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

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

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This Newsletter is also available on our Internet website:
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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®.

As the Feature article, we have included a brief report from a recent WHO-led pharmacovigilance training event.

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## Carbamazepine

### Risk of Stevens Johnson’s Syndrome.

**India**: The Central Drugs Standard Control Organisation (CDSCO) and the Signal Review Panel of the Pharmacovigilance Programme of India-Indian Pharmacopoeia (SRP-PvPI-IPC) have requested that all manufacturers of carbamazepine should include Stevens Johnson’s Syndrome as an adverse reaction in the package inserts and on the official websites.

Carbamazepine is used as an anticonvulsant used in patients with epilepsy and in patients with trigeminal neuralgia.

In India, there are 122 reports of life threatening or fatal skin reactions (Stevens Johnson’s Syndrome, Toxic Epidermal Necrolysis) that may have been caused by the use of carbamazepine formulations. Although Stevens Johnson’s Syndrome is a known adverse effect of carbamazepine and is already included in some package inserts, the Subject Expert Committee (SEC) have recommended that all manufacturers should include the same information on this adverse effect. The CDSCO/PvPI have decided that it was necessary to revise the package insert to include screening of HLA-B* 1502 prior to initiating the carbamazepine treatment, as HLA-B* 1502 is a known factor for carbamazepine-induced Stevens Johnson’s Syndrome.

(See WHO Pharmaceuticals Newsletters No.1, 2013: Potential risk of serious skin reactions associated with the HLA-A* 3101 allele in United Kingdom)

**Reference:**
Central Drugs Standard Control Organisation, February 2016 (www.cdsco.nic.in)

## Cisplatin

### Risk of blood clots in the veins (venous thromboembolism)

**Canada**. Health Canada has recommended that the prescribing information for cisplatin products should be updated to include warnings about the increased risk of venous thromboembolism.

Cisplatin, in combination with other treatments, is used to treat advanced bladder, testicular and ovarian cancers.

Health Canada conducted a review investigating a possible risk of venous thromboembolism with cisplatin treatment, following an update of prescribing information published in Japan.

The review concluded that cisplatin is linked to a higher risk of venous thromboembolism when used to treat patients with advanced bladder, testicular and ovarian cancers. Health Canada has therefore asked manufacturers of cisplatin products to update their prescribing information to include warnings about this risk.

At the time of the review, Health Canada had received 18 reports of venous thromboembolism with the use of cisplatin. All cases were determined to be possibly related to cisplatin. Among the reported cases, five had a fatal outcome, but the cause of death was inconclusive.

The WHO Global Individual Case Safety Report (ICSR) Database, Vigibase® had 520 reports of venous thromboembolism cases linked with cisplatin at the time of this review.

A published study in the literature also reported a greater risk of venous thromboembolism with patients treated with cisplatin, compared to non-cisplatin treated patients when used to treat solid tumours.

**Reference**:

## Entecavir hydrate

### Risk of hepatic function disorder

**Japan**. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for entecavir hydrate (Baraclude®) should be revised to include risk of hepatic function disorder as a clinically significant adverse reaction.

Entecavir hydrate is used to suppress the replication of hepatitis B virus in chronic hepatitis B patients with confirmed hepatic function associated with active viral replication.

Cases of elevated liver enzymes AST and ALT have been reported during treatment with entecavir hydrate in Japan. Although it is difficult to distinguish whether the cause is due to entecavir or the primary disease (can also elevate levels of AST and ALT), the causality due to the drug could not be ruled out.

The package insert will be updated to include: Hepatic function disorder: AST and ALT may become elevated during treatment with this drug. If elevation of AST and ALT are observed, patients should be carefully monitored by conducting more frequent liver function tests, etc. If there are no signs of improvement in hepatic function based on test values, etc., appropriate measures such as discontinuation of
Eribulin mesylate

Risks of oculomucocutaneous syndrome (Stevens-Johnson Syndrome) and erythema multiforme

Japan. The MHLW and PMDA have announced that the package insert for eribulin mesylate (Halaven®) will be revised to include risks of oculomucocutaneous syndrome (Stevens-Johnson Syndrome) and erythema multiforme.

Eribulin mesylate is used for unresectable or recurrent breast cancer.

The MHLW/PMDA stated that cases of oculomucocutaneous syndrome have been reported in Japan and cases of both oculomucocutaneous syndrome and erythema have been reported in other countries.

The package insert will be updated to include:
- Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme:
- Oculomucocutaneous syndrome or erythema multiforme 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, 16 February 2016 (www.pmda.go.jp/english/)

Esomeprazole magnesium hydrate

Risk of rhabdomyolysis

Japan. The MHLW and PMDA have announced that the package insert for esomeprazole magnesium hydrate (Nexium®) will be revised to include risk of rhabdomyolysis as a clinically significant adverse reaction.

Esomeprazole magnesium hydrate is used to treat: ulcers (gastric, duodenal, anastomotic); reflux oesophagitis, and Zollinger-Ellison syndrome. It is also used to suppress the relapse of gastric or duodenal ulcers when prescribing non-steroid anti-inflammatory drugs (NSAIDs) or low-dose aspirin.

In addition, it is indicated for the eradication of Helicobacter pylori, in combination with antibiotics.

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

The package insert will be updated to include:
- Rhabdomyolysis:
  - Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feeling of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 16 February 2016 (www.pmda.go.jp/english/)

Flunitrazepam

Precautionary measures for respiratory depression; and risk of apnoea, respiratory depression, and glossoptosis

Japan. The MHLW and the PMDA have requested that the package insert for flunitrazepam (Rohypnol®) should be revised to include advice on using precautionary measures to prepare and monitor for respiratory depression. In addition the package insert should be updated to include reports of apnoea, respiratory depression and glossoptosis.

Flunitrazepam is used for induction of general anaesthesia and sedation during topical anaesthesia.

Cases of respiratory depression with serious outcomes in patients, and cases of insufficient monitoring and delayed therapeutic measures have been reported with the use of flunitrazepam in Japan.

During the last three fiscal years in Japan, a total of 11 cases associated with respiratory depression have been reported (including eight cases for which a causal relationship to the product could not be ruled out; however, six of these cases used the drug for a condition not included as an approved indication).

A summary of the MHLW/PMDA’s recommendations are as follows:
- Need for preparation of emergency analeptic drugs and flumazenil prior to administration as well as need for continuous monitoring of cardiorespiratory dynamics should be added as an important precaution to the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 16 February 2016 (www.pmda.go.jp/english/)
• Reports of serious outcomes and need for appropriate measures with apnoea, respiratory depression and glossoptosis should be added as clinically significant adverse reactions to the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 22 March 2016 (www.pmda.go.jp/english/)

Furosemide

Risk of interstitial pneumonia

Japan. The MHLW and the PMDA have requested that the risk of interstitial pneumonia is added as a clinically significant adverse reaction to the package insert for furosemide (Lasix® and Eutensin®) as a clinically significant adverse reaction.

Furosemide is used for treatment of several diseases and symptoms such as hypertension, oedema, premenstrual tension, stimulating excretion of urinary calculus, and oliguria due to acute or chronic renal failure.

Cases of interstitial pneumonia have been reported in patients treated with furosemide in Japan. In the last three fiscal years in Japan, a total of six cases associated with interstitial pneumonia have been reported (including two cases for which a causal relationship to the product could not be ruled out).

Reference:
Revision of Precautions, MHLW/PMDA, 22 March 2016 (www.pmda.go.jp/english/)

Fusafungine nose and mouth sprays

Risk of serious allergic reactions

EU. The European Medicines Agencies (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the marketing authorizations for fusafungine-containing medicines are revoked, so that the medicines can no longer be marketed in the EU. This recommendation follows a review by the PRAC which concluded that the benefits of fusafungine did not outweigh its risks, particularly the risk of serious allergic reactions.

Fusafungine is an antibiotic and anti-inflammatory nose and mouth spray used to treat upper airway infections such as rhinopharyngitis (common cold).

Serious allergic reactions have occurred soon after the use of these sprays and involved bronchospasm (excessive and prolonged contractions of the airway muscles leading to difficulty breathing). Although serious allergic reactions are rare, they can be life-threatening, and no measures have been identified to sufficiently reduce this risk. Evidence for beneficial effects of fusafungine is weak, and upper airway diseases are generally mild and self-limiting.

