



World Health
Organization

WHO Pharmaceuticals NEWSLETTER

2017

No. 5

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

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

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

Safety and Vigilance: Medicines,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pvsupport@who.int

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

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

This newsletter includes two brief reports, on the Pharmacovigilance Workshop held in Seoul for APEC countries and the workshop on ATC/DDD and drug utilization research held in Rabat.

Contents

Regulatory matters

Safety of medicines

Signal

Feature

© World Health Organization 2017

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: “This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition”.

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization.

Suggested citation. WHO Pharmaceuticals Newsletter No.5, 2017: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Printed in Switzerland

Regulatory Matters

Atypical antipsychotics	5
Azithromycin.....	5
Combined use of buprenorphine or methadone with benzodiazepines or CNS depressants	5
Dabigatran	6
Doxycycline	6
Gadolinium based contrast agents for MRI.....	6
Hyoscine butylbromide ampoule	6
Ibrutinib.....	7
Laninamivir.....	7
Methylprednisolone injections containing lactose	7
Palivizumab	7
Paracetamol (modified- or prolonged-release).....	8
Riociguat.....	8
Selexipag	8
Sodium polystyrene sulfonate	9
Trimebutine based medicines.....	9
Warfarin.....	9

Safety of Medicines

Brivudine.....	10
Corticosteroids	10
Desloratadine.....	10
Direct-acting antivirals (DAAs)	11
Fluindione.....	11
Iron isomaltoside.....	11
Ketamine.....	12
Lithium	12
Obeticholic acid.....	12
Pembrolizumab	12
Prasugrel.....	13
Teriflunomide.....	13

Signal

Amitriptyline and dry eyes – an ADR overlooked in labelling 14

Insufficiently labelled ADRs: abdominal pain, chest pain and headache
while using noscapine 15

Complete loss of libido reported for women on systemic hormonal
contraceptive 15

Feature

APEC Harmonization Center (AHC) Pharmacovigilance Workshop, Seoul,
11-12 September 2017 19

The second workshop to integrate Anatomical Therapeutic Chemical (ATC)
and Defined Daily Dose (DDD) in drug utilization research..... 21

Atypical antipsychotics

Potential risk of sleep walking and sleep-related eating disorder

Canada. Health Canada recommends that the product safety information for all atypical antipsychotics should be updated to include risks of sleep walking (SW) and sleep-related eating disorder (SRED).

Atypical antipsychotics are used to treat mental disorders such as schizophrenia, bipolar disorder and depression. Health Canada reviewed the potential risk of SW and SRED with the use of atypical antipsychotics, following the publication of a case report which described these events in a patient treated with ziprasidone.

At the time of the review, Health Canada had received a total of 13 unique Canadian reports of SW and SRED suspected to be linked to the use of atypical antipsychotics. In the review it was suggested that of these 13 reports, two cases of sleep disorder were likely to be linked to atypical antipsychotics use. The patients recovered when they stopped the treatment. Six reports, out of 13, were found to have a possible link. Other risk factors such as pre-existing conditions, history of sleep disorders or use of other medications could have contributed to the events; however, a link could not be ruled out. The five remaining reports could not be assessed due to insufficient information.

This safety review evaluated information from 413 international reports of SW and SRED suspected to be associated with the use of atypical antipsychotics, but these reports provided limited additional information.

In addition, Health Canada found 23 published case reports of SW and SRED suspected to be associated

with the use of atypical antipsychotics. In the majority of these reports, patients recovered when they stopped the treatment and in some cases, the events returned when patients resumed the treatment. The drug was taken as recommended and the events appeared to happen more often with higher doses. Overall, the review of these case reports suggested a link between the use of atypical antipsychotics and SW or SRED.

Reference:

Summary Safety Review, Health Canada, 21 September 2017 (www.hc-sc.gc.ca)

Azithromycin

Risk of acute generalized exanthematous pustulosis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for azithromycin (Zithromax®) has been updated to include the risk of acute generalized exanthematous pustulosis as a clinically significant adverse reaction.

Azithromycin is an antimicrobial used for a number of bacterial infections caused by strains of genus *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Neisseria gonorrhoeae*, *Moraxella (Branhamella) catarrhalis*, *Haemophilus influenzae*, *Legionella pneumophila*, *Peptostreptococcus*, *Prevotella*, *Chlamydia*, and *Mycoplasma*.

One case of acute generalised exanthematous pustulosis has been reported in Japan. A causal relationship could not be excluded in this case. In addition, the company core datasheet (CCDS) has been updated.

Reference:

Revision of Precautions, MHLW/PMDA, 8 August 2017 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.5, 2016: Risk of acute generalized exanthematous pustulosis in India)

Combined use of buprenorphine or methadone with benzodiazepines or CNS depressants

Medication management can reduce risks of serious adverse effects

USA. The US Food and Drug Administration (FDA) has required that drug labels for buprenorphine and methadone medicines (medication assisted treatment, MAT) are updated to include detailed recommendations for minimizing the use of MAT medicines and benzodiazepines together.

Medicines containing buprenorphine or methadone as the active ingredient are FDA-approved to treat opioid addiction and dependency. MAT should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS), despite the risk of serious adverse effects, as harm caused by untreated opioid addiction usually outweighs risks.

Careful medication management by health-care professionals can reduce these risks.

The FDA recommended that health-care professionals should take several actions and precautions and develop a treatment plan when buprenorphine or methadone is used in combination with benzodiazepines or other CNS depressants.

Reference:

Drug Safety Communication, US FDA, 6 September 2017 (www.fda.gov)

Dabigatran

Risk of acute hepatic failure, hepatic function disorder, and jaundice

Japan. The MHLW and the PMDA have announced that the package insert for dabigatran (Prazaxa®) has been updated to include the risks of acute hepatic failure, hepatic function disorder and jaundice as clinically significant adverse reactions.

Dabigatran is used to reduce the risk of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

A total of five cases associated with acute hepatic failure, hepatic function disorder and jaundice have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:

Revision of Precautions, MHLW/PMDA, 12 September 2017 (www.pmda.go.jp/english/)

Doxycycline

Risk of fixed drug eruptions

Saudi Arabia. The Saudi Food and Drug Authority (SFDA) has updated the summary of product characteristics and patient information leaflet for doxycycline to include the risk of fixed drug eruptions (FDE).

Doxycycline is a tetracycline broad-spectrum antibiotic with bacteriostatic characteristics. It is used as treatment or prophylaxis against a wide range of susceptible strains of gram-negative and gram-positive bacteria and other microorganisms.

The SFDA initiated the investigation based on a signal observed in a published case report examining potential associations between doxycycline and risk of FDE. As a result, the SFDA reviewed the available evidence related

to this safety issue including screening of the WHO global database of Individual Case Safety Reports, VigiBase. In addition, a literature review was conducted.

The SFDA concluded that the available evidence suggests a probable association between doxycycline and FDE.

Reference:

Based on the communication from Saudi Food and Drug Authority, December 2016

Gadolinium based contrast agents for MRI

Retention of gadolinium in the brain

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) has updated the data sheet for gadolinium based contrast agents (GBCAs) with information about the retention of gadolinium in the brain. Medsafe has stated that although GBCAs enter the brain, and so far no harm has been identified due to retention, use should be restricted.

GBCAs are used to enhance magnetic resonance (MR) images.

Medsafe and the Medicines Adverse Reactions Committee (MARC) recently conducted a safety review of GBCAs. It was concluded that the use of GBCAs should be restricted to situations where they are expected to provide additional information so that the patient's condition is diagnosed or monitored correctly.

Medsafe will continue to monitor the safety of GBCAs, provide more information and take further action if necessary.

Reference:

Safety Information, Medsafe, 21 August 2017 (www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletters No.4, 2017: Restrictions on use in EU, No harmful effects identified with brain retention in the US and No.5, 2015: Possible risk of brain deposits with repeated use in the US)

Hyoscine butylbromide ampoule

Caution of use in patients with pre-existing cardiac conditions

Australia. The Therapeutic Goods Administration (TGA) has updated product information for hyoscine butylbromide (Buscopan®) to include a caution regarding the use of hyoscine ampoules in patients with pre-existing cardiac conditions (for example cardiac failure, coronary heart disease). The Australian product information for hyoscine butylbromide already lists tachycardia, decreased blood pressure and anaphylaxis as potential adverse effects, but the product information has been updated to include a stronger warning in the precautions section because these adverse events can be more serious in patients with cardiac conditions. Monitoring of these patients is advised and emergency equipment and personnel trained in its use must be readily available.

Hyoscine butylbromide ampoules, administered by intramuscular or slow intravenous injection, are used to treat gastrointestinal tract, biliary and renal spasms, and are used as a diagnostic in radiology.

There are 28 cases describing tachycardia and/or hypotension relating to use of hyoscine butylbromide in the TGA's adverse events database. An additional four cases describe anaphylactic reactions. There is insufficient clinical information provided to determine whether or not these reactions occurred in people with pre-existing cardiac conditions. None of

these cases reported death, cardiac arrest or myocardial infarction.

Reference:

Medicines Safety Update, TGA, Vol. 8, No. 4, August-September 2017 (www.tga.gov.au)

(See WHO Pharmaceuticals Newsletter No.2, 2017: Risk of serious adverse effects in patients with underlying cardiac disease in the United Kingdom)

Ibrutinib

Reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and opportunistic infections

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated the product information of ibrutinib (Imbruvica®) to include ventricular tachyarrhythmia (common) and hepatitis B virus reactivation (uncommon) as adverse reactions.

Opportunistic infections are already listed in the product information of ibrutinib.

Ibrutinib is indicated for the treatment of adult patients with:

- mantle cell lymphoma who have received at least one prior therapy
- chronic lymphocytic leukaemia (CLL), including CLL with deletion 17p
- Waldenström's macroglobulinaemia

A routine European review examined the safety profile of ibrutinib. Data from randomised controlled trials and the scientific literature were assessed. Worldwide spontaneous suspected adverse drug reaction (ADR) reports were also reviewed.

In a 2017 study of case reports of relevant events from post-marketing sources and clinical trial data, the authors identified 11 cases of ventricular tachycardia/ventricular fibrillation and six cases of

sudden cardiac death in patients exposed to ibrutinib. The review also identified two spontaneous ADRs of ventricular tachyarrhythmia in which the role of ibrutinib could not be excluded.

The review identified eight cases of hepatitis B reactivation in which the role of ibrutinib was considered probable or possible.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 1: 1, August 2017 (www.gov.uk/mhra)

Laninamivir

Risk of bronchial spasm, and dyspnoea

Japan. The MHLW and the PMDA have announced that the package insert for laninamivir (Inavir®) has been updated to include the risk of bronchial spasm and dyspnoea as clinically significant adverse reactions.

Laninamivir is indicated for treatment and prophylaxis of influenza A and B virus infection.

Eight cases associated with bronchial spasm and dyspnoea have been reported in Japan. Of these, a causal relationship could not be excluded in three cases.

Reference:

Revision of Precautions, MHLW/PMDA, 8 August 2017 (www.pmda.go.jp/english/)

Methylprednisolone injections containing lactose

Contraindication to patients allergic to cow's milk proteins.

EU. The European Medicines Agency (EMA) has made an announcement that the product information for methylprednisolone injections

containing lactose will be revised to include a contraindication in patients allergic to cow's milk proteins. In addition, the vial and packaging of these medicines will be clearly marked with a warning against use in patients with cow's milk allergy.

Methylprednisolone injections are used to treat the symptoms of severe allergic reactions and other inflammatory conditions.

In a review it was found that methylprednisolone injections containing lactose derived from cow's milk may also contain traces of cow's milk proteins which can trigger allergic reactions. This is of particular concern in patients already being treated for an allergic reaction as they are more prone to developing new allergic reactions.

Considering that methylprednisolone is used for the treatment of severe allergic reactions in an emergency setting where details of the patients' allergies may not always be known, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) confirmed that the most effective way of minimising any risk is to remove cow's milk proteins from the preparation. Companies have been asked to provide data allowing the replacement of formulations containing lactose from cow's milk; this data should be provided by the middle of 2019.

Reference:

News and press releases, EMA, 1 August 2017 (www.ema.europa.eu)

Palivizumab

Risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced that the package insert for palivizumab (Synagis®) has been updated to include the risk of thrombocytopenia as a

clinically significant adverse reaction.

Palivizumab is indicated for: prevention of serious lower respiratory tract diseases caused by respiratory syncytial virus infection in high-risk neonates and infants and children.

A total of four cases associated with thrombocytopenia have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:

Revision of Precautions, MHLW/PMDA, 12 September 2017 (www.pmda.go.jp/english/)

Paracetamol (modified- or prolonged-release)

Modified- or prolonged-release preparations should be suspended from marketing

EU. The EMA has recommended that modified- or prolonged-release paracetamol products should be suspended from the market. This is in view of the risks to patients from the complex way these medicines release paracetamol into the body after an overdose.

Paracetamol is a medicine that has been widely used for many years to relieve pain and fever in adults and children.

The review of modified-release paracetamol has been carried out by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC evaluated published studies and reports of overdose with these medicines, consulted experts in the management of poisoning and assessed how overdose with paracetamol is managed in the EU and other parts of the world.

In many cases, it may not be known whether an overdose of paracetamol involves

immediate-release or modified-release products, making it difficult to decide what type of management is needed. The committee could not identify a way to minimise the risk to patients, or a feasible and standardised way to adapt the management of paracetamol overdose across the EU to allow for treatment of cases that involve modified-release preparations. It concluded on balance that the risk following overdose with these medicines outweighs the advantage of having a longer-acting preparation.

Reference:

News and press releases, EMA, 1 September 2017 (www.ema.europa.eu)

Riociguat

Increased incidences of serious adverse events and fatal outcomes

Japan. The MHLW and the PMDA have announced that the package insert for riociguat (Adempas®) should be updated to include an important precaution on the risk of serious adverse events and fatal outcomes.

Riociguat is indicated to treat inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or postoperative persistent or recurrent CTEPH, and pulmonary arterial hypertension.

A clinical study in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias (RISE-IIP Study) was terminated early due to increased incidences of serious adverse events and fatal outcomes observed in patients receiving riociguat compared with patients receiving placebo. Similar risks are expected in patients with pulmonary arterial hypertension associated with interstitial pneumopathy and the risks

may outweigh the benefits in some patients.

One case associated with adverse reactions has been reported in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias in Japan.

Reference:

Revision of Precautions, MHLW/PMDA, 3 August 2017 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletters No.1, 2017: Contraindicated for use in patients with pulmonary hypertension associated with idiopathic interstitial pneumonia in Malaysia and No. 5, 2016: Contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias in the United Kingdom)

Selexipag

Contraindication with potent inhibitors of cytochrome P450 2C8

Spain. The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) has informed health-care professionals that the concomitant use of selexipag (Uptravi®) with potent cytochrome P4502C8 (CYP2C8) inhibitors (for example, gemfibrozil) is contraindicated as exposure to the active metabolite of selexipag can be increased causing adverse reactions.

Selexipag is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adults (in combination, or, as monotherapy in certain cases).

In a pharmacokinetic study, the number and severity of adverse reactions reported following concomitant administration of selexipag and gemfibrozil (a potent CYP2C98 inhibitor) were higher than those reported with selexipag alone. This is consistent with increased levels of the active metabolite.

Regarding use in conjunction with CYP2C8 inducers, it was observed that the concomitant use of rifampicin and selexipag does not affect blood levels of selexipag but reduces levels of the metabolite and it may be necessary to adjust the dose of selexipag if used concomitantly with rifampicin or other inducers of CYP2C8 (e.g. carbamazepine, phenytoin, efavirenz and St. John's wort).

The AEMPS has advised health-care professionals to follow the recommendations for use established in the technical data sheet of selexipag and in particular, guidance on interactions with other medicinal products which may result in a need for dosage adjustment.

Reference:

Información dirigida a profesionales sanitarios, AEMPS, 14 June 2017, Spain (www.aemps.gob.es)

Sodium polystyrene sulfonate

Potential drug-drug interaction

USA. The US FDA has updated the drug labels for sodium polystyrene sulfonate (Kayexalate®) to include information warning patients to avoid taking this medicine at the same time as other oral medicines.

Sodium polystyrene sulfonate is used to treat hyperkalaemia, a serious condition in which the amount of potassium in the blood is too high.

A study found that sodium polystyrene sulfonate binds to many commonly prescribed oral medicines, decreasing the absorption and therefore effectiveness of those oral medicines. To reduce this likelihood, the FDA has recommended separating the dosing of sodium polystyrene sulfonate from other orally administered medicines by at least 3 hours.

Reference:

Drug Safety Communication, US FDA, 6 September 2017 (www.fda.gov)

(See WHO Pharmaceuticals Newsletter No6, 2015: Potential risk of drug interaction in US)

Trimebutine based medicines

Contraindication in children under two years of age

France. L'Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) has stated that the use of trimebutine based medicines in children under two years of age is contraindicated.

Trimebutine is an antispasmodic indicated in gastroenterology.

Cases with neurological (drowsiness and seizures) and cardiac (bradycardia) adverse drug reactions have been reported, particularly in children under the age of two years. These were due to overdoses that occurred following a medication error.

Due to low level of evidence of efficacy and the risk of serious adverse drug reactions in children under the age of two years, trimebutine-based medicines are now contraindicated in this age group.

Reference:

Point d'information, ANSM, 28 July 2017, France (www.anism.sante.fr)

Warfarin

Risk of calciphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for warfarin has been updated to include the risk of calciphylaxis as a clinically significant adverse reaction.

Warfarin is used for treatment and prevention of thromboembolism (including venous thrombosis, myocardial infarction, pulmonary embolism, brain embolism and, slowly progressive cerebral thrombosis).

Eleven cases associated with calciphylaxis have been reported in Japan and there is an overseas report published in the literature describing calciphylaxis with the use of warfarin. In addition, package inserts in Europe and the United States have been revised.

