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Prepared in collaboration with the WHO Collaborating Centre for International Drug Monitoring, Uppsala Sweden

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

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

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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also includes write-ups on 'Signals' from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

This newsletter includes three feature articles describing: the 38th meeting of the WHO International Working Group for Drug Statistics Methodology; Pre-conference Workshop on WHO ATC/DDD Methodology and Drug Utilization Research; and the 38th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

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Aripiprazole

Risk of certain impulse control behaviours

Canada. Health Canada has updated the Canadian prescribing information for aripiprazole (Abilify®) to include a warning statement of risk of pathological gambling and uncontrollable sexual behaviours (hypersexuality).

Aripiprazole is an oral medication and is used to treat:

- manic-depressive illness (bipolar I disorder) in adults and adolescents of 13 years and older. This condition is characterised by periods of elevated moods (mania) and depression;
- schizophrenia in adults and adolescents of 15 years and older;
- depression in adults when used in combination with other drugs.

Health Canada conducted a safety review following the European Medicines Agency (EMA)'s warning (product label update) of the risk of pathological gambling and the inclusion of hypersexuality as an adverse effect.

At the time of the review, Health Canada received five reports of pathological gambling and/or hypersexuality, suspected of being linked with aripiprazole. Upon review of these cases, no conclusions could be made regarding what role, if any, the drug may have played due to limited information.

Among 14 of the 18 cases of pathological gambling, and 5 of 6 cases of hypersexuality linked to aripiprazole identified in the scientific and medical literature, the behaviours resolved or improved when the treatment with aripiprazole was stopped or the dosage was reduced.

Health Canada will continue to monitor adverse effect information involving aripiprazole to investigate potential harms.

Reference:
Summary Safety Review, Health Canada, 2 November 2015 (*www.hc-sc.gc.ca*)

Asunaprevir and daclatasvir

Risk of interstitial pneumonia

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced the revision of the package insert for asunaprevir (Sunvepra®) and daclatasvir (Daklinza®) to include risk of interstitial pneumonia.

Asunaprevir and daclatasvir are co-administered for treatment of serogroup 1 (genotype 1) chronic hepatitis C or compensated cirrhosis type C.

The MHLW/PMDA stated that cases of interstitial pneumonia have been reported in patients treated with asunaprevir and daclatasvir in Japan.

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

Interstitial pneumonia: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia, abnormal chest sound (crepitations) etc. are observed, examinations including chest X-ray, chest CT scan, or serum marker test should be performed. If interstitial pneumonia is suspected, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Azithromycin

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

Singapore. The Health Sciences Authority (HSA) has informed health-care professionals of the risk of eosinophilia and systemic symptoms (DRESS) associated with the use of azithromycin.

Azithromycin (Zithromax®) is a macrolide antibiotic (azalide subclass) used to treat upper and lower respiratory tract infections and other infections sensitive to azithromycin.

In April 2014, Health Canada updated package inserts (PI) of azithromycin-containing products to include information on DRESS. This was based on a report of DRESS suspected to be associated with azithromycin in Canada, and a review of published literature.

To date, the HSA has not received any reports of DRESS associated with the use of azithromycin, but initiated a labelling update for azithromycin to warn of reports of DRESS.

The HSA has recommended health-care professionals to be vigilant to the signs and symptoms of DRESS in patients who are prescribed azithromycin. These may include rash, fever, lymphadenopathy, haematological abnormalities and multi-organ involvement. Early and prompt discontinuation of the offending drug is important to achieve the best outcome in patients with DRESS.

Reference:
Product Safety Alerts, HSA, 30 September 2015 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.5, 2015: Risk of drug-induced hypersensitivity syndrome in Japan and No.6, 2014: Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS) in Canada)

Ceftriaxone

Risk of acute generalised exanthematous pustulosis

Japan. The MHLW and the PMDA have announced the revision of the package insert ceftriaxone to include risk of acute generalised exanthematous pustulosis.

Ceftriaxone is an antimicrobial used to treat infections such as: sepsis, pharyngitis/ laryngitis, tonsillitis, acute bronchitis, pneumonia, lung abscess and pyothorax by several strains.

The MHLW/PMDA stated that cases of acute generalised exanthematous pustulosis have been reported in patients treated with ceftriaxone sodium hydrate in Japan and in other countries. In addition, the company core datasheet (CCDS) has been updated.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the "Acute generalised exanthematous pustulosis" to the section of the "Clinically significant adverse reaction" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Clopidogrel

Long-term treatment does not change risk of death

USA. A US Food and Drug Administration (FDA) review has determined that long-term use of the blood-thinning drug clopidogrel (Plavix®) does not increase or decrease overall risk of death in patients with, or at risk of heart disease. The FDA evaluation of the Dual Antiplatelet Therapy (DAPT) trial and several other clinical trials also does not suggest that clopidogrel increases the risk of cancer or death from cancer. The FDA has been working with the manufacturers of clopidogrel to update the label to reflect the results of the mortality meta-analysis.

Clopidogrel is an antiplatelet medicine used to prevent blood clots in patients who have had a heart attack, stroke, or problems with the circulation in the arms and legs. It works by helping to keep the platelets in the blood from sticking together and forming clots that can occur with certain medical conditions.

In order to investigate the increased risk of death and cancer-related death reported with clopidogrel in the DAPT trial, the FDA examined the results of the DAPT trial and other large, long-term clinical trials of clopidogrel with data available on rates of death, death from cancer, or cancer reported as an adverse event.

The FDA performed meta-analyses of other long-term clinical trials to assess the effects of clopidogrel on death rates from all causes. The results indicate that long-term (12 months or longer) dual antiplatelet therapy with clopidogrel and aspirin do not appear to change the overall risk of death when compared to short-term (6 months or less) clopidogrel and aspirin, or aspirin alone. Also, there was no apparent increase in the risks of cancer-related deaths or cancer-related adverse events with long-term treatment.

The FDA has recommended that health-care professionals should consider the benefits and risks of available antiplatelet medicines before starting treatment.

Reference:
Drug Safety Communication, US FDA, 6 November 2015 (*www.fda.gov*)

Codeine

Suspension of use

Ethiopia. The Ethiopian Food, Medicine and Healthcare Administration and Control Authority (FMHACA) has suspended the use of codeine for all patients due to the risk of death and life threatening adverse effects.

The suspension is based on the US FDA reports of children who developed serious adverse effects after taking codeine for pain relief after tonsillectomy and/or adenoidectomy. These children had evidence of an inherited ability to convert codeine into morphine very rapidly.

Codeine is converted to morphine in the cytochrome P450 2D6 (CYP2D6). Some people have genetic background that makes this enzyme more active. These "ultra-rapid metabolizers" are more likely to have higher blood level of morphine after taking codeine. A study showed that Ethiopians are one of "ultra-rapid metabolizers", therefore Ethiopians are more susceptible for inadvertent adverse effects of codeine.

Even though the standard treatment guideline sets codeine as an alternative medicine for pain management

and dry cough, the FMHACA has decided to suspend the use of codeine for all patients in Ethiopia considering the genetic background.

Reference:
Communication from FMHACA to WHO, 25 November 2015

(See WHO Pharmaceuticals Newsletters No.3 and 4, 2015, No.5 and 4, 2013 and No.5, 2012 for related information)

Dipeptidyl peptidase-4 (DPP-4) Inhibitors

Risk of severe joint pain

Egypt. Egyptian Pharmaceutical Vigilance Center (EPVC) recommends the addition of a warning label to products containing dipeptidyl peptidase-4 (DPP-4) inhibitors, to include Joint Pain (Arthralgia).

DPP-4 inhibitors (e.g. sitagliptin, saxagliptin, linagliptin, and alogliptin) combined with diet and exercise are used to lower blood sugar in adults with type 2 diabetes. These medicines are available as single-ingredient products and in combination with other diabetes medicines such as metformin.

This recommendation was based on the US FDA warning of severe and disabling joint pain associated with the use of DPP-4 inhibitors.

Reference:
Newsletter, EPVC, Volume 6, Issue 11, November 2015

(See WHO Pharmaceuticals Newsletter No.5, 2015: DPP-4 inhibitors for Type 2 diabetes may cause severe joint pain in the United States of America)

Dutasteride

Risk of hepatic function disorder and jaundice

Japan. The MHLW and the PMDA have announced the revision of the package insert for dutasteride (Avolve® and Zagallo®) to include risk of hepatic function disorder and jaundice.

Dutasteride is used for benign prostatic hyperplasia and male pattern hair loss (androgenetic alopecia).

The MHLW/PMDA stated that cases of hepatic function disorder and jaundice have been reported in patients treated with dutasteride in Japan.

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

Hepatic function disorder, jaundice:
Hepatic function disorder or jaundice associated with increased levels of AST (GOT), ALT (GPT), bilirubin, etc. may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Galantamine

Risk of rhabdomyolysis

Japan. The MHLW and the PMDA have announced the revision of the package insert for galantamine (Reminyl®) to include risk of rhabdomyolysis.

Galantamine is used to suppress progression of dementia symptoms in patients with mild to moderate Alzheimer's type dementia.

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

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

Rhabdomyolysis:
Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feelings of weakness, increased creatine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Hepatitis C treatments (Viekira Pak® and Technivie®)

Risk of serious liver injury

USA. The US FDA has issued a warning that hepatitis C treatments, a fixed-dose combination of dasabuvir, ombitasvir, paritaprevir and ritonavir (Viekira Pak®) and a fixed-dose combination of ombitasvir, paritaprevir and ritonavir (Technivie®) can cause serious liver injury in patients with underlying advanced liver disease.

Cases of hepatic decompensation and liver failure in patients with underlying liver cirrhosis were identified in patients who were taking these medicines. Some of these events resulted in serious outcomes including, liver transplantation or death, mostly in patients taking Viekira Pak® with evidence of advanced cirrhosis even before starting treatment.

At least 26 worldwide cases submitted to FDA Adverse Event Reporting System were considered to be possibly or probably related to these medicines. Some of the cases occurred in patients for whom these medicines were contraindicated or not recommended.

The FDA requires manufacturers to include information about serious liver injury adverse events to the Contraindications, Warnings and Precautions, Postmarketing Experience and Hepatic Impairment sections of the Viekira Pak® and Technivie® labels.

Reference:
Drug Safety Communication, US FDA, 22 October 2015 (*www.fda.gov*)

Iodine-containing contrast agents for medical imaging

Rare cases of underactive thyroid in infants

USA. The FDA has approved changes to the labels of all iodinated contrast media (ICM) products to include information on cases of underactive thyroid in infants following the use of contrast media containing iodine (contrast dye).

Iodinated contrast media contain iodine and are given to patients to enhance the ability to see blood vessels and organs in medical images such as X-rays or computed tomography (CT) scans.

In all of the reported cases, the infants were either premature or had other serious underlying medical conditions. Based on available evidence the FDA believes that this rare occurrence is usually temporary and resolves without treatment or any lasting effects.

The FDA will continue to evaluate this issue. Manufacturers of ICM products are required to conduct a study to investigate this further.

The FDA has recommended that health-care professionals should continue to follow the label recommendations for ICM products and continue to use clinical judgment to determine if testing for underactive thyroid is necessary.

Reference:
Drug Safety Communication, US FDA, 17 November 2015 (*www.fda.gov*)

Magnesium oxide

Risk of hypermagnesaemia

Japan. The MHLW and the PMDA have requested the revision of the package insert for magnesium oxide and magnesium oxide-containing medicines to include risk of hypermagnesaemia.

Magnesium oxide is used for constipation, prevention of the formation of calcium oxalate urinary stone and as an antacid.

The MHLW/PMDA stated that cases of hypermagnesaemia have been reported in patients treated with magnesium oxide in Japan. Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of "Geriatrics" to the section of the "Careful administration" and addition of precautions regarding hypermagnesaemia to the "Use of geriatrics" section in the package insert.

The MHLW/PMDA also recommended the addition of the following precaution to the section of the "Important precaution" in the package insert.

- Use of the product should be kept to a minimum.
- Patients should be instructed to seek medical attention if they experience any symptoms, such as vomiting, bradycardia, muscular weakness, and somnolence.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Mirabegron

Risk of severe hypertension, associated cerebrovascular and cardiac events

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that mirabegron is now contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg, or both). The MHRA recommends blood pressure should be measured before starting treatment, and regularly during treatment, especially in patients with hypertension.

Mirabegron (Betmiga®) is a beta 3-adrenoceptor agonist used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome.

This follows a review of the latest safety data in the EU.

Mirabegron is known to increase blood pressure. Cases of severe hypertension have been reported, which include hypertensive crisis associated with reports of cerebrovascular and cardiac events (mainly transient ischaemia attack or stroke), some with a clear temporal relation to mirabegron use.

Data are limited regarding use of mirabegron in patients with stage 2 hypertension (i.e. systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg) and it should therefore be used with caution in this group.

Reference:
Drug Safety Update, MHRA, Volume 9, issue 3: 1, October 2015 (*www.gov.uk/mhra*)

Roxithromycin

Risk of QT prolongation, ventricular tachycardia (including torsades de pointes) and pseudomembranous colitis

Japan. MHLW and the PMDA have announced the revision of the package insert for roxithromycin (Rulid®) to include risk of QT prolongation, ventricular tachycardia (including torsades de pointes) and pseudomembranous colitis.

Ceftriaxone is an antimicrobial used for treatment of superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma by strains of genus *Staphylococcus*, genus *Streptococcus*, *Pneumococcus*, *Moraxella (Branhamella) catarrhalis*, *Propionibacterium acnes*, and *Mycoplasma pneumoniae*.

The MHLW/PMDA stated that cases of pseudomembranous colitis, QT prolongation and ventricular tachycardia (including torsades de pointes) have been reported in patients treated with roxithromycin in Japan and in other countries. In addition, the company core datasheet (CCDS) has been updated.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of "QT prolongation and ventricular tachycardia (including torsades de pointes)" and "Pseudomembranous colitis" to the section of the "Clinically significant adverse reaction" in the package insert.

The MHLW/PMDA also recommended the addition of the "Patients with risk of prolonged QT" to the section of the "Careful administration" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 20 October 2015 (*www.pmda.go.jp/english/*)

Sodium glucose co-transporter 2 (SGLT2) inhibitors

1. Risk of acute kidney injury

Canada. Health Canada is working with manufacturers on updating the Canadian prescribing information for canagliflozin (Invokana®) and dapagliflozin (Forxiga®) to strengthen the warning related to the risk of kidney injury. This reflects conclusions drawn from a safety review conducted by Health Canada.

Canagliflozin and dapagliflozin are SGLT2 inhibitors, and can be used as single agents with diet and exercise or with other products to decrease blood sugar levels in adults with type 2 diabetes.

The review was triggered following new post market safety information received from the manufacturer of canagliflozin. Reports of serious acute kidney injury, acute renal failure and renal failure (severe renal impairment) were investigated. These kidney problems occur when the kidneys suddenly become unable to filter waste products from the blood.

At the time of the review, Health Canada had received two reports of acute kidney injury in canagliflozin users.

Additional international reports of kidney injury associated with the use of either canagliflozin or dapagliflozin were identified. In the review, the evidence indicated a link between events of acute kidney injury and the use of these SGLT2 inhibitors.

A review of the scientific literature linking canagliflozin or dapagliflozin to acute kidney injury provided limited evidence on this topic, although their renal effects were noted as a potential problem.

In the Health Canada's safety review, it was concluded that the evidence supported the existence of a link between the use of SGLT2 inhibitors and the risk of acute kidney injury.

(Also see information from TGA on pages 13-14)

Reference:
Summary Safety Review, Health Canada, 16 October 2015 (*www.hc-sc.gc.ca*)

2. Interim update on risk of serious ketoacidosis

Singapore. The HSA is reviewing the current available information and seeking expert opinion from local clinicians on risk of serious ketoacidosis to determine if there is a need for further regulatory action. Licence holders have issued 'Dear Health-Care Professional Letters' (DHCPLs) to warn of serious and sometimes life-

threatening cases of diabetic ketoacidosis (DKA) during treatment with SGLT2 inhibitors.

In Singapore, SGLT2 inhibitors, namely canagliflozin (Invokana®), dapagliflozin (Forxiga®) and empagliflozin (Jardiance®), are indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus, as monotherapy, add-on combination therapy with other glucose-lowering agents including insulin, and/or initial combination therapy with metformin.

In Singapore, the HSA has monitored the safety profile of the SGLT2 inhibitors following their registration. As of August 2015, HSA has received three local reports of serious DKA associated with SGLT2 inhibitors.

HSA will provide an update on the outcome of its review when completed.

Reference:
Product Safety Alerts, HSA, 30 September 2015 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.5, 2015: Risk of ketoacidosis and sepsis in Japan and No.4, 2015: Risk of diabetic ketoacidosis in the United Kingdom)

Strontium

Risk of heart and circulatory side effects

Canada. Health Canada recommends that labels of all products containing strontium (>4mg elemental/day) should be updated to include advice against the use of strontium products in patients who have, or are at high risk for, heart disease, circulatory problems, or blood clots, as a precautionary measure. This risk currently remains uncertain.

Strontium is a naturally occurring mineral classified as a natural health product in Canada. It is available in different salt forms over the counter and is used to support bone health.

Following the precautionary advice by the EMA, for use of strontium ranelate at the prescription dose of 680mg per day, Health Canada conducted a safety review.

At the time of the review, there were no reports of heart or circulatory adverse effects associated with strontium salts (citrate, lactate, and gluconate).

Health Canada's review did not find information available on cardiovascular risk with the strontium ranelate form at doses less than 680 mg/day, or with other non-ranelate forms of strontium at any dose. Strontium plays an active role in the body, and the salt components (ranelate, lactate, citrate, and gluconate) help with absorption of the strontium. There is not enough information available to compare absorption of different strontium salts and/or the risk of heart or circulatory adverse effects with low dose strontium.

Health Canada will continue to monitor safety information involving all salt forms of strontium and will take additional actions, if warranted.

Reference:
Summary Safety Review, Health Canada, 22 October 2015 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.1, 2 and 4, 2014, No.3 and 4, 2013 for related information from other countries and regions)

Testosterone

Further investigations are necessary: risk of cardiovascular events

Singapore. The HSA has informed health-care professionals of the possible risk of cardiovascular (CV) events associated with use of testosterone-containing products. The information is based on changes in product labels and safety reviews conducted in Canada, Europe, New Zealand and the United States. Testosterone is a steroid hormone involved in androgenic and anabolic processes. It is mainly indicated for replacement therapy in males with primary and secondary hypogonadal disorders. Some of the testosterone-containing products are also indicated for osteoporosis caused by androgen deficiency, or for masculinisation in female to male transsexuals.

The HSA has received one local ADR report of myocardial infarction (MI) associated with the use of testosterone. No local ADR reports of venous thromboembolism associated with the use of testosterone have been received.

HSA has also consulted local experts (urologists and cardiologists) regarding the potential risk of CV events with testosterone. Some of the experts were of the opinion that methodological limitations and biases may have impacted results from the observational studies conducted. In general, evidence of the risk of CV events associated with use of testosterone remains weak and further investigations are needed.

HSA is working with companies to ensure that the warnings and precautions relating to CV events are adequately highlighted across the package inserts of testosterone-containing products.

Reference:
Product Safety Alerts, HSA, 30 September 2015 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.2, 2015 and No.2, 2014 for related information from the United States of America)

Ustekinumab

Risk of serious skin conditions

Australia. The Therapeutic Goods Administration (TGA) has announced that the Product Information for ustekinumab (Stelara®) has been updated to include a precaution regarding serious skin conditions.

Ustekinumab is a human monoclonal antibody that is indicated for the treatment of:

- moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy;
- signs and symptoms of active psoriatic arthritis (used alone or in combination with methotrexate) in adults where response to previous non-biological disease-modifying antirheumatic drug therapy has been inadequate.

This update follows an investigation conducted by the TGA, that examined the association of serious skin conditions, namely exfoliative dermatitis (also known as erythroderma) and erythrodermic psoriasis with ustekinumab treatment. This was also investigated by other regulators such as the EMA and Health Canada.

Up until 20 May 2015, the TGA has received one report of erythrodermic psoriasis and no reports of exfoliative dermatitis suspected to be associated to ustekinumab use.

The TGA's investigation of this safety concern found that there was insufficient information at this point in time to establish a definite causal relationship between exfoliative dermatitis or erythrodermic psoriasis and treatment with ustekinumab. However, given the seriousness of these adverse events and their potential reversibility after cessation of the inciting medicine, the TGA considered that health-care professionals should be made aware of this possible association.

The updated ustekinumab Product Information states that patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 5, October 2015 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.4, 2015: Risk of rare but serious skin reactions in Singapore, No.2, 2015: Risk of exfoliative dermatitis in the United Kingdome and No.1, 2015: Serious skin disorders (Exfoliative dermatitis and erythrodermic psoriasis) in Canada)

Vemurafenib

Risk of pancreatitis

Singapore. The HSA has updated the local package insert (PI) to include information on patient monitoring and detection of pancreatitis.

Vemurafenib (Zelboraf®) is a low molecular weight inhibitor of BRAF serine-threonine kinase. (BRAF is a human gene)

This update follows updates to product labels by the EMA and Health Canada to list the risk of pancreatitis as an adverse reaction. This action was based on separate reviews conducted by the market authorization holder and Health Canada.

To date, HSA has not received any adverse reaction reports of pancreatitis associated with vemurafenib.

The HSA has advised health-care professionals to remain vigilant to the possible signs and symptoms of pancreatitis in patients who are prescribed vemurafenib, and to consider the possibility of pancreatitis in the event of unexplained abdominal pain.

Reference:
Product Safety Alerts, HSA, 30 September 2015 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.2, 2015: Risk of pancreatitis in Canada and No.3, 2014: Association of vemurafenib use with drug induced liver injury (DILI) in Canada)

Crizotinib

Risk of cardiac failure

The United Kingdom. The MHRA has announced that severe, sometimes fatal cases of cardiac failure in patients treated with crizotinib (Xalkori®) have been reported.

Crizotinib is licensed to treat adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer.

A review by European medicines regulators of data from clinical trials and reports from clinical practice has concluded that this adverse effect is common (i.e. occurs in between 1 in 10 and 1 in 100 patients who take crizotinib).

Up until 25 February 2015 forty cases of cardiac failure have been reported globally. In some of these cases, symptoms of cardiac failure resolved on stopping crizotinib (positive de-challenge), and symptoms reoccurred when it was reintroduced (positive re-challenge).

The MHRA has provided the following advice for health-care professionals:

- Monitor all patients for signs and symptoms of heart failure (including dyspnoea, oedema, or rapid weight gain from fluid retention).
- Consider reducing the dose, or interrupting or stopping treatment if symptoms of heart failure occur.

Reference:
Drug Safety Update, MHRA, Volume 9, issue 4: 1, November 2015 (*www.gov.uk/mhra*)

(See WHO Pharmaceuticals Newsletter No.4, 2015: Risk of cardiac failure in Japan)

Entacapone

No clear evidence: increased cardiovascular risks

USA. The US FDA has found no clear evidence of an increased risk of heart attacks, stroke, or other cardiovascular events associated with the use of entacapone. As a result, information in product labels for entacapone (Comtan®) and a combination of entacapone, carbidopa, and levodopa (Stalevo®) will remain the same.

Entacapone-containing products are used to treat symptoms of Parkinson's disease, such as muscle stiffness, tremors, spasms, and poor muscle control.

The FDA issued an alert to patients and health-care professionals warning of a possible increased risk of cardiovascular events and death with entacapone treatment in August 2010. This alert was triggered from observations in a clinical trial, Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) and in a meta-analysis that combined the cardiovascular-related findings from 15 clinical trials comparing a combination of entacapone, carbidopa, and levodopa to carbidopa/levodopa. The FDA was concerned that the entacapone was responsible for these cardiovascular risks because the comparison drugs do not show evidence of an increased risk of cardiovascular events.

Manufacturers were requested by the FDA to conduct a study to investigate the potential for cardiovascular risk with entacapone use. After examining results from the requested study and all available evidence the FDA concluded that there is no evidence of an increased risk of cardiovascular adverse events with entacapone. The original meta-analysis (STRIDE-PD), which was not designed to assess cardiovascular risks does not represent a true increase in risk due to entacapone and results were likely due to chance.

Reference:
Drug Safety Communication, US FDA, 26 October 2015 (*www.fda.gov*)

Infliximab

Limited evidence: risk of cancer (lymphoma, hepatosplenic T-Cell lymphoma, and leukaemia)

Canada. Health Canada has conducted a safety review to evaluate the risk of developing three types of cancers (lymphoma, hepatosplenic T-cell lymphoma, and leukaemia) associated with the use of infliximab (Remicade®) when used to treat autoimmune diseases of the skin (i.e. psoriasis) in adults. Investigators did not find evidence of an association between lymphoma, hepatosplenic T-cell lymphoma, or leukaemia, and the use of infliximab to treat psoriasis.

Infliximab is a unique immune system protein (monoclonal antibody), which works by blocking a naturally occurring chemical TNF-α (Tumour Necrosis Factor-alpha). TNF-α causes inflammation which can occur due to the body's own defence system attacking the skin, joints, intestines, or stomach (autoimmune disease).

At the time of the review, the Canada Vigilance Program received 77 reports of lymphoma, five reports of a type of lymphoma (Non-Hodgkin's Lymphoma) that also included cases of

hepatosplenic T-cell lymphoma, and eight reports of leukaemia associated with the use of infliximab to treat autoimmune diseases. Health Canada's analysis of the reports found no association between these cancers with infliximab use for psoriasis.

A review of international data from the WHO's global database retrieved 413 reports of lymphoma, 73 reports of Non-Hodgkin's Lymphoma that included cases of hepatosplenic T-cell lymphoma, and 50 reports of leukaemia associated with infliximab treatment of autoimmune diseases. Health Canada's evaluation of these reports and a review of the scientific and medical literature did not indicate an association between these cancers and infliximab treatment particularly when used for psoriasis or psoriatic arthritis. However, the current safety review of reports is limited by several factors, including an increased risk of cancer in patients having certain underlying diseases or having taken, or currently taking other medications.

Health Canada will continue to monitor side effect information involving infliximab to identify and assess potential harms.

Reference:
Summary Safety Review, Health Canada, 29 September 2015 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletter No.5, 2015: Risk of non-melanoma skin cancers, particularly in psoriasis patients in Australia)

Newer rotavirus vaccines (Rotarix® and RotaTeq®)

Risk of intussusception

Singapore. The HSA has advised health-care professionals to be vigilant to symptoms that are indicative of intussusception (e.g. vomiting, palpable abdominal mass, abdominal pain or diarrhoea) following rotavirus vaccination. The HSA requests health-care professionals to inform parents or caregivers to seek treatment early if the child experiences abdominal pain or bloating, often accompanied with persistent or bouts of crying, vomiting, blood in the stool or change in bowel movements at any time after each dose of the vaccine.

Safety concerns of intussusception with rotavirus immunization were first announced in 1999 with the RotaShield® preparation. This led to its withdrawal from the market. The risk of intussusception was estimated at 10-20 cases per 100,000 Rotashield® recipients. Consequently, two newer oral rotavirus vaccines, the monovalent (RV1) Rotarix® and the pentavalent (RV5) RotaTeq®, underwent large-scale clinical trials to ensure that there was no elevated risk of intussusception prior to market approval in many countries (including the United States, Europe and Singapore).

However, recent post-licensure studies in some settings, namely Latin America (Mexico and Brazil), Australia and the United States, have estimated the attributable risk of intussusception after rotavirus vaccination to be approximately 1.5 to 6 per 100,000 infants vaccinated.

A study conducted in Asian immunized infants with intussusception showed similar incidence rates. To date, the HSA has received 16 reports of intussusception suspected to be associated with this vaccine, eleven of which occurred within eight days of vaccination. Of these 11 cases, eight cases were reported after the first dose and three cases after the second dose. The remaining five cases occurred beyond the 21-day risk period identified with rotavirus vaccination. There were also three reports of intussusception associated with RV5, which is less commonly used in Singapore. All the patients had either recovered or were recovering at the time of reporting.

Reference:
Product Safety Alerts, HSA, 30 September 2015 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.6, 2013: Risk of intussusception in Australia)

Sodium glucose co-transporter 2 (SGLT2) inhibitors

Risk of diabetic ketoacidosis

Australia. The TGA has announced that serious cases of diabetic ketoacidosis (DKA) have been reported in patients being treated with inhibitors of SGLT2. In some of these cases, the presentation of diabetic ketoacidosis was atypical.

SGLT2 inhibitors, such as canagliflozin, dapagliflozin and empagliflozin, belong to a class of medicine that improves glycaemic control in patients with type 2 diabetes mellitus. These medicines have the following indications:

- as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is contraindicated, or not tolerated;
- as combination therapy in patients with type 2 diabetes with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

This announcement follows a statement published on the TGA website on 13 August 2015, with additional information for health professionals.

The number of reports of DKA associated with SGLT2 inhibitors is low. However, DKA is a serious, potentially life-threatening complication and there is a risk of delay in diagnosis and treatment as a result of its presentation being atypical in some cases.

In some of the reported cases, just before or at the same time as the DKA occurred, patients experienced acute illness (such as, urinary tract infection, urosepsis, gastroenteritis, influenza, trauma or surgery), reduced caloric or fluid intake, and/or reduced insulin dose.

The underlying mechanism for SGLT2 inhibitor-associated DKA has not been established.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 5, Ocotber 2015 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.5, 2015: Risk of ketoacidosis and sepsis in Japan and No.4, 2015: Risk of diabetic ketoacidosis in the United Kingdom)

Sodium polystyrene sulfonate

Potential risk of drug interaction

USA. The US FDA requests that the manufacturer of sodium polystyrene sulfonate (Kayexalate®) conduct studies to investigate its potential to bind to other medications administered by mouth. This could cause drug interactions, and decrease the effects of the medication.

Sodium polystyrene sulfonate is used to treat hyperkalaemia, a serious condition in which the amount of potassium in the blood is too high. It works by binding potassium in the large intestine so it can be removed from the body.

To reduce this potential risk, prescribers and patients should consider separating sodium polystyrene sulfonate dosing from other medications taken by mouth by at least 6 hours. This includes both prescription medications, such as antibiotics, blood pressure lowering agents and blood thinners, and those purchased over-the-counter without a prescription, such as antacids and laxatives. Health-care professionals should monitor blood levels or clinical response to the other medications when appropriate.

If the studies conducted by the sodium polystyrene sulfonate manufacturer confirm significant interactions with other medications, the FDA will require all manufacturers of sodium polystyrene sulfonate products to update product information labels to include this information.

Reference:
Drug Safety Communication, US FDA, 22 October 2015 (*www.fda.gov*)

Tramadol

Risk of slowed or difficult breathing in children

USA. The US FDA has been investigating the use of tramadol in children aged 17 years and younger, for risk of slowed or difficult breathing. This risk may be increased in children treated with tramadol for pain after surgery to remove their tonsils and/or adenoids.

Tramadol is not approved for use in children in USA, however, data show it is being used "off-label" in the paediatric population.

There is a genetic variation in the metabolism of tramadol, and some individuals convert tramadol to the active form of the opioid, called O-desmethyltramadol faster than usual. This can lead to higher blood levels, resulting in breathing difficulties that may lead to death.

The FDA has recommended that parents and caregivers of children taking tramadol who notice any signs of slow or shallow breathing, difficult or noisy breathing, confusion, or unusual sleepiness should stop tramadol and seek medical attention immediately by taking their child to the emergency room or calling the ambulance.

The FDA is evaluating all available information and will communicate final conclusions and recommendations to the public when the review is complete.

Reference:
Drug Safety Communication, US FDA, 21 September 2015 (*www.fda.gov*)

(See WHO Pharmaceuticals Newsletter No.5, 2015: Tramadol oral drops not for children under the age of 12 years in Australia)

Vemurafenib

Risk of potentiation of radiation toxicity

The United Kingdom. The MHRA has warned prescribers of the risk of radiation toxicity with vemurafenib (Zelboraf®) when given before, during, or after radiotherapy.

Vemurafenib is indicated as monotherapy for the treatment of adults with BRAF V600 mutation-positive unresectable or metastatic melanoma.

A review of global data by EU medicines regulators concluded that vemurafenib can potentiate radiation toxicity. In phase III and phase IV clinical

trials, approximately 1 in 20 patients who received vemurafenib had a radiation-related injury, (either radiation recall or radiation sensitisation).

These cases occurred in patients who received radiation before, during, or after treatment with vemurafenib. Most cases were confined to the skin, but some involved visceral organs and resulted in a fatal outcome (including one case of radiation necrosis of the liver and two cases of radiation oesophagitis). Most patients had received doses of radiation ≥2 Gy/day.

Up until October 2015, the MHRA has received two reports of radiation injury and related events in patients receiving vemurafenib.

The MHRA has advised health-care professionals that vemurafenib should be used with caution when given before, during, or after radiotherapy and prescribers should be aware of the risk of potentiation of radiation toxicity.

Reference:

Drug Safety Update, MHRA, Volume 9, issue 4: 2, November 2015 (*www.gov.uk/mhra*)

A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®. The database contains over 10 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase® is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase® data is performed in accordance with UMC's current routine signal detection process.
More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 31). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC's vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information, visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

Atomoxetine and neutropenia in paediatric patients

Dr Ian Boyd, Australia

Summary

Atomoxetine is a relatively potent inhibitor of the presynaptic noradrenaline transporter, a moderate inhibitor of 5HT uptake, and a weak inhibitor of dopamine uptake with minimal affinity for the other noradrenergic receptors. It is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults. After the elimination of duplicates, there are currently (4 February 2015) 25 individual case safety reports (ICSRs) in the WHO Global ICSR database, VigiBase® of neutropenia in association with atomoxetine in children and adolescents. The reports are from Canada, Finland, Germany, Ireland, Switzerland, the United Kingdom and the United States. Atomoxetine was the only drug suspected in 20 of the 25 cases. The outcome of the neutropenia was indicated in 15 reports. The patients were reported as recovered or recovering in 10 cases and not recovered in the remaining five cases. In the cases where recovery was reported, the drug was withdrawn in seven cases, the dose increased in one case and the fate of the drug was unknown in the remaining two cases. Time to onset showed a clustering around 14-27 days.

Case reports in VigiBase® suggest that there is a possible signal for the association of atomoxetine and neutropenia. The fact there was a positive dechallenge in seven of the 10 reports where recovery was documented is suggestive of a drug-induced effect. This is supported by the time to onset of 14-27 days which is consistent with drug-induced neutropenia. However, the possible association of atomoxetine with neutropenia appears predominantly in the adolescent and paediatric population.

Introduction

Atomoxetine is a relatively potent inhibitor of the presynaptic noradrenaline transporter, a moderate inhibitor of 5HT uptake, and a weak inhibitor of dopamine uptake with minimal affinity for the other noradrenergic receptors. Atomoxetine has moderate affinity for 5HT2 and GABAA receptors but poor affinity for most other receptors. It is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults. The most frequent adverse reactions reported during clinical trials of atomoxetine in children and adolescents including gastrointestinal reactions, increased blood pressure and heart rate, decreased appetite, decreased weight and skin reactions. The product information does not refer to blood disorders.[1]

Neutropenia is a high level term in WHO-ART with preferred terms consisting of neutropenia, granulocytopoenia and leukopenia.

The preferred term, neutropenia, which is the subject of this signal, is defined as a decrease to less than 1.5×10^9/L of segmented polymorphonuclear and band cells. Neutropenia is considered as "severe" below 0.5×10^9/L.[2]

Reports in VigiBase®

As of 4 February 2015, there are a total of 35 individual case safety reports (ICSRs) of neutropenia in association with atomoxetine in the

WHO Global ICSR database, VigiBase®. Out of these reports, after the elimination of duplicates, there are 25 cases of neutropenia in children and adolescents up to 17 years of age (Table 1). Of the remaining reports, ages range from 22 years to 65 years in seven cases and the remaining case has reported age unknown. The reports from children and adolescents were submitted from the United Kingdom (9 reports), United States (7), Finland (4), Canada (2), Germany, Ireland and Switzerland (1 each). The patients ranged in age from 6 to 17 years with a median of 12 years. There were 23 males and 2 females.

Atomoxetine was the only drug suspected in 20 of the 25 cases. There were other drugs also suspected in the remaining five cases and they included drugs for treatment of psychotic disorders (olanzapine, risperidone) in two cases, an antidepressant (fluoxetine) in one case, an anticonvulsant (valproic acid) in one case and another drug for the treatment of ADHD (methylphenidate) in the remaining case. Three of these drugs, olanzapine, risperidone and valproic acid, refer to neutropenia in their product information and these drugs may each be a possible cause in the three cases where these drugs are suspect (Cases 5, 7 and 24). Concomitant drugs were reported in 10 of the 25 cases and showed a similar trend to that observed with the co-suspected drugs with use of antipsychotic, anticonvulsant, and antidepressant drugs along with the use of other treatments for ADHD.

Time to onset was reported in 11 of the reports and ranged from 14 days to 10 months. The median time was 50 days and there was a clustering of five cases between 14 and 27 days.

The outcome of the neutropenia was indicated in 15 reports. The patients were reported as recovered or recovering in 10 cases and not recovered in the remaining five cases. In the cases where recovery was reported, the drug was withdrawn in seven cases, the dose was increased in one case and the fate of the drug was unknown in the remaining two cases. In the five cases where the patient had not recovered, the drug had been discontinued in four cases and the fate of the drug was unknown in the remaining case.

The indication for use was stated in 15 reports and was ADHD in all 15 cases. Dosage ranged from 18 mg to 100 mg including some cases in which the dose was escalated.

Other reactions were reported in 19 of the 25 reports. Other blood disorders were reported in 15 of these cases and these were mostly other white cell disorders, particularly leucopoenia, in 14 cases although thrombocytopenia was reported in five cases and red cell disorders in three cases. Hepatic reactions were reported in five cases and weight decrease was reported in four cases.

Literature and Labelling

The product literature does not refer to neutropenia nor does it mention other blood disorders.[1] No reports of neutropenia in association with atomoxetine could be found in the literature.

Discussion

Case reports in VigiBase® suggest that there is a possible signal for the association of atomoxetine and neutropenia in children and adolescents. Atomoxetine was the only drug suspected in 20 of the 25 cases. In three of the remaining five cases, there were co-suspected drugs for which neutropenia is labelled.

Time to onset was reported in 11 of the reports and ranged from 14 days to 10 months. The median time was 50 days and there was a clustering of five cases between 14 and 27 days. This is consistent with drug- induced neutropenia.

The outcome of the neutropenia was indicated in 15 reports. The patients were reported as recovered or recovering in 10 cases and not recovered in the remaining five cases. In the cases where recovery was reported, the drug was withdrawn in seven cases, the dose was increased in one case and the fate of the drug was unknown in the remaining two cases. In the five cases where the patient had not recovered, the drug had been discontinued in four cases and the fate of the drug was unknown in the remaining case. The seven cases with a positive dechallenge is supportive of a drug-induced effect. The reports without recovery may simply represent cases that have been reported before the reaction had resolved. Drug-induced neutropenia usually resolves after 10 days.[3]

The possible association of atomoxetine with neutropenia appears predominantly in the adolescent and paediatric population. After the elimination of duplicates, there is a total of 33 reports of neutropenia in association with atomoxetine in the total population. Twenty-five of these reports were reported in the adolescent and paediatric age groups which represents 75.8% of all the reports. While it may be considered that atomoxetine is used preferentially in the younger age groups, overall reporting in VigiBase® indicates that of the 16,504 reports submitted, the age group from 2 to 17 years represents 60% of the total reports.

Table 1. Case overview of reports from children and adolescents in VigiBase® of neutropenia in association with atomoxetine

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reactions (WHO-ART preferred terms)	Outcome
1*	14/M	Sertraline (C)	Neutropenia, abdominal pain, bone marrow aplasia, fatigue, hepatitis, thrombocytopenia	Recovering
2	12/M	Pipamperone (C)	Neutropenia, anaemia, leukopenia, lymphocytes atypical	Unknown
3	12/M	Fluoxetine (S)	Neutropenia	Unknown
4	11/M	None	Neutropenia, alopecia, weight decrease	Recovered
5	14/M	Risperidone (S)	Neutropenia	Unknown
6*	14/F	Sertraline (C)	Neutropenia, hepatitis cholestatic, hepatic fibrosis, hepatitis viral, thrombocytopenia, educational problem***	Recovered
7	13/M	Olanzapine (S) Aripiprazole, escitalopram, guaifenesin (C)	Neutropenia, alkaline phosphatase increased, ALT increased, AST increased, lymphocytosis, monocytosis, blood calcium abnormal#, protein total abnormal***	Unknown
8	17/M	Valproic acid, sertraline (C)	Neutropenia, lymphocytosis	Unknown
9	9/M	None	Neutropenia, abdominal pain, flatulence, gastroenteritis, haematemesis, hypotension, intestinal obstruction, leukopenia, peripheral ischaemia, systemic inflammatory response syndrome, tachycardia, thrombocytopenia	Recovered
10	11/M	Methylphenidate (S)	Neutropenia, leukopenia	Unknown
11	16/M	None	Neutropenia, leukopenia	Recovering
12	10/M	None	Neutropenia, leukopenia, thrombocytopenia	Not recovered
13	11/M	None	Neutropenia, abdominal pain, agitation, anorexia, fatigue, hallucination, weight decrease	Recovered
14	12/M	Risperidone (C)	Neutropenia, leukopenia, weight decrease	Not recovered
15	12/F	None	Neutropenia, leukopenia	Recovered
16	11/M	None	Neutropenia, leukopenia	Recovered
17**	11/M	Salbutamol (C)	Neutropenia	Recovering
18	6/M	None	Neutropenia, leukopenia, rash	Recovered
19	7/M	Methylphenidate (C)	Neutropenia, peripheral ischaemia	Unknown
20	10/M	None	Neutropenia	Unknown
21**	11/M	Methylphenidate, salbutamol (C)	Neutropenia	Not recovered
22	11/M	None	Neutropenia, alkaline phosphatase increased, hypotension postural, urticaria	Recovered
23	15/M	Methylphenidate (C)	Neutropenia	Not recovered
24	14/M	Valproic acid (S) Valproic acid (C)	Neutropenia, bilirubinaemia, epilepsy, lymphopenia, thrombocytopenia, weight decrease	Not recovered
25	12/M	Melatonin, methylphenidate (C)	Neutropenia	Not recovered
26	15/M	None	Neutropenia, leukopenia	Unknown
27	10/F	None	Neutropenia, ALT increased, anaemia, AST increased, blood disorder, Epstein-Barr virus, hepatic function abnormal, hepatomegaly, monocytopenia, thrombocytopenia	Unknown

**Cases 1 and 6 are duplicates*
***Cases 17 and 21 are duplicates*
****MedDRA terms*

Conclusion

In summary, there are 25 reports from children and adolescents associating neutropenia with the use of atomoxetine. Atomoxetine was the only drug suspected in 20 of the 25 cases. The fact there was a positive dechallenge in seven of the 10 reports where recovery was documented is suggestive of a drug-induced effect. The clustering of five cases with an onset between 14 and 27 days is consistent with drug-induced neutropenia. However, the possible association of atomoxetine with neutropenia appears predominantly in the adolescent and paediatric population.

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Response from Eli Lilly & Company

Thank you for the opportunity to provide our comments on the possible signal that has been generated from the UMC's VigiBase® safety database and the thorough assessment conducted by Dr Boyd. Eli Lilly & Company (Lilly) routinely queries reported adverse events in Lilly's internal safety database and the FDA Adverse Event Reporting System for early signs of potential adverse drug reactions in patients treated with Lilly drugs. Lilly recognizes the importance of early signal detection and also acknowledges that database queries are only one method that can be employed. Additionally, Lilly's review of the reported adverse events involves medical assessment of the narratives where information provided and not captured in the standard fields often helps to refine the assessment.

Consistent with the UMC, Lilly recognizes that signals are uncertain and preliminary in nature (UMC, Signals selected by UMC and the clinical review panel: How the process works). This is because, for any given adverse event report considered in generating a signal, there is no certainty that the adverse event was caused by the suspected drug. Rather, the adverse event could have resulted from the underlying condition being treated, a comorbid condition, a concomitant medication, or may simply be the result of chance.

Lilly has completed two reviews of blood dyscrasias including neutropenia which involved assessment of individual case narratives, as well as all available information from other data sources. The first review was conducted in 2006 and covered the period from 26 November 2002 to 26 November 2005, with a second review completed in 2014. As both reviews revealed similar findings and conclusions, we are providing the high level results of the second review as an illustrative example of the evaluations undertaken. Of note, the results of the last review were submitted to the EU Regulatory Agencies in 2014 and no further questions were raised or further actions deemed necessary at that time.

In the second assessment, cases reported between 26 May 2008 and 26 May 2013 and coded to the MedDRA preferred term "neutropenia" were reviewed. Time to onset ranged from approximately 2 months to 11 months, and did not reflect a pattern indicative of a treatment-emergent trend. Thirteen neutropenia cases were identified, but 7 (54%) of those cases either did not provide adequate information to assess the event or presented medical history, historical, or concurrent use of other medication that may provide an alternative explanation for the onset of neutropenia, for example, medical conditions that reduce cell line counts such as human immunodeficiency virus, a family history of autoimmune disorders, or use of medications such as risperidone or valproate. Of the remaining 6 cases, which involved adolescent patients, 5 described neutropenia and 1 neutropenia/leukopenia. Of the 6 patients, 4 patients discontinued atomoxetine treatment while 2 patients continued atomoxetine. Although in 3 of the 4 patients who discontinued atomoxetine the event resolved, these cases did not provide sufficient information, for example, medical history, concomitant medication use, and/or the patient's baseline laboratory values to permit adequate medical assessment. Importantly, without baseline measurements, it is impossible to know whether the condition existed before the patients began taking atomoxetine.

Based on the evaluations summarised above, Lilly has concluded from its previous reviews that there is not sufficient evidence to support a causal association or increased risk between atomoxetine treatment and neutropenia in the treated population. Available information would indicate that the events reported are either incidental findings or may possibly be related to other causes including pre-existing conditions or concomitant medications, as mentioned above, though more information in these cases is needed. In addition, as Dr Boyd mentioned in his article, no reports of neutropenia in association with atomoxetine could be found in the literature. Case reports and other sources of information that include suspected neutropenia adverse events in atomoxetine-treated patients will be reviewed by Lilly and continue to be monitored through routine pharmacovigilance.

Deferasirox and pancreatitis in paediatric patients

Dr Ian Boyd, Australia

Summary

Deferasirox is an orally active chelator that is highly selective for iron (III). Deferasirox promotes excretion of iron, primarily in the faeces. It is indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major aged 6 years and older and for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate. There are currently (March 2015) 14 individual case safety reports (ICSRs) in the WHO Global ICSR Database, VigiBase® of pancreatitis in children and adolescents in association with deferasirox. The reports are from France, Germany, South Africa, the United Kingdom and the United States. Deferasirox was the only drug suspected in 11 of the 14 cases. The outcome of the pancreatitis was indicated in 10 reports. The patients were reported as recovered or recovering in nine cases and the outcome was fatal in the remaining case. In the cases where recovery was reported, the drug was withdrawn in six cases and continued in the other three cases.

Case reports in VigiBase® suggest that there is a signal for the association of deferasirox and pancreatitis. Time to onset is consistent with a drug-induced effect and although it does appear to be longer than usual in some cases, this is consistent with other reports of drug-induced pancreatitis. The response to dechallenge is supportive of a drug-induced effect. However, the possible association of deferasirox with pancreatitis appears predominantly in the paediatric population.

Introduction

Deferasirox is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the faeces. It is indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major aged 6 years and older and for the treatment of chronic iron overload due to blood trans- fusions when deferoxamine therapy is contraindicated or inadequate. The most frequent reactions reported during chronic treatment with deferasirox in adult and paediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhoea or abdominal pain), skin rash in about 7% of patients and increases in serum creatinine in about 36% of patients. Gallstones and related biliary disorders were reported in about 2% of patients. Serious acute pancreatitis may potentially occur as a complication of gallstones (and related biliary disorders).[1]

Acute pancreatitis is an inflammatory disease of the pancreas, characterized by abdominal pain, frequently severe and of sudden onset, and almost always accompanied by increased pancreatic enzymes in the blood and urine. Although in about 80% of cases the disease is mild, severe attacks may lead to shock with renal and pulmonary insufficiency, which may prove fatal. In non-fatal cases, clinical, morphological and functional recovery usually occurs. Drug-induced pancreatitis is usually an acute condition. The clinically suspected diagnosis of acute pancreatitis should always be confirmed by biochemical investigations. Chronic pancreatitis is in most cases characterized by recurrent or persisting abdominal pain. The diagnosis cannot be satisfactorily established unless there is evidence of persistent morphological change or pancreatic insufficiency, manifested by, for example, steatorrhoea or diabetes mellitus. Pancreatic enzymes in blood or urine are usually increased during attacks of acute pain, but usually to a less extent than in acute pancreatitis.[2]

Gallstones are the leading cause of acute pancreatitis (30-60% in most series). Alcohol is the second most common cause, responsible for 15-30% cases in the United States. Other more common causes include endoscopic retrograde choliangiopancreatography, hypertriglyceridaemia, trauma, surgery and drugs.[3] Approximately 0.1-2% of cases of acute pancreatitis are drug-related.[4] Responsible drugs include azathioprine, 6-mercaptopurine, oestrogens, tetracycline, valproic acid, sulindac, ACE inhibitors, HMG-CoA reductase inhibitors, isoniazid and anti-HIV medications.[3,4]

Reports in VigiBase®

As of March 2015, after the elimination of duplicates, there are a total of 14 individual case safety reports (ICSRs) of pancreatitis in association with deferasirox in children and adolescents in the WHO Global ICSR Database, VigiBase® (see Table 1). The reports describe pancreatitis in 10 female and 4 male subjects aged from 4 to 16 (median: 12) years old. The reports were submitted from the United Kingdom (6 reports), France (4), South Africa (2), Germany and the United States (1 each).

Deferasirox was the only drug suspected in 11 of the 14 cases. There were other drugs also suspected in the remaining three cases and they included azithromycin, ceftriaxone and hydroxycarbamide in one case, amoxicillin, clarithromycin and omeprazole in another case, and deferoxamine in the remaining case. Concomitant drugs were reported in four cases and included folic acid (3 cases) and antibiotics (3).

Time to onset was reported in nine of the reports and ranged from 17 days to over five years (median: 11 months). The outcome of the pancreatitis was indicated in 10 reports. The patients were reported as recovered or recovering in nine cases and the outcome was fatal in the remaining case. In the cases where recovery was reported, the drug was withdrawn in six cases and continued in the other three cases. In the case where the patient died, the drug was withdrawn.

The indication for use was stated in 11 reports and indicated iron overload in four cases, sickle cell disease in four cases, thalassaemia major in two cases and diamond-blackfan anaemia in the remaining case. Dosage was stated in 12 reports and ranged from 250 mg daily to 2000 mg daily (median: 813 mg).

Other reactions were reported in seven reports and included hepatic reactions in six reports and abdominal pain in five reports. Renal complications were reported in four cases, vomiting was reported in three cases with fever and increased amylase was present in two cases.

Table 1. Case overview of reports in VigiBase® of pancreatitis in association with deferasirox

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reactions (WHO-ART preferred terms)	Outcome
1	4/F	None	Pancreatitis	Died
2	8/F	None	Pancreatitis	Recovering
3	5/M	None	Pancreatitis	Unknown
4	16/F	Azithromycin, ceftriaxone, hydroxycarbamide (all S)	Pancreatitis, fever, hepatitis cholestatic, hepatocellular damage, hepatomegaly	Recovered
5	16/F	Benzoyl peroxide, benzoyl peroxide/ clindamycin phosphate, folic acid, hydrocortisone, hydroxycarbamide, tetracycline (all C)	Pancreatitis, abdominal pain, azotaemia, coagulation time increased, diabetes mellitus, disseminated intravascular coagulation, fluid overload, hepatic function abnormal, INR increased, renal failure acute, respiratory insufficiency	Recovered
6	12/F	None	Pancreatitis	Unknown
7	16/M	None	Pancreatitis, abdominal pain, back pain, jaundice, hepatitis	Recovered
8	12/M	Amoxicillin, clarithromycin, omeprazole (all S)	Pancreatitis, abdominal pain, amylase increased, fever, vomiting	Recovered
9	16/M	Ascorbic acid, copper (both C)	Pancreatitis, abdominal pain, coagulation disorder, gastritis, hepatic function abnormal, hepatocellular damage, nephropathy toxic, vomiting	Unknown
10	12/F	Codeine, diclofenac, folic acid, paracetamol, phenoxymethylpenicillin (all C)	Pancreatitis	Recovered
11	12/F	None	Pancreatitis	Unknown
12	12/F	Folic acid, phenoxymethylpenicillin (both C)	Pancreatitis	Recovering
13*	14/F	Deferoxamine (S)	Pancreatitis, abdominal pain, ALT increased, amylase increased, anaemia, ascites, azotaemia, bilirubinaemia, C-reactive protein increased, hepatic enzymes increased, hepatitis, hypoproteinaemia, iron metabolism disorder, leukocytosis, lymphopenia, splenomegaly, urticaria, vomiting, blood creatinine decreased**	Recovering
14*	14/F	Deferoxamine (C)	Pancreatitis, abdominal pain, ALT increased, amylase increased, anaemia, ascites, azotaemia, bilirubinaemia, C-reactive protein increased, hepatic enzymes increased, iron metabolism disorder, leukocytosis, lymphopenia, splenomegaly, urticaria, vomiting, blood creatinine decreased**, ultrasound abdomen abnormal**	Recovering
15	7/F	None	Pancreatitis, acidosis, hepatocellular damage, renal failure acute	Recovered

**Cases 13 and 14 are duplicates*
***MedDRA terms*

Literature and Labelling

The product literature does not refer to pancreatitis although it does indicate that gallstones and related biliary disorders were reported in about 2% of patients and that serious acute pancreatitis may potentially occur as a complication of gallstones (and related biliary disorders).[1]

In the literature, Galanello and co-workers reported on a Phase II clinical trial on the safety and tolerability of deferasirox in paediatric patients with transfusion-dependent beta thalassaemia major. Of the 39 patients studied, one developed pancreatitis but this was considered by the authors to be either a typical complication of thalassaemia or an incidental medical problem. It was not considered to be treatment-related and did not lead to discontinuation.[5]

Chang and colleagues reported on a study which evaluated whether twice daily deferasirox treatment showed increased efficacy or tolerability in unresponsive or intolerant patients. Seven of the 25 patients received twice-daily deferasirox because of intolerance to the once-daily dose. One of these patients had developed pancreatitis in which only elevated amylase levels were noted.[6]

Vichinsky et al. evaluated the long-term safety and efficacy of deferasirox in patients with sickle cell disease (SCD) who first completed a 1-year, Phase II, randomized, deferoxamine (DFO)-controlled study and then entered a 4-year extension, continuing to receive deferasirox, or switching from DFO to deferasirox. Of the 185 patients assessed, one withdrew from the study due to pancreatitis which had a suspected relationship to deferasirox treatment. Another patient developed increased blood amylase also suspected to be related to deferasirox treatment.[7]

Discussion

Case reports in VigiBase® suggest that there is a signal for the association of deferasirox and pancreatitis in paediatric patients. Deferasirox was the only drug suspected in 11 of the 14 cases. There were other drugs also suspected in the remaining three cases and they included azithromycin, ceftriaxone and hydroxycarbamide in one case, amoxicillin, clarithromycin and omeprazole in another case and deferoxamine in the remaining case. Azithromycin, ceftriaxone, hydroxycarbamide and clarithromycin have a reference to the possibility of pancreatitis as a possible adverse reaction in their product information.[8,9,10,11] In case 4, ceftriaxone was used for only two days and ceased five days before onset and azithromycin was also only used for two days and ceased one day before onset. These would appear to be unlikely causes. Hydroxycarbamide was initiated at the same time as deferasirox and was continued along with deferasirox and would seem to be a possible cause. In case 8, pancreatitis occurred eight days after omeprazole was commenced and at the end of a seven day course of clarithromycin and amoxicillin while deferasirox had been taken for up to three years. Recovery occurred after the withdrawal of deferasirox while omeprazole was continued. In case 13, deferoxamine, although a suspected drug, had been withdrawn 18 days before onset and appears an unlikely cause as it was only after it was replaced by deferasirox that pancreatitis occurred.

Time to onset was reported in nine of the reports and ranged from 17 days to over five years (median: 11 months). This is reasonably consistent with a drug-induced effect although onset in some cases appears to be rather longer than anticipated. However, Tatley noted that time to onset may be six (or even nine) months after commencement of the suspected causative medicine.[12] Moreover, Balani and Grendell also observed that onset can be delayed. Pancreatitis in association with HMG-CoA reductase inhibitors rarely occurs early, onset of pancreatitis in association with ACE inhibitors ranges from five weeks to a year, onset of pancreatitis with valproic acid ranges from three to 17 months and onset of pancreatitis with oestrogen and sulindac ranges from a few weeks to five years.[4]

The outcome of the pancreatitis was indicated in 10 reports. The patients were reported as recovered or recovering in nine cases and the outcome was fatal in the remaining case. In the cases where recovery was reported, the drug was withdrawn in six cases and continued in the other three cases. This is reasonably supportive of a drug-induced reaction. In case 5, however, both folic acid and tetracycline were withdrawn on the same date as deferasirox. Although neither were suspected, pancreatitis is listed in the product information for tetracycline and is a possible cause.[13]

The product literature does not refer to pancreatitis although it does indicate that gallstones and related biliary disorders were reported in about 2% of patients and that serious acute pancreatitis may potentially occur as a complication of gallstones (and related biliary disorders).[1] None of the patients reported in this series, however, appeared to have gallstones. There are three reports in the literature in which isolated patients in clinical trials of deferasirox developed pancreatitis. One of these was a paediatric patient.[5] In the other reports, the age of the patients developing pancreatitis was not stated but 7 of the 11 patients included in the efficacy analysis reported by Chang et al. were aged from 12 to 20 years while 48.6% of the patients reported by Vichinsky et al. were aged 16 years or less.[6,7]

The possible association of pancreatitis with deferasirox appears predominantly in the adolescent and paediatric population. There is a total of 62 reports of pancreatitis in association with deferasirox in the total population. The age is reported in 28 of them. The fact that 14 of these reports were reported in the adolescent and paediatric age groups represents 50% of these reactions in this age group. While it is possible that deferasirox is used preferentially in the younger age groups, overall reporting in VigiBase® indicates that of the 7,148 deferasirox reports submitted where the age was known, the age group from 2 to 17 years represents only 16.8% of the total reports.

Conclusion

In summary, there are 14 cases associating pancreatitis with the use of deferasirox in paediatric and adolescent patients. Deferasirox was the only drug suspected in 11 of the 14 cases. Time to onset is consistent with a drug-induced effect and although it does appear to be longer than usual in some cases, this is consistent with other reports of drug-induced pancreatitis. The response to dechallenge is supportive of a drug-induced effect. There is some support in the literature for the association with three reports in which isolated patients in clinical trials of deferasirox developed pancreatitis. However, the possible association of deferasirox with pancreatitis appears predominantly in the paediatric population.

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Response from Novartis

In response to a WHO signal evaluation on the association of deferasirox and pancreatitis in paediatric patients, Novartis presents the Company analysis of this signal. To date, the patient exposure of deferasirox (Exjade) is estimated to be over 245,000 patient-treated-years including > 7,200 in clinical trials. Novartis has reviewed 38 cases of pancreatitis in paediatric patients in the Novartis safety database

(spontaneous, clinical trial, and literature reports). In 3 cases there were no identifiable confounders to exclude a possible causal relationship; therefore Novartis cannot exclude an association between events of acute pancreatitis in paediatric patients and treatment with Exjade.

Background

Pancreatitis has several causes and symptoms. Acute Pancreatitis (AP) is defined by the presence of 2 of the 3 following criteria (Harrison's Principles of Internal Medicine, 18th Edition):

- Abdominal pain characteristic of AP;
- Serum amylase and/or lipase >3 times the upper limit of normal (ULN); and
- Characteristic findings of AP on cross-sectional abdominal imaging (preferably by computed tomography (CT) scan).

The prevalence of acute pancreatitis in adults ranges between 6 and 45/100,000 person-years in various populations and ages, with lesser rates reported in younger patients. In children, the estimated incidence of pancreatitis ranges between 3.6 and 13.2/100,000 children (Morinville 2012). The etiologies of pancreatitis are quite varied in childhood, and differ from those seen in adults.

In a review by Latif, the most common etiologies of AP in children were biliary (32.6%), medication toxicity (25.6%), and idiopathic (22.3%) (Latif 2008). Inflammatory bowel disease presenting as acute pancreatitis was more frequent among the paediatric population (Broide, 2011). Hereditary pancreatitis is the second most common congenital pancreatic disorder following cystic fibrosis in children (Dayal, 2013).

Three possible etiological factors for pancreatitis in the population treated with Exjade include biliary sludge formation, haem-induced inflammatory cytokines, and hypoxia.

Biliary sludge may be an antecedent of gallstones and also lead to pancreatitis even in the absence of gallstones (Lee 1988). Infections are frequent in patients with thalassemia or SCD, requiring the frequent use of antibiotics, including ceftriaxone, which seems to promote sludge formation.

Haem released from hame proteins has been shown to promote a systemic inflammatory response and organ failure. The important role of inflammatory cytokines in the pathogenesis of acute pancreatitis is well known (Saruc 2003).

Reduced perfusion of the pancreas leading to hypoxia and ischemia is a well-described mechanism causing or worsening pancreatitis. The pathological oxygen saturation of haemoglobin in thalassaemia has been described (Löhr 2014). AP has been depicted as a rare manifestation of vaso-occlusive painful crisis in SCD (Ahmed S 2003).

Patients with transfusional iron overload resulting from haemolytic conditions (including thalassaemia and sickle cell disease [SCD]) have an increased risk of biliary-mediated pancreatitis with rates reaching 20-40% (Silva 2015, Cosentini 2005). Patients with SCD have an increased risk of cholelithiasis from bilirubin stones that result from increased haemolysis and serum bilirubin concentration (Amoako 2013).

As stated in the current label, cholelithiasis has been uncommonly reported in clinical trial patients treated with Exjade, and there have been post-marketing reports of serious acute pancreatitis which occurred as a complication of gallstones (and related biliary disorders). Both cholelithiasis and biliary-mediated pancreatitis are documented as adverse events in the product information.

Preclinical data

Inflammatory and degenerative changes in the gallbladder and bile ducts were seen in marmosets at high doses of deferasirox that generally resulted in morbidity/mortality. Similar findings were observed in the intra-hepatic bile ducts in transgenic mice at 100 mg/kg (standard diet) after 4 and 26 weeks of treatment.

In pre-clinical toxicity testing, the pancreas was not identified as a target organ.

Individual case safety reports from Novartis safety database.

Due to the unavailability of exposure data by age group, an estimated reporting rate in the paediatric population (age below 18 years) cannot be calculated.

As of 4 June 2015, there are 38 cases of Exjade-pancreatitis drug-event combinations in paediatric patients in the Novartis safety database (spontaneous, clinical trial, literature reports). In eleven cases, there was limited information, questionable diagnosis, or negative rechallenge for Exjade. In 13 cases, there was evidence of biliary tract etiology for pancreatitis. Three cases were temporarily associated with other medication known to induce pancreatitis. One had a prior history of chronic pancreatitis. Seven patients developed pancreatitis in the setting of concurrent acute illness associated with pancreatitis (sickle cell crisis – 2; acute renal failure – 1; new onset Crohn's disease – 1; acute systemic infection – 3)

In the remaining three cases with sufficient information for assessment (two with underlying beta-thalassaemia, and one with SCD), no confounding factor could be identified, and a causal association with Exjade could not be excluded.

Conclusions

While the majority of sufficiently documented cases included alternative explanations and/or were confounded, three cases contained no identifiable confounder; a causal relationship could therefore not be excluded between acute pancreatitis and deferasirox treatment in the paediatric population.

Although it is recognized that the underlying disease in Exjade-treated patients could present a contributing factor to the etiology of pancreatitis, via haemolysis- induced biliary complications, possible hame-induced inflammatory mediators, or ischemia-mediated effects (particularly in sickle cell crises), Novartis considers it pertinent to add "Acute pancreatitis" to the label as an adverse drug reaction derived from post-marketing reports with an unknown frequency due to the severity and specificity of the event.

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Desloratadine and aggressive reaction

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Summary

As of March 2015, the WHO Global Individual Case Safety Report (ICSR) database, VigiBase®, included 17 ICSRs of aggressive reaction associated with desloratadine. Desloratadine is a selective peripheral histamine (H1) receptor antagonist, indicated for the relief of symptoms associated with allergic rhinitis and urticaria in children and adults. Ten of the VigiBase® reports involved children, of which six presented with a supportive temporal relationship and positive dechallenge, and of those, two reported a subsequent positive rechallenge. The adult reports were less convincing in supporting a signal, but one of the cases represented a rapid onset, positive dechallenge as well as positive rechallenge, and thus this signal is not limited to children. Central nervous system (CNS) adverse reactions have previously been reported for desloratadine, hence penetration into the brain and the possibility of other clinically relevant CNS

effects cannot be ruled out. Additional loratadine reports in VigiBase® and the fact that aggression is a known adverse reaction for cetirizine, another second-generation antihistamine, contribute to suspicions of a possible class effect.

Introduction

Desloratadine is a non-sedative, selective peripheral histamine (H1) receptor antagonist, indicated for the relief of symptoms associated with allergic rhinitis and urticaria.[1] This second-generation antihistamine was authorized throughout the European Union and the United States in 2001 and is currently available in large parts of the world, including Latin America, Africa and Asia.[1,2,3] Desloratadine is the primary active metabolite of loratadine, a widely used antihistamine which was introduced in 1993 and is now available over the counter.[4,5] Desloratadine is still subject to medical prescription.[1,2]

In the European Union desloratadine is approved for use in adults, adolescents and children over the age of 1 year.[1] In the United States the drug is approved for patients of 6 months and older.[2] The recommended daily dose for adults and adolescents (12 years of age and over) is 5 mg, for children from 6 to 11 years 2.5 mg, from 1 to 5 years 1.25 mg and from 6 to 11 months 1 mg.[1,2] Desloratadine reaches maximum plasma concentration after approximately three hours, and the half-life is about 27 hours. The enzyme responsible for the metabolism is still unknown, so interactions with other medicinal products cannot be excluded.[1]

The most common adverse reactions reported in clinical trials were fatigue, dry mouth and headache (frequency ≥ 1/100 to < 1/10). Additional psychiatric and nervous system adverse reactions reported during the post-marketing period include hallucinations, dizziness, somnolence, insomnia, psychomotor hyperactivity and seizures (frequency < 1/10,000).[1] Aggressive reaction is not listed as an adverse reaction, neither for desloratadine nor loratadine.[1,2,4,5]

Aggression is a wide term and is not a diagnosis in itself. It may instead be a symptom of or related to many different conditions, such as attention-deficit hyperactivity disorder (ADHD) or dementia, and it may overlap with other terms, such as irritability and emotional lability.[6,7] Aggressive behaviour can manifest throughout life and may be part of the natural development process in children. For toddlers and pre-school children aggression generally peaks at 18 to 24 months and slowly decreases by the age of 5.[7] The nature of aggressive behaviour is complex and involves genetic and environmental factors, different neural circuits, and several neurotransmitters, including serotonin (5-HT), dopamine, and GABA.[8]

Reports in VigiBase®

As of March 2015 the WHO Global Individual Case Safety Report (ICSR) database, VigiBase®, included 17 ICSRs of the WHO-ART preferred term 'aggressive reaction' associated with desloratadine. The first report entered VigiBase® in 2002 and reports have continuously been submitted to VigiBase® up to 2014. The majority of the reports (12) originate from Europe (Austria, Croatia, France, Greece, Germany, the Netherlands, Norway, and Sweden), three reports are from the United States, and two from Canada. The cases represent 6 females and 11 males and patient ages range from 1 to 79 years (median age 12 years). The majority of the cases are reported by physicians (7 reports), pharmacists (4), or consumers/non-health professionals (3).

Paediatric reports

Ten of the reports involve children, all but two of them being 8 years of age or younger. The characteristics of these cases are presented in Table 1. All paediatric reports are from 2006 or more recent. Three of the reports were classified as serious by the reporter.

Six of the reports describe that the patient had recovered or was recovering from the reaction at the time of reporting, all of them upon withdrawal of the drug. Two of the cases describing a positive dechallenge also report a positive rechallenge and one of those describes a repeated positive rechallenge. In the remaining four cases, desloratadine was withdrawn but the patients had not recovered at the time of reporting (3 reports) or the outcome was unknown (1).

Time to onset varies from one or a few days up to seven months. One report does not provide precise time to onset information but the duration of desloratadine use is about one year. For the six reports with positive dechallenge, time to onset is "during administration" (1 report), one to two days (2), three days (2) and a few weeks (1). Desloratadine is the sole suspect drug in all of these six cases; however two of them report concomitant medication previously associated with aggressive behaviour (budesonide) or mood changes (cyamemazine).[5,9] In the latter case, cyamemazine had been used for one year together with risperidone for autism; after adding desloratadine the reaction was experienced two days later. Only one of the remaining four cases reports co-suspected drugs: montelukast, for which aggressive reaction is a labelled adverse reaction, and chlarithromycin, which has been associated with irritability.[5] Chlarithromycin treatment was however stopped about two weeks before reaction onset. Fluticasone, for which aggressive reaction is labelled, is concomitantly used in one case and pseudoephedrine, for which irritability is mentioned as a symptom of overdosage, is concomitantly used in another case.[5]

One report (case 2) describes an 8 year-old female who experienced aggression and irritability following administration of desloratadine for allergic rhinitis, with a latency of one to two days after start of treatment. Desloratadine was withdrawn after six days and the patient recovered within one day. Concomitant medication was not reported and the patient had no known medical history. The past drug therapy indicated that the patient had experienced aggression after a previous intake of a cetirizine tablet and a loratadine tablet on different occasions. The case was reported by a specialist physician and the reaction was assessed as probably related to desloratadine.

Another report (case 4) concerns a 20 month-old female and is reported by the patient's mother. The child was given desloratadine several times in periods of five to seven days for about 1.5 years, mainly for allergic reactions to insect bites. No other medication was reported. The mother described that the child was always rather irritable and aggressive when taking the drug, and at night she seemed to go through something like a nightmare. The sender of the report assessed the reaction as certainly related to desloratadine, because of positive rechallenge.

Adult reports

Seven of the reports concern adults. Two of these present with multiple possible confounders or other more likely reasons for the reaction. For another three adult cases the reported information is sparse, and thus the prerequisites to make proper assessments of these cases are limited. One of them however reports a time to onset of one month.

One case, reported by a specialist doctor, indicates a possible interaction effect from concomitant use of desloratadine and risperidone. The case describes a 38 year-old male who had used desloratadine for years when adding risperidone for autistic disorder. A few hours after the first dose of risperidone the patient experienced violent thoughts, difficulty in standing, dystonia, sedation, trismus and salivation. After withdrawal of risperidone the reactions abated. The patient had previously experienced violent thoughts while on another antipsychotic drug. The reactions may be explained by risperidone alone in this case, however in the light of the paediatric case 1, which also has risperidone co-reported, the interaction hypothesis may also be worth consideration.

The remaining report describes a 32 year-old male presenting with aