

- prevention of herpes zoster (shingles) in people aged 50 years and older
- prevention of post-herpetic neuralgia (nerve pain due to damage caused by the varicella-zoster virus) and for reduction of acute and chronic zoster-associated pain in individuals 60 years of age and older.

The TGA has received a report of a death occurring in a person with pre-existing compromised immune function after receiving Zostavax® that is used to prevent shingles and prevention/treatment of nerve pain associated with the virus.

Reference:
Alert/Advisory, TGA, 7 March 2017 (www.tga.gov.au)
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 14 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 26). 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.

Idelalisib and Leukoencephalopathy
Dr Rebecca E Chandler, Uppsala Monitoring Centre

Summary
Idelalisib is a first-in-class lipid kinase inhibitor which was granted marketing authorisation in the US and in Europe for the treatment of relapsed chronic lymphocytic leukaemia and certain lymphomas in 2014. The licence applications included interim results in two pivotal trials; accelerated approval pathways were used to allow earlier patient access to the medicine and final results of the ongoing clinical trials are expected in the post marketing period.

As of September 2016 a total of seven cases of leukoencephalopathy were included in VigiBase®, the WHO international database of suspected adverse drug reactions; five of which were John Cunningham (JC) virus PCR positive cases of progressive multifocal leukoencephalopathy (PML). Cases arose from both the clinical trial setting as well as from spontaneous sources.

PML is associated with both the underlying disease for which idelalisib is indicated as well as the medication, rituximab, whose concomitant use is required in the approved indication for idelalisib. However, current data suggest that the total number of reports of PML received for idelalisib in the context of its limited post marketing exposure may be greater than expected even in the presence of these confounding factors. The purpose of the communication of this signal is to encourage further investigation to determine if there is an additive risk for PML and consideration for additional risk minimization measures as have been suggested for other agents with higher risks of PML.

Finally, the communication of this signal exemplifies the role of post-marketing pharmacovigilance in the rapid access to medicines whose approval has been based upon more limited clinical trial data.

Introduction
Idelalisib is a reversible, highly selective inhibitor of the delta isoform of phosphatidylinositol-3-kinase (PI3K), whose expression is restricted to hematopoietic cells and is central to B-cell homeostasis and function. Given that the PI3K pathway is overactive in B-cell malignancies, it is an attractive drug target for the treatment of CLL and lymphoma.1

In July 2014 the U.S. Food and Drug Administration (FDA) approved idelalisib for the treatment of patients with relapsed chronic lymphocytic leukaemia (CLL), in combination with rituximab, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities; an accelerated approval was also for the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) or relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies.2 The European Medicines Agency (EMA) also granted approval through an accelerated approval procedure in July 2015 for the same indications; the EMA licence also allows for first-line use in CLL in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy.3 The total number of patients included in the clinical safety database at the time of approval was only 752 patients.4

The effects of idelalisib appear to be multiple: interference with BCR (B-cell receptor) signalling through a decrease in phosphorylation of downstream pathways such as AKT and mitogen-activated protein kinase (MAPK)5, promotion of caspase-dependent apoptosis5,6, hindrance of the secretion of...
cytokines and chemokines which disrupts the communication and chemotaxis, and inhibition of survival signals from stromal derived factors CD40 ligand, BAFF, tumour necrosis factor, and fibronectin. Furthermore, although T-cell and natural killer cell viability are not affected by idelalisib, their production of inflammatory and anti-apoptotic cytokines such as IL-4, IL-6, IL-10 and interferon gamma (IFNy) is diminished.

Progressive multifocal leukoencephalopathy (PML) is a manifestation of an infection of the white matter of the brain with the John Cunningham (JC) virus which results in progressive demyelination. Although most people have been infected with the JC virus by the age of 10, PML is a rare disease which is typically seen only in people with severely depressed cell-mediated immunity caused either by HIV/AIDS, certain malignancies (such as CLL), and certain medications, such as immune therapy with monoclonal antibodies (e.g.: natalizumab, rituximab) and various other immunosuppressants, including prednisone, cyclophosphamide, methotrexate, and cyclosporine. The symptoms of PML are clumsiness, hemiparesis, dysarthria and visual field defects. The disease is progressive and typically culminates in death, usually within months after symptoms begin. Treatment of PML is supportive, with treatment of underlying disease or discontinuance of medicines which have been associated with PML.