In addition there are concerns for the potential for fusafungine to promote antibiotic resistance. The evidence of this is weak, however the risk cannot be ruled out.

Patients and health-care professionals should note that medicines will remain available while a final decision is pending. Further information will be issued in due course.

Reference:
Press release, EMA, 12 February 2016 (www.ema.europa.eu)

Idelalisib

Risk of a particular type of lung infection (Pneumocystis jirovecii pneumonia)

EU. The EMA’s PRAC has issued provisional advice for doctors and patients using the cancer medicine idelalisib (Zydelig®) to ensure that it continues to be used as safely as possible.

In the EU, idelalisib is authorised for the treatment of:
• chronic lymphocytic leukaemia in patients who have received previous treatment as well as in previously untreated patients who have certain genetic mutations in their cancer cells. It is used in combination with rituximab.
• a type of non-Hodgkin lymphoma called follicular lymphoma where it is used on its own.

The PRAC recommends that all patients treated with idelalisib should receive antibiotics to prevent a particular type of lung infection (Pneumocystis jirovecii pneumonia). Patients should also be monitored for infection and have regular blood tests for white cell counts (low counts can increase their risk of infection). Idelalisib should not be started in patients with a generalised infection. It should also not be started in previously untreated patients with chronic lymphocytic leukaemia (CLL) whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation).

These are provisional recommendations which the PRAC has issued, as a precaution, to protect patients
while the medicine is being reviewed. The review was initiated after an increase in the rate of serious adverse events including deaths (mostly due to infection) was observed in three clinical trials.

Further information on the review of idelalisib will be provided as necessary and once the review is concluded.

Reference:

Imatinib mesylate

Decline in kidney function during long-term treatment

Canada. Health Canada is working with manufacturers of imatinib mesylate (Gleevec®) to include additional safety information on the decline of kidney function into the Canadian Product Monograph.

Imatinib is a tyrosine kinase inhibitor. It is used as a chemotherapy agent to treat several solid tumours or blood cancers, such as chronic myeloid leukaemia (CML).

Following a publication in the medical literature, Health Canada conducted a safety review which concluded that there is sufficient evidence to consider a potential causal link between imatinib and decline in kidney function during long-term treatment.

At the time of the review, Health Canada had received 30 reports of decreased or abnormal kidney function linked with imatinib use. The manufacturer found an additional 63 reports worldwide. The study of these cases provided limited evidence of a causal relationship due to insufficient information and the presence of other potential risk factors.

Information from six clinical trials suggested that patients on long-term treatment with imatinib gradually lost some of their kidney function at a rate that may be faster than normal. The progressive loss of kidney function was greatest in the first year of therapy. Over time, gradual losses of kidney function linked with imatinib treatment may contribute to the development or worsening of some kidney diseases.

The following safety information will be included into the Canadian Product Monograph:

- Long term treatment with imatinib may result in decline in renal function. Patients treated with imatinib in clinical studies had a decrease over time in estimated glomerular filtration rate (eGFR).
- Monitoring for renal function should be undertaken before initiating therapy and periodically thereafter.

Reference:

Inhaled corticosteroids for chronic obstructive pulmonary disease

Risk of pneumonia

EU. The EMA’s PRAC has recommended that the product information for inhaled corticosteroids is updated to include advice on the increase in risk of pneumonia when used to treat chronic obstructive pulmonary disease (COPD).

COPD is a long-term disease of the lungs in which the airways and air sacs in the lungs become damaged or blocked, leading to breathing difficulties.

Corticosteroids are anti-inflammatory medicines used for a wide range of conditions. Beclometasone, budesonide, flunisolide, fluticasone propionate and fluticasone furoate are authorised and marketed as inhalation formulations for use in COPD.

The recommendation follows a review by PRAC which confirms that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the Committee’s view is that the benefits of inhaled corticosteroids continue to outweigh their risks. The PRAC also looked whether there were any differences in the risk of pneumonia between different corticosteroid containing medicines, and did not find conclusive evidence of a difference. Pneumonia remains a common side effect for all of them.

PRAC recommend that there should be no changes to the way these medicines are used; however, doctors and patients should be vigilant for signs and symptoms of pneumonia in patients with COPD as the clinical features of pneumonia overlap with those of exacerbations of the underlying disease.

Reference:

Loxoprofen

Risk of stenosis and obstruction of small and large intestine

Japan. The MHLW and the PMDA have requested that risk of stenosis and obstruction of the small and large intestines are included as clinically significant adverse reactions in
the package for loxoprofen (Loxonin® and generics).

Loxoprofen is used as an anti-inflammatory/analgesic for symptom relief of several diseases, post-surgery, post-trauma and after a dental extraction.

Cases of stenosis and obstruction of small and large intestines have been reported in patients treated with loxoprofen sodium hydrate in Japan. In the last three fiscal years in Japan, a total of six cases associated with stenosis and obstruction of small and large intestines have been reported (including five cases for which a causal relationship to the product could not be ruled out). No fatality has been reported.

Reference: Revision of Precautions, MHLW/PMDA, 22 March 2016 (www.pmda.go.jp/english/)

Methylphenidate hydrochloride

Risks of hepatic failure and hepatic function disorder

Japan. The MHLW and PMDA have announced that the package insert for methylphenidate hydrochloride (Concerta® and Ritalin®) should be revised to include risks of hepatic failure and hepatic function disorder as a clinically significant adverse effect.

Methylphenidate hydrochloride is used for the treatment for attention deficit/hyperactivity disorder (AD/HD) and narcolepsy.

The MHLW/PMDA stated that cases of hepatic failure and hepatic function disorder have been reported in patients treated with Concerta® in countries other than Japan, and it’s company core datasheet (CCDS) has been updated. In addition, cases have also been reported in patients treated with Ritalin® (countries other than Japan).

The package insert will be updated to include:

- Hepatic failure and hepatic function disorder:
  - Hepatic failure (including acute hepatic failure) or hepatic function disorder 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, 16 February 2016 (www.pmda.go.jp/english/)

Mirabegron

Risk of hypertension

Japan. The MHLW and the PMDA have requested that the package insert for mirabegron (Betanis®) is revised to include the risk of hypertension.

Mirabegron is indicated for urgency, urinary frequency, and urge urinary incontinence in patients with overactive bladder.

The Summary of Product Characteristics (SmPC) has been revised in Europe. In addition, cases of hypertension have been reported in patients treated with mirabegron in Japan. In the last three fiscal years in Japan, a total of 16 cases associated with hypertension have been reported (including seven cases for which a causal relationship to the product could not be ruled out). No fatality has been reported.

The MHLW/PMDA have recommended:

- Precautions regarding blood pressure measurement should be added as an important precautions in the package insert.
- Hypertension should be added as Clinically significant adverse reaction in the package insert.

(See WHO Pharmaceuticals Newsletters No.6, 2015: Risk of severe hypertension, associated cerebrovascular and cardiac events in the United Kingdom)

Reference: Revision of Precautions, MHLW/PMDA, 22 March 2016 (www.pmda.go.jp/english/)

Mycophenolate mofetil

Contraindications relating to pregnancy and breastfeeding

Australia. The Therapeutic Goods Administration (TGA) has informed health-care professionals that new contraindications relating to pregnancy and breastfeeding have been added to the Product Information for mycophenolate mofetil due to its mutagenic and teratogenic potential.

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid, and is used as an immunosuppressant. It is indicated for the prophylaxis of solid organ rejection in adults receiving allogeneic organ transplants and in paediatric patients (aged 2-18 years) receiving allogeneic renal transplants.

Mycophenolate mofetil is now contraindicated in the following situations:

- During pregnancy
- In women of childbearing potential who are not using two reliable forms of contraception (including at least one highly effective method).
In women who are breastfeeding.

The TGA has recommend that all patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and be counselled regarding pregnancy prevention and planning. The TGA provides advice on: using two forms of contraception for female patients; timing and form of pregnancy test before and during treatment; contraception for male patients.

Before starting treatment, female patients of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL. The second test should be performed 8–10 days after the first one and immediately before starting treatment. Repeat pregnancy tests should be performed during routine follow-up visits. Patients should be instructed to contact you immediately should they become pregnant.

Use during breastfeeding is also contraindicated as a precaution based on studies in rats which have shown that mycophenolate mofetil can be excreted in milk. It is not known whether this medicine is excreted in human milk.