Reference:

Revision of Precautions, MHLW/PMDA, 8 August 2017 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletters No.2, 2017: Risk of calciphylaxis in Malaysia and No.4, 2016: Reports of calciphylaxis in the US)

Brivudine

Drug-drug interaction with anti-neoplastic chemotherapy agents or topical 5-fluorouracil preparations

Spain. The AEMPS has reminded health-care professionals that brivudine (Nervinex®) should not be administered to patients receiving anti-neoplastic chemotherapy, especially if they are treated with 5-fluorouracil, including topical preparations.

Brivudine is indicated for the early treatment of acute herpes zoster in immunocompromised adults.

In June 2012, the AEMPS issued an information note alerting health-care professionals about the potentially fatal interaction between brivudine and antineoplastic drugs containing 5-fluoropyrimidines: 5-fluorouracil and a combination of medicinal products containing these active ingredients or other 5-fluoropyrimidines.

Despite the information note, the Spanish pharmacovigilance system continues to receive reports of fatal cases due to co-administration of brivudine and 5-fluoropyrimidines containing antineoplastics. Since the issue of the note in 2012, seven new fatal cases have been reported in Spain.

Reference:

Notas informativas, AEMPS, 7 September 2017, Spain (www.aemps.gob.es)

Corticosteroids

Rare risk of central serous chorioretinopathy

The United Kingdom. The MHRA has provided advice to health-care professionals on the risk of central serous chorioretinopathy (CSCR) with

local as well as systemic administration of corticosteroids.

Corticosteroids are indicated for a wide variety of indications in the treatment or suppression of inflammatory and allergic disorders, commonly including:

- asthma and allergic rhinitis
- systemic inflammatory disorders, for example, rheumatoid arthritis
- skin conditions, for example, eczema

CSCR is a rare adverse effect that occurs with all formulations and has been described after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal and periocular routes. Although blurred vision is a symptom of CSCR, it is also an established adverse effect of steroid treatment. The causes of blurred vision are various and can also include cataract and glaucoma.

The MHRA has recommended that patients are provided with guidance to report any vision problems or disturbances. If a patient has received treatment with local administration of a corticosteroid and presents with visual symptoms, referral to an ophthalmologist should be considered.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 1: 2, August 2017 (www.gov.uk/mhra)

Desloratadine

Potential risk of QT interval prolongation: not enough evidence

Canada. Health Canada has carried out a safety review to look at the potential risk of QT interval prolongation with the use of over-the-counter (OTC) desloratadine-containing products. This safety review was triggered by a signal publication in the WHO Pharmaceuticals Newsletter

No.2, 2015, describing cases of abnormal heart rhythm suspected to be associated with the use of loratadine and desloratadine. Desloratadine is used to relieve symptoms of seasonal allergy or allergy caused by pollen or dust (hay fever).

At the time of the review, Health Canada had received 10 Canadian reports of abnormal heart rhythm suspected to be associated with desloratadine use. Of these, one case was further assessed. The review of this case found a possible link between desloratadine and abnormal heart rhythm. However, other factors such as concomitant medicines may have played a role. The remaining nine reports were excluded from further review because the test results to confirm the abnormal heart rhythm were not available.

In addition, Health Canada reviewed 13 international reports of abnormal heart rhythm suspected to be associated with the use of desloratadine that were provided by the manufacturer. Of these, four reports were further assessed. A link between these four reports and abnormal heart rhythm could not be established due to other factors that may have played a role such as: concomitant medicines, underlying heart conditions, and administration of higher than recommended doses of desloratadine.

A search in the WHO database of Individual Case Safety Reports, VigiBase identified 35 cases of abnormal heart rhythm suspected to be associated with desloratadine use. A link between the use of desloratadine and the abnormal heart rhythm could not be established, as there was not enough information in the reports to draw conclusions.

Published scientific studies have shown that desloratadine is not associated with abnormal heart rhythm in humans.

Health Canada's review of the available information did not establish a link between the use of desloratadine and abnormal heart rhythm.

Reference:

Summary Safety Review, Health Canada, 10 August 2017 (www.hc-sc.gc.ca)

Direct-acting antivirals (DAAs)

Interaction with warfarin

New Zealand. Medsafe has warned that recent evidence indicates that the use of direct-acting antivirals (DAAs) together with warfarin may result in changes in international normalised ratio (INR). In most cases decreases in INR were reported during concomitant treatment.

DAA regimens are used for the treatment of chronic hepatitis C infection. Warfarin (Coumadin® and Marevan®) is a vitamin K antagonist and is widely used as an anticoagulant.

Medsafe is continuing to monitor reports of adverse reactions to DAAs and is working with companies to ensure that all DAA data sheets and consumer medicine information include information on this safety concern.

Medsafe has recommended increasing the frequency of INR monitoring during concomitant treatment and making adjustments when necessary. Frequent monitoring of INR is also required in the post-treatment follow-up period, particularly if any warfarin dose adjustment has occurred.

Reference:

Safety Information, Medsafe, 25 August 2017 (www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.6, 2016: Interaction potential with warfarin and other vitamin K antagonists: changes to INR in Ireland)

Fluindione

Risk of allergic reaction

France. The ANSM has encouraged health-care professionals to be cautious when initiating therapy with fluindione due the risk of allergic reactions, particularly during the first six months of treatment.

Fluindione (Préviscan®) is an antivitamin K (AVK) class anticoagulant. It is indicated for atrial fibrillation (heart rhythm disorder), venous thrombosis or pulmonary embolism.

A survey carried out by the Regional Centre for Pharmacovigilance in Lyon found that the use of fluindione is more frequently associated with the occurrence of rare but often severe DRESS-type immuno-allergic attacks, in particular renal, hepatic, haematological or dermatological disorders.

In France, 82% of patients treated with AVK received fluindione, 13% of warfarin and 5% of acenocoumarol. These data are based on the number of daily defined doses consumed in 2016. Warfarin is the most widely used AVK in the rest of the world.

