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

The aim of the Newsletter is to disseminate 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,

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

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

This newsletter also includes a short report from a recent training activity for strengthening pharmacovigilance in Botswana.

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Regulatory Matters

Safety of medicines

Signal

Amoxicillin

Risk of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

Singapore. The Health Sciences Authority (HSA) has announced that the package inserts for amoxicillin containing products (Amoxil®) and amoxicillin/clavulanate (Augmentin®) will be updated to include the risk of eosinophilia and systemic symptoms (DRESS) syndrome as an adverse drug reaction.

Amoxicillin is indicated for the treatment of commonly occurring bacterial infections such as respiratory tract, genitourinary, skin, and soft tissues infections.

The European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) conducted a safety review and recommended that the package inserts for amoxicillin-containing products should be updated to include the risk of DRESS syndrome.

HSA has received six serious local reports of DRESS syndrome associated with the use of amoxicillin/clavulanate. Two of the six cases described visceral involvements (hepatitis and myositis).

Reference:
Product Safety Alerts, HSA, 14 September 2018 (*http://www.hsa.gov.sg/*)

Ampicillin and ampicillin prodrugs

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 inserts for ampicillin (Viccillin®), bacampicillin (Viccillin-S®), and sultamicillin (Pengood®) should be revised to include acute generalized exanthematous pustulosis as an adverse drug reaction.

Ampicillin, bacampicillin and sultamicillin are antibiotics used to treat several conditions, such as sepsis, infective endocarditis and superficial skin infections.

A total of two cases involving acute generalized exanthematous pustulosis have been reported in patients treated with preparations containing ampicillin or bacampicillin in Japan during the previous three fiscal years. As bacampicillin and sultamicillin are prodrugs of ampicillin, MHLW/PMDA concluded that the revision of the package inserts was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 18 September 2018 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.5, 2017, No.1, 2016 and No.6 and No.3, 2015: Risk of acute generalized exanthematous pustulosis in Japan; No.5, 2016: Risk of acute generalized exanthematous pustulosis in India)

Apremilast

Risk of severe diarrhoea

Japan. MHLW and PMDA have announced that the package insert for apremilast (Otezla®) should be revised to include severe diarrhoea as an adverse drug reaction.

Apremilast is indicated for treatment of psoriasis vulgaris in patients who were not sufficiently responsive to topical therapies for treatment of psoriatic arthritis.

Cases of severe diarrhoea have been reported in overseas patients treated with apremilast, but no cases have been reported in Japan. Taking into account the existing text concerning severe diarrhoea in the US and EU package inserts for apremilast, MHLW/PMDA concluded that revision of the package insert was necessary based on currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 2 August 2018 *(www.pmda.go.jp/english/)*

Azithromycin

Increased risk of cancer relapse in donor stem cell transplant patients

USA. The US Food and Drug Administration (FDA) has advised health-care professionals not to prescribe azithromycin (Zithromax® and Zmax®) for long term use in patients who undergo donor stem cell transplants due to the potential risk of cancer relapse and death.

Azithromycin is an antibiotic used to treat many types of infections affecting the lungs, sinuses, skin and other parts of the body. Although not approved, azithromycin has been used for prophylaxis of bronchiolitis obliterans syndrome in patients who undergo donor stem cell transplants.

Results of a clinical trial show an increased rate of relapse in cancer affecting blood and lymph nodes, and deaths in these patients.

Reference:
Safety Alerts for Human Medical Products, US FDA, 3 August 2018 *(www.fda.gov)*

Beta-lactam antibiotics

Risk of severe cutaneous adverse reactions (SCAR)

Canada. Health Canada has announced that there is evidence of a link between the use of beta-lactam antibiotics and the risk of severe cutaneous adverse reactions (SCAR).

Beta-lactam antibiotics are a widely prescribed group of antimicrobial agents and are indicated to treat many types of bacterial infections. Beta-lactam antibiotics include ampicillin, amoxicillin, piperacillin and penicillin.

Health Canada reviewed the risk of SCAR with beta-lactam antibiotics because information submitted by a manufacturer suggested a potential risk of SCAR with amoxicillin/clavulanic acid. Because the risk of SCAR is included in the product information for some beta-lactam antibiotics, Health Canada decided to review all beta-lactam antibiotics, focusing on products that do not already include SCAR in their product information.

Health Canada has received 45 Canadian reports of SCAR in patients exposed to beta-lactam antibiotics.. At the time of the review there were 8,855 Individual Case Safety Reports (ICSRs) in the WHO global database for ICSRs, VigiBase®. The review established a possible link between the use of beta-lactam antibiotics and the risk of SCAR.

Reference:
Summary Safety Review, Health Canada, 7 August 2018 (*www.hc-sc.gc.ca*)

Ceftriaxone

Risk of convulsions and involuntary movements

Japan. MHLW and PMDA have announced that the package insert for ceftriaxone (Rocephin®) should be revised to include neuropsychiatric symptoms such as convulsions and involuntary movements as adverse reactions.

Ceftriaxone is active against microorganisms of genera: *Streptococcus*, *Pneumococcus*, and *Escherichia coli*. It is indicated for the treatment of bacterial infections such as sepsis, pharyngitis, tonsillitis and acute bronchitis.

A total of 19 cases of neuropsychiatric symptoms have been reported in Japan during the previous three fiscal years, and a causal relationship with ceftriaxone could not be excluded for 11 cases. Also, there are cases of neuropsychiatric symptoms reported in patients treated with ceftriaxone overseas.

MHLW/PMDA concluded that revision of the package insert was necessary based on currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 2 August 2018 *(www.pmda.go.jp/english/)*

Corticosteroids

Risk of central serous chorioretinopathy (CSCR)

New Zealand. Medsafe has informed health-care professionals of reports of central serous chorioretinopathy (CSCR) with the use of both topical and systemic corticosteroids.

Corticosteroids are widely used to treat various symptoms such as, inflammation, immunosuppression and proliferation.

The Centre for Adverse Reactions Monitoring (CARM) received reports for one case of CSCR and two cases of retinal detachment associated with corticosteroid use.

Symptoms of CSCR include blurred or distorted vision, blind spots, micropsia, sensitivity to bright light and reduced contrast sensitivity.

Medsafe is working with sponsors to include safety information about CSCR in the New Zealand data sheets for all corticosteroid-containing products.

Reference:
Prescriber Update, Medsafe, September 2018 *(www.medsafe.govt.nz/)*
(See WHO Pharmaceuticals Newsletter No.5, 2017: Rare risk of central serous chorioretinopathy in UK)

Dolutegravir

Risk of hepatic impairment and jaundice

Japan. MHLW and PMDA have announced that the package inserts for dolutegravir containing products (dolutegravir (Tivicay®) and dolutegravir sodium/abacavir sulfate/lamivudine (Triumeq Combination®)) should be revised to include hepatic impairment and jaundice as adverse reactions.

Four cases of hepatic impairment have been reported in patients exposed to dolutegravir containing products in Japan during the previous three fiscal years.

Reference:
Revision of Precautions, MHLW/PMDA, 18 September 2018 *(www.pmda.go.jp/english/)*

Iodine contrast media (ICM)

Risk of hypothyroidism

Singapore. HSA has announced that the package inserts for products containing iodine contrast media (ICM) will be updated to include warnings of ICM-induced thyroid function changes.

ICM products are used to enhance visualization of vascular structures and organs during radiographic procedures such as angiography and computed tomography. The iodine in ICM products can interfere with thyroid hormone production, which may in turn affect growth and development in infants; and metabolic activity in children and adults.

In April 2017, Health Canada issued a safety alert on the rare potential risk of

hypothyroidism with the use of ICM in certain patients, particularly infants.

HSA has not received any local reports of thyroid dysfunction associated with the use of ICM.

Reference:
Product Safety Alerts, HSA, 14 September 2018 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.1, 2018: Possible risk of hypothyroidism in infants in New Zealand)

Isotretinoin

Risk of obsessive compulsive disorder (OCD)

New Zealand. Medsafe has placed oral isotretinoin (Oratane® and Isotane®) on the Medicines Monitoring scheme due to the risk of obsessive compulsive disorder (OCD).

Isotretinoin is indicated to treat severe acne.

CARM has received a report of a 14 year old male who developed OCD and other anxiety symptoms after starting treatment with oral isotretinoin for acne.

There are 106 ICSRs that report OCD with isotretinoin use in the WHO global database for ICSRs, VigiBase. The Medicines Adverse Reactions Committee (MARC) reviewed available information and agreed that at present there is insufficient evidence of a causal association between isotretinoin and OCD. However, the MARC recommended additional monitoring to encourage reporting of OCD cases in patients taking oral isotretinoin.

Reference:
Safety Information, Medsafe, 14 August 2018 *(www.medsafe.govt.nz/)*

(See WHO Pharmaceuticals Newsletter No.5, 2016: Potential risk of psychiatric adverse events in Australia; No.1, 2015: Possible risk of psychiatric disorders in UK)

Methadone

Risk of serious harm in children breastfed by mothers being treated with methadone

Canada. Health Canada has announced a possible link between methadone (Methadose®, Metadol-D®) exposure in children through breast milk and the risk of serious harm (including death).

Methadone is used to treat addiction to opioids, such as heroin, in adults. It works by preventing withdrawal symptoms.

Health Canada reviewed a published article that reported two Canadian cases of death in children who had increased levels of methadone in their blood because they were being breastfed by mothers being treated for opioid addiction. Health Canada also reviewed 13 international cases of methadone toxicity in children exposed through breast milk, 10 of which reported death. A possible link between methadone and the risk of serious harm in children was found in 12 of these cases.

Health Canada's review of the available information found that there may be a link between methadone and the risk of serious harm in children breast fed by mothers taking methadone. Health Canada will be working with the manufacturers of methadone containing products to strengthen the product information, to warn of the risk of serious harm.

Reference:
Summary Safety Review, Health Canada, 3 August 2018 (*www.hc-sc.gc.ca*)

Methotrexate

Risk of teratogenicity

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information and Package Leaflet for oral methotrexate will be updated to reflect current knowledge in relation to teratogenicity, use of methotrexate in women of child bearing potential, and in male patients.

Oral methotrexate is indicated for the treatment of active rheumatoid arthritis, adult psoriasis and in a number of oncology related indications. Methotrexate is a known teratogen and is contraindicated for use during pregnancy and lactation.

Women are advised not to become pregnant while taking methotrexate and effective contraception should be used throughout treatment and for at least six months after treatment cessation. It is also advised that male patients taking methotrexate are recommended to use reliable contraception.

HPRA recommends that methotrexate should be administered as a once weekly dose only for rheumatology and dermatology indications.

