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

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

Safety and Vigilance,
EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pals@who.int

This Newsletter is also available on our Internet website:
http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring
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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®

This newsletter includes three feature articles describing: WHO-UMC-HSA Inter-Regional Pharmacovigilance Training in Singapore; the 2nd annual meeting for strengthening pharmacovigilance in Eastern Mediterranean region; and capacity building workshop in the Republic of Congo.

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Amantadine hydrochloride

Risk of rhabdomyolysis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced the revision of the package insert for amantadine hydrochloride (Symmetrel®) to include risk of rhabdomyolysis.

Amantadine hydrochloride (Symmetrel®) is used for Parkinson’s disease, improvement of hypobulia or decreased initiative associated with sequela of cerebral infarction and Type A influenza virus infection in Japan.

The MHLW/PMDA stated that one case of rhabdomyolysis has been reported in a patient treated with amantadine hydrochloride in Japan. A causal relationship to the product could not be ruled out. Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the following text to the subsection of the “Clinically significant adverse reaction” in the section of “Adverse reaction” in the package insert.

Rhabdomyolysis:
Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feelings of weakness, increased creatine kinase (creatinine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

Reference:
Revision of Precautions, MHLW/PMDA, 15 September 2015 (www.pmda.go.jp/english/)

Asunaprevir and daclatasvir

Risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced the revision of the package insert for asunaprevir (Sunvepra®) and daclatasvir (Daklinza®) to include risk of thrombocytopenia.

Asunaprevir and daclatasvir as a combination are used for the treatment of chronic hepatitis C virus (HCV) infection, in patients with serogroup 1 (genotype 1), or compensated cirrhosis type C.

The MHLW/PMDA stated that cases of thrombocytopenia have been reported in patients treated with asunaprevir and daclatasvir hydrochloride in Japan. Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the following text to the subsection of the “Clinically significant adverse reaction” in the section of “Adverse reaction” in the package insert.

Thrombocytopenia:
Thrombocytopenia may occur. Patients should be carefully monitored through periodic blood tests, etc. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted. The reactivation of viruses including Human Herpes Virus 6 (HHV-6) has been frequently found associated with DIHS. Symptoms such as rash, pyrexia, and/or hepatic

Reference:
Revision of Precautions, MHLW/PMDA, 15 September 2015 (www.pmda.go.jp/english/)
Who Pharmaceuticals Newsletter No. 5, 2015

Regulatory Matters

Function disorder may relapse or be prolonged even after discontinuation of administration, and therefore, caution should be exercised.

Reference:
Revision of Precautions, MHLW/PMDA, 15 September 2015
(www.pmda.go.jp/english/)
(See WHO Pharmaceuticals Newsletter No. 6, 2014 for Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS) in Canada)

Canagliflozin

Increased risk of bone fractures and new information on risk of decreased bone mineral density

USA. The US Food and Drug Administration (FDA) has strengthened the warning for the type 2 diabetes medicine canagliflozin (Invokana® and Invokamet®) related to the increased risk of bone fractures, and added new information relating to risk of decreased bone mineral density. To address these safety concerns, the FDA added a new Warning and Precaution and revised the Adverse Reactions section of the canagliflozin drug labels.

Canagliflozin is a prescription medicine used in combination with diet and exercise to lower blood sugar in adults with type 2 diabetes. It belongs to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors. Canagliflozin is available as a single-ingredient product and also in combination with the diabetes medicine metformin.

The FDA is continuing to evaluate the risk of bone fractures with other drugs in the SGLT2 inhibitor class, including dapagliflozin and empagliflozin, to determine if additional label changes or studies are needed. Healthcare professionals and patients are urged to report side effects involving canagliflozin or other SGLT2 inhibitors.

The FDA has recommended that healthcare professionals should consider factors that contribute to fracture risk prior to starting patients on canagliflozin and that patients should talk to their healthcare professionals about factors that may increase the risk for bone fracture. Patients should not stop or change their diabetes medicines without first talking to their healthcare professional.

Reference:

Clozapine

Modifications for monitoring neutropenia

USA. The US FDA has changed the requirements for monitoring, prescribing, dispensing, and receiving clozapine, to address continuing safety concerns of severe neutropenia (dangerously low number of neutrophils and white blood cells).

Clozapine is an antipsychotic medicine used to treat symptoms of schizophrenia in patients who do not respond adequately to standard antipsychotic treatment. It is also effective in reducing risk of repeated suicidal behaviour in patients with schizophrenia or schizoaffective disorder.

The changes include:
Modification of the prescribing information for clozapine to clarify and enhance explanations on how to monitor for neutropenia and manage clozapine treatment, and approval of a shared risk evaluation and mitigation strategy (REMS) called the Clozapine REMS Program. The shared REMS is expected to reduce the burden and possible confusion related to having separate registries for individual clozapine medicines.

The FDA has informed that patients who are currently treated with clozapine will be automatically transferred to the Clozapine REMS Program. Prescribers and pharmacies that dispense clozapine will be required to be certified in the Clozapine REMS Program according to a specific transition schedule starting 12 October 2015.

Reference:

Deferasirox

Risk of gastrointestinal perforations

Japan. The MHLW and the PMDA have announced the revision of the package insert for deferasirox (Exjade®) to include risk of gastrointestinal perforations.

Deferasirox is indicated for chronic iron overload due to blood transfusions (when iron chelating agents such as desferrioxamine is contraindicated or inadequate).

The MHLW/PMDA stated that cases of gastrointestinal perforations have been reported in patients treated with deferasirox both in Japan and other countries and that the CCDS has been updated.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the “gastrointestinal perforations” to the subsection of “Gastric ulcer (including multiple ulcers), duodenal ulcer, and gastrointestinal haemorrhage” in the section of
“Clinically significant adverse reaction” in the package insert.

**Reference:**
Revision of Precautions, MHLW/PMDA, 6 August 2015 (www.pmda.go.jp/english/)

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**Fingolimod**

1. Risk of progressive multifocal leukoencephalopathy (PML)

**USA and Japan.** The US FDA, the MHLW and the PMDA have announced label changes for fingolimod (Gilenya® and Imusera®). The changes inform health-care professionals and the public of two cases of progressive multifocal leukoencephalopathy (PML) reported in patients with multiple sclerosis (MS) that were treated with fingolimod.

These are the first cases of PML reported in patients taking fingolimod, who had not been previously treated with an immunosuppressant drug for MS or any other medical condition.

Fingolimod is an immunomodulator shown to benefit patients with relapsing forms of MS.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the following text to the subsection of the “Clinically significant adverse reaction” in the section of “Adverse reaction” in the package insert.

Progressive multifocal leukoencephalopathy (PML): PML may occur. Patients should be carefully monitored during and after treatment with this drug. If symptoms such as disturbed consciousness, cognitive disorder, symptoms of paralysis (hemiplegia or quadriplegia), or speech and language disorder are observed, imaging diagnostics with MRI and cerebrospinal fluid tests should be performed. In addition, administration of this drug should be discontinued, and appropriate measures should be adopted.

The FDA has recommended that health-care professionals should stop fingolimod and perform a diagnostic evaluation if PML is suspected.

**References:**
Drug Safety Communication, US FDA, 4 August 2015 (www.fda.gov)
Revision of Precautions, MHLW/PMDA, 15 September 2015 (www.pmda.go.jp/english/)

2. Risk of abnormal tissue growth (neoplasms)

**Canada.** The Canadian product monograph for fingolimod has been updated to include information on an increased risk of lymphomas and other malignant cancers (particularly the skin) following results of a safety review.

Health Canada has requested additional safety information from the manufacturer and will continue to monitor this issue.

At the time of the review, there were 16 reports of neoplasms linked to fingolimod in Canada. The World Health Organization (WHO) global database of individual case safety reports (ICSRs), VigiBase® presented 62 cases of skin cancer at the time of the review.

A review of the scientific and medical literature identified two published case reports, three clinical trials, and four safety reviews that describe cases of neoplasms in patients treated with fingolimod. In two of the clinical trials, participants receiving fingolimod had a higher occurrence of skin cancers than those who did not.

Numerous patient medical reports received from the manufacturer link skin cancer to fingolimod since it was first approved for sale. In addition, reports of skin cancer have increased recently in patients treated with fingolimod.

Adverse effects such as neoplasms are rare and could take a long time to develop or be detected. Therefore, additional safety information from the manufacturer of fingolimod about the risk of neoplasms has been requested by Health Canada.

Furthermore, Health Canada will continue to monitor adverse event information involving fingolimod.

**Reference:**

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**Hydroxyzine-containing medicines**

**Risk of prolonged QT interval and ventricular tachycardia**

**Japan.** The MHLW and the PMDA have announced the revision of the package insert for hydroxyzine-containing medicines (Atarax®) to include risk of prolonged QT interval and ventricular tachycardia.

Hydroxyzine-containing medicines are used for urticaria, pruritus associated with skin disease, anxiety, tension, depressed mood in neurosis.

The MHLW/PMDA stated that cases of prolonged QT interval and ventricular tachycardia have been reported in patients treated with hydroxyzine-containing medicines in Japan and in other countries. In addition, European Medicines Agency (EMA) have taken
action to minimize the risks of effects on heart rhythm with hydroxyzine-containing medicines.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of “Patients with prolonged QT interval (including those with long QT interval syndrome congenital), patients being administered drugs known to prolong QT interval, and patients with significant bradycardia or hypokalaemia” to the section of the “Careful administration” in the package insert.

The MHLW/PMDA also recommended the addition of the following text to the subsection of the “Clinically significant adverse reaction” in the section of “Adverse reaction” in the package insert.

QT interval prolongation and ventricular tachycardia (including torsades de pointes):

QT interval prolongation or ventricular tachycardia (including torsades de pointes) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 6 August 2015 (www.pmda.go.jp/english/)
(See WHO Pharmaceuticals Newsletter No.3, 2015 for Risks of effects on heart rhythm in Europe and Risk of QT interval prolongation and Torsade de Pointes in the United Kingdom)

<table>
<thead>
<tr>
<th>Infliximab</th>
<th>Ingenol mebutate gel</th>
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<tr>
<td><strong>Risk of non-melanoma skin cancers, particularly in psoriasis patients</strong></td>
<td><strong>Risk of severe allergic reactions and herpes zoster (shingles)</strong></td>
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<td><strong>Australia.</strong> The Therapeutic Goods Administration (TGA) has announced**</td>
<td><strong>USA. The US FDA has requested that the product</strong></td>
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<td>that the Product Information for infliximab has been updated to provide</td>
<td><strong>label for Ingenol mebutate gel (Picato®) is updated to include</strong></td>
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<td>further information about the risk of skin cancers, particularly in</td>
<td><strong>a warning of an increased risks of severe allergic reactions and herpes zoster</strong></td>
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<td>psoriasis patients who have undergone phototherapy.**</td>
<td><strong>(shingles). In addition, instructions on the safe an appropriate application</strong></td>
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<td><strong>Infliximab (Remicade®) is a chimeric human-murine monoclonal antibody</strong></td>
<td><strong>of the gel should also be provided.</strong></td>
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<td>that binds to human tumour necrosis factor alpha (TNFα) and is indicated</td>
<td><strong>Ingenol mebutate is used to treat actinic keratosis, a scaly, crusty lesion on</strong></td>
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<td>for treatment of rheumatoid arthritis in adults, ankylosing spondylitis,</td>
<td><strong>the skin that may be red or yellow in colour.</strong></td>
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<td>psoriatic arthritis, psoriasis, Crohn’s disease, refractory fistulising</td>
<td><strong>The FDA has received reports of cases of severe eye injuries and skin reactions</strong></td>
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<td>Crohn’s disease and ulcerative colitis.**</td>
<td><strong>associated with the application of ingenol mebutate gel. Some cases were</strong></td>
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<td>The changes included updating the ‘Precautions’ section to include the</td>
<td><strong>associated with ingenol mebutate gel not being used according to the instructions</strong></td>
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<td>statement ‘Psoriasis patients should be monitored for non-melanoma skin</td>
<td><strong>for use on the label.</strong></td>
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<td>cancers (NMSCs), particularly those patients who have had prior prolonged</td>
<td><strong>The FDA has recommended that patients who experience a severe allergic reaction</strong></td>
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<td>phototherapy treatment.**</td>
<td><strong>should stop using ingenol mebutate gel and seek immediate medical attention.</strong></td>
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<tr>
<td>In addition, basal cell carcinoma and squamous cell carcinoma were added to</td>
<td><strong>The allergic reaction may include throat tightness, difficulty breathing,</strong></td>
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<td>the ‘Adverse events’ section with the frequency listed as unknown.**</td>
<td><strong>feeling faint, or swelling of the lips or tongue. The FDA also recommended</strong></td>
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<td>The TGA has reminded prescribers to monitor patients who have been</td>
<td><strong>that patients should stop using the product and contact a health-care professional if</strong></td>
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<td>prescribed infliximab for any new or changed skin lesions, and to ensure</td>
<td><strong>they develop hives, itching, or severe skin rash.</strong></td>
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<td>patients with any suspicious lesions undergo further investigations.**</td>
<td><strong>Reference:</strong></td>
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<td><strong>Reference:</strong></td>
<td>Drug Safety Communication, US FDA, 21 August 2015 (<a href="http://www.fda.gov">www.fda.gov</a>)</td>
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<td>Medicines Safety Update, TGA, Vol. 6, No. 4, August 2015</td>
<td>(<a href="http://www.tga.gov.au">www.tga.gov.au</a>)</td>
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### Regulatory Matters

#### Laninamivir octanoate and zanamivir

**Risk of anaphylaxis**

**Japan.** The MHLW and the PMDA have announced the revision of the package insert for laninamivir octanoate (Inavir®) and zanamivir (Relenza®) to include risk of anaphylaxis.

Laninamivir octanoate and zanamivir are indicated for treatment and prophylaxis of influenza A and B virus infections.

The MHLW/PMDA stated that cases of anaphylaxis have been reported among patients treated with laninamivir octanoate hydrate and zanamivir hydrate who have an allergy to milk products in Japan.

Based on expert advice and available evidence, the MHLW/PMDA recommended the addition of the "Patients with a history of hypersensitivity to milk products" to the section of the "Careful administration" in package insert.

This drug is using the lactose hydrate which contains milk proteins. There have been reports of anaphylaxis upon administration of this drug to patients with a history of hypersensitivity to milk products. Therefore, caution should be exercised when administering this drug to such patients.

**Reference:** Revision of Precautions, MHLW/PMDA, 6 August 2015 (www.pmda.go.jp/english/)

#### Memantine hydrochloride

**Risk of rhabdomyolysis**

**Japan.** The MHLW and the PMDA have announced the revision of the package insert for memantine hydrochloride (Memary®) to include risk of rhabdomyolysis.

Memantine hydrochloride is used to suppress symptoms of dementia in patients with moderate to severe Alzheimer’s type dementia.

The MHLW/PMDA stated that cases of rhabdomyolysis have been reported in patients treated with memantine hydrochloride in Japan.

Based on expert advice and available evidence, the MHLW/PMDA recommended the addition of the following text to the subsection of the “Clinically significant adverse reaction” in the section of “Adverse reaction” in the package insert.

Rhabdomyolysis:

Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feelings of weakness, increased creatine kinase (creatine phosphokinase), or increased myoglobin blood and urine are observed, administration of this drug should be discontinued and appropriate measures should be adopted. In addition, caution should be exercised for development of acute renal failure due to rhabdomyolysis.

**Reference:** Revision of Precautions, MHLW/PMDA, 6 August 2015 (www.pmda.go.jp/english/)

#### Nivolumab

**Risks of myasthenia gravis and myositis, colitis and severe diarrhoea**

**Japan.** The MHLW and the PMDA have announced the revision of the package insert for nivolumab (Opdivo®) to include risks of myasthenia gravis and myositis, colitis and severe diarrhoea.

Nivolumab is used for radically unresectable malignant melanoma.

The MHLW/PMDA stated that:

- due to the T cell activation effect of this drug, various diseases or conditions caused by excessive immunoreaction are expected to occur;
- cases of adverse reactions due to an excessive immunoreaction have been reported in patients treated with nivolumab in Japan; and
- the CCDS and package inserts of other countries should include precautions regarding adverse reactions due to the immunological mechanism of this drug.

Based on expert advice and available evidence, the MHLW/PMDA recommended the addition of the following text to the section of the “Important Precautions” in the package insert.

Various diseases or conditions may occur due to excessive immunoreaction caused by T cell activation effect of nivolumab. Patients should be carefully monitored. If any abnormalities are observed, appropriate differential diagnosis should be conducted taking into consideration that the adverse reaction may be caused by an excessive immunoreaction. If an adverse reaction due to an excessive immunoreaction is suspected, appropriate measures such as administration of adrenal
corticosteroids should be considered.

The MHLW/PMDA also recommended the addition of the following texts to the subsection of the “Clinically significant adverse reaction” in the section of “Adverse reaction” in the package insert.

Myasthenia gravis and myositis: Myasthenia gravis or myositis may occur, and there have been reports of cases where these complications have occurred. Muscular weakness, eyelid ptosis, dyspnoea, dysphagia, increased creatine kinase (creatine phosphokinase), etc. should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures such as dose reduction, drug suspension, or discontinuation of administration should be adopted.

Reference: Revision of Precautions, MHLW/PMDA, 6 August 2015 (www.pmda.go.jp/english/)

Panitumumab

Risk of toxic epidermal necrolysis (TEN)

Japan. The MHLW and the PMDA have announced the revision of the package insert for panitumumab (Vectibix®) to include risk of toxic epidermal necrolysis (TEN).

Panitumumab is indicated for KRAS wild-type, metastatic colorectal cancer.

The MHLW/PMDA stated that cases of TEN have been reported in patients treated with panitumumab in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the "Toxic epidermal necrolysis (TEN)" to the section of the "Clinically significant adverse reaction" in the package insert.

Reference: Revision of Precautions, MHLW/PMDA, 6 August 2015 (www.pmda.go.jp/english/)

Protein pump inhibitors

Very low risk of subacute cutaneous lupus erythematosus

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has warned that proton pump inhibitors (PPIs) are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE), a non-scarring dermatosis that can develop in sun-exposed areas.

PPIs reduce the secretion of stomach acid and are widely used medicines for management of acid-related conditions, including: reflux oesophagitis; gastric and duodenal ulcers; and Zollinger-Ellison syndrome.

Drug-induced SCLE can occur weeks, months or even years after exposure to the drug.

A Swedish case-control study that linked a patient register with a prescription-drug
patients with vascular or mixed dementia

Australia. The TGA has updated the Product Information for risperidone to reflect that the indication is limited to Alzheimer type dementia, and that duration of use is restricted to short-term management (up to 12 weeks).

Risperidone is an atypical antipsychotic drug belonging to the benzisoxazole-derivative class. It is a selective monoaminergic antagonist with high affinity for serotoninergic 5-hydroxytryptamine2, dopaminergic D2 and alpha1-adrenergic receptors.

Results from controlled clinical studies that were submitted to the TGA by the sponsor found an increased risk of cerebrovascular adverse events for patients being treated with risperidone for vascular or mixed dementia. The odds ratio for patients with vascular or mixed dementia was 5.26 (95% confidence interval [CI] 1.18-48.11), compared with those taking it for Alzheimer's dementia, with a comparative odds ratio of 2.23 (95% CI 0.85-6.88).

From 1993 to 18 May 2015, the TGA has received 17 reports of cerebrovascular adverse events in patients being treated with risperidone. In nine of these cases, the indication was dementia or behavioural management related to dementia, one of the nine reports stated the diagnosis as Alzheimer's disease, while another referred to fronto-temporal dementia. Otherwise, the type of dementia was not specified in the remaining seven reports.

To Product Information was modified by removing the implicit indication for use in patients with vascular or mixed dementia. Furthermore, the Product Information includes a stipulation that the duration of risperidone treatment for this indication should not exceed 12 weeks, and that it should be used to treat persistent agitation or aggression only if the symptoms are unresponsive to non-pharmacological approaches.

Reference:
Medicines Safety Update, TGA, Vol. 9, No. 2, September 2015
(www.tga.gov.au)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Risk of ketoacidosis and sepsis

Japan. The MHLW and the PMDA have announced the revision of the package insert for sodium-glucose co-transporter 2 (SGLT2) inhibitors to include risks of ketoacidosis and sepsis.

SGLT2 inhibitors (canagliflozin hydrate (Canagluz®), dapagliflozin propylene glycolate hydrate (Forxiga®), empagliflozin (Jardiance®), ipragliflozin L-proline (Suglat®), luseogliflozin hydrate (Lusefi®) and tofogliflozin hydrate (Apleway®)) are used for type 2 diabetes mellitus.

The MHLW/PMDA stated that cases of ketoacidosis have been reported in patients treated with SGLT2 inhibitors and cases of sepsis from pyelonephritis have been reported in patients treated with some SGLT2 inhibitors in Japan.

Based on expert advice and available evidence, the MHLW/PMDA recommended the addition of the following text on ketoacidosis to the subsection of the “Clinically significant adverse reaction” in the section of “Adverse reaction” in the package insert.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 4, August 2015 (www.tga.gov.au)
Ketoacidosis: Ketoacidosis (including diabetic ketoacidosis) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

The MHLW/PMDA have also recommended the addition of a description of sepsis to the “Adverse Reaction” and “Important Precautions” sections, under “pyelonephritis” and “ketone bodies increase and diabetic ketoacidosis” subsections respectively, in the package insert.

Reference: Revision of Precautions, MHLW/PMDA, 15 September 2015 (www.pmda.go.jp/english/)
(See WHO Pharmaceuticals Newsletter No.4, 2015 for Risk of diabetic ketoacidosis in the United Kingdom)

Sterile talc

Risk of interstitial lung disease

Japan. The MHLW and the PMDA have announced the revision of the package insert for sterile talc (Unitalc®) to include risk of interstitial lung disease.

Sterile talc is suspended with saline and injected into the pleural cavity for use in the prevention of recurrent malignant pleural effusion.

The MHLW/PMDA stated that cases of interstitial lung disease have been reported in patients treated with sterile talc in Japan. In addition, exacerbation of interstitial lung disease after the treatment with sterile talc has been reported in some patients who had the complication of interstitial lung disease prior to treatment.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the “Patients with interstitial lung disease” to the “Careful administration” section and the addition of the following text to the subsection of the “Clinically significant adverse reaction” in the section of “Adverse reaction” in the package insert.

Interstitial lung disease: Interstitial lung disease may occur. Patients should be carefully monitored for clinical symptoms such as cough, dyspnoea, and pyrexia. If any abnormalities are observed, tests such as chest X-rays or chest computed tomography (CT) scans should be conducted. If interstitial lung disease is suspected, appropriate measures such as administration of adrenal corticosteroids should be adopted.