Reference:

Point d'information, ANSM, 19 June 2017, France (www.anism.sante.fr)

Iron isomaltoside

Do not start new treatment with iron isomaltoside

Spain. The AEMPS has recommended that health-care professionals should not start any new treatment with iron isomaltoside (Monoferro®) as a precautionary measure.

In Spain, the following iron preparations for intravenous administration are available: iron-carboxymaltose (Ferinject®), iron-dextran

(Cosmofer®), iron-isomaltoside (Monoferro®) and iron-sucrose (Feriv®, Venofer®). These products are used to treat and prevent iron deficiency.

Recently, the Spanish Pharmacovigilance System (Sistema Español de Farmacovigilancia; SEFV) has received large number of reports of suspected serious hypersensitivity reactions associated with iron-isomaltoside administration.

Specifically, as of 5 July 2017, after a search in the database of SEFV, Farmacovigilancia Española, Datos de Reacciones Adversas (FEDRA), a total of 108 reported cases of severe anaphylactic reactions or, of serious clinical situations related to anaphylaxis/shock associated with the administration of one of the intravenous iron preparations were identified.

Of these 108 severe adverse drug reaction reports, 44 were related to the administration of iron-isomaltoside. The rate of reporting on severe hypersensitivity reactions (reported cases in relation to treated patients) is much higher than for other intravenous iron preparations.

All available data are currently being analyzed in detail, and as a precaution, AEMPS recommends that healthcare professionals should not start any new treatment with iron-isomaltoside.

The AEMPS will report on the final decision to be taken based on the detailed evaluation of all available data.

Reference:

Notas informativas, AEMPS, 19 July 2017, Spain (www.aemps.gob.es)

Ketamine

Risk of severe liver injury with repeated and/or prolonged high-dose use

France. The ANSM has received reports of serious liver injury potentially related to the repeated and/or prolonged use of high dose ketamine. The ANSM has reminded health-care professionals that good practice recommendations for use of ketamine should be implemented.

It is essential to observe the recommended dosages and monitor the liver function closely.

Ketamine is indicated as an anaesthetic agent, alone or in combination with other anaesthetics.

Ten cases of serious liver injuries, including four cases leading to liver transplantation, have been reported by health-care professionals since 2014. These are cholestatic type cholangitis, which may be linked to the repeated and/or prolonged administration of ketamine.

Reference:

Point d'information, ANSM, 20 June 2017, France (www.ansm.sante.fr)

Lithium

Risk of toxicity

Australia. The TGA has reminded health-care professionals to remain vigilant for potential signs of lithium toxicity, particularly in patients with risk factors. Early symptoms of lithium toxicity can occur close to or within the serum therapeutic range.

Lithium (Quilonum® and Lithicarb®), is indicated for the treatment of acute mania, hypomania and for the prophylaxis of manic-depressive illness. The risk of lithium toxicity is adequately addressed in the product

information for lithium. A patient died in 2013 as a result of lithium toxicity and has prompted this reminder.

As of 17 May 2017, the TGA has received 58 reports in which lithium was suspected of causing toxicity. Two of these cases resulted in death.

Interactions with other medicines were identified as a contributing factor in 17 cases, and may have played a role in four other cases.

Inappropriate dosing was found to be a contributing cause of toxicity in two cases, and may have contributed to a third case.

Reference:

Medicines Safety Update, TGA, Vol. 8, No. 4, August-September 2017 (www.tga.gov.au)

Obeticholic acid

Risk of serious liver injury

USA. The US FDA has warned that obeticholic acid (Ocaliva®) is being incorrectly dosed in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death.

Obeticholic acid is used to treat a rare, chronic liver disease known as primary biliary cholangitis (PBC).

The FDA stated that some patients are receiving excessive doses, at a higher than recommended frequency. Obeticholic acid may also be associated with liver injury in some patients with mild disease who are receiving the correct dose. The recommended dosing and monitoring for patients on obeticholic acid are described in the current drug label. The FDA is working with the drug manufacturer, Intercept Pharmaceuticals, to address these safety concerns.

Reference:

Drug Safety Communication, US FDA, 21 September 2017 (www.fda.gov)

Pembrolizumab

Risk of using pembrolizumab for multiple myeloma in combination with immunomodulatory agents

USA. The US FDA has informed the public, health-care professionals and oncology clinical investigators about the risks associated with the use of pembrolizumab (Keytruda®) in combination with dexamethasone and an immunomodulatory agent (lenalidomide or pomalidomide) for the treatment of patients with multiple myeloma.

Pembrolizumab is used for certain types of cancers, but is not approved for treatment of multiple myeloma.

The FDA statement is based on a review of data from two clinical trials evaluating the use of pembrolizumab combined with other treatments in patients with multiple myeloma.

On 3 July 2017, the FDA required that all patients in these trials should be discontinued from further investigation with this drug because, interim results from both trials demonstrated an increased risk of death for patients receiving pembrolizumab when it was combined with an immunomodulatory agent as compared to the control group.

The manufacturer was made aware of the issue through an external data monitoring committee recommendation and suspended the trials to enrolment on 12 June, 2017.

Other multiple myeloma clinical trials of pembrolizumab and other combinations are currently undergoing clinical evaluation.

Reference:

Drug Safety Communication,
US FDA, 31 August 2017
(www.fda.gov)

Prasugrel**Potential risk of severe cutaneous adverse reactions (SCAR): not enough evidence**

Canada. Health Canada has carried out a safety review on the potential risk of severe cutaneous adverse reactions (SCAR) with the use of prasugrel (Effient®) following cases reported by the manufacturer.

Prasugrel is used with low-dose acetylsalicylic acid, such as aspirin, to reduce the risk of stroke, heart attacks or dying from a disease related to the heart or blood vessels.

At the time of the review, Health Canada had not received any Canadian reports of SCAR linked to the use of Prasugrel.

The safety review looked at 11 international reports of SCAR in patients treated with prasugrel. In seven of the 11 reports, the link between SCAR and the use of prasugrel was considered to be possible; however other factors such as the advanced age of the patients and the use of other medications at the same time may have played a role. For the remaining four reports, the condition was considered unlikely linked to prasugrel use or there was not enough information to assess the link.