Reference:
Drug Safety Newsletter, HPRA, August 2018 (*https://www.hpra.ie*)

Neuromuscular blocking agents

Prevention of unintended paralysis through medication errors

Australia. The Therapeutic Goods Administration (TGA) has announced that package labels for medicines containing neuromuscular blocking agents (NMBAs) will include a warning indicating that the product is a paralysing agent.

NMBAs, such as suxamethonium, pancuronium, and vecuronium, are used to cause paralysis during anaesthesia. Errors in the administration of NMBAs present significant risk to patient safety due to potential

for unintended paralysis, respiratory arrest, severe permanent harm and/or death.

Administration errors involving these medicines in Australia can be caused by look-alike selection errors.

Reference:
Medicines Safety Update, TGA, Vol. 9, No. 3, August-September 2018 (*www.tga.gov.au*)

Oseltamivir and other anti-influenza medicines

Potential risk of abnormal behaviour

Japan. MHLW and PMDA have announced that the package insert for oseltamivir (Tamiflu®) should be revised to remove the contraindication for use in patients aged 10 to 19 years. Instead, additional text informing patients and health-care professionals of reports of severe abnormal behaviour (e.g. falls) in male school-age children will be included in the package inserts for oseltamivir and other anti-influenza medicines such as amantadine (Atenegine® and Symmetrel®), baloxavir marboxil (Xofluza®), favipiravir (Avigan®), laninamivir (Inavir®), peramivir (Rapiacta®) and zanamivir (Relenza®).

The contraindication for use of oseltamivir in patients aged 10 to 19 years occurred following reports of abnormal behaviours (e.g. falls) in this age group. A causal relationship was unclear.

MHLW reviewed the available information and could not find a conclusive association between the use of oseltamivir and abnormal behaviours.

Reference:
Revision of Precautions, MHLW/PMDA, 21 August 2018 *(www.pmda.go.jp/english/)*

Pembrolizumab

Risk of immune-mediated adverse reactions

New Zealand. Medsafe has announced that the data sheet for pembrolizumab (Keytruda®) has been updated to include advice on dose modifications in the occurrence of immune-mediated and/or infusion-related adverse reactions.

Pembrolizumab is a monoclonal antibody used to treat some metastatic cancers including melanoma, non-small cell lung carcinoma, classical Hodgkin lymphoma and urothelial carcinoma.

As of 30 June 2018, CARM received 21 reports suspected to be related to the use of pembrolizumab. Reported adverse reactions include: changes in renal function, diabetes related reactions, symptoms of hypophysitis and, a fatal case of pneumonitis.

Reference:
Prescriber Update, Medsafe, September 2018 *(www.medsafe.govt.nz/)*

(See WHO Pharmaceuticals Newsletter No.5, 2017: Risk of using pembrolizumab for multiple myeloma in combination with immunomodulatory agents in USA; No.4, 2017: Reports of organ transplant rejection in UK)

Prednisone, prednisolone

Risk of scleroderma renal crisis (SRC) in patients with systemic sclerosis

Canada. Health Canada has informed health-care professionals of a possible link between the use of oral prednisone and prednisolone, and the risk of scleroderma renal crisis (SRC) in patients with systemic sclerosis.

Prednisone and prednisolone are indicated to treat allergies and inflammation. The announcement was triggered following an update of the product safety information for oral and injectable prednisone and prednisolone products by the EMA in July 2017. Health Canada reviewed the potential risk of SRC with the use of oral prednisone and prednisolone products in patients with systemic sclerosis. Two Canadian reports and six published international reports were reviewed and a link between the use of oral prednisone and prednisolone, especially at higher doses, and the risk of SRC in patients with systemic sclerosis was found.

Health Canada will be working with the manufacturers to update the Canadian product safety information for oral prednisone and prednisolone products to inform health-care professionals and patients about this risk.

Reference:
Summary Safety Review, Health Canada, 7 August 2018 (*www.hc-sc.gc.ca*)

Radium-223 dichloride

New restrictions for use

1. Ireland. The HPRA has announced that further restrictions on the use of radium-223 (Xofigo®) will be applied due to the increased risk of fractures.

Radium-223 is used to treat prostate cancer in adult men.

A previous restriction consisted of making the combined use of radium-223, abiraterone acetate (Zytiga®) and prednisone/prednisolone a contraindication. This contraindication remains, and the additional restriction is to limit use as monotherapy, or in combination with luteinising hormone releasing hormone (LHRH) analogue, for a number of different indications such as: the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known

visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC, or ineligible for any available systemic mCRPC treatment.

Radium-223 is not recommended in patients with a low level of osteoblastic bone metastases and in patients with only asymptomatic bone metastases. It is also not recommended in combination with other systemic active cancer therapies other than LHRH analogues.

Reference:
Drug Safety Newsletter, HPRA, August 2018 (*https://www.hpra.ie*)

2. Japan. MHLW and PMDA have announced that the package inserts for radium-223 (Xofigo®) should be revised to include a cautionary statement concerning co-administration of radium-223 with abiraterone acetate and prednisolone in chemotherapy-naive patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer accompanied by bone metastases.

A multi-regional phase III study investigating administration of radium-223 chloride in combination with abiraterone acetate plus prednisone or prednisolone to chemotherapy-naive patients showed a tendency for a higher mortality rate and incidence of bone fracture compared to the patients who were taking placebo.