Congenital malformations, including multiple malformations in live births of children of patients exposed to mycophenolate mofetil (in combination with other immunosuppressants), and spontaneous abortions (mainly in the first trimester) in patients exposed to mycophenolate mofetil have been reported at an estimated risk of 23–27% and 45–49% respectively. The risk of malformation in live births for the overall population is estimated to be 2% and the risk of spontaneous abortion in solid organ transplant patients treated with other immunosuppressants is reported at a rate of 12–33%.

(See WHO Pharmaceuticals Newsletters No.1, 2016: New pregnancy-prevention advice for women and men in the United Kingdom)

**Reference:**


### Opioid pain medicines

#### Several safety issues require label changes

**USA.** The US Food and Drug Administration (FDA) has issued a warning about several safety issues with the entire class of opioid medicines. The FDA has also requested that labels of all opioid drugs should contain warnings about risks of potentially harmful interactions with other medications, problems with adrenal glands, and decreased sex hormone levels.

Opioids are narcotic pain medicines that are used to treat moderate to severe pain, (unresponsive to other pain medication).

Opioids can interact with antidepressants and migraine medicines to cause serotonin syndrome. Cases of serotonin syndrome in the FDA Adverse Event Reporting System (FAERS) database were reported more frequently with the opioids fentanyl and methadone used at the recommended doses. Some opioids, (e.g. tramadol) already have warnings about serotonin syndrome, however there are cases reported with other opioids. Therefore, the labels of all opioid medications will be updated to include information about serotonin syndrome as a drug interaction and adverse reaction.

Opioids can lead to adrenal insufficiency, and the FDA will add warnings of this to all opioid labels. A search of FAERS for the period January 1, 1969, to February 5, 2014, identified 37 cases of adrenal insufficiency reported with the use of opioids. Twenty-seven cases reported opioid monotherapy, and 10 reported use of more than one opioid at the same time.

The FDA reviewed published studies that assessed levels of sex hormones in patients taking opioids chronically; however, all studies were limited by difficulty in determining whether the symptoms were caused by the opioids or other factors. The FDA is now adding decreased sex hormone levels as an adverse reaction to all opioid product labels.

**Reference:**


### Natalizumab

#### Risk of the rare brain infection Progressive multifocal leukoencephalopathy (PML)

**EU.** The EMA’s PRAC has recommended new measures to minimize this risk of progressive multifocal leukoencephalopathy (PML) in patients taking natalizumab (Tysabri ®).

PML is a rare and very serious brain infection caused by John Cunningham (JC) virus.

Natalizumab is a medicine used to treat adults with highly active multiple sclerosis (MS), a disease of the nerves in which inflammation destroys the protective sheath surrounding the nerve cells.

New data from large clinical studies also suggest that, the blood level of antibodies...
against JC virus (‘antibody index’) relates to the level of risk for PML, in patients who have not been treated with immunosuppressants (medicines that reduce the activity of the immune system) before starting natalizumab.

Patients are considered at higher risk of developing PML if they: have tested positive for JC virus, and have been treated with natalizumab for more than two years, and either have used an immunosuppressant before starting natalizumab, or have not used immunosuppressants and have a high JC virus antibody index.

The EMA recommends, that for patients at higher risk of PML more frequent MRI scans (e.g. every three to six months) performed using simplified protocols, should be considered. If lesions suggestive of PML are discovered, the MRI protocol should be extended to include ‘contrast-enhanced T1-weighted MRI’, and testing the spinal fluid for the presence of JC virus should also be considered.

In patients at higher risk of developing PML, treatment with natalizumab should only be continued if benefits outweigh the risks.

If PML is suspected at any time, treatment with natalizumab must be stopped until PML has been excluded.

EMA’s recommendations are based on an initial review by PRAC, which has then been confirmed by the Committee for Medicinal Products for Human Use (CHMP). The European Commission will make a legally-binding decision based on these recommendations.


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**Piperacillin and tazobactam combination**

**Risk of bronchospasm and hypokalaemia**

**India:** The CDSCO has requested that bronchospasm and hypokalaemia are included as adverse reactions in the package insert for combination products of piperacillin and tazobactam. The request follows the recommendation received from the Pharmacovigilance Programme of India - Indian Pharmacopoeia Commission (PvPI-IPC).

Piperacillin and tazobactam are used as antibiotics in combination.

Based on available evidence and advice of the subject expert committee, CDSCO/PvPI have decided that it was necessary to revise the package insert to add hypokalaemia and bronchospasm as clinically significant adverse reactions.

**Reference:** Central Drugs Standard Control Organisation, February 2016 (www.cdsco.nic.in)

**Piperacillin containing products (alone or in combination with tazobactam)**

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

**Canada.** Health Canada has updated the prescribing information for the drug combination piperacillin-tazobactam to include a warning statement for the risk of drug reaction/rash with eosinophilia and systemic symptoms (DRESS), and as a potential adverse effect for piperacillin alone.

Piperacillin is an antibiotic that is available alone or in combination with a product that enhances piperacillin activity (tazobactam). Both products are administered into a vein (intravenously) or in a muscle (intramuscularly) and are used to treat different types of infections.

Health Canada carried out a safety review to evaluate the potential link between the antibiotic drug combination piperacillin and tazobactam or piperacillin alone and DRESS. At the time of Health Canada’s review, two cases of DRESS suspected of being linked with the drug combination piperacillin and tazobactam were reported in Canada. Both cases were considered to be linked to the piperacillin-tazobactam drug combination.

In the published literature 17 cases of DRESS linked with the drug combination piperacillin and tazobactam were also identified. One case out of 17 resulted in death; however a direct association with the drug combination could not be established due to pre-existing health problems. In 10 cases, the patients recovered after stopping the combination treatment with or without additional treatment. The six remaining cases could not be assessed further because the information contained in the reports was incomplete. Additional investigation of a subset of the 17 cases suggests that the role played by piperacillin alone could not be excluded.

Health Canada concluded that there is evidence of a link between the drug combination piperacillin and tazobactam and Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS).
Simeprevir

Risk of severe liver problems

Canada. Health Canada has updated the prescribing information for simeprevir (Galexos®) by adding warnings about the risk of severe liver problems and related death. Health Canada has also reminded health-care professionals to frequently monitor patients for liver problems when using this drug.

Simeprevir is a drug used to treat chronic hepatitis C.

A safety review was carried out by Health Canada after Japan published a risk communication on severe liver problems and related death with simeprevir use.

At the time of the review, Health Canada had received 11 reports originating from Canada, of severe liver problems, including two deaths, suspected of being linked with simeprevir. Upon review of these cases, no conclusions could be made regarding what role, if any, the drug may have played, due to limited information from these cases.

In Japan, eight cases of severe blood bilirubin levels and three deaths had been reported in association with simeprevir. Ethnic differences in susceptibility to liver problems exist, therefore the information from these cases need to be interpreted with caution when considering the risk of simeprevir for other populations.

Information was also received from the manufacturer about cases of severely abnormal bilirubin levels suspected of being linked with simeprevir. In some of these cases, the contribution of simeprevir to the adverse effect could not be ruled out.

Based on all the information reviewed, Health Canada concluded that the prescribing information should be updated to reflect the level of evidence related to the risk of severe liver problems.

The prescribing information of simeprevir has been updated to:

- warn about the risk of severe liver problems and related death
- advise health-care professionals to do blood tests to check for liver function before and during treatment, and
- not use simeprevir in patients who have moderate or severe liver damage.

(See WHO Pharmaceuticals Newsletters No.1, 2015: Increase in blood bilirubin levels in Japan)

Reference:

Sodium-glucose co-transporter-2 (SGLT2) inhibitors

Risk of diabetic ketoacidosis

EU. The EMA’s PRAC has made recommendations to minimize the risk if diabetic ketoacidosis with the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors.

SGLT2 inhibitors are medicines used to treat type 2 diabetes. They block a protein in the kidneys called SGLT2, which absorbs glucose back from the urine into the bloodstream as the blood is filtered in the kidneys. This causes more glucose to be removed through the urine, thereby reducing the levels of glucose in the blood.

There are currently three SGLT2 inhibitors authorised in the EU (canagliflozin,
dapagliflozin and empagliflozin).

Diabetic ketoacidosis is a serious complication of diabetes and can be life-threatening.

If diabetic ketoacidosis is suspected or confirmed, treatment should be stopped immediately and should not be re-started unless another cause for the ketoacidosis is identified and resolved.