Reference: Revision of Precautions, MHLW/PMDA, 6 August 2015 (www.pmda.go.jp/english/)

Treanda® Injection

Not compatible with closed system transfer devices, adapters, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene

USA. The US FDA has warned health-care professionals not to use bendamustine hydrochloride injection (Treanda® injection 45 mg/0.5 mL or 180 mg/2 mL solution) with closed system transfer devices (CSTD), adapters, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS). Most marketed CSTDs contain either polycarbonate or ABS and are not compatible with Treanda® Injection (45 mg/0.5 mL or 180 mg/2 mL solution).

Bendamustine hydrochloride for injection is an alkylating drug indicated for treatment of patients with:
- Chronic lymphocytic leukaemia. Efficacy relative to first line therapies other than chlorambucil has not been established.
- Indolent B-cell non-Hodgkin’s lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

Treanda® is available in two formulations, a solution, Treanda® Injection (45 mg/0.5 mL or 180 mg/2 mL solution); and a lyophilized powder, Treanda® for Injection (25 mg/vial or 100 mg/vial lyophilized powder).

N, N-dimethylacetamide (DMA), an ingredient in Treanda® Injection (45 mg/0.5 mL or 180 mg/2 mL solution), is incompatible with polycarbonate or ABS. Devices that contain polycarbonate or ABS dissolve when coming into contact with DMA. This can lead to device failure, possible product contamination, and potential serious adverse health consequences, including skin reactions in health-care professionals preparing and administering this product and the risk of small blood vessel blockage in patients.

The FDA has required label changes for both the solution and the powder formulations of Treanda® to reflect safe preparation information.

The FDA has recommended that health-care professionals only use a polypropylene syringe with a metal needle and polypropylene hub to withdraw and transfer Treanda® Injection and should stop using Treanda® Injection (45 mg/0.5 mL or 180 mg/2 mL solution) with CSTDs or vial syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS).
adapter and syringes containing polycarbonate or ABS

If a CTSD or adaptor is to be used as supplemental protection during preparation, only Treanda® for Injection (25mg/vial or 100 mg/vial lyophilized powder) should be used and not the solution formulation.

**Reference:**
**Bortezomib**

**Potential link with flesh-eating disease (necrotising fasciitis)**

**Canada.** Health Canada has completed a safety review to assess the potential association between flesh-eating disease and bortezomib (Velcade®).

Bortezomib is used to treat cancers of the bone marrow (multiple myeloma) and the lymphatic system (mantle cell lymphoma).

At the time of the review, no cases of flesh-eating disease in association with bortezomib were reported in Canada, however, 11 cases were reported in Europe. A review of the scientific and medical literature identified two additional medical case reports relevant to the topic of flesh-eating disease linked with the use of bortezomib.

In all the cases reviewed, other potential confounding factors were present such as: use of other medications, the presence of diabetes, alcohol use, smoking, obesity, immune suppression of the immune system (body’s ability to fight infection), chronic steroid use and blood circulation diseases affecting blood vessels. Hence, it was not possible to link the use of bortezomib alone and flesh-eating disease, at the time of the review.

Health Canada has requested additional safety information from the manufacturer for review and will continue to monitor bortezomib for the risk of flesh-eating disease.

**Reference:**


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**Brintellix® (vortioxetine) and Brilinta® (ticagrelor)**

**Similar drug names leading to potential medication errors.**

**USA.** The US FDA has warned health-care professionals and patients of the potential confusion between the antidepressant vortioxetine known as, Brintellix® and a different medication with a similar brand name Brilinta® (ticagrelor) which is used as an anti-blood clotting agent.

The confusion between these two medications with similar brand (proprietary) names has resulted in reports of prescribing and dispensing errors. None of the reports indicates that a patient ingested the wrong medication.

Brintellix® (vortioxetine) is a selective serotonin reuptake inhibitor (SSRI) used to treat major depressive disorder (MDD) in adults. Brilinta® (ticagrelor) is an antiplatelet /anti-blood clotting medication used to lower the risk of having another heart attack, or dying from a heart problem after a heart attack or severe chest pain.

The FDA has advised that health-care professionals can reduce the risk of name confusion by including the generic (established) name of the medication, in addition to the brand name, and the indication for use when prescribing these medications. Patients should check their prescriptions to ensure that the correct medication was dispensed.

**Reference:**


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**DPP-4 Inhibitors for Type 2 Diabetes**

**May cause severe joint pain**

**USA.** The US FDA has warned that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling. The FDA has added a new Warning and Precaution about this risk to the labels of all medicines in this drug class, called dipeptidyl peptidase-4 (DPP-4) inhibitors.

DPP-4 inhibitors are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes. These medicines are available as single-ingredient products and in combination with other diabetes medicines such as metformin.

The FDA advised health-care professionals to consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue the drug if appropriate. The FDA also advised that patients should not stop taking their DPP-4 inhibitor medicine, but should contact their health-care professional right away if they experience severe and persistent joint pain.

**Reference:**


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**Eltrombopag**

**Limited evidence: Risk of serious skin reactions**

**Canada.** Health Canada has conducted a safety review to evaluate the potential link between serious skin reactions and the use of eltrombopag (Revolade®). Results of the review show limited evidence of a risk of serious skin reactions.
Safety of Medicines

Reactions associated with the use of eltrombopag. Eltrombopag is a medicine used to help increase the number of platelets or thrombocytes in patients with immune thrombocytopenia purpura, severe aplastic anaemia and hepatitis C virus infection.

At the time of the review, Health Canada had received two reports of serious skin reactions other than SJS, TEN or DRESS in eltrombopag. Similar international reports suspected to be linked with eltrombopag use were provided by manufacturers of eltrombopag (Revolade®).

In addition a review of the literature identified two studies that reported four cases of serious skin reactions linked with eltrombopag use. Health Canada concluded that the evidence of an increase in risk of serious skin reactions with use of eltrombopag was limited due to incomplete reports and use of concomitant medications.

The Canadian prescribing information for eltrombopag already describes that rashes and the abnormal loss of skin cell are linked to eltrombopag use.


Etanercept

Limited evidence: Potential risk of schizophrenia like symptoms

Canada. Health Canada has conducted a safety review to evaluate harmful effects (adverse reactions) related to schizophrenia like symptoms with the use of etanercept (Enbrel®). Results of the review show limited evidence of an association.

The safety review was triggered by a published case report of a 54-year old woman taking etanercept who developed symptoms similar to schizophrenia.

Etanercept is an immune system protein (monoclonal antibody) which works by blocking a chemical TNF-α (Tumour Necrosis Factor-alpha) that causes pain and swelling (inflammation). Etanercept is used to treat inflammation of joints and skin caused by the body’s own defence system in conditions such as arthritis and psoriasis.

At the time of the review, 25 cases of psychiatric disorders, two of which were psychosis originated from Canada. A review of data from WHO global database of ICSRs, VigiBase®, identified 209 cases of psychiatric disorders, including anxiety, depression, and psychosis. However, Health Canada’s evaluation of both international and Canadian cases did not indicate that schizophrenia was linked to the use of etanercept.

Analysis of reports were limited due to incomplete reports, presence of other diseases and/or a past history of psychiatric disorders, and concomitant medications.

Health Canada will continue to monitor for adverse reactions associated with etanercept.


Gadolinium-based Contrast Agents for Magnetic Resonance Imaging (MRI)

Possible risk of brain deposits with repeated use

USA. The US FDA has announced that they are investigating the risk of brain deposits following repeated use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI). Recent publications in the medical literature have reported that deposits of GBCAs remain in the brains of some patients who undergo four or more contrast MRI scans, long after the last administration. It is unknown whether these gadolinium deposits are harmful or can lead to adverse health effects.