In the literature, there was no evidence of increased risk of SCAR with the use of prasugrel.

Health Canada's review concluded that there was not enough information available to establish a link between the risk of SCAR and the use of prasugrel.

Reference:

Summary Safety Review,
Health Canada, 28 August
2017 (www.hc-sc.gc.ca)

Teriflunomide**Potential risk of acute renal injury or nephrolithiasis: not enough evidence**

Canada. Health Canada has reviewed the potential risk of sudden onset of acute renal injury or nephrolithiasis with the use of teriflunomide (Aubagio®) following safety information received from the manufacturer.

Teriflunomide is used to treat patients with multiple sclerosis (MS).

At the time of the review, Health Canada received, 55 reports (all were international) of suspected sudden onset of kidney injury and 135 reports (eight of these were Canadian) of suspected nephrolithiasis with teriflunomide use from the manufacturer. No additional reports were found in Health Canada's Vigilance database.

Upon review, only two reports of patients with sudden onset of renal injury were considered to be possibly related to the use of teriflunomide. The review of reports of nephrolithiasis did not show a link related to the use of teriflunomide. In these reports, other factors could have played a role, such as the MS itself or problems with the bladder. In addition, information in the reports that described the health of the patient's kidneys before taking teriflunomide was limited.

In the published scientific literature, there were no reports or studies related to the possible association of sudden onset of renal injury or nephrolithiasis with the use of teriflunomide.

There was limited evidence to suggest that MS patients may be at greater risk of renal

injury or nephrolithiasis when taking teriflunomide.

Health Canada's review of the available information did not establish a link between the use of teriflunomide and a risk of sudden onset of renal injury or nephrolithiasis.

Reference:

Summary Safety Review,
Health Canada, 4 August 2017
(www.hc-sc.gc.ca)

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 reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 16 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. Signals are first communicated to National Pharmacovigilance Centres through SIGNAL (a restricted document from UMC), before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 18). 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. 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.

Amitriptyline and dry eyes – an ADR overlooked in labelling

Dr Henric Taavola, Uppsala Monitoring Centre

During the joint UMC/Lareb signal detection sprint focusing on patient reports, the adverse reaction 'dry eyes' was highlighted for the drug amitriptyline in the WHO global database of individual case safety reports, VigiBase. As of January 2017, there were 40 reports on this drug and adverse drug reaction (ADR) combination in VigiBase, and if the search is extended to all similar drugs with the same ATC code (N06AA non-selective monoamine reuptake inhibitors) the number increases to 60.

Amitriptyline belongs to the class of tricyclic antidepressants and is used for the treatment of depression, anxiety and chronic pain. It has anticholinergic effects, inhibiting the neurotransmitter acetylcholine present in the central and peripheral nervous systems. This inhibition has effects on several autonomous functions such as decreased saliva production, decreased mucus production in the nose and throat, decreased sweating, increased body temperature, dilation of the pupils and reduced bowel movements. As well as these effects, there is also the reduced production of tears, causing the eyes to feel dry.¹ The official labelling in the United States and the United Kingdom both mention the anticholinergic effects of amitriptyline in general along with some examples, but neither of them mention dry eyes or reduced tear production.^{2,3}

For the similar drugs clomipramine and maprotiline, the Swedish labels, under the section "Warnings and precautions", state that contact lens wearers can sustain injuries to the cornea due to the reduced production of tears. However, there is no

direct mention of dry eyes or reduced tear flow in the section for adverse reactions.^{4,5}

Of the 40 reports of dry eyes in relation to amitriptyline in VigiBase, 37 concern female patients, two male patients, while one lacks information on patient sex. Half of the reports come from the United States, one from New Zealand and the remainder from various European countries. Among the 40 reports for the combination, 14 have amitriptyline as the only suspected drug, nine reports have a positive dechallenge and one report has a positive rechallenge. One report told the story of a patient sustaining a corneal ulceration due to eye dryness, a marked reduction in visual acuity and longstanding eye-problems. Another patient described the eye dryness as painful. There was also a case where a pre-existing problem with dry eyes was aggravated by the use of amitriptyline.

One reason, why this adverse reaction may have been overlooked in the labelling, could be that it is well known to many health-care professionals as being a consequence of the anticholinergic effect of amitriptyline, especially since 'anticholinergic effect' itself is labelled. However, as it would be far from obvious to patients, it would be useful to update the patient information leaflet and summary of product characteristics of amitriptyline to explicitly list eye dryness as an adverse effect.

References

1. Rang HP, Dale MM. Rang and Dale's Pharmacology. 6th ed. Edinburgh: Churchill Livingstone; 2007.
2. US DailyMed: Product label for amitriptyline. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=61d2da8d-b435-4ada-a013-401786f7cace>. Accessed: 24 January 2017.
3. Electronic Medicines Compendium: Summary of product characteristics for amitriptyline. Available from: <https://www.medicines.org.uk/emc/medicine/25741>. Accessed: 24 January 2017.
4. FASS. Summary of Product Characteristics for klomipramin (synonym for clomipramine, Anafranil®). Available from: <http://www.fass.se/LIF/product?userType=0&nplId=19741004000068>. Accessed: 24 January 2017.
5. FASS. Summary of Product Characteristics for maprotilin (synonym for maprotiline, Ludiomil®). Available from: <http://www.fass.se/LIF/product?userType=0&nplId=19790406000046>. Accessed: 24 January 2017.

Insufficiently labelled ADRs: abdominal pain, chest pain and headache while using noscapine

Ms Ellen Ederveen, the Netherlands Pharmacovigilance Centre Lareb

During the joint UMC/Lareb signal detection sprint in October 2016, focusing on patient reports, noscapine, a drug indicated for cough, and various adverse drug reactions (ADRs) were highlighted in VigiBase, the WHO global database of individual case safety reports. The most notable ADRs that were reported were abdominal pain, headache, chest pain and chest discomfort, with a total of 130 individual case safety reports as of 1 November, 2016. Of the reports, 99.2% originated from five countries: Sweden, Norway, Germany, Denmark and the Netherlands, although noscapine is marketed in several countries worldwide. In the latter two countries, these ADRs are not sufficiently labelled. Several patients highlighted the severity of the symptoms. For instance, "terrible pain, I was quite sure I had a heart attack or an aneurysm", "feels like I can hardly breathe", "terrible abdominal pain, I cried out because of the intense pain", and

"very painful, feels like your belly/stomach is wrung out".

The reported ADRs are not listed in every summary of product characteristics (SmPC) or patient information leaflet (PIL). Also, the severity of some of these ADRs is not sufficiently described in the label information for all products. Therefore, it is advisable to mention these adverse reactions and to highlight the possible severity in all SmPCs and PILs.

The countries with insufficient labelling have been sent a full assessment. Should it be of interest, the full assessment is available upon request.

Please email signals@who-umc.org.

Complete loss of libido reported for women on systemic hormonal contraceptive

Ms Sarah Watson, Uppsala Monitoring Centre

The MedDRA preferred term 'loss of libido' was initially highlighted for two systemic hormonal contraceptives (desogestrel and ethinylestradiol/levonorgestrel) in the joint UMC/Lareb signal detection sprint focusing on patient reports that took place in October 2016. Although the terms 'decreased libido', 'increased libido' or 'changes in

libido' are covered in most summary of product characteristics and patient information leaflets for systemic hormonal contraceptives, a complete loss of libido as reported and described by these patients is rarely mentioned.^{1,2}

Many health-care professionals may know that most systemic hormonal contraceptives are known to be able to affect the libido and in some cases cause a complete loss of libido. The full extent of this effect does not, however, always seem to be known among the women using these products. A decrease in libido, as listed in many of the patient information leaflets, may be acceptable to some patients, but a loss of libido as an adverse effect of contraceptive use would be less so.

As of 6 October 2016, there were 694 reports of loss of libido for hormonal contraceptives for systemic use (ATC code G03A) in VigiBase, the WHO global database of individual case safety reports (ICSRs). The top 10 reported drugs within this category are shown in Table 1. All have a positive IC_{025} value, which means that the adverse reaction is reported more often for that drug than what would be expected compared to the background of the database, with a statistical significance.³ The reports originate from all continents. Most of the reports concern women in the 18 to 44 age group (65%, with an even distribution within the age group), which is consistent with the age group most commonly using hormonal contraceptives. The five most commonly co-reported terms are depression, headache, mood swings, weight increased and anxiety. Depression is a confounder for loss of libido and was co-reported on 245 of the reports. The term "libido decreased" has 1743 reports for hormonal contraceptives for systemic use in VigiBase, and "libido increased" has 55 reports. Whether or not decrease and loss of libido are more common as adverse drug reactions than an increase in libido, or that they are a more serious problem which makes patients more prone to report, is not possible to say from this data.

The majority of the 694 reports in VigiBase lack information about any actions taken with the hormonal contraceptives. There are, however, 114 reports where the causal relationship between the drug and the adverse drug reaction is strengthened by positive de- or rechallenges of loss of libido. For 112 of the reports, there is a recorded positive dechallenge and two of them documents a positive rechallenge. Reports with depression co-reported are included in these figures and concern 44 of these reports. Seventy-seven of the 112 reports were submitted by consumers/non health professionals. The women describe in their own words how the complete loss of libido affected their lives and that they were not aware of a possible correlation to their contraceptive.

One user switched from an oral contraceptive with which she had experienced a decrease in libido to another oral contraceptive and as a result suffered a complete loss of libido during a period of one year. Once she had stopped the second contraceptive regime for a month, her libido returned and she realised that the loss of libido probably was related to her contraceptive drug. She questioned the information about this potential side effect and commented that the pills are of no use when you

experience this adverse drug reaction: "Why use birth control pills if you never want to have sex?". The risk of non-compliance in cases like this is quite evident if the primary reason for the patient to take the contraceptive is to prevent a pregnancy.

Another female described how her libido gradually disappeared over two years while taking her hormonal contraceptive. When she started to have unexpected bleedings, she stopped taking the contraceptive and her libido returned completely after about one week.

A third woman explained that her libido did return after discontinuation of the hormonal contraceptive, but that she was still struggling in her sex life because the reaction to the effects of the contraceptive had become associated with so many negative emotions.

Different needs among women and couples influence their decision on which contraceptive method to use. The potential risk of hormonal contraceptives influencing their libido needs to be communicated to women when prescribing, to enable women who experience this problem to reconsider their choice of contraceptive method. In a response to one of the patient reports the manufacturer made the following statement: "Since 'libido decreased' is listed, therefore loss of libido is considered listed". However, this does not seem to be sufficiently informative to patients.

Although depression could be a confounder for loss of libido, there is a sufficient number of reports in VigiBase without this confounder present. There are also several with depression co-reported that have recorded positive dechallenges.

These reports highlight the importance of helping consumers make well-informed decisions about their treatments and being aware of potential adverse reactions. Users who lose their libido while on these contraceptives might need to change their method of birth control in order to sustain their life quality and reduce the risk of non-compliance. A clearer message in the patient information leaflet about the potential loss of libido is recommended.

References

1. Electronic Medicines Compendium: Summary of Product Characteristics for systemic hormonal contraceptives. Available from: www.medicines.org.uk/emc/. Accessed: 1 November 2016.
2. US DailyMed: Product label for systemic hormonal contraceptives. Available from: <https://dailymed.nlm.nih.gov/dailymed/>. Accessed: 1 November 2016.

3. Norén GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. *Stat Methods Med Res.* Feb 2013;22(1):57-69.

Table 1. Top 10 reported systemic hormonal contraceptives (ATC G03A) for the MedDRA preferred term loss of libido in Vigibase

Drug	No of reports	IC₀₂₅	No of reporting countries
Levonorgestrel	406	3.37	17
Medoxprogesterone	87	2.80	4
Drospirenone/Ethinylestradiol	52	1.68	9
Etonorgestrel	43	2.04	7
Ethinylestradiol/Etonorgestrel	31	2.22	8
Ethinylestradiol/Levonorgestrel	29	1.90	10
Desogestrel	23	3.84	3
Ethinylestradiol/Norelgestromin	16	0.47	3
Ethinylestradiol/Norgestimate	9	1.11	2
Desogestrel/Ethinylestradiol	7	0.20	4

CAVEAT DOCUMENT

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

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring (PIDM). The information is stored in VigiBase, the WHO international database of suspected adverse drug reactions (ADRs). It is important to understand the limitations and qualifications that apply to this information and its use.

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

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

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

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

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

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

Confidential data

According to WHO policy and UMC Guidelines, ADR reports sent from the WHO PIDM member countries to VigiBase are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

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

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

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

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

APEC Harmonization Center (AHC) Pharmacovigilance Workshop, Seoul, 11-12 September 2017



The 2017 Asia-Pacific Economic Cooperation (APEC) Harmonization Center (AHC) Pharmacovigilance workshop was held 11-12 September, 2017 in Seoul, Republic of Korea.

This workshop was organized by AHC as part of the APEC Regulatory Harmonization Steering Committee (RHSC) under the Roadmap to promote regulatory convergence on Pharmacovigilance (PV) framework. The AHC, in partnership with APEC RHSC, has been providing similar workshops for building PV capacity and serving as an educational platform for regulatory priorities among APEC member economies since 2012.

The aim of this two day workshop was to impart knowledge and understanding of the best practices in PV, including the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) 'E2 series' guidelines, as well as the ongoing efforts for strengthening collaboration among stakeholders.

There were approximately 260 participants from regulatory authorities, academia, industry and national PV centres, representing 20 economies. Experts from the Ministry of Food and Drug Safety (MFDS) in Korea, US Food and Drug Administration (US FDA), WHO, The WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, the International Society of Pharmacovigilance (ISoP), among others, presented and facilitated the programme.

The topics covered during the two-day workshop included:

- Understanding ICH Guideline
- Risk management in pharmacovigilance
- Pharmacovigilance in biotherapeutics
- Assessing the impact of pharmacovigilance
- Promoting international partnership in pharmacovigilance
- Collaborative efforts among regulatory authorities, patients, industry and academia

The workshop was officially opened by Dr Sun Hee Lee, Director of the AHC, followed by remarks from Dr Hee-Mok Won, Chairman of the Korea Pharmaceutical and Bio-Pharma Manufacturers Association, and keynote speech from Mr Sang-Hyun Kim, Deputy Director of the Pharmaceutical Safety Division, MFDS.





On Day 1, PV specialists, speakers from the European Medicines Agency (EMA) and the US FDA and others introduced concept of ICH E2-series guidelines, its application and challenges in practice. Key principles and history of revisions were presented in detail, and considerations for local requirements were shared. A session on risk management provided an overview of current practices from regulatory and industry perspectives. Challenges in global and local environments were shared and the HSA highlighted the importance of timely and accurate communication. Lastly, PV in biotherapeutics covered unique characteristics and considerations for biotherapeutic products. Varying approaches and measures among regulatory authorities were presented, and the importance of PV at the levels of products and batches was emphasized.

Day 2 of the program consisted of topics on measuring the impact of PV and efforts for international collaboration. In the morning, key findings and challenges from assessment of PV activities were introduced, and the Pharmaceuticals and Medical Devices Agency (PMDA) shared Japan's experiences in utilizing electronic medical records. In subsequent sessions, updates on international activities and collaborative efforts were provided. Building a trusted and constructive relationship with stakeholders was highlighted as a key feature to such partnerships, and WEB-RADR was introduced as a new platform for mobile phone-based reporting ADR. Furthermore, existing gaps in national PV systems and WHO's PV activities beyond APEC region were presented to raise awareness on the continuous need for harmonization.



The participants expressed that the workshop provided valuable opportunity to broaden their knowledge and understanding on ICH guidelines and current international activities. In particular, participants found the session on risk management in PV practical and relevant to their daily work.

Feedback and comments from the participants and speakers will be analyzed and used to modify the program so that it addresses the needs of APEC economies. The AHC expressed its commitment to continue to provide training programs for regulatory convergence to support this important dialogue.

WHO will continue to support PV activities in the APEC region as well as other PV activities with regional cooperation.



The second workshop to integrate Anatomical Therapeutic Chemical (ATC) and Defined Daily Dose (DDD) in drug utilization research

The second workshop to integrate the ATC/DDD system, pharmacovigilance and drug utilization research for promoting the quality use of medicine was held on 20-21 September 2017 in Rabat, Morocco.



The two-day workshop on the ATC/DDD methodology to integrate its use in pharmacovigilance and drug utilization research consisted of lectures, discussions and interactive hands-on exercises. Experts from the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC in Oslo; Norwegian Institute of Public Health), WHO Collaborating Centre for Strengthening Pharmacovigilance Practices (WHOCC in Rabat; Centre Anti Poison et de Pharmacovigilance du Maroc) and WHO facilitated this workshop.

The aims of the workshop were;

- to introduce the principles of ATC classification and DDD; and their use in drug utilization monitoring and research, including pharmacovigilance
- to introduce the principles of drug utilization research, data sources and methods for collecting data on drug use
- to introduce the principles of investigating quality use of medicines, and to share country experiences on medicines use surveillance for selected products (e.g. anti-influenza products).

This workshop targeted pharmacovigilance and health-care professionals in low and middle income countries participating in the WHO Programme for International Drug Monitoring. In order to allow for good interactive learning, a small number of participants (around 20 in total) were invited to the workshop. The participants were from; Burkina Faso, Ethiopia, Ghana, Kenya, Mali, Morocco, Senegal, Sudan, and Uganda.



Overall, there was positive feedback from participants. Given the need to promote and support the use of this tool, WHO will continue to organise workshops on ATC/DDD system in collaboration with WHOCC in Oslo, WHOCC in Rabat and other experts. This will be in addition to the annual course in Oslo (<https://www.whocc.no/courses/>).

Please visit the following websites to learn about the ATC/DDD system and methodology:

- <http://www.who.int/medicines/regulation/medicines-safety/utilization/en/>
- <http://www.who.int/medicines/regulation/medicines-safety/toolkit/en/>
- <https://www.whocc.no/>