Reference:
Revision of Precautions, MHLW/PMDA, 18 September 2018 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.2, 2018: Not to be used together with abiraterone and prednisone/prednisolone in Europe; No.1, 2018: Risk of death and fractures in UK)

Sedating antihistamines

Contraindication for use in children under two years

New Zealand. Medsafe has announced that sedating antihistamines are now contraindicated in children aged under two years and are no longer indicated for the treatment of anxiety due to risk of sedation and respiratory depression.

Sedating antihistamines include: alimemazine, brompheniramine and ketotifen. They are indicated to treat conditions such as cough and insomnia.

The MARC reviewed available information and recommended that sedating antihistamines should be contraindicated in children aged less than two years. Additionally, the Medicines Classification Committee (MCC) recommended that statements indicating that sedating antihistamines can be used for the treatment of anxiety should be removed from the pharmacist-only (restricted) medicines.

Reference:
Prescriber Update, Medsafe, September 2018
(www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.2, 2018: Potential for fatal respiratory depression in children under two years of age in Australia)

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

Risk of serious infection of the genital area

USA. The US FDA has recommended that the prescribing information and patient medication guides for all sodium-glucose cotransporter-2 (SGLT2) inhibitors should include a new warning about the risk of a rare but serious infection of the genital area.

SGLT2 inhibitors include canagliflozin, dapagliflozin, empagliflozin and ertugliflozin, and are indicated to treat type-2 diabetes.

Cases of the infection of the genital area have been reported.

Reference:
Safety Alerts for Human Medical Products, US FDA, 29 August 2018 *(www.fda.gov)*

Sunitinib

Risk of acute cholecystitis

Japan. MHLW and PMDA have announced that the package insert for sunitinib (Sutent®) should be revised to include acute cholecystitis as an adverse reaction.

Sunitinib is indicated for imatinib-resistant gastrointestinal stromal tumor, unresectable or metastatic renal cell carcinoma, and pancreatic neuroendocrine tumor.

Five cases involving acute cholecystitis have been reported in Japan during the previous three fiscal years, and a causal relationship to the product could not be excluded in two of these cases.

Reference:
Revision of Precautions, MHLW/PMDA, 18 September 2018 *(www.pmda.go.jp/english/)*

Ulipristal

New measures to minimize risk of liver injury

1. Europe. The EMA has recommended that several measures should be put in place to minimize the risk of rare but serious liver injury with the use of ulipristal acetate (Esmya®).

Ulipristal is indicated to treat moderate to severe symptoms

of uterine fibroids (benign tumors of the womb).

The minimization measures include: contraindication in women with known liver problems; and introducing liver function tests before, during and after treatment. Additionally, the use of ulipristal for more than one treatment course has been restricted to women who are not eligible for surgery.

The review of ulipristal was conducted by EMA's PRAC following reports of serious liver injury, including liver failure leading to transplantation. The PRAC concluded that ulipristal may have contributed to the development of some cases of serious liver injury.

Reference:
EMA, 26 July 2018
(www.ema.europa.eu)

2. Canada. Health Canada has recommended that health-care professionals monitor the liver function of patients taking ulipristal during and after treatment. Ulipristal is not recommended for use in patients with liver disease.

Health Canada's review of the available information concluded that there may be a link between ulipristal use and risk of serious liver injury.

Reference:
Summary Safety Review, Health Canada, 7 September 2018 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletter No.4, 2018: New measures to minimise the risk of liver injury in Europe; No.2, 2018: Potential risk of liver injury in Europe)

Valproate

Risk of teratogenicity

Singapore. The HSA has placed several local risk mitigation measures to manage the teratogenic risks of valproate (Epilim®).

Valproate is indicated for the treatment of various types of epileptic seizures, such as generalised and partial seizures. Valproate is a known teratogen that has been associated with congenital malformations and developmental disorders in children born to women taking the medicine during pregnancy.

The measures include: strengthening warnings of the risk of teratogenicity and precautions against its use during pregnancy in the Singapore package inserts for valproate.

This decision follows the EMA's recommendation to introduce new measures.

HSA has not received any local cases of adverse events associated with the exposure of valproate during pregnancy.

Reference:
Product Safety Alerts, HSA, 14 September 2018
(*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.3, 2018: Contraindicated in women and girls of childbearing potential in UK; No.3, 2017: Risk of developmental disorders in UK; No.2, 2016: Risk of abnormal pregnancy outcomes in UK; No2, 2015: Risk of abnormal pregnancy outcomes in UK; 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 UK)

Valsartan

Update on recall due to contamination with N-nitrosodiumethylamine (NDMA)

Europe. The EMA has issued an update on the recall of valsartan medicines containing the active substance from Zhejiang Huahai and Zhejiang Tianyu Pharmaceuticals in China. The recall initially occurred after an impurity N-nitrosodimethylamine (NDMA) was found in the active substance in products manufactured by Zhejiang Huahai Pharmaceuticals.

EMA has also learnt that low levels of NDMA have been detected in the valsartan medicines containing the active substance manufactured by another company, Zhejiang Tianyu. The NDMA levels detected in batches of valsartan from Zhejiang Tianyu are much lower than levels seen in the active substance from Zhejiang Huahai in China.

Additionally, another impurity, N-nitrosodiethylamine (NDEA), has been detected in valsartan made by Zhejiang Huahai. NDEA and NDMA are classified as probable human carcinogens.

Medicines containing valsartan from Zhejiang Huahai and Zhejiang Tianyu have been recalled and are no longer being distributed in the EU.

The EU authorities have conducted inspections of the manufacturing sites of both companies in China.

EMA continues to work closely with national authorities and international partners to gather information.

It is important to note that there is no immediate risk to patients. Patients taking the affected medicines who have not yet switched to an alternative should not stop taking their medicines without consulting their doctor or pharmacist.

Reference:
EMA, 2 and 10 August, 13 September 2018
(www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletter No.4, 2018: Recalled due to the contamination with N-nitrosodimethylamine (NDMA) in Europe)

Varenicline

Risk of loss of consciousness

1. Europe. The PRAC has recommended that the summary of product characteristics and package leaflet of varenicline (Champix®) should be updated

to include the risk of transient loss of consciousness.

PRAC considered available evidence in EudraVigilance® and literature with regards the risk of loss of consciousness.

Reference:
EMA, 9 July 2018
(www.ema.europa.eu)

2. Ireland. The HPRA has announced that PRAC recommended that the product information (SmPC and PL) for varenicline (Champix®) should be updated to include the risk of transient loss of consciousness.

Varenicline is indicated for smoking cessation in adults.

The review by PRAC considered that an association between varenicline and loss of consciousness could not be excluded. The potential association is biologically plausible (varenicline is a partial nicotinic receptor agonist, and these receptors are known to be involved in both excitatory and inhibitory neurotransmission). Furthermore, dose-dependent effects were observed in non-clinical trial studies.

Reference:
Drug Safety Newsletter, HPRA, August 2018
(*https://www.hpra.ie*)

Dolutegravir

Possible risk of neural tube defects

1. New Zealand. Medsafe has issued a warning about a potential risk of neural tube defects when dolutegravir (Tivicay® and Triumeq®) is taken in early pregnancy.

Dolutegravir is used in combination with other antiretroviral agents in the treatment of HIV infection in adults and children over 12 years of age.

Preliminary results of a study in Botswana suggest a possible increased risk of neural tube defects in infants born to women who were taking dolutegravir at the time of conception.

The study reported that four babies of 426 (0.9%) women who became pregnant while taking dolutegravir had a neural tube defect. On the other hand, 14 (0.1%) babies were born with a neural tube defect in 11,173 women taking other medicines for HIV.

Medsafe will continue to monitor this issue and will produce updated advice for health-care professionals and consumers as necessary.

Reference:
Safety Information, Medsafe, 6 August 2018
(www.medsafe.govt.nz/)

2. Europe. PRAC confirmed its precautionary advice issued earlier this year on the use of dolutegravir in pregnant women and women who can become pregnant. Women who can become pregnant should use effective contraception while taking dolutegravir. Additionally, women should undergo pregnancy testing before starting treatment and the medicine should not be used during the first trimester of pregnancy unless there is no alternative.

Reference:
EMA, 5 October 2018
(www.ema.europa.eu)

Also, WHO issued a follow on statement to the one that was issued on 18 May 2018 on dolutegravir.

Reference:
Full List of WHO Medical Product Alerts, WHO, October 2018
(http://www.who.int/medicines/publications/drugalerts/DTG_followon_may2018.pdf?ua=1)

(See WHO Pharmaceuticals Newsletter No.4, 2018: Potential risk of neural tube birth defects in USA and in Europe)

Febuxostat

Interaction with azathioprine or mercaptopurine

New Zealand. Medsafe has issued a warning about the interaction between febuxostat (Adenuric®) and azathioprine or mercaptopurine. When used in combination, febuxostat could potentially increase blood levels of mercaptopurine.

Febuxostat is used for the treatment of chronic hyperuricaemia in patients with gout. Febuxostat is not recommended in patients concomitantly treated with azathioprine or mercaptopurine.

Azathioprine is first metabolized to 6-mercaptopurine, which in turn is converted to inactive products by xanthine oxidase. Inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine, leading to toxicity.

As on 30 June 2018 there have been no reports of this interaction in New Zealand.

Reference:
Prescriber Update, Medsafe, September 2018
(www.medsafe.govt.nz/)

Rotavirus vaccines

Potential risk of intussusception

New Zealand. Medsafe has announced that 11 cases of intussusception associated with rotavirus vaccines (RotaTeq® and Rotarix®) were reported.

Rotavirus vaccine is an oral vaccine used against rotavirus infection.

Intussusception is the most common abdominal emergency in young children. About 1-6 in 100,000 children may experience intussusception due to vaccination with rotavirus vaccine.

In Ten of the 11 cases, patients recovered (the outcome was unknown in one case). The time between vaccination and onset of the reaction ranged from four days to two months.

The benefits of rotavirus vaccination continue to outweigh the risks of harm.

Parents and guardians should be advised to seek prompt medical assistance if any of the symptoms of intussusception occur.

Reference:
Prescriber Update, Medsafe, September 2018
(www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.5, 2016: Risk of intussusception in India; No.6, 2015: Risk of intussusception in Singapore; No.6, 2013: Risk of intussusception in Australia)

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 18 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.

Desogestrel and severe psychiatric disorders: panic attack, suicidal ideation and self-injurious behaviour

Sarah Watson, Uppsala Monitoring Centre

Summary

"Tried antidepressants on three occasions without success and sought months of therapy including cognitive behavioural therapy. Severe depression, high anxiety and suicidal thoughts. Changed to combined contraceptive pill and feel better."

Altered and depressed mood are listed adverse drug reactions (ADRs) for the contraceptive drug desogestrel, but the more severe reactions – suicidal ideation and panic attack – are not. These ADRs were highlighted as potential adverse drug reactions for desogestrel in the joint UMC/Lareb signal detection sprint on patient reports in October 2016. As on 1 November 2016, VigiBase, the WHO global database of individual case safety reports, contained 23 reports of panic attacks of which 21 had desogestrel as the only suspected drug and in 14 of the reports it was documented that the patients improved when the drug was withdrawn. For suicidal and self-injurious behaviour there were 34 reports of which 22 had desogestrel as the only suspected drug, and there were 20 cases describing improvement after withdrawal of the drug. The cases are further strengthened by the patients' stories, and send a strong signal to prescribers to be aware of potentially more severe psychiatric disorders for desogestrel and an update of the labelling should be considered.

Introduction

The terms panic attack and suicidal ideation were highlighted for the drug desogestrel in the joint UMC/Lareb signal detection sprint on patient reports in October 2016. Desogestrel is a hormonal contraceptive progestin drug used to prevent pregnancies. It is used on its own or in combination with ethinylestradiol and marketed in all parts of the world either on its own or as a combination product. This assessment has focused on the reports in VigiBase, the WHO global database of individual case safety reports, of desogestrel on its own.

The contraceptive effect of desogestrel is, in contrast to traditional progestogen-only pills, achieved primarily by inhibition of ovulation. Other effects include increased viscosity of the cervical mucus and decreased estradiol levels, to a level corresponding to the early follicular phase. Desogestrel is considered to be best suited for use during breast feeding and for women who may not or do not want to use oestrogens.[1]

Listed side effects within the MedDRA system organ class Psychiatric disorders are mood changes, depressed mood and decreased libido. All are considered common.[1] There is however nothing in the summary of product characteristics (SmPCs) or patient information leaflets about anxiety, more severe anxiety leading to panic attacks, or about risks of severe depression leading to suicidal thoughts or suicide attempts, as seen in the reports from patients in VigiBase.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a panic attack is defined as a discrete period of intense

fear or discomfort, often accompanied by physical symptoms such as palpitations and trembling. Experiencing repeated, consistent panic attacks that get in the way of everyday functioning is considered a defining symptom of panic disorder.[2]

Suicidal ideation could be translated to thoughts of harming oneself or bringing about one's own death and is most closely associated with major depression or chronic dysphoria. The prevalence is highest among adolescents and the elderly. Among adolescents it is approximately 12%. Symptoms and signs include depression, poor sleep, anxiety, decreased appetite and mood changes. Among adolescents who experience thoughts of suicide, girls and young women suffer about twice as often as boys. About one in three persons who have suicidal ideations actually tries to commit suicide.[3]

Reports in VigiBase

Panic attacks

In VigiBase there were 18 reports for the MedDRA preferred term (PT) 'panic attack' reported for desogestrel as of 1 November 2016. Widening the search to look at all reports within the high level term (HLT) 'panic attacks and disorders' revealed five more reports which are also included in this assessment and gives 23 reports in total. The reports are all from Europe and concern women between the ages of 22 to 48 years. In 16 cases desogestrel is the single reported drug and in all but two of the reports desogestrel is the single suspected drug. In both cases where another drug was co-suspected, the other drug seems to have been taken around the same time, but no exact dates were provided. In one of the cases the co-suspect was another contraceptive drug; ethinylestradiol/levonorgestrel and in the other case it was an antibiotic; lymecycline. None of the drugs have 'panic attack' listed as an adverse drug reaction (ADR).[4,5]

Only one person had a documented medical history of panic attacks but she had not had a panic attack for five years. Fifteen days after starting desogestrel she experienced a panic attack. There are 14 reported positive dechallenges and one mentioning of a rechallenge for psychiatric problems. For all but one report, the panic attacks occurred within the first two months of treatment. Co-reported terms are often anxiety, depression and/or mood swings.

One of the women described her suspected adverse reactions as *"Severe depression, anxiety and panic attacks. Sought additional treatment for depression/anxiety from general practitioner but symptoms abated once stopped taking Cerazette."*

Similarly, another patient reported her panic attacks while on desogestrel and how they disappeared when she stopped taking the drug as *"Episodes of anxiety, panic and panic attacks in pressured situations. I connected this to my current life situation before I stopped Cerazette in January 2015. At the same time the panic attacks I anticipated in certain situations did not occur. I did never suspect Cerazette to have any role in my anxiety or panic attacks before I stopped the drug and realized that my problems went away. Thinking back, I realize that my problems started in the same period as I started taking Cerazette."*

There is also a report from a woman which describes a rechallenge of this type of symptom: *"Depressive episode, anxiety aggravated, judgement impaired and panic attacks. This is the second time I have tried this birth control method, and the second time I have had mental health issues immediately afterwards. It has brought on my depression and anxiety after being free for about 12 months."*

Widening the search to look at all hormonal contraceptives for systemic use (ATC G03A) and the PT 'panic attack' in VigiBase revealed that with several other contraceptives panic attacks were also reported more often than expected compared to the background of the database (i.e. had positive IC_{025} values; IC_{025} being the 95% credibility interval for the information component that describes disproportionate reporting in VigiBase[6]). These were drospirenone/ethinylestradiol, ethinylestradiol/etonogestrel, ethinylestradiol/iron/norethisterone, norethisterone, levonorgestrel and ethinylestradiol/norgestimate. For the combination product ethinylestradiol/iron/norethisterone it was found for one of many products that the adverse reactions 'panic attack' as well as 'suicidal ideation' were included in the label as post marketing experience.[7]

Suicidal ideation and self-injurious behaviour

As of 1 November 2016 there were 26 reports for the MedDRA PT 'suicidal ideation' in VigiBase. One of these reports also mentioned panic attacks and are therefore counted twice for both ADRs. Looking at the HLT suicidal and self-injurious behaviour revealed eight more reports with the PTs 'intentional self-injury', 'self-injurious ideation' and 'suicide attempt'. These reports were also included in this assessment. There were no reports of completed suicides. The reports come from women aged between 18 and 51, and all from Europe.

Among the 34 reports, 19 had desogestrel as the only reported drug. Desogestrel was the only suspected drug in 27 reports including one of five reported suicide attempts where the patient had ingested several drugs but only desogestrel was reported as suspected for the reaction. The other suspected drugs were other contraceptives for two patients, topiramate in one case, citalopram in one, escitalopram in one and in two cases multiple drugs in two of the suicide attempts.

The time to onset (where this information was

recorded) ranged from one day to five months. In 20 cases the patients reported a positive dechallenge and in one case there is a mention of a rechallenge, although it is not clear if it was from the same contraceptive drug.

In three of the cases there was a recorded medical history of depression, depressive episodes and panic disorder respectively although all had documented positive dechallenges upon removal of desogestrel.

One patient detailed her experiences while on desogestrel as follows: *"Anxiety, intrusive disturbing thoughts, suicidal ideation. Having always slept well I was suddenly only able to sleep for two or three hours per night. I felt constantly anxious, shaky, palpitations, constantly feeling the need to run away, couldn't concentrate on work or anything else. Most disturbingly I began to experience sudden vivid flashing images of me harming my young children - this is something I would never ever do and it upset me greatly. I have no history at all of mental health problems. I began to think this might be hormonal because the psychological symptoms were at their worst the day before my period started. This lead me to search the internet (my next step would have been to seek medical help) and I found accounts by other women who had experienced the same while taking Cerazette/Cerelle. I am really shocked by how much better I feel just a couple of days after having stopped taking it."*

An overview of the HLT 'suicidal and self-injurious behaviour' for all systemic hormonal contraceptives in VigiBase showed that desogestrel is one out of three drugs that is reported more often than expected compared to the rest of the database (with a 95% credibility interval: IC_{025} 1.19). The two other drugs both contain norethisterone; the combined oral contraceptive norethisterone acetate/ethinylestradiol/ferrous fumarate and norethisterone alone.

Literature

Although no recorded cases of desogestrel and panic attack, suicidal ideation or self-injurious behaviour were found while searching PubMed, there were several documented cases of psychiatric problems, including panic disorder, in the literature for another progestin – levonorgestrel – from which desogestrel is derived. Wagner *et al.* described in 1994 two cases of major depression and panic disorder while on levonorgestrel. In 1996 the same author published another article about five women who all developed major depression and where two also developed obsessive-compulsive disorder and one of these women also developed agoraphobia, while using levonorgestrel. These women had no prior psychiatric history and all the ADRs resolved after removal of levonorgestrel.[8,9]

Discussion and Conclusion

The adverse reactions 'mood changes' and 'depressed mood' are listed as *common* in the SmPCs and patient information leaflets for desogestrel. However, the much more severe 'panic attack', 'suicidal ideation' and 'self-injurious behaviour' are not mentioned at all and nothing relevant was found in a PubMed search for desogestrel related to these terms. Although many people feel less depressed and anxious while on contraceptive drugs, some women do suffer from psychiatric problems while starting this type of treatment. That depression is listed in the SmPC does not rule out the possibility that some of these patients might suffer a more severe depression while on desogestrel and that thoughts of self-harm or even suicide could occur. Anxiety may manifest as a symptom of depression and both conditions often occur together. Panic attacks are essentially intensified anxiety that has escalated into intense fear or discomfort. The fact that panic attacks and suicidal ideation are mentioned under post marketing experience for the hormonal contraceptive drug containing ethinylestradiol/iron/norethisterone and the case reports of another progestin levonorgestrel – causing panic attacks as well as other unlabelled psychiatric problems further strengthen a possible causal relationship between desogestrel and the highlighted adverse reactions.

The VigiBase reports contain narratives that describe women with symptoms of both depression, anxiety and panic attacks as well as self-harm. The majority of the reports also mention that the patients improved upon discontinuation of desogestrel. These reports send a strong signal to prescribers to be aware of potentially more severe psychiatric disorders for desogestrel. Further investigations for these type of ADRs for hormonal contraceptives in general would be useful.

**Part of this signal was published as a "Letter to the Editor" in the British Journal of Clinical Pharmacology, August 2018:*
https://bpspubs.onlinelibrary.wiley.com/doi/abs/10.1111/bcp.13617

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Edoxaban – Incorrect dose administered

Alem Zekarias, Uppsala Monitoring Centre

Edoxaban is an anti-coagulant drug indicated to prevent thromboembolic disease in patients diagnosed with atrial fibrillation, including one or more risk factors such as history of stroke or transient ischaemic attack, age 75 years or older, diabetes mellitus or hypertension. The drug is also approved for treatment of deep vein thrombosis and pulmonary embolism.[1]

The recommended dose differs according to the indication but ranges between 30 mg and 60 mg once a day. In patients with body weight lower than 60 kg, or taking P-glycoprotein inhibiting drugs, such as ciclosporin, dronedarone, erythromycin, ketoconazole, or suffering from moderate or severe renal impairment, the dose should be reduced to 30 mg daily.[1,2]

Thirty-six individual case safety reports have been submitted to the VigiBase, the WHO global database for individual case safety reports, up until February 2018 describing patients given the wrong dose of edoxaban.

An age was provided in 16 of the 36 cases, and these patients were 67 years or older. The reports describe patients having been given a dose that was inappropriate to either their medical condition, body weight or health condition. The consequences of such errors included cerebral bleeding, gastric bleeding and urethral bleeding. In most of the cases the drug was either withdrawn and changed to another anticoagulant or the edoxaban dose was decreased.

In one fatal case, an 83-year-old female who was taking a dose of 60 mg edoxaban for an unknown indication experienced cerebral mass bleeding with ventricular bleeding a year after she started taking edoxaban. The cause of death was reported as cerebral bleeding.

It is stated in both the Summary of Product Characteristics and in the product information leaflet that different dose adjustments for edoxaban are needed/recommended.[1,2] Despite the prescribing information, we have noted reports in VigiBase with inappropriate prescription leading to severe and serious outcomes.

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Metamizole – Documented hypersensitivity to administered product

Alem Zekarias, Uppsala Monitoring Centre

Metamizole contains the active substance dipyrone. The drug is a non-opioid agent with anti-inflammatory, analgesics, spasmolytic and antipyretic properties indicated to treat both acute and chronic pain in human and in veterinary medicine.[1,2] Metamizole is available in different formulations, both as a prescription and as an over-the-counter medicine, in several countries.[3,4]

Countries such as Japan, the United States of America, the United Kingdom, Sweden, Australia and Iran have withdrawn the drug from the market due to the risk of agranulocytosis and anaphylaxis. In the US the drug was withdrawn in 1977. This decision was based on studies that showed a 0.79%-0.86% frequency rate of metamizole-induced agranulocytosis together with a 0.57% mortality rate. In Sweden metamizole was first withdrawn 1974, due to an estimated incidence of agranulocytosis of 1 in 3,000 patients. The drug was then re-approved in 1995 because a much lower incidence rate was seen in an International Agranulocytosis and Aplastic Anaemia Study. A couple years after the second approval, the drug was once again withdrawn due to spontaneous reporting of blood dyscrasias.[3,5,6]

It is known that metamizole can cause severe adverse reactions such as Stevens-Johnson syndrome and anaphylactic shock, with fatal consequences. The risk for developing an anaphylactic reaction has been estimated to be 1 in 5,000 treated patients given the drug parenterally.[3]

In VigiBase, the WHO database for international drug monitoring, there are 19 individual case safety reports submitted from Spain (12 cases) and Germany (7) describing problems related to hypersensitivity together with metamizole as of February 2018. All patients, 15 females and 4 males, were between 24 and 93 years of age, with one of unknown age, who received metamizole despite having a documented hypersensitivity to the drug. Most of the patients (13) received the drug orally while five of them had an intravenous administration. In one case the route of administration is unknown. Five patients suffered anaphylactic shock, two of them with asystole, seven suffered mild skin reactions, two had dyspnea. In three cases agranulocytosis/low white cell count was reported, and a similar reaction was noted in these patients' medical history. In two patients the reaction is not described in detail. Seventeen patients recovered, and in two cases the outcome was not reported.

Anaphylactic reactions with metamizole are described in detail in the Summary of Product Characteristics.[3,7]

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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.

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Strengthening Pharmacovigilance in Botswana

Recognizing the need for robust pharmacovigilance (PV) frameworks and processes, the Ministry of Health and Wellness of Botswana invited the World Health Organization (WHO) to support PV strengthening activities using dolutegravir as a pathfinder. WHO staff working in safety and vigilance for medicines and HIV from the WHO Country Office in Botswana, WHO Regional Office for Africa, WHO Headquarters, together with technical staff from WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre jointly organized and facilitated two PV workshops (one succeeding the other) in Gaborone, Botswana from 26 to 29 June 2018.

The first workshop was a basic PV course that lasted two and a half days. Training focused on reporting, use of different reporting methods and management of adverse drug reactions (ADRs). The basic course was attended by health-care professionals (HCPs) who treat HIV patients, and staff from the National regulatory authority, Botswana Medicines Regulatory Agency (BoMRA), Ministry of Health and Welfare, and the National HIV disease programme. The second PV workshop was more advanced and lasted one and a half days. The advanced PV workshop targeted staff from BoMRA and experts from the National HIV programme. Training focused on causality assessments and signal detection.

Participants noted learning about reporting methods, and how pharmacovigilance enhances the healthcare system as a whole to be very useful. Participants gained a better understanding of the importance of reporting and conveyed that they intend to incorporate the knowledge and skills gained during the workshop into everyday practice. A train the trainer course will be developed to increase awareness and enhance reporting within the country. Although the workshop was focused more on the antiretroviral therapy and dolutegravir in particular, the PV system as a whole was presented to the participants, which was highly appreciated.