Health-care professionals should exercise caution in patients with risk factors for ketoacidosis and inform patients of the risk factors. These include low reserve of insulin-secreting cells, conditions that restrict food intake or can lead to severe dehydration, a sudden reduction in insulin or an increased requirement for insulin due to illness, surgery or alcohol abuse.

In addition, PRAC has recommended temporarily stopping SGLT2-inhibitor treatment in patients in hospital for major surgical procedures or due to serious illness.

The benefits of SGLT2 inhibitors continue to outweigh their risks in the treatment of type 2 diabetes. PRAC reminds health-care professionals that these medicines are not authorised for treating type 1 diabetes, noting that some cases of ketoacidosis had occurred with off-label use.

(See WHO Pharmaceuticals Newsletters No.1, 2016: Risk of acid in blood and serious urinary tract infections in the USA, No.6, 2015: Interim update on risk of serious ketoacidosis in Singapore and Risk of diabetic ketoacidosis in Australia, No.5, 2015: Risk of ketoacidosis and sepsis in Japan and No.4, 2015: Risk of diabetic ketoacidosis in the United Kingdom)

Reference:
Press release, EMA, 12 and 26 February 2016 (www.ema.europa.eu)

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**Verteporfin**

**Risk of convulsions**

**Japan.** The MHLW and the PMDA have requested that the package insert for verteporfin (Visudyne®) should be revised to include the risk of convulsions as a clinically significant adverse reaction.

Verteporfin is indicated for age-related macular degeneration in association with subfoveal choroidal neovascularisation.

Cases of convulsions have been reported in patients treated with verteporfin both in other countries and in Japan. In addition, the company core datasheet (CCDS) has been updated.

Reference:
Revision of Precautions, MHLW/PMDA, 22 March 2016 (www.pmda.go.jp/english/)
**Bcr-Abl tyrosine kinase inhibitors**

**Assessment of potential harm to the fetus**

Canada. Health Canada has announced the conclusions of a safety review, which further assessed the risk of fetal harm associated with Bcr-Abl tyrosine kinase inhibitors, after receiving additional safety information from the manufacturer.

Bcr-Abl tyrosine kinase inhibitors imatinib (Gleevec® and generics), dasatinib (Sprycel®), nilotinib (Tasigna®) and bosutinib (Bosulif®) are used to treat blood cancers in Canada. The potential for these drugs to cause harm to the fetus is known and is included in the Canadian label. The label also advises women to use effective birth control during treatment.

At the time of the review, a total of 27 published international studies and case reports of pregnant women treated with imatinib were found in the scientific literature. Overall healthy babies were the most reported outcomes (50.2%), followed by elective abortions (30.7%), miscarriages (10.6%) and birth defects (8.4%).

No Canadian cases of harm to the fetus have been received through the Canada Vigilance program with any Bcr-Abl tyrosine kinase inhibitors.

Following the completion of the safety review, the manufacturer has updated the prescribing information for Gleevec® to tell doctors to confirm by pregnancy test that female patients are not pregnant before starting treatment. No modifications were recommended for the prescribing information of the other tyrosine kinase inhibitors at this point in time based on the lack of evidence of increased fetal harm and because of differences in the mechanism of action of these medications.

**Reference:**

**Levonorgestrel-releasing intrauterine systems**

**Should be prescribed by brand name**

**The United Kingdom.** The MHRA has recommended that levonorgestrel-releasing intrauterine systems (IUS) should always be prescribed by brand name. This is because products have different indications, durations of use, and insertion devices.

A levonorgestrel-releasing IUS has been available as the brand Mirena® for a number of years. Recently, a second product called Levosert® was licensed for use in the United Kingdom.

Mirena® is licensed for five years’ use and Levosert® is licensed for three years’ use for contraception or idiopathic menorrhagia. Mirena® is also licensed for four years’ use for endometrial protection as part of a hormone-replacement therapy regimen.

Mirena® and Levosert® have different introducers/insertion devices, requiring different insertion techniques. Insertion (and removal) of any intrauterine device (IUD) may be associated with pain, bleeding, and in some cases perforation of the uterus. Therefore, IUDs should only be inserted by health-care professionals who are experienced in insertion or who have had training in the relevant insertion techniques.

A smaller IUS that contains smaller amounts of levonorgestrel (called Jaydess®) has also been marketed since 2014 and is licensed for three years’ use as contraception, only in the United Kingdom.

**Reference:**
Drug Safety Update, MHRA, Volume 9, issue 6: 2, January 2016 (www.gov.uk/mhra)

**Nicorandil**

**Now second-line treatment for angina-risk of ulcer complications**

**The United Kingdom.** The MHRA has updated the advice to health-care professionals for the use of nicorandil, following a review on nicorandil-induced ulceration.

Nicorandil is indicated in adults for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or have a contraindication or intolerance to first-line anti-anginal therapies (e.g. beta-blockers or calcium antagonists).

Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula, or abscess. Almost two-thirds of reported gastrointestinal ulcerations are serious. Ulcers caused by nicorandil do not respond to conventional treatment, including surgery.

The MHRA advises health-care professionals to stop nicorandil treatment if ulceration occurs, and consider the need for alternative treatment or specialist advice if angina symptoms worsen. In addition the use of nicorandil for treatment of stable angina should only be in: patients whose angina is inadequately controlled by first line anti-anginal therapies, or who have a contraindication or...
intolerance to first line anti-anginal therapies such as beta-blockers or calcium antagonists.

Reference:
Drug Safety Update, MHRA, Volume 9, issue 6: 1, January 2016 (www.gov.uk/mhra)

Pseudoephedrine containing over-the-counter products

Assessment of potential risk of inflammation and ischemic colitis

Canada. Health Canada published findings from a safety review which concluded that there is very limited evidence of ischemic colitis with the occasional use of pseudoephedrine at recommended doses and duration, in the absence of other risk factors.

Pseudoephedrine is a medicinal ingredient in over-the-counter products that is used to treat the blockage of nasal passages due to excess fluid or mucus (nasal congestion). Ischemic colitis is an inflammation and injury of the large intestine (colon) due to reduced blood flow.

The review was triggered following a serious case of ischemic colitis published in the scientific literature. At the time of the review, no Canadian cases of ischemic colitis were reported with the use of pseudoephedrine. A review of international data from the WHO Global ICSR Database, VigiBase® identified 24 cases of ischemic colitis, seven of which involved the use of pseudoephedrine as a single ingredient. These 24 cases could not be assessed due to limited information provided. In the scientific and medical literature, there were nine cases of ischaemic colitis associated with use of pseudoephedrine. Six cases contained other risk factors, two were not assessable due to limited information and in one case, ischemic colitis was assessed to be probably caused by pseudoephedrine.

Reference:

Rivaroxaban

Benefit-risk balance of rivaroxaban: unchanged

EU. The EMA has announced that the overall safety or benefit-risk balance of rivaroxaban (Xarelto®) has not changed, following recent knowledge of a defect in the international normalised ratio (INR) device used in the ROCKET study.

Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. The ROCKET study was the main clinical trial underpinning the use of this anticoagulation medicine in patients with non-valvular atrial fibrillation (irregular heartbeat). In the study, which compared rivaroxaban with warfarin, the INR device was used to measure blood clotting in patients taking warfarin. Because of the defect, there were concerns that the INR device could have provided lower INR values in some of the warfarin group patients. The lower values could in turn have led investigators to give too high a dose, increasing their risk of bleeding and so giving a false impression of the comparative safety of rivaroxaban.

After further analyses of the ROCKET study data taking into account the defect in the INR device, EMA's CHMP concluded that any incorrect measurements obtained with the defective device would have had only a marginal effect on the study results, and the safety of rivaroxaban remains unchanged. In addition, data from other large studies confirmed the comparative safety of the medicine and showed similar rates of bleeding in their warfarin groups. The CHMP therefore considered that the benefit-risk balance of rivaroxaban in patients with non-valvular atrial fibrillation remains unchanged.

(See WHO Pharmaceuticals Newsletters No.6, 2013: Risk of serious haemorrhage - clarified contraindications apply to Apixaban, dabigatran and rivaroxaban in the United Kingdom)

Reference:
Press release, EMA, 5 February 2016 (www.ema.europa.eu)

Spironolactone and renin-angiotensin system drugs

Risk of potentially fatal hyperkalaemia

The United Kingdom. The MHRA has reminded healthcare professionals that the concomitant use of spironolactone with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB) is not recommended as routine treatment because of the risks of severe hyperkalaemia, particularly in patients with marked renal impairment. Spironolactone is indicated for congestive heart failure. It is a competitive aldosterone antagonist that increases sodium excretion while
Reducing potassium loss at the distal renal tubule. Due to this mechanism of action hyperkalaemia can occur, particularly in patients with impaired renal function.

ACEIs are mainly indicated in patients with hypertension or heart failure. ARBs are also indicated in hypertension and some are also indicated in heart failure. Recognised adverse effects of ACEi and ARB include renal dysfunction and an increase in serum potassium. Risk factors for hyperkalaemia, such as renal insufficiency and diabetes mellitus, are more common in patients who require treatment with ACEi or ARB.

Between January 1998 and December 2015, the MHRA has received 82 spontaneous reports of abnormal blood potassium in patients using spironolactone as well as an ACEi (n=63) or ARB (n=25), 70 of which describe hyperkalaemia. Three patients taking spironolactone and ACEi had a fatal outcome.

The number of cases reported increased in the last two years. This could reflect an increase in co-administration of spironolactone and ACEi or ARB, or it could represent stimulated reporting due to increased awareness of the risks, following recommendations from an European review. The review concluded that combination use of ACEi and ARB (which both inhibit the renin-angiotensin system) is not recommended because of an increased risk of hyperkalaemia, hypotension, and impaired renal function.

Health-care professionals are reminded to:

- Use the lowest effective doses of spironolactone and ACEi or ARB if co-administration is considered essential
- Regularly monitor serum potassium levels and renal function

Interrupt or discontinue treatment in the event of hyperkalaemia

Spironolactone should not be used in patients with severe renal impairment or pre-existing hyperkalaemia.

(See WHO Pharmaceuticals Newsletters No.2, 2014: New warnings regarding Aliskiren, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in Canada)

Reference:
Drug Safety Update, MHRA, Volume 9, issue 6: 2, February 2016 (www.gov.uk/mhra)

Ticagrelor

Possible association with depression / suicidality

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) is placing a safety concern about the possible association of depression and suicidality with the use of ticagrelor (Brilinta®) on the medicines monitoring scheme, to obtain further information on these possible adverse reactions.

Ticagrelor, co-administered with acetylsalicylic acid (aspirin), is indicated for the prevention of blood clots in adult patients with acute coronary syndromes (such as unstable angina and myocardial infarction (heart attack).

Reports in the WHO Global ICSR Database, VigiBase® from New Zealand and from various other countries may suggest a possible safety concern regarding ticagrelor and depression/suicidality. Suicidality includes suicidal thoughts and tendencies, thoughts of self-harm and self-harm.

The current overall benefit-risk balance of ticagrelor remains positive. Placement of ticagrelor on the medicines monitoring scheme will last until 30 September 2016.

Reference:
Safety Information, Medsafe, 1 March 2016 (www.medsafe.govt.nz/)

Trametinib

Risk of gastrointestinal perforation and colitis

The United Kingdom. The MHRA has warned health-care professionals that trametinib should be used with caution in patients with risk factors for gastrointestinal perforation.

Trametinib (Mekinist®), authorised as monotherapy or combined with dabrafenib, is indicated for the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation in adults.

The warning follows a review of clinical studies in the literature and all reported cases of suspected adverse drug reactions (up to November 2015). Four deaths from gastrointestinal perforation while receiving trametinib were identified and the EU medicines regulators concluded that trametinib can cause gastrointestinal perforation or colitis.

Thirteen of the case reports for gastrointestinal perforation were considered to have a likely causal relation with trametinib. Most of these cases had documented risk factors (gastrointestinal metastases, diverticulitis, or use of concomitant medicines that can cause gastrointestinal perforation e.g. non-steroidal anti-inflammatory drugs or corticosteroids). The risk of these adverse reactions seems to be highest within the first two months of starting trametinib, either as monotherapy or combined with dabrafenib.
Safety of Medicines

It is thought that gastrointestinal perforation occurs due to the inhibitory effects of trametinib on angiogenesis (formation of new blood vessels from pre-existing vessels) and gastrointestinal epithelial cell proliferation. Another possible mechanism is rapid tumour shrinkage in patients with metastases, resulting in intestinal perforation at the site of metastases.

Reference:
Drug Safety Update, MHRA, Volume 9, issue 8: 1, March 2016 (www.gov.uk/mhra)

Valproate

Risk of abnormal pregnancy outcomes

The United Kingdom. The MHRA has requested that health-care professionals use new communication materials (listed below) to discuss the risk of developmental disorders and congenital malformations in children exposed to valproate in utero. This measure is to improve awareness of the risks of valproate in pregnancy, following an earlier notification of risks in January 2015.

The communication materials include: booklet for health-care professionals, consultation checklist, guide and card to give to patients.

Valproate is used for treatment of mania associated with bipolar disorder.

The MHRA have summarised the risks and precautions as follows:

- Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and congenital malformations (in approximately 10% of cases).
- Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.
- Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
- Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.

Health-care professionals must ensure that all female patients are informed of and understand:

- the risks associated with valproate during pregnancy;
- the need to use effective contraception;
- the need for regular review of treatment;
- the need to rapidly consult if she is planning a pregnancy or becomes pregnant

The MHRA has informed health-care professionals that the outer packaging for medicines containing valproate will include a warning for women on the risk of adverse pregnancy outcomes later in 2016.

(See WHO Pharmaceuticals Newsletters No.2, 2015: Risk of abnormal pregnancy outcomes in the United Kingdom, No.1, 2015: Further restriction of the valproate use in women and girls in Ireland, No.5, 2014: Fetal exposure and cognitive impairment in Australia, No.6, 2013: Risk of neurodevelopmental delay in children following maternal use in the United Kingdom and No.3, 2013: Contraindicated for pregnant women for prevention of migraine headache in the USA)

Reference:
Drug Safety Update, MHRA, Volume 9, issue 6: 1, February 2016 (www.gov.uk/mhra)

Vit.D3® (colecalciferol)

Risk for patients with a peanut or soya allergy

New Zealand. Medsafe highlighted the safety concern of Vit.D3® and allergic reactions for patients with peanut or soya allergy.

Vit.D3® is a prescription only colecalciferol containing product and now available in New Zealand. Colecalciferol is indicated for the prevention and treatment of vitamin D deficiency.

Vit.D3® contains soya oil inside the capsule. Some people are allergic to soya oil and some people with peanut allergy also react to soya oil. This product should not be used by people who are allergic to peanut or soya.

Reference:
Safety Information, Medsafe, 2 March 2016 (www.medsafe.govt.nz/)
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 database of ICSRs, VigiBase®. The database contains over 12 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 ICSR, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 25). 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.

Levetiracetam and impaired renal function
Dr Imti Choonara, United Kingdom and Dr Kristina Star, Uppsala Monitoring Centre

Summary
Levetiracetam and acute renal failure (ARF) was highlighted as a potential signal in the paediatric signal detection sprint. The paediatric population and ARF was the starting point for this assessment but the signal expanded to cover reports of all ages as well as encompassing interstitial nephritis. There are more than 150 reports on levetiracetam with ARF and/or interstitial nephritis in the WHO Global database of Individual Case Safety Reports, VigiBase®, although many of these reports turned out to be duplicates. We assessed a subset of 39 reports more in-depth and found reports supporting a possible causal relationship between levetiracetam and impaired renal function, and more specifically, interstitial nephritis. Impaired renal function or related events are not described as adverse reactions in the product information for levetiracetam. Although these events may occur only rarely, it would be beneficial to inform clinicians that levetiracetam has the potential to impair renal function.

Introduction
Levetiracetam is one of the newer generation antiepileptic drugs (AEDs). It is considered to be safer than many of the older AEDs. It is an effective anticonvulsant and its main adverse drug reactions are tiredness and behavioural changes. The active substance of levetiracetam is a pyrrolidone derivate. The mechanism of action is not fully elucidated but in vitro studies suggest that an interaction between levetiracetam and the synaptic vesicle protein 2A results in antiseizure activity. Levetiracetam is excreted primarily via urine by glomerular filtration followed by tubular reabsorption. Elimination of levetiracetam is correlated to creatinine clearance.¹

Acute renal failure (ARF) is a life-threatening condition. Renal insufficiency is impairment of renal function that is less severe. ARF can be classified as: prerenal ARF with diminishing circulating arterial volume caused by conditions such as dehydration, sepsis and cardiac failure; or intrinsic renal ARF with renal parenchymal damage resulting from glomerulonephritis, rhabdomyolysis, acute interstitial nephritis; or postrenal ARF with obstruction to the urinary tract from for example tumors or posterior urethral valves. Medicines can negatively affect the renal function directly by reducing the blood flow, or indirectly by inducing for example allergic reactions to the renal tissues. Examples of nephrotoxic medicines that are known to cause ARF are aminoglycosides, acetaminophen, cisplatin, lithium, and vancomycin. Medicines known to induce interstitial nephritis are antimicrobials (e.g. cephalosporins, penicillins and sulphonamides), NSAIDs, diuretics and certain anticonvulsants (carbamazepine, phenytoin). Topiramate is an example of a medicine inducing nephrothiasis.²

Reports in VigiBase®
Up to February 2015, and before exclusion of duplicates, the WHO Global database of Individual Case Safety Reports, VigiBase® included 35 reports for children (0-17 years) with
levetiracetam and the WHO adverse reaction terminology (ART) preferred terms (PT) 'Renal failure acute' (n=29); 'Azotaemia' with the included term 'Creatinine blood increased' (n=1); and 'Renal function abnormal' with the included term 'Renal impairment' (n=5). Original reports were used in the evaluation of the reports issued for children. A total of 90 reports for adults (≥ 18 years), including reports where age was unspecified, with PT 'Renal failure acute' were retrieved, of which 12 reports were well-documented, according to VigiGrade³ (score > 0.80), and further assessed in-depth. The PT 'Nephritis interstitial' was co-reported in some of the reports, so a separate analysis was made on those 49 reports with any ages.

**Disproportionality**

For levetiracetam and 'Renal failure acute', the lower limit of the 95% credibility interval of the Information Component (IC₂₅) was positive for the subgroups of ages 12-17 years (IC = 2.28; IC₂₅ = 1.63) and 18-44 years (IC = 1.05; IC₂₅ = 0.59), which constituted the age groups with most reports for this combination. The IC was not positive for 'Renal failure acute' when basing the calculation on the full database. The IC for levetiracetam and 'Nephritis interstitial' was 2.43 (IC₂₅ = 2.01) based on the full database.

**Renal failure in children**

After removal of 21 duplicates, 14 reports on children from five countries remained and were evaluated more in-depth. Four cases were reported with ARF, of which one also had interstitial nephritis, six with renal failure, three with creatinine increased, and one with renal impairment. Five reports referred to published case reports. Ages ranged from 6 weeks to 17 years with a median of 10.5 years. Seven reports were for females, five for males, and gender was not specified in two reports. Levetiracetam was reported as the single suspect drug in six reports. Nine cases were co-reported with other AEDs: lacosamide (n=4), valproic acid (n=3), phenobarbital (n=3), diazepam (n=3), lamotrigine (n=2), phenytoin (n=2), thiopental (n=2), topiramate (n=1), clonazepam (n=1), and clobazam (n=1). Note that one report can be reported with more than one AED. Hepatic disorders were co-reported in five reports. The daily dose was recorded in nine reports and ranged from 54 mg for a 6-week-old premature baby to 2000 mg for one of the 17-year-old cases.

Three cases where levetiracetam was reported as the single suspect drug with a positive dechallenge:

- A 17-year-old published female case report (case 1), resulting in eight duplicate reports, had the most likely causal relationship.⁴ The patient had been treated with levetiracetam for 10 days when diagnosed with ARF and biopsy-confirmed interstitial nephritis. She sought health care because of vomiting, loose stools and abdominal pain for the past two days. Creatinine levels were normal before she started levetiracetam and declined after withdrawal of the drug and treatment with prednisone. The authors of this publication stated that she had no prior history of renal problems or used other medications that could have explained the event.

- A 12-year-old female (case 2) was admitted to hospital for ARF, metabolic acidosis, respiratory distress and confusion, which was described in a published abstract.⁵ A few hours after admission she became encephalopathic. Levetiracetam levels were found to be high and the probable cause of encephalopathy. Levetiracetam was stopped and replaced with valproate and patient improved after about five days. The focus in the abstract was on the encephalopathy, and it was unclear what the origin of the ARF was.

- A 6-week-old premature baby (case 3) was diagnosed with ARF after 16 days treatment with levetiracetam. Reaction abated when the drug was withdrawn. Prematurity could contribute to the susceptibility.

Further information on the above cases is given in Table 1.

In another report, where levetiracetam was the single suspect drug, a 16-year-old was described to be hospitalized for encephalopathy and chorea. The patient was placed on phenytoin, and then transitioned to valproic acid and later to levetiracetam. Serum creatinine started to increase thereafter. This report did not include any other co-reported drugs. Time to onset and dechallenge information was missing for this report.

Another six cases included alternative causes for the ARF:

- In four cases, the influence of levetiracetam in relation to the impaired renal function could not entirely be ruled out. The cases had a reasonable time to onset (3, 5, 4, 17 days) and a positive dechallenge, but levetiracetam was co-reported with drugs known to cause renal problems. One case started and stopped aciclovir during the same dates as levetiracetam. In the second case, the creatinine values peaked when the doses were highest for the suspect drugs levetiracetam, topiramate, and thiopental, and started to decrease when topiramate was withdrawn, followed by a continuous decrease after stopping levetiracetam and thiopental some days later. The third case was a 7-week-old premature baby with a complex history, who recovered from increased creatinine levels three weeks after levetiracetam had been stopped and one week after dose reduction of
meropenem, which is listed with renal disorders. The fourth case was a published case reporting a suspected interaction between methotrexate and levetiracetam and where the time to onset for levetiracetam was uncertain but most likely three days.\(^5\)

- In two reports, the increased creatinine and renal impairment was most probably the secondary event to DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms), which is listed in the product information for levetiracetam.\(^7\) These cases had additional co-suspected AEDs: phenytoin, lacosamide and valproic acid, also known to be reported with DRESS-syndrome.

One report was unassessable because of lack of information. In three cases, levetiracetam was most likely not related to the ARF, in which two reported fatal outcome:

- A 9-year-old male experienced status epilepticus with metabolic acidosis and developed rhabdomyolysis and hepatorenal failure.\(^6\)

- A 3-year-old female where the focus was on status epilepticus and the sudden interruption of lacosamide treatment.\(^7\)

**Renal failure in adults**

A total of 90 reports for adults, or with unknown age, with levetiracetam and the WHO-ART PT 'Renal failure acute' have been received from 11 countries in North America, Europe, Oceania and Asia. Twelve of the 90 reports were well-documented according to vigiGrade\(^3\) (score \(>0.80\)) and were included in the analysis.

Ten cases reported ARF, one renal failure, and another renal insufficiency. Ages ranged from 21 to 73 years with a median of 45 years. Five reports were for females and seven for males. Levetiracetam was reported as the single suspect drug in five reports. Six cases were co-reported with other AEDs: lamotrigine (n=3), valproic acid (n=2), phenytoin (n=2), clonazepam (n=1), clobazam (n=1), oxcarbazepine (n=1), lacosamide (n=1); one report can be recorded with more than one AED. In eight reports, the reaction abated thereafter. Patient started with carbamazepine and the WHO

Five cases were co-reported with other AEDs: phenytoin (n=2), clonazepam (n=1), clobazam (n=1); one report can be recorded with more than one AED. In five reports were for females and seven for males. Levetiracetam was reported as the single suspect drug in five reports. Six cases were co-reported with other AEDs: lamotrigine (n=3), valproic acid (n=2), phenytoin (n=2), clonazepam (n=1), clobazam (n=1), oxcarbazepine (n=1), lacosamide (n=1); one report can be recorded with more than one AED. In eight reports, the reaction abated thereafter. Patient started with carbamazepine and re-started losartan and gliclazide.

See Table 1, for further information on these cases (4-6).

In seven cases, alternative causes for the renal failure or insufficiency were reported, such as other drugs (n=2); other main events associated with the renal failure (DRESS syndrome (n=2), rhabdomyolysis and status epilepticus (n=1)), or confounding factors such as cancer (n=2). Two cases were reported with QT prolongation in connection to the renal failure.

**Interstitial nephritis in children and adults**

Forty-nine reports with levetiracetam and 'Nephritis interstitial' were retrieved from VigiBase\(^®\). Among the reports for children, one report had already been accounted for in the review of ARF and the remaining 17 reports were likely duplicates with the published 17-year-old female.\(^4\) For the adults, or reports without a given age, 13 reports were evaluated following removal of 16 duplicate reports of another published case of a 45-year-old,\(^6\) and additionally two duplicates for other cases. Ages ranged from 20 to 76 years with a median of 51 years. Nine reports were for males and four for females. Levetiracetam was reported as the single suspect drug in six reports. Five cases were co-reported with other AEDs: valproic acid (n=5), carbamazepine (n=2), topiramate (n=1), clobazam (n=1); one report can be recorded with more than one AED. In five
reports, the reaction abated after drug withdrawal. Time to onset could be assessed in five reports and ranged from 1 to 12 months.

In three reports, levetiracetam was reported as the single suspect drug with a positive dechallenge. See Table 1 and cases 7-9 for more information.

In two cases levetiracetam was reported as the single suspect drug with a long time to onset and lacked complete dechallenge information.

- A 52-year-old female was diagnosed with interstitial nephritis after five months treatment with levetiracetam 2000 mg daily. Drug was stopped 10 months after event start. Patient had not recovered at the time of report. Reported concomitant drugs were: tramadol, citalopram, simvastatin, folic acid and iron. No dates were given for these drugs.
- A 37-year-old male was diagnosed with interstitial nephritis and renal interstitial fibrosis after about four months of treatment with levetiracetam. It is unknown if the drug was stopped. Patient had not recovered at the time of report. Reported concomitant drugs were: valproic acid and carbamazepine. No dates were given for these drugs.

### Table 1. Renal failure and interstitial nephritis reported with single suspect levetiracetam: nine cases with a positive dechallenge

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Suspected (S) or concomitant (C) drugs</th>
<th>Indication</th>
<th>Daily dose</th>
<th>Reactions (WHO-ART preferred terms)</th>
<th>Time to onset</th>
<th>Dechallenge outcome/ Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^</td>
<td>17/F</td>
<td>Levetiracetam (S)</td>
<td>Convulsion</td>
<td>500 mg</td>
<td>Renal failure acute, abdominal pain, diarrhea, fatigue, nephritis interstitial, palp, renal function abnormal, vomiting</td>
<td>10 days</td>
<td>Reaction abated after drug withdrawal and corticosteroid treatment. No history of renal problems and no other medications. Changed antiepileptic treatment to oxcarbazepine.</td>
</tr>
<tr>
<td>2^</td>
<td>12/F</td>
<td>Levetiracetam (S)</td>
<td>Epilepsy</td>
<td>-</td>
<td>Renal failure acute, acidaosis, confusion, drug level increased, dyspnoea, EEG abnormal, encephalopathy, medicine ineffective, muscle contractions involuntary, somnolence, tremor</td>
<td>-</td>
<td>Patient returned to baseline after drug withdrawal. Unclear why she was admitted for acute renal failure. Had a history of Chiari II, myelomeningocele, shunted hydrocephalus, renal tubular acidaosis and well-controlled epilepsy on levetiracetam.</td>
</tr>
<tr>
<td>3</td>
<td>6 weeks 6^</td>
<td>Levetiracetam (S)</td>
<td>Seizure</td>
<td>54 mg</td>
<td>Renal failure acute</td>
<td>16 days</td>
<td>Reaction abated after drug withdrawal. Prematurity could contribute to susceptibility. Renal failure reported as transient.</td>
</tr>
<tr>
<td>4</td>
<td>73/M</td>
<td>Levetiracetam (S), gliclazide, losartan, aspirin (all C)</td>
<td>Epilepsy</td>
<td>-</td>
<td>Renal failure acute, nephritis</td>
<td>1 day</td>
<td>Reaction abated after drug withdrawal. The patient had a history of arterial hypertension and Type 2 diabetes mellitus, and a long-time treatment with gliclazide, losartan and aspirin. Losartan is known to cause renal failure.</td>
</tr>
<tr>
<td>5</td>
<td>21/M</td>
<td>Levetiracetam (S)</td>
<td>Epilepsy</td>
<td>250 mg for some weeks, increased to 500 mg</td>
<td>Renal failure acute</td>
<td>~20 days</td>
<td>Reaction abated after drug withdrawal.</td>
</tr>
<tr>
<td>6</td>
<td>60/F</td>
<td>Levetiracetam (S)</td>
<td>Petit mal epilepsy</td>
<td>500 mg</td>
<td>Renal failure acute</td>
<td>4 days</td>
<td>Reaction abated after drug withdrawal.</td>
</tr>
<tr>
<td>7</td>
<td>20/M</td>
<td>Levetiracetam (S)</td>
<td>-</td>
<td>750 mg and 1000 mg</td>
<td>Nephritis interstitial</td>
<td>-</td>
<td>Reaction abated after drug withdrawal. Dates were not given for the different dosages.</td>
</tr>
<tr>
<td>8</td>
<td>45/F</td>
<td>Levetiracetam (S)</td>
<td>Epilepsy</td>
<td>1000 mg</td>
<td>Nephritis interstitial, renal acidaosis tubular</td>
<td>-</td>
<td>Reaction abated after drug withdrawal.</td>
</tr>
<tr>
<td>9</td>
<td>45/M</td>
<td>Levetiracetam (S), dexamethasone, temozolomide (both C)</td>
<td>Seizure prophylaxis</td>
<td>1000 mg start dose increased over a 2-month period to 3000 mg</td>
<td>Nephritis interstitial, renal failure acute</td>
<td>2 months</td>
<td>Reaction abated after drug withdrawal. Levetiracetam was changed to lacosamide and patient improved clinically and the creatinine normalized over 1 month.</td>
</tr>
</tbody>
</table>
In another report, levetiracetam was the single suspect drug and most likely the spontaneously reported published 69-year-old case described later in this signal.10

In three reports, levetiracetam was co-suspect with other drugs but because dates were lacking it was not possible to assess which of the drugs were more likely to have induced the event. The co-suspect drugs were valproic acid, topiramate, fluconazole. Interstitial nephritis is not labelled for any of these drugs.

In three additional reports, the co-suspect drugs; melperone, oesomeprazole and carbamazepine, respectively, were more likely the drugs inducing the interstitial nephritis in these cases.

The main event for a 32-year-old was DRESS syndrome that was co-reported with the interstitial nephritis. Co-suspect drugs for this patient were vancomycin and valproic acid.

**Literature and Labelling**

In addition to the published case reports on levetiracetam with ARF and/or interstitial nephritis4,8,9 included in this assessment, there is a possible renal tubular disorder reported in a 23-year-old male who developed hypokalaemia and hypomagnesaemia but had normal serum creatinine.11 Another 23-year-old received 1000 mg levetiracetam and 2 mg lorazepam at the hospital for new onset seizures.12 Creatinine was normal before admission to hospital and started to increase the following day. Patient recovered after stopping levetiracetam and changing to phenytoin. A 69-year-old woman, who after two weeks treatment with levetiracetam presented with severe mouth mucosal ulceration secondary to herpes simplex virus, and feeling unwell with wide spread rash, elevated creatinine, leukocyte count and because of worsening azotaemia she needed haemodialysis. Levetiracetam was changed to valproic acid and her renal function gradually improved.10

Impaired renal function or related events are not described as adverse reactions in the product information for levetiracetam.1,13

**Discussion**

More than 100 reports with levetiracetam and ARF and/or interstitial nephritis have been reported to VigiBase® and several related published cases have been highlighted in the literature.4,5,8,9,12 The high number of reports in itself creates a suspicion of a possible nephrotoxic effect from levetiracetam. However, in many of the evaluated VigiBase® reports, levetiracetam was reported with other co-suspect drugs known to cause nephrotoxicity. The reported ARF was part of a more complex disease process in many of the reports, such as rhabdomyolysis in association with status epilepticus, and DRESS-syndrome.

When it comes to the quality of data, duplication of reports was a particular obstacle in the assessment of these reports. More than 50 duplicate reports were found among the evaluated reports that to a large extent were generated from three published case reports, and there might be more duplicates among the unassessed adult cases. However, in nine of the 39 evaluated unique reports, we found support for at least a possible causal relationship between levetiracetam and impaired renal function.

ARF was reported more frequently than expected for adolescents (12-17 years) and young adults (18-44 years). However, the IC in the adolescent age group is most likely driven by the high number of duplicates from the 17-year-old and 12-year-old published cases.4,8 Reports with levetiracetam and interstitial nephritis was reported more frequently than expected based on the overall reporting in VigiBase®, although this case series also included many duplicates.

ARF is not a well-defined reaction but support for a more specific event was found for interstitial nephritis, reported for some of the ARF cases and also singly in the reports under assessment. The short time to onset for some of the cases suggests an allergic response to the drug, which supports the case of interstitial nephritis. Possible toxicity to the renal tubules in connection to levetiracetam-induced hypokalaemia and hypomagnesaemia was suggested in a published case,11 additional to this reviewed case series. In the evaluated VigiBase® reports in this assessment, there was no mentioning of kidney stone formation but more so of allergic nephritis or interstitial nephritis.

A temporal relationship was reasonable in most reports where a time to onset could be calculated. The time to onset ranged from one day to two months among the nine cases that supported a possible relationship. The time to onset of two months related to a case with increasing dose during this time period.9

Experimental evidence for this signal was supported by several cases from VigiBase® and the literature where the renal impairment improved after the drug had been withdrawn and where some reports described normal creatinine before start of levetiracetam, followed by an increase after treatment and a decrease when levetiracetam was withdrawn. Also, biological plausibility was suggested in cases where the increasing dose seemed to have triggered the development of the renal event.

There is insufficient information to be certain of the pathophysiology of levetiracetam toxicity on the kidney. The placebo-controlled clinical studies summarised for the Keppra product,14 with over

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700 levetiracetam-treated patients, did not highlight any statistically significant laboratory findings, although in open studies abnormal values in haematocrit, haemoglobin, white blood cell counts and eosinophil counts were found. Creatinine levels were not mentioned. These studies might however include too few patients in order to detect ARF and particularly interstitial nephritis.

It should be noted that only a subset of the 90 VigiBase® reports with ARF for adults were assessed in this review and that full details of the reports were only assessed for the paediatric reports, so additional supporting cases might exist.

**Conclusion**

The majority of the cases included in the evaluated case series had alternative explanations for the renal impairment such as other drugs; confounding factors such as prematurity; or occurred secondary to DRESS or rhabdomyolysis. However, nine cases supported the hypothesis of a possible causal relationship between levetiracetam and impaired renal function. The pharmacological mechanism behind this signal needs to be further elucidated.

**References**

Benznidazole and severe skin reactions
Dr Pia Caduff-Janosa, Uppsala Monitoring Centre

Benznidazole is a nitroimidazole derivative indicated for the treatment of Chagas disease (American Trypanosomiasis), a tropical protozoan infection with *Trypanosoma cruzi* endemic in Central and South America. The drug shows good efficacy in the acute stage of the disease but limited therapeutic success in chronic disease. The acute stage often goes unnoticed as it manifests with unspecific symptoms, if any. In the chronic stage, less than half of the patients will develop life-threatening cardiomyopathy and digestive disease (megaoesophagus and megacolon).  

Drugs available for treatment are nifurtimox and benznidazole. Commercial preparations of benznidazole have been available in Central and Latin America since 2012, ending a long period of shortage after the first commercialized products were discontinued in 1998, more than 25 years after their appearance on the market. The product information leaflet of Abarax®, dated 2012, lists mostly benign cutaneous eruptions among possible side effects, with the recommendation to discontinue treatment if fever and/or adenopathy occur.  

Severe skin reactions such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) are not listed. Several publications on the treatment of Chagas disease document rash as a frequent adverse reaction to benznidazole without any mention of SJS or TEN.

The combination benznidazole and the WHO-ART preferred term erythema multiforme (EM) was highlighted in the WHO Global ICSR Database, VigiBase®, as standing out statistically (IC\(_{25}\) 0.09). A total of eight reports were analysed after including also reports with SJS and TEN.

Two reports originate from Argentina, the other six from Spain (one patient explicitly reported to be of Latin-American origin), and refer to patients (seven women, one man) between 16 and 55 years of age (median 32.5 years). Three cases reported erythema multiforme (one erythema multiforme major), three SJS and two TEN. Benznidazole was the only suspected medication reported in all but one case, where posaconazole had been administered concomitantly for seven days. Time to onset could not be calculated in one report and varied between 8 and 46 days in the remaining seven reports (median time to onset 28 days). Benznidazole was discontinued by all patients and four were reported to have recovered, one with sequelae. One further patient was recovering at the time of reporting, two are reported as not recovered, and in one case the outcome was unknown.

In one report ‘Drug Reaction with Eosinophilia and Systemic Symptoms’ (DRESS syndrome) was co-reported approximately three weeks before developing SJS under treatment, and the patient, who was concomitantly treated with posaconazole for seven days, also developed hepatitis and neutropenia (from which she recovered). Both hepatitis and neutropenia are known side effects of azole anti-infective.

A possible causal association for severe skin reactions and benznidazole is further supported by the fact that SJS and TEN have been associated with imidazole derivatives, and are listed in the Summary of Product Characteristics of metronidazole.

Due to the scarce information available on medications used for neglected tropical diseases, we would like to signal this association.

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 database of Individual Case Safety Reports, 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.

Confidential data

According to WHO policy and UMC Guidelines, ICSRs 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). 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

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.

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.

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

WHO Collaborating Centre for International Drug Monitoring, Box 1051, SE-751 40 Uppsala, Sweden
Seasonal Malaria Chemoprevention and Pharmacovigilance, Rabat, Morocco, February 2016

Seasonal malaria chemoprevention (SMC, previously known as intermittent treatment), is defined as the intermittent administration of full treatment courses of antimalarial medicines during the malaria season to prevent malaria illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk (1).

In 2012, WHO made a recommendation for the implementation of SMC in areas of highly seasonal malaria transmission across the Sahel sub-regions. This consists of a combination of amodiaquine and sulfadoxine-pyrimethamine (AQ + SP) which will be administered to children aged between 3 and 59 months at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the malaria transmission season, provided both drugs retain sufficient antimalarial activity. The policy also recommends that Pharmacovigilance (PV) should be strengthened where it exists, and where there is no PV, it should be instituted (1).

ACCESS-SMC is a UNITAID-funded project, led by the Malaria Consortium in partnership with Catholic Relief Services (CRS), which is scaling up access to SMC across the malaria endemic sub-Saharan countries (2). The project started in 2015 and will last three years in collaboration or with technical support from the London School of Hygiene and Tropical Medicine (LSHTM), Centre de Support de Santé International, Management Sciences for Health, Medicines for Malaria Venture, and Speak Up Africa. In 2015 there was a target of 30 million SMC treatments to be given to 7.5 million children under five years of age in Burkina Faso, Chad, the Gambia, Guinea, Mali, Niger and Nigeria. In preparation for the SMC programme a workshop was held in 2015 by the WHO Collaborating Centre for Strengthening Pharmacovigilance Practices, in Rabat, as a system
stirngthening activity (3). Participants from the National PV Centre and National Malaria Programmes from each country attended. At the end of the workshop, each country produced a PV plan for integrating PV into the SMC programme. A second workshop was organized in 2016 so that countries could share experiences and lessons learnt after the first year of SMC. Participants who attended the first workshop in May 2015 were invited back to Rabat, in February 2016.

The 2016 workshop was hosted by the WHO Collaborating Centre for Strengthening Pharmacovigilance Practices, in Rabat and organized in collaboration with WHO and LSHTM. Representatives from Ghana and Senegal also joined. Representatives from the: WHO Collaborating Centre for 1) International Drug Monitoring, Uppsala and 2) the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra; researchers; project leads from LSHTM and members of CRS and Malaria Consortium also joined the workshop.

The workshop lasted three days and started with a presentation of safety activities implemented by each of the countries. Countries presented their key achievements and challenges associated with integrating PV. Discussions on the reporting flow, referral systems and capacity for performing laboratory investigations when needed were held. Feedback on PV training during the SMC campaign was provided. In addition, examples of different reporting tools, e.g. e-reporting, phone-reporting and SMS-reporting were presented. Finally, a plan to form a regional safety committee was consolidated. Moving forward, it was agreed that more time needs to be allocated to PV training in future campaigns, and that training should extend to doctors/nurses/pharmacists in district hospitals. Technology was identified as a key tool to assist with reporting, for example the use of e-reporting. WHO will be using the WHO ISOP PV curriculum to update existing PV modules to assist with PV training in SMC (4). In addition e-reporting will be made available to VigiFlow® users with no additional costs.