The FDA is working with the research community and industry to understand the mechanism of gadolinium retention and to determine if there are any potential adverse health effects. Based on the need for additional information, at this time, the FDA is not requiring manufacturers to make changes to the labels of GBCA products.

To reduce the potential for gadolinium accumulation, the FDA has advised health-care professionals to consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary. Health-care professionals are also urged to reassess the necessity of repetitive GBCA MRIs in established treatment protocols.

**Pseudoephedrine and ephedrine**

**Update on managing the risk of misuse**

The United Kingdom. The MHRA has provided an update on measures taken to manage the risk of misuse of pseudoephedrine and ephedrine in the United Kingdom.

Pseudoephedrine and ephedrine are nasal decongestants, and are available from pharmacies without a prescription. Between 2007 and 2008, the MHRA introduced restrictions on use of these substances because of concerns that medicines containing these active substances could be used in the illicit manufacture of the class A controlled drug methylamphetamine.

Since April 2008, after public consultation and following advice from the Commission on Human Medicines (CHM), the following sales restrictions have been in place to manage the risk of misuse of pseudoephedrine and ephedrine:

- it is illegal to sell or supply any product that contains more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription;
- it is illegal to sell or supply a combination of products that between them add up to more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription;
- it is illegal to sell or supply a product that contains pseudoephedrine and a product that contains ephedrine in one transaction.

Furthermore, the Royal Pharmaceutical Society advises that the sale and supply of these products must be made by a pharmacist or a suitably trained pharmacy staff member under the supervision of a pharmacist.

It is recommended that existing levels of monitoring, education and awareness measures by pharmacists should be maintained.

**Reference:**
Drug Safety Update, MHRA, Volume 9, issue 2: 3, September 2015 (www.gov.uk/mhra)

**Rivaroxaban**

**Possible risk of liver injury**

Canada. Health Canada has completed a safety review to evaluate whether using rivaroxaban (Xarelto®) is linked to a risk of liver injury. A clear link between the use of rivaroxaban and liver injury could not be established.

The review was initiated after the publication of two studies in the literature described liver injury linked to the use of rivaroxaban in a total of 16 patients.

Rivaroxaban is used to:

- prevent blood clots from forming in patients who have had hip or knee replacement surgeries;
- prevent and treat blood clots forming in a deep vein, usually in the leg (deep vein thrombosis), or in a blood vessel that supplies the lungs (pulmonary embolism);
- prevent stroke in patients with abnormal heart rhythm (atrial fibrillation).

At the time of the review, there were 61 reports originating from Canada, that described liver-related harmful effects (adverse events) in patients taking rivaroxaban.

In addition, a review global reports obtained in the WHO global database, VigiBase® showed 431 cases of liver injury, and rivaroxaban was reported as the only suspected drug used in 23 of these cases. However, a clear link between rivaroxaban and liver injury could not be determined, due to incomplete information in reports.

In some of the reports published in the scientific literature, patients had underlying liver diseases before using rivaroxaban or were taking other medications that may have contributed to the liver injury.

Health Canada will continue to monitor safety information involving rivaroxaban.

**Reference:**
Summary Safety Review, Health Canada, 26 August 2015 (www.hc-sc.gc.ca)

**Tramadol oral drops**

**Not for children under the age of 12 years**

Australia. The TGA has reminded health-care professionals that tramadol oral drops (Tramal®) are not approved for use in children under the age of 12 years and no dosing instructions are provided for this age group in the Product Information.

Tramadol is a centrally-acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects.

The reminder follows the death of a two-year-old Australian child as a result of tramadol toxicity following treatment with tramadol oral drops.

The TGA has provided the following information for health-care professionals:

- Tramadol oral drops are safe and appropriate for use in adult and adolescent patients for whom the medicine is approved, however, given the concentration of the drops...
Safety of Medicines

(100 mg/mL), there is a potential risk of overdose in children.

- The dosing recommendations in the Product Information for tramadol oral drops are only valid for adults and adolescents over the age of 12 years.
- Use of tramadol oral drops in children under the age of 12 years is off-label.
- This medicine should only be prescribed for patients in the approved age group.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 4, August 2015 (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 the WHO Global ICSR database, VigiBase®. The database contains over 10 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 23). 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.

Dextromethorphan and serious neurological disorders in children
Ms Lovisa Sandberg and Ms Sarah Watson, Uppsala Monitoring Centre

In the screening of paediatric individual case safety reports (ICSRs) from the WHO Global ICSR database, VigiBase® the adverse drug reaction (ADR) ataxia was highlighted for the drug dextromethorphan. The substance is used in many cough, cold and flu products sold over the counter globally. It is approved for children and adults above 6 years of age in the United Kingdom and above 4 years of age in the United States.1,2 Most dextromethorphan containing products in the United Kingdom are however indicated from the age of 12.1

Widening the search in VigiBase® to include reports on the whole WHO-ART System Organ Class (SOC) Neurological disorders revealed several serious ADRs. As of February 2015 there were 110 reports for children under the age of 6 years for the whole SOC. The reports originate from Asia, Europe, Latin and North America. Among the reported terms were ataxia, convulsions, dyskinesia and coma. There were 29 reports for the WHO-ART High Level Term (HLT) ataxia and 10 reports for the HLT coma (all reports of coma were for children of 2 years of age or less). For all children (younger than 18 years) there were 51 reports for the HLT ataxia, and 19 reports with the HLT coma. In the summary of product characteristics (SmPC) for several products containing multiple ingredients including dextromethorphan, coma is listed in the section for overdoses but for drugs containing only dextromethorphan in the United Kingdom, coma is not listed as a possible ADR other than as a contraindication in patients using MAO-inhibitors.1

In 2008/2009 the MHRA and the CHM in the United Kingdom advised that children under 6 years should not be given over-the-counter cough and cold medicines containing dextromethorphan.3 Nonetheless, reports on dextromethorphan associated with serious ADRs within the SOC Neurological disorders for children below the age of 6 have continued to be reported to VigiBase® after 2009 (the latest submitted in 2014). The majority of these reports are not co-reported with accidental intake of the drug or overdose.

Continuous reporting of serious neurological ADRs associated with off-label use of dextromethorphan in young children suggests that the risk-benefit balance for dextromethorphan is not clear to parents. Further revisions of the patient information leaflets are advised to clearly highlight the risk of serious neurological reactions in young children.

References
Olanzapine and accidental drug intake by children
Ms Lovisa Sandberg and Ms Sarah Watson, Uppsala Monitoring Centre

In the screening of paediatric ICSRs from the WHO Global ICSR database, VigiBase® the ADR miosis was highlighted for the drug olanzapine in young children. Olanzapine is not indicated for children and adolescents due to lack of data on safety and efficacy.1 As of March 2015 there were eight reports of miosis for children below the age of 6 years. The signs of miosis reflect the anticholinergic properties of olanzapine. An assessment of the reports revealed that the WHO-ART preferred terms (PT) accidental drug intake by child, accidental overdose, or medication error was co-reported in six out of the eight reports. Widening the search to the WHO-ART HLT medication error related problems revealed 20 reports for olanzapine within the age group excluding two suspected duplicates. More than half of those reports represented accidental drug intake (by child, accidental exposure to product or accidental overdose). The reports originated from Asia, Europe, North America and Oceania.

Accidental overdose with olanzapine in children is well described in the literature, including several published case reports (of which a few are also present in VigiBase®).2,3 This notice aims to further highlight the issue of a continuing problem with children getting access to potentially harmful drugs. This is especially important to bear in mind when prescribing drugs to parents for indications likely to reflect decreased risk awareness. It should be stressed that, when available, blister packages are the preferred choice for parents with young children.