The pathogenesis of PML remains incompletely elucidated, but it is thought to comprise of the following steps: initial infection with JC virus; establishment of a latent or persistent infection; gene rearrangement to express a neurotropic form of the virus; re-expression of the virus from the sites of latency or persistence; entry of the virus into the brain; establishment of productive infection of glial tissues; failed central nervous system immunosurveillance.

Reports in VigiBase®

As of September 2016 there were a total of five idelalisib cases included in VigiBase®, the WHO database of suspected adverse drug reactions, in association with the MedDRA Preferred Term (PT) “progressive multifocal leukoencephalopathy” and three cases which describe the event with the MedDRA PT “leukoencephalopathy”. These cases were identified using the Standardized MedDRA Query “demyelination” (broad). The IC value for idelalisib and PML is calculated to be 2.67 with IC_{025} of 1.15, while the IC value for idelalisib and leukoencephalopathy is calculated to be 2.36 (IC_{025}=0.31).

One of the cases of leukoencephalopathy was identified to be a duplicate of one of the cases of PML. Therefore, there are a total of seven unique reports included in this review.

The first report was received in VigiBase® in June 2015 and the most recent was received in July 2016. Three of the reports were ”spontaneous” and four were from clinical studies.

The cases arise from multiple countries: United States (two cases), Germany, Spain, Portugal, Switzerland, and the United Kingdom (one case each). There were five males and two females; the age range was between 56 and 80 years.

In six cases, idelalisib and rituximab were both considered to be suspect agents; in one case (case 1), additional agents were also considered to be suspect (fludarabine, cyclophosphamide, benmustine, alemtuzumab, and ibrutinib). One report (case 6) does not report rituximab as either past or concomitant therapy; in this case, obinutuzumab is the co-suspected medication.

Three of the seven cases had a fatal outcome, and two of the cases note that patients were recovering at the time of the report.

Case narratives

1. 72-year-old female with CLL was initiated on treatment with idelalisib and rituximab. Three months after starting therapy with this combination, she was admitted to the hospital with left-sided facial palsy and weakness of the arm. Computerized tomographic scan showed evidence of an ischemic stroke and this was initially entertained as the cause of the patients’ symptoms. However, within a few weeks of this diagnosis, there was concern for PML, and cerebrospinal fluid (CSF) was positive for copies of the JC virus. The patient died the next month of a “respiratory infection”. The patient’s CLL had been diagnosed approximately three and a half years prior, and she had been treated initially with rituximab, fludarabine and cyclophosphamide (five cycles). Her recurrent CLL disease was subsequently treated with a variety of sequential regimens: rituximab and cyclophosphamide (four months), and rituximab and bendamustine (three months). It is also noted that she received steroids for approximately five months which were stopped in the month prior to diagnosis of PML. The case report notes a number of complications potentially related to CLL/treatment: COPD, heart failure, autoimmune haemolytic anaemia, herpes zoster, respiratory infections with aspergillosis and Stenotrophomonas. Concomitant medications at the time of the report were atorvastatin, bisoprolol, furosemide, propylthiouracil, escitalopram, sulfamethoxazole, and voriconazole.
2. 71-year-old male with progressive CLL was initiated on treatment with idelalisib and rituximab. Therapy with rituximab lasted two months; therapy with idelalisib lasted three months. Three months after starting therapy, he was diagnosed with PML. Idelalisib was stopped at the time of diagnosis. The patient died approximately three months later. Cause of death was labelled as PML.

3. 73-year-old male with progressive CLL was initiated on treatment with idelalisib and rituximab. Therapy with rituximab was discontinued after two months, while therapy with idelalisib was continued for another five months. Six months after the initiation of treatment, while the patient was on idelalisib monotherapy, the patient developed a visual field defect and neurologic neglect syndrome. CSF was positive for JC virus and PML was diagnosed. Idelalisib was discontinued and therapy with mefloquine and mirtazapine was initiated. The patient was reported to be improving. The patient’s CLD had been treated in the past with fludarabine monotherapy (two cycles), bendamustine monotherapy (three cycles and then four cycles several years after), and combination rituximab and bendamustine (five cycles).

4. 77-year-old male with CLL was initiated on therapy with idelalisib and rituximab. Six months after the start of treatment, the patient was diagnosed with PML. The event of PML resulted in a fatal outcome. Concomitant medications included rosuvastatin, montelukast, iron, fenoibrate, ergocalciferol, escitalopram, tiotropium, omeprazole, simethicone, fenofibrate, ergocalciferol, escitalopram, tiotropium, omeprazole, simethicone, formoterol fumarate/budesonide, and famotidine.

5. 74-year-old male was initiated on idelalisib and rituximab for an unknown indication. Two weeks after beginning therapy, the patient experienced progressive and rapid neurological deterioration and muscular weakness of the lower limbs. The patient also had loss of mobility and urinary incontinence. The physician suspected a leukoencephalopathy. Lumbar puncture results were pending at the time of the report. Both idelalisib and rituximab were discontinued. Concomitant medications included dabigatran, digoxin, carvedilol, trimethoprim/sulfamethoxazole, acyclovir, omeprazole, and torasemide. There was no information included in the report regarding the outcome of the event.

6. 56-year-old female who was enrolled in a clinical trial and was treated with obinutuzumab and idelalisib for CLL, stage 3. The patient received escalating doses of obinutuzumab at 100 mg and concomitant idelalisib 150 mg (two per day) on day 1, obinutuzumab 900 mg on day 2 and obinutuzumab 1000 mg daily on day 8 which continued for 7 days. The date of the event of leukoencephalopathy is noted to have occurred two weeks after the first dose of obinutuzumab and idelalisib. Concomitant medications included dexamethasone, methylprednisolone, diphenhydramine, allopurinol, omeprazole, losartan, ciprofloxacin, ibuprofen, colecaltferol, paracetamol, amlodipine, and potassium. It is noted that the patient is recovering from the event.

7. 80-year-old male who was diagnosed with CLL in 2003. He was initiated on therapy in late 2015 with five cycles of rituximab. He had also received prednisone in variable doses. The patient was then initiated on combination therapy with rituximab and idelalisib in January 2016. The patient experienced blurred vision which resulted in consultation with a neurologist. After undergoing numerous neurological tests, he was diagnosed with PML with radiographic findings and with lumbar puncture revealing the presence of JC virus in CSF. Treatment with idelalisib was discontinued.

**Literature and Labelling**

The label for idelalisib approved in the EU contains warnings for transaminase elevations, pneumonitis and colitis. Section 4.8 notes also that “infections” and “neutropenia” occurred in clinical trials with a frequency of “very common” (even grade 3 abnormalities) in patients treated with idelalisib alone or in combination with anti-CD20 monoclonal antibodies. The label for idelalisib approved in the US contains a black box warning for hepatic toxicity, severe diarrhoea, colitis, pneumonitis, and intestinal perforation as well as additional warnings for severe cutaneous reactions and neutropenia. Section 6 notes that the following events occurred at a higher frequency in patients in clinical trials receiving rituximab+idelalisib compared to rituximab+placebo: pneumonia, nasal congestion, sepsis, bronchitis, sinusitis, and urinary tract infection, as well as neutrophil count decreased, lymphocyte count increased and lymphocyte count decreased. Given that all patients in this case series received the combination of idelalisib and rituximab, it should be mentioned that PML is included as a warning in the labelling for rituximab in both the EU and the US.

**Discussion and Conclusion**

Within the last 10 years, PML has been increasingly reported in association with the use of immunosuppressive and biologic agents. The first recognition were reports of PML in patients being treated with natalizumab for multiple sclerosis and Crohn’s disease in 2005. Since that time there have been reports with other agents, such as rituximab, which are
used to treat autoimmune diseases and lymphoproliferative disorders. Given the complex pathogenesis of PML and the differences in underlying diseases as well as drug targets, the risk for PML appears to differ among these agents and among the various types of patients being treated.

A recent paper by Chanin and Berger describes a risk classification scheme to classify agents according to their risk of PML and to aid clinicians in the decision-making process. Three distinct categories or classes of agents have been proposed. Differences between classes were established based on the frequency with which PML is observed, the nature of the underlying illness being treated (whether it predisposed to PML in the absence of the specific drug), and the time to onset from treatment initiation and the development of PML.

Class I agents have been associated with PML and are used in patients without known disorders that predispose to PML; they typically exhibit a latency of several months to years from the time to initiation prior to the onset of PML. Furthermore, the incidence of PML associated with the use of these agents is relatively high (1/100-1/1000). Natalizumab is an example of a class I agent. Class II agents are those that are used in patients with an underlying condition that predisposes to PML, or with concurrent or prior use of other immunosuppressive therapies. The development of PML can occur at any time, and the incidence of PML is relatively low compared to class I agents (>1/10,000). Rituximab is an example of a class II agent. Finally, class III agents are similar to class II in that they are used in the treatment of conditions or in conjunction with drugs that already carry a risk of PML; however, thus far the risk for PML has been too low to be quantified. This class includes agents such as TNF-alpha blockers.

A plan for risk minimisation has been suggested for use of the different classes of agents. Use of class I agents should be prefaced with JC virus serological testing. If serology is negative at the time of initiation of therapy, repeat serology should be performed every three to six months; if serology is positive, consideration of past immunosuppressant use should be considered (if no past use, therapy can be considered for up to two years with routine serological testing). Risk minimisation with use of class II and class III agents depends upon the underlying condition and the presence of concomitant immunosuppressant use. However, with use in high-risk patients, individual benefit/risk calculations are recommended as there is currently no strong evidence to recommend JC serological testing in these patients.

Recently the EMA provided new guidance for risk management with the use of natalizumab, as recent studies have suggested that early detection and treatment of asymptomatic PML may improve patients' outcomes. Given that asymptomatic cases of PML can be detected on MRI scans, and that simplified MRI protocols permit the identification of PML lesions, the EMA has recently recommended that, in addition to yearly MRI scans which are current recommended, there should be consideration for patients at higher risk of PML to undergo more frequent MRI scans (e.g. every three to six months). Furthermore, if lesions suggestive of PML are discovered, a contrast-enhanced T1-weighted MRI should follow as well as testing the spinal fluid for the presence of JC virus.

In the case of idealisib and PML, the obvious confounders are both the underlying disease of CLL and the concomitant therapy of rituximab. Therefore, the question at hand is whether there is any further increased risk with the use of idealisib in patients pre-disposed by their underlying disease who are concomitantly receiving a drug which has previously been associated with PML. Data on the incidence of PML in CLL patients as well as the reporting rate of PML occurrence with rituximab are available. The incidence of PML in patients with CLL has been estimated to be 11.1 (0.28-61.74) per 100,000 person-years. Published data on the incidence of PML with rituximab has been estimated for patients with systemic lupus erythematosus (2 cases per 8000) and for rheumatoid arthritis (1/25,000). It has been written in several sources that such estimates in patients receiving rituximab for treatment of CLL are difficult to ascertain.

Although actual post marketing exposure data is not publically available, taking into account the relatively small amount of time the drug has been available, six case reports may indicate a higher incidence of occurrence than expected even taking into consideration the confounding factors of CLL and concomitant rituximab. Furthermore, three of the cases did not report current use of rituximab at the time of diagnosis of PML (cases 2 and 3), and one of the cases has no documented history of rituximab use (case 6).

Concern for an additive risk for PML has not been limited to idealisib. A recent publication using data from the FDA's Adverse Event Reporting System (FAERS) reported elevated measures of disproportionality in reporting of PML for several targeted cancer therapies which are commonly used in combination with other drugs that cause PML. Significant proportional reporting ratio signals were found among seven (14.6%) biological and targeted cancer therapies including: brentuximab (24.5, CI:14.8-40.6), ofatumumab (16.3, CI:9.6-27.4), alemtuzumab (9.9, CI:6.0-16.4), obinutuzumab (7.4, CI:2.4-22.8), ibrutinib (5.6 CI:3.0-10.5), belimumab (4.5 CI:2.3-9.0), and idealisib (4.1, CI:1.3-12.6). The purpose of the communication of this signal is to encourage further studies to elucidate if there is an additive risk of PML with the use of idealisib in combination with rituximab in patients with CLL. If a further
increased risk is present, additional risk minimisation measures, such as JC serology monitoring, and periodic MRI brain scans, as is recommended for high risk patients taking class I agents, may be considered. Knowledge of JC serology status at the time of initiation of combination therapy with idelalisib and periodic MRI scanning could be important in the early recognition of asymptomatic disease, discontinuation of offending agents, and perhaps initiation of treatment of PML with mirtazapine and mefloquine (as in case 3) and potentially avoiding a fatal outcome from PML.

References

Response from Gilead

On 15 September 2016, the Uppsala Monitoring Centre (UMC) notified the Marketing Authorization Holder (MAH) for Zydelig (idelalisib) (Gilead Sciences, Inc.) of a potential product safety signal, Leukoencephalopathy, and invited the MAH to comment on their analysis and interpretation.

Progressive multifocal leukoencephalopathy (PML) is a manifestation of a brain white-matter John Cunningham (JC)-virus infection which results in progressive demyelination. Although most patients have been infected with JC virus by age 10, PML reactivation is a rare and often fatal disease which typically occurs in people with severely depressed immunity, either from a comorbid disease or from the treatment for a co-morbid disease (such as malignancy). Patients with chronic lymphocytic leukaemia (CLL) are at a significantly increased risk of PML due to manifestations of their disease and the chemoimmunotherapy (including anti-CD20 monoclonal antibodies [mAbs]) they often receive successively.

In the European Union (EU), Zydelig is indicated in combination with an anti-CD20 mAb (rituximab or ofatumumab) for the treatment of patients with relapsed CLL who have received at least one prior therapy and in front-line patients with CLL with 17p deletion or TP53 mutation who are not eligible for any other therapies. Zydelig is also indicated as monotherapy in patients with refractory follicular lymphoma (FL). In these relapsed/refractory populations, patients have lived with their disease for a median of 7 years and have received a median of 3 prior therapies (range 1-12).

The UMC has identified 7 unique cases of PML in the WHO global database (VigiBase®) of suspected Zydelig adverse drug reactions; in 5 of the cases JC virus test was positive. Three were spontaneous reports and 4 were from clinical studies. Six patients received Zydelig for CLL and one patient received Zydelig for an unknown indication. In 6 cases the anti-CD20 mAb, rituximab, was a co-suspect medication and in the remaining case, the anti-CD20 mAb, obinutuzumab, was co-suspect. The underlying disease, CLL, and the anti-CD20 mAbs, rituximab and obinutuzumab, are each associated with increased risk of PML.

A search of the Gilead safety database using the standardized broad MedDRA query for Demyelination identified 10 cases with reported PML or leukoencephalopathy (inclusive of all 7 cases, discussed above, from VigiBase). All 10 cases reported concomitant medication with rituximab or obinutuzumab. One of the 10 cases was a duplicate. Of the 9 unique cases: 2 cases lacked sufficient information to assess causality; in 4 cases, the patients started Zydelig and rituximab or obinutuzumab at the same time. Of the remaining 3 cases: one patient received multiple rituximab courses prior to Zydelig, and PML started 2 months after initiation of Zydelig and 3 months after the last rituximab dose; another patient experienced PML 5 months after the last dose of rituximab; and the remaining patient was diagnosed with PML 83 days after the last dose of rituximab. Given the lingering plasma half-lives associated with mAb therapies and time to presentation of PML reactivation manifestations, a contributory role for Zydelig could not be temporally distinguished from a causal role for the anti-CD20 mAb in these 9 cases of PML or leukoencephalopathy.

Within the Gilead-sponsored randomized, controlled Phase 3 development program, 3 trials of idelalisib involving 893 subjects, reported 2 PML events. Both events occurred in the anti-CD20 mAb-alone arms and not in the idelalisib treatment arms.

Gilead uses disproportionality analysis (DPA) as part of the signal detection process to monitor the United States Food and Drug Administration Adverse Event Reporting System database (FAERS) for the emergence of new safety signals. DPA of spontaneous data in FAERS is conducted using the Multi Item Gamma Poisson Shrinker algorithm. Gilead monitors the FAERS data on a quarterly basis for new Zydelig safety signals. For events that occur ≥ 3 times in the database, the scores of disproportional reporting for drug-event pairs are evaluated (an EB05 score ≥ 2.0 is taken as a safety signal). Neither PML nor leukoencephalopathy have emerged as Zydelig safety signals from this routine DPA surveillance of FAERS.

Gilead used DPA methodology to investigate PML-drug pairs in FAERS. The eight drugs (as per the WHO Signal document) with their resulting EB05 scores in descending order were: rituximab, 41.93; alemtuzumab, 29.85; brentuximab, 19.79; ofatumumab, 18.31; ibritinib, 3.96; belimumab, 2.86; idelalisib, 1.25; obinutuzumab, 1.17. A similar analysis performed by Gilead on VigiBase® yielded: rituximab, 66.02; alemtuzumab, 14.38; brentuximab, 12.86; ofatumumab, 6.51; belimumab, 3.14; ibritinib, 2.66; idelalisib, 1.24; obinutuzumab, analysis not done, < 3 cases reported. Thus, in these DPA analyses, idelalisib did not meet the positive cut-off of EB05 ≥ 2. Of note, rituximab, which is very frequently used in combination with idelalisib for treatment of CLL, resulted in the strongest DPA signal in both databases, suggesting that anti-CD20 mAb treatments (especially rituximab) are important confounding factors for the observed PML cases in CLL patients treated with Zydelig.

Gilead estimated the incidence of PML in ‘real-world’ CLL patients during treatment with the same set of 8 drugs between August 2014 and February 2016 using a US-based IMS healthcare claims database. For rituximab there were two PML cases during 1,847 patient-years. For obinutuzumab there was one case during 314
controlled clinical trials data, disproportionality analyses on FAERS and VigiBase® databases and healthcare claims data, does not provide evidence suggestive of an additive risk for Zydelig, over the known association with anti-CD20 mAbs, in the causality of PML in CLL patients. Zydelig safety information received from all sources by the MAH is carefully evaluated on an ongoing basis for any new safety signals and the prescribing information is updated as soon as adverse drug reactions are identified.

**Panic attacks with levothyroxine**

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**Summary**

Close to 200 reports in VigiBase®, the WHO global database of individual case safety reports, describe patients who have suffered panic attacks while on levothyroxine treatment. Among these are detailed accounts where the panic attacks have ceased upon stopping levothyroxine treatment or lowering the dose, and sometimes recurred after repeated exposure. The impact on patients’ well-being and daily activities can be significant, with repeated hospital admissions, extended sick-leave, impaired social life and more. Some patients had been on stable treatment for years without change in product or dose before the problems began, which delayed the consideration of a causal association. Palpitations, tremor and sweating are known adverse drug reactions to levothyroxine, so a causal association is plausible, and may be viewed by health professionals as expected. However, patients may fail to associate their severe experiences with the listed symptoms. They should be made aware that panic attacks while on levothyroxine could be related to the medicine, and that those who suffer these symptoms should consult their treating physicians about possibly lowering their dose. Physicians should be reminded that panic attacks associated with therapeutic overdoses of levothyroxine may have a significant effect on the patient’s well-being, to the point that patients themselves might experiment with dose changes or treatment termination. The signal was identified in the joint UMC/Lareb signal detection sprint, in October 2016.

**Introduction**

Thyroxxine is the hormone responsible for maintaining the metabolic rate of the body. Levothyroxine is a synthetic preparation of T4 L-thyroxine used for lifelong hormone replacement therapy in patients with hypothyroidism. It is also used for the treatment of enlarged thyroid glands (goiter) and for the treatment of some types of thyroid cancer. The prevalence of spontaneous hypothyroidism is between 1 and 2%, and up to 10 times as common in women as in men.1 Levothyroxine doses need to be carefully titrated, and the symptoms of overdose reflect those of hyperthyroidism. Many of these are similar to the symptoms and signs of adrenergic excess and include nervousness, palpitations, hyperactivity, increased sweating, insomnia, and more.2 Panic attacks are brief periods with a sudden onset of intense discomfort, anxiety or fear. They are accompanied by somatic symptoms such as chest pain, dizziness, and palpitations; and by cognitive symptoms such as fear of dying, fear of going crazy, and depersonalization. Up to 10% of the population have been estimated to suffer one or more panic attacks in a single year. It may also work the other way around, in which case a sudden onset of palpitations or chest pain triggers anxiety in predisposed patients.

**Reports in VigiBase®**

As of November 2016, there were 187 reports of ‘Panic attacks and disorders’ (MedDRA high level term) with levothyroxine in VigiBase®, the WHO global database of individual case safety reports. In 80% of the cases, levothyroxine was the single suspected drug and in just over 50% of the cases it was the only reported drug. 90% of the reports were for women, which correlates well with the overall proportion of reports for women for levothyroxine (85%), especially since there are also more reports of panic attacks for women than for men in VigiBase®. The patients were between 16 and 81 years old (median 51), and 80% were between 18 and 64, in line with the overall reporting patterns for levothyroxine and
for 'Panic attacks and disorders'. 112 reports were from the United States (US), 30 from the Netherlands, 14 from the United Kingdom (UK) and 13 from Germany. Beyond that, there were 6 reports from Canada, 4 from Italy, and 3 from Sweden, as well as single reports from Austria, Switzerland, Denmark, Norway and Spain. The highest yearly rate was 41 reports in 2014; 135 reports were submitted from 2011 and onward. This is in line with the overall reporting patterns in VigiBase® for levothyroxine and/or panic attacks and disorders.

One noteworthy feature of the reports on levothyroxine together with 'Panic attacks and disorders' in VigiBase® is that 80% come directly from patients, as compared with 56% for levothyroxine overall and 56% for panic attacks and disorders overall. In contrast, only 9% of the reports come from physicians, as compared with 24% for levothyroxine overall and 23% for 'Panic attacks and disorders' overall.

Another noteworthy feature of the reports on levothyroxine together with 'Panic attacks and disorders' in VigiBase® is that 26% also involve palpitations, as compared with 10% for levothyroxine reports overall and only 8% for reports on 'Panic attacks and disorders' overall. This supports our hypothesis that these reported adverse effects reflect a more severe presentation of the known adverse reactions to levothyroxine.

Several reports note that the panic attacks stopped after levothyroxine treatment was discontinued or the dose was lowered. In at least two cases, the panic attacks recurred when the levothyroxine treatment was re-introduced:

A woman of 48 years had been on stable levothyroxine treatment for hypothyroidism for six years when she began to suffer from confusion, impairment of memory and impairment of concentration, along with restlessness, paranoia and panic reactions. By her own account, she stopped levothyroxine, upon which the symptoms resolved. When she restarted treatment, the symptoms returned.

A woman of 50 years initiated levothyroxine treatment for latent hypothyroidism. Within hours, she suffered panic attacks, tremor, and unrest. She was more than once admitted to hospital, and she mentioned that her social life was almost impossible. The dose was subsequently reduced, and finally the therapy was discontinued leading to regression of the symptoms. At a later stage the medication was restarted with recurrence of the adverse effects within a week after start of treatment. She was then switched to drops and recovered completely.

The severe impact on quality of life for many of the affected patients, and the observation that many remained undiagnosed as probable adverse drug reactions for long periods of time, are illustrated by the following examples:

A woman of 28 years initiated levothyroxine treatment and suffered gradual symptoms of anxiety and panic attacks, to the point where she described neglecting her job, and eventually going on 50% sick leave. She also lost weight from a BMI of 25 to 19. After more than a year she herself associated the panic attacks and anxiety with her levothyroxine treatment and lowered the dose, after which all reactions abated and had not since returned.

A woman of 51 years suffered severe anxiety and panic attacks, along with muscle pain, cramps, and extreme tiredness, while on levothyroxine. She suspected that her dose was possibly too high, but the doctor had said that her levels were normal. The symptoms forced her to work part-time, reduce her leisure activities, and seek help for depression.

A woman of unknown age had been on levothyroxine treatment for two years and suffered trembling inside, paraesthesia and panic reactions. She suspected that the symptoms might be caused by levothyroxine, and consulted several physicians on the matter, but felt that they did not pay attention to the symptoms. Against their recommendation, she temporarily stopped her levothyroxine treatment on several occasions, but always resumed therapy. The outcome of these dechallenge and rechallenge interventions was not reported.

Many of the 30 cases from the Netherlands are part of a larger case series where a change in packaging from bottles to blister packs is suspected to have led to better preservation of the active substance, causing higher effective doses at the same nominal strength of the tablets. This would be consistent with the hypothesis that the panic attacks were mainly the result of a therapeutic over-dose. However, in several of these cases, the problems are reported to have remained despite a lowering of the dose, which could appear inconsistent from a pharmacological viewpoint, but might indicate that once developed into a clinical problem the pattern of panic attacks may not immediately reverse with removal of the causal agent.

**Literature and Labelling**

The most recent patient information leaflet for levothyroxine products in the UK states that levothyroxine may worsen existing heart problems, such as fast or irregular heartbeats, awareness of beating of the heart, and chest pain. Nervousness, excitability, restlessness, and difficulty sleeping are also mentioned as possible adverse drug reactions. Beyond that, anxiety and confusion are highlighted as the adverse effects of accidentally taking too many tablets at once. 'Panic attacks and disorders' are not mentioned.

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Similarly, the drug label information directed to consumers for a levothyroxine sodium tablet in the US lists headache, hyperactivity, nervousness, anxiety, irritability, emotional lability and insomnia as adverse drug reactions related to the central nervous system; palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction and cardiac arrest are mentioned as cardiovascular adverse drug reactions. It does not explicitly mention panic attacks and disorders.  

A PubMed search for ‘levothyroxine panic’ returned 25 results but none that appeared to be related to a possible causal association between levothyroxine treatment and ‘Panic attacks and disorders’. It did highlight papers that have studied the relationship between thyroid function and panic disorder, such as that by Kikuchi et al, which found significant correlation between thyroid hormone levels and the severity of anxiety or panic attacks in non-medicated patients with panic disorder.

**Discussion and Conclusion**

Panic attacks may be viewed as expected adverse effects of levothyroxine therapeutic overdoses, considering the known adverse drug reactions, which include palpitations, tremor, and sometimes anxiety. However, the risk of panic attacks seems not to be explicitly mentioned in patient information leaflets, and patients may not associate their severe experience with the listed adverse drug reactions. Indeed, we have identified several cases where neither the patient nor the doctor linked the panic attacks to a levothyroxine treatment, or at least did not attempt to alleviate the symptoms by considering to lower levothyroxine dose. The severe impact on quality of life in many of these cases warrants careful consideration. Patients should be made aware that panic attacks while on levothyroxine could be related to the medicine, and that those who suffer these symptoms should consult their treating physicians about possibly lowering their dose; further, that physicians be reminded that panic attacks associated with therapeutic overdoses of levothyroxine may have a significant impact on the patient’s well-being and daily living, to the point that patients themselves might experiment with dose changes or treatment termination, and be vigilant of such symptoms in their patients.

**References**


CAVEAT DOCUMENT

Accompanying statement to data released from VigiBase®, the WHO international database of suspected adverse drug reactions

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (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 (PIDM). The information is stored in VigiBase®, the WHO international database of suspected adverse drug reactions (ADRs). 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.

If in doubt or in need of help for interpretation of country specific data, UMC recommends to contact the concerned NC before using the data.

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, ADR reports 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). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

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

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.

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

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.