References

Temozolomide and Oesophagitis
Prof Alfonso Carvajal, Spain

Summary
Temozolomide is an oral alkylating agent used in a radiation-containing regimen as the first-line treatment for glioblastoma. Oesophagitis is not listed in the EMA SmPC or FDA label, while, related reactions such as stomatitis, dysphagia and gastroenteritis are. In a series of nine cases from the WHO Global ICSR database, VigiBase®, a relationship between temozolomide and oesophagitis has been highlighted through the vigiRank screening method. Though the information coming from this series is not fully conclusive by itself and there is no clear evidence in the literature of this combination, both biological plausibility and analogy to a structurally similar drug indicate that this reaction could be correlated to temozolomide; further studies should be pursued to characterize it.

Introduction
In September 2014, the UMC signal detection for the first time screened reports issued for paediatrics. This screening, using the vigiRank screening method, highlighted an association between temozolomide and oesophagitis. Since the drug is not restricted to paediatric use and multiple age groups were associated with the adverse event, this evaluation was conducted on patients of all ages.

Temozolomide is an oral triazene alkylating agent that has been available since the early 2000s; coupled with radiotherapy it is the first-line treatment for glioblastoma, the most common primary brain cancer in adults, against which its efficacy has been proven.1,2 At physiological pH, temozolomide is converted to the monomethyl-triazene metabolite, MTIC, which exerts the main cytotoxic action by methylating DNA at a number of sites. Temozolomide shares this metabolite and structural similarities with another triazene alkylating agent, dacarbazine.3 In early clinical
development it was observed that the administration of a single dose of temozolomide induced myelosuppression.

Oesophagitis is a potentially serious inflammation of the oesophagus that can occur due to different causes, from infections to physical injury resulting from radiation therapy.

**Reports in VigiBase®**

Twelve cases of oesophagitis (WHO-ART PT) in association with temozolomide were identified in the WHO Global ICSR database, VigiBase®, in October 2014. Based on age, sex, country, type of report and other features, one duplicate (case 1) and one triplicate (case 8) have been identified. Thus, there are nine primary cases containing the reaction of interest (Table 1); in one, the reaction was reported as "oesophageal pain".

Age and sex were known in five cases while two cases only reported patient gender (Table 1). Two cases concerned children, an 8-year-old female and a 10-year-old male, while three involved male adults aged 62, 67 and 69; two cases of unknown age were female, while two cases had no information on the patient. No age or sex patterns emerge.

In all cases the reaction appeared after the intake of the drug. Two reported time to onset (19 days and 31 days); in none was the reaction reported alone. Temozolomide was the only suspected drug in three of the reports. The drug was withdrawn in four cases: the outcome was unknown for two cases (1, 8), recovery as concerns one (case 2, which was reported as positive dechallenge) and no recovery in another (case 3). There is no information on dechallenge in case 7, however the outcome was recovery. No cases mention positive rechallenge. All cases except one, case 3, were considered as serious. In two cases the patient died due to severe myelosuppressive reactions.

In November 2014 VigiBase® was also queried for oesophagitis (WHO-ART) in association with dacarbazine, obtaining seven cases. Additionally, this combination was highlighted through a disproportionality analysis with an IC of 1.29 and IC25 of 0.03.

**Table 1. Characteristics of reports for temozolomide and oesophagitis in VigiBase®**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Other Suspected (S) or concomitant (C) drugs</th>
<th>Other reported reactions (WHO-ART preferred terms)</th>
<th>Time to onset</th>
<th>Action taken/ Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62/M</td>
<td>Cisplatin, gemcitabine, methyldprednisolone, paclitaxel (all S) Acetylsalicylic acid, therapeutic radiopharmaceuticals (both C)</td>
<td>Venous thrombosis, thrombocytopenia, pancytopenia, myopathy, hiatus hernia, chest pain, ulcer*</td>
<td>-</td>
<td>Drug withdrawn/ Unknown</td>
<td>Oesophageal candidiasis</td>
</tr>
<tr>
<td>2</td>
<td>67/M</td>
<td>Zolpidem, amiodipine, naproxen, tolterodine, vitamins nos, trovaprost, paracetamol (all C)</td>
<td>Vomiting, nausea, haematemeses, gastro-intestinal disorder nos, erythema, constipation, chest x-ray abnormal, aortic disorder*</td>
<td>-</td>
<td>Dechallenge positive</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>69/M</td>
<td>Metamizole, corticosteroids, omeprazole, tramadol, therapeutic radiopharmaceuticals (all C)</td>
<td>Thrombocytopenia</td>
<td>31 days</td>
<td>Drug withdrawn/ Not recovered</td>
<td>Not serious</td>
</tr>
<tr>
<td>4</td>
<td>-/F</td>
<td>Bevacizumab, irinotecan, therapeutic radiopharmaceuticals, fluticasone, levethoxyine, simvastatin, docetaxel, methotrexate, tinidol, gefitinib, citalopram, phenytoin, bupropion, tolterodine, paracetamol/hydrocodone bitartrate, trazodone, omeprazole (all S)</td>
<td>Wbc abnormal nos, urinary tract infection, neutrophil count*, haemoglobin*</td>
<td>19 days</td>
<td>-</td>
<td>Developed oesophagitis after stopping temozolomide (duration 4 days). Sepsis.</td>
</tr>
<tr>
<td>5</td>
<td>-/F</td>
<td>Topotecan, bevacizumab (both S) Sertraline, metoprolol (both C)</td>
<td>Thrombocytopenia, sepsis, renal failure, oesophagitis, neutropenia, neoplasm progression*, mucosal inflammation, mental status changes*, febrile neutropenia, thrombosis venous deep</td>
<td>-</td>
<td>-</td>
<td>Febrile neutropenia, death due to infection</td>
</tr>
<tr>
<td>6</td>
<td>10/M</td>
<td>Irinotecan, carboplatin, etoposide, cyclophosphamide (all S) Hydromorphone (C)</td>
<td>Mucosal inflammation, febrile neutropenia, platelet count decreased, appetite decreased, oesophageal pain, abdominal pain upper, anaemia</td>
<td>-</td>
<td>-</td>
<td>Oesophageal pain</td>
</tr>
<tr>
<td>7</td>
<td>-/-</td>
<td>-</td>
<td>Incorrect technique in drug usage process, angioedema, oesophagitis</td>
<td>-</td>
<td>-/Recovered</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>8/F</td>
<td>Nimotuzumab (S)</td>
<td>Dermatitis, leucopenia, thrombocytopenia</td>
<td>-</td>
<td>Drug withdrawn/ Rechallenge/-</td>
<td>Death due to disease progression</td>
</tr>
<tr>
<td>9</td>
<td>-/-</td>
<td>Bevacizumab (S)</td>
<td>Vomiting, transaminase nos increased, dehydration, wound infection, healing impaired, intestinal perforation, haemorrhage nos, fatigue, venous thrombosis, neutropenia, thrombocytopenia</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*MedDRA terms
Temozolomide is indicated for use in children from three years of age and in adults. Oesophagitis is not labelled for the drug in adults or in children, neither in the UK SPC nor the FDA label, however, stomatitis, dysphagia and gastroenteritis are listed as adverse drug reactions. Using the keywords “temozolomide” and “oesophagitis” (or “oesophag*”) no articles were retrieved in PubMed (November, 2014). In two separate clinical studies, two cases of oesophagitis associated with temozolomide were reported; it is difficult to ascertain if these cases are the ones that have been reported and stored in VigiBase®. At least one, case 8, that was presented in Reactions Weekly, has already been sent to VigiBase®.

Discussion and Conclusion
Oesophagitis can be a serious reaction that may have many causes; among them, radiation therapy that is usually employed along with temozolomide for the treatment of brain tumours. Another cause is myelodepression and subsequent neutropenia, which in turn can give rise to infections. Medications, through different mechanisms, have also been associated with oesophagitis; particularly antitumourals. Myelodepression, for instance, can be induced by different drugs; in fact, some of the cases in the present series (1, 5, 6, 9) developed neutropenia or candidiasis. Direct damage could be another possibility, as temozolomide is administered by the oral route. Thus, based on the pathophysiology of the reaction and the mechanism of this alkylating agent, there exists the possibility that this reaction was cause-related.

The present series is composed of nine cases; some of the cases (2, 3, 6, 9) come from clinical studies and are well described, as is the one from the literature (case 8). However, there is only one case (case 7) in which temozolomide is the only reported drug; since this case is not sufficiently complete, the possibility of unreported concomitants cannot be excluded. Although there is one positive dechallenge, there is no case with a positive re-challenge: based on this particular series, drawing a conclusion proves to be difficult.

In the literature there are some cases of oesophagitis, but once again, it is difficult to pinpoint the reaction to temozolomide since most of the patients were being treated with multiple drugs.

All in all, the best evidence could be pharmacological plausibility. Many anticancer drugs are able to interfere with the cellular cycle, and in this manner interrupt the cellular growth; this is particularly evident in rapidly growing tissues. For these drugs, stomatitis, oesophagitis, gastritis and enteritis would be a continuum depending on the route, dose and time of exposure. With this in mind, it would be expected for similar adverse reactions to occur. In fact, stomatitis, dysphagia and gastroenteritis are already labelled for temozolomide.

Oesophagitis is therefore a possible reaction in connection with temozolomide. Moreover, an error in the administration could possibly account for this reaction. In fact, one of the cases mentions an “incorrect technique in drug usage process”; the SmPC does warn about this possibility: the capsules have to be swallowed as they are, with water; they must not be opened or chewed.

References
CAVEAT DOCUMENT

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

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

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

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

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

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

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

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

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

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

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

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase®.
WHO-UMC-HSA Inter-Regional Pharmacovigilance Training, Singapore,
30 September - 2 October 2015

The World Health Organization (WHO), the Uppsala Monitoring Centre (UMC) and the Health Sciences Authority (HSA) of Singapore hosted the WHO-UMC-HSA Inter-Regional Pharmacovigilance Training in Singapore, from 30th September to 2nd October 2015.

Pharmacovigilance (PV) is the key to monitoring and evaluating adverse reactions to medicinal products (ADRs). PV can identify and assess the risk-benefit balance related to the use of medicinal products in whole population or in specific population groups. PV activities are imperative to improve patient safety and thus public health with regard to the use of pharmaceutical products.

The Association of Southeast Asian Nations’ (ASEAN) member countries and Asia Pacific countries have different levels of PV capacity. Therefore sharing the current PV status, practices and challenges would contribute in further development in the areas of reporting, data quality, assessment of Individual Case Safety Reports (ICSRs), detection of Signals, preventing ADRs, communication with stakeholders and patient safety. Training in these areas is therefore an important component of the WHO Programme.

Since 2010, WHO, the UMC and the HSA of Singapore have been collaborating to conduct PV training for regulators and National PV Centres in ASEAN and Asia Pacific countries with the aim of building PV capabilities in countries within this region.

Speakers included experts from WHO, the UMC and the HSA, and from Japan’s Pharmaceuticals and Medical Devices Agency (PMDA).

The aim of this three-day training course was to impart knowledge and understanding of the various essential elements in PV, as well as the necessity to collaborate with stakeholders. In addition, there were sessions dedicated to the role and the importance of effective communication. Communication plays a critical role in PV as information needs to be relayed to the various stakeholders in a manner that it can be understood, to influence and effect changes in behaviour.

There were approximately 60 participants from regulatory authorities and National PV Centres, representing Brunei Darussalam, Cambodia, Fiji, Hong Kong, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Tuvalu, Vietnam. Experts from WHO, the UMC, the HSA (Singapore) and the PMDA (Japan) and Associate Professor Thoon Koh Cheng, an Adverse Events Following Immunisation (AEFI) specialist from the KK Women’s and Children’s Hospital, Singapore presented and facilitated the training programme. The topics covered during the 3-days programme included:

- Pharmacovigilance Methods
- WHO Programme for International Drug Monitoring (PIDM)
- Substandard / spurious / falsely-labelled / falsified / counterfeit (SSFFC) Medicinal Products
- Management of Individual Case Safety Reports (ICSRs)
- Immunisation Programmes
- Effective Communication in Pharmacovigilance, including communication in crisis.
- Patient Safety and Medication Errors

The training was officially opened by the Chief Executive Officer of HSA, Dr Mimi Choong.

On Day 1, presentations from the HSA and the PMDA introduced the national PV centre in the country, its organization, roles, responsibilities and PV activities. Fundamental PV methods were presented, and WHO’s activities in PIDM were introduced. Also, there was a presentation on WHO programmes on SSFFC. Presentations on developing a positive ADR reporting culture and ways to collect ADRs highlighted the importance of active and collaborative relationships between all stakeholders. Data exchange in a global PV environment session provided information on data format and terminologies used in PV.
Day 2 consisted of interactive sessions on causality assessment. In the morning, two sessions provided the basic principles on how to select, use and analyse ICSRs. After these sessions, participants were divided into smaller groups that consisted of about 5 - 6 individuals. They learned the concept, methodology, tips and implementation of causality assessments, detection and interpretation of Signals and data mining.

The "PV in public health programme -AEFI-" and "patient safety and medication errors" were covered on Day 3. Subsequently, an intense presentation on communication in PV was provided. Participants learned some examples of miscommunications that could occur during the PV activities, how to avoid miscommunication, and importance of good and appropriate communication and preparations for it.

Most participants found the training useful. Some have asked for the training to be conducted on a regular (e.g. annual) basis.

In particular, a few participants highlighted the topics of causality assessment and communication practices as interesting or valuable to them. The sessions related to causality assessment and signal detection were "practical" and "relevant" to their daily work.

There were also comments that the training has enabled them to pick up new ways of starting a pharmacovigilance system in their countries.
One of the recommendations revisited in the 2015 meeting included harmonizing and coordinating vigilance systems to form a single reporting portal.

Pharmacovigilance systems in the Eastern Mediterranean Region

There are 22 countries in the Eastern Mediterranean (EM) region, 10 are full members of the WHO Programme for International Drug Monitoring (PIDM), five are associate members and seven are not in the Programme. The first country to join the WHO PIDM was Morocco in 1992, where the first EM regional meeting was held in 2014. This brought together countries in the region to discuss pharmacovigilance (PV) topics and strategies to advance PV. One of the recommendations revisited in the 2015 meeting included harmonizing and coordinating vigilance systems to form a single reporting portal. Other recommendations include: encouraging more countries in the region to join PIDM, building global vigilance systems in countries where PV does not exist, and harmonizing terminology in the Arabic language.

The workshop

Day 1 The meeting started with a warm welcome from the Head of the CAPM on behalf of the Morocco Ministry of Health. The PV ambience was set with an overview of global and regional PV for medicines, vaccines and medical devices. An update of activities from four Pharmacovigilance WHO Collaborating Centres (WHO Collaborating Centres for: Advocacy and Training in PV, Accra; International Drug Monitoring, Uppsala; PV in Education and Patient Reporting, Lareb; and Strengthening PV Practices, Rabat) was provided with a focus on developments in the EM region. In the afternoon, the recently published "WHO Guideline on Pharmacovigilance Indicators: A Practical Manual for Assessment of Pharmacovigilance Systems" was introduced and preliminary results of a survey on national PV systems in EM region using the indicators were shared. Nineteen countries responded to the survey and the findings highlighted the variability in PV levels across the region.
The workshop continued...

Day 2

Countries shared their experiences and approach to aspects of PV such as establishing a federal system, regional centres, risk management plans, medication errors, and clinical practice. The 2014 recommendation from the first Eastern Mediterranean Regional meeting on integrating vigilance systems was visited and participants were split into groups to discuss and explore the concept of integrating vigilance systems. Participants in groups worked together to identify potential opportunities and challenges to help create a road map for establishing an integrated vigilance system.

Day 3

In the morning, participants either made site visits or met with representatives of the Moroccan anti-poison centre, hospitals and pharmaceutical companies to discuss pharmacovigilance in these areas. This generated interesting discussions, providing a practical perspective of PV. The remainder of the day focused on vaccines safety. Recent concepts were introduced, and an intense session on the technical aspects of Adverse Events Following Immunization (AEFI) surveillance, causality assessments and signal detection was conducted. Participants were split into groups and worked together to apply concepts to exercises which aimed to make AEFI surveillance systems functional in countries with variable health care systems.

Day 4

The day started with further presentations focusing on vaccine safety monitoring during pregnancy, actions after causality assessment and the vaccine safety blueprint. The afternoon consisted of a plenary session. During this session group work carried out on day 2 was shared amongst all participants. Through engaged discussions, participants agreed on a draft of recommendations and next steps for establishing an integrated vigilance system. In addition an online vigilance platform for sharing information and building a network in the EM region was launched.

2015 Recommendations for pharmacovigilance in the Eastern Mediterranean region

The following recommendations were made by the meeting participants:

Integrated Systems

- WHO should define the broad elements of an integrated vigilance system.
- To the extent possible countries should adopt a step wise, integrated approach to medicinal products surveillance.
- Where vigilance systems exist, collaborative platforms to support integrated approaches should be developed.
- Where there is no functional vigilance system in place, countries should develop a functional and sustainable vigilance system towards an integrated system in the long-term.
- An integrated vigilance model should be established; the CAPM may serve as a reference.

Vaccinovigilance

- A national AEFI committee should be established if non-existent.
- The 22 AEFI variables should be included in adverse event reporting form.
- AEFI data should be reported to both WHO/UNICEF Joint Reporting Form and the national database.
- The performance indicator: AEFI reporting ratio for 100,000 surviving infants should be monitored.
- The management of serious AEFI cases should be harmonized.
Pharmacovigilance in CEMAC countries

The Economic and Monetary Community of Central Africa (CEMAC) is made up of six Member States: Central African Republic (CAR), Gabonese Republic, Republic of Cameroon, Republic of Chad, Republic of Congo, and Republic of Equatorial Guinea. These countries cover a total surface of approximately three million km² with a total estimated population of 37 million. CEMAC was created in 1994 and was established to promote economic integration among countries that share a common currency.

Organization of coordination for control of Endemic Diseases in Central Africa (OCEAC) is an organization responsible for public health issues in CEMAC countries, and was mandated in 2005 by the Council of CEMAC Ministers to lead the harmonization process of National Pharmaceutical Policies (NPP) in central Africa. In June 2013, the CEMAC Heads of States adopted an additional act to the CEMAC treaty to include regulations on pharmacovigilance (PV). The objective of the PV regulation is to set up an efficient PV systems for monitoring unexpected adverse effects of pharmaceuticals in the CEMAC Member States.

Four of the CEMAC countries have not yet joined the WHO Programme for International Drug Monitoring (PIDM) (Central African Republic, Gabonese Republic, Republic of Congo, and Republic of Equatorial Guinea). Republic of Chad has recently become an associate member (August 2015) and Republic of Cameroon has been a full member of the programme since 2010.

Building Pharmacovigilance in Member States of Economic and Monetary Community of Central Africa (CEMAC)

Workshop in Brazzaville, Republic of Congo, 28 September-02 October 2015

A pharmacovigilance (PV) workshop for countries of the Economic and Monetary Community of Central Africa (CEMAC) was organized jointly between Organization of Coordination for Control of Endemic Diseases in Central Africa (OCEAC), WHO Africa Regional Office, WHO Country Office in Republic of Congo and WHO Headquarters. The workshop was facilitated by the WHO Collaborating Centre for Strengthening Pharmacovigilance Practices, Centre Anti Poison de Pharmacovigilance du Maroc (CAPM), Rabat.

Participants from all six OCEAC countries were appointed by their country’s Ministry of Health. The participants, facilitators from the CAPM, WHO Headquarters and from OCEAC travelled to Brazzaville, Republic of Congo where the workshop took place, from 28 September-02 October 2015. Pharmacovigilance training has been expressed as a requirement by the OCEAC countries, many of which do not have a PV system. The purpose of the workshop was to improve PV skills, provide technical support to countries and help countries setup or enhance PV systems.

The workshop

Day one: The workshop commenced with a grand opening ceremony where a representative of the Minister of Health from the Republic of Congo presented a speech. He emphasized the need for medicines safety where everyone at both national and regional levels should take responsibility. Representatives from each of the six countries presented their country’s current pharmacovigilance (PV) situation. Following this an introduction to the fundamentals of PV, definitions used, and the role of the WHO Programme for International Drug Monitoring (PIDM) were presented.

Day two: The morning sessions started with an introduction on the essential elements of a reporting form. Participants were then split into groups to evaluate reporting forms. Two countries had already designed their own reporting forms, and the remaining countries were yet to create one. Constructive feedback on existing forms were presented. The day ended with a practical session on casualty assessments, in which participants practised using the French imputability method. The exercises reaffirmed the need for complete information in reporting forms.

Day three: This was an intensive day, starting with a session on ATC/DDD classification of medicinal products, followed by hands-on training on VigiFlow®. VigiFlow is a web-based data management system for Individual Case Safety Reports (ICSR) designed by the Uppsala Monitoring Centre for national PV centres. Participants were also introduced to the concept of disproportionality during the session on signal detection.
**Day four:** The first presentation of the day focused on integrating PV into public health programmes. This sparked spirited discussions, as many of the countries run public health programmes and mass drug administration campaigns which require PV. Following the second presentation on medication errors, the importance of raising awareness of medication errors and introducing a no-blame culture was expressed. The day progressed with presentations on phytovigilance, detection of Spurious/Falsely-labelled/Falsified/counterfeit (SSFFC) medicines and using a one-stop integrated vigilance system. Discussions on these topics were extremely important, as CEMAC countries face difficult challenges with SSFFCs. In addition, many patients resort to herbal and natural remedies which require a vigilance system. In the afternoon, participants split into groups again. They formulated an action plan to build PV in their countries using the concepts learned.

**Day five:** A representative from each country presented their action plan for PV to the group of participants. The day ended with a closing ceremony.

**Pharmacovigilance in the Republic of Congo**

The Republic of Congo is not yet a member of the WHO Programme for International Drug Monitoring (PIDM). However, pharmacovigilance (PV) activities have started. As part of a PV pilot, two medical doctors working at the university hospital in Brazzaville, received PV training in May 2015. Since then, five, reports of suspected adverse drug reactions have been made. There are plans to extend this training to clinicians in two other hospitals. Currently, there is a focal person for haemovigilance but not PV. Representatives from Republic of Congo who attended the meeting revealed plans to assign a PV focal person and join the WHO PIDM in the near future.

*Participants and facilitators at the pharmacovigilance capacity building seminar for CEMAC countries, Brazzaville, Republic of Congo, 28 September – 2 October 2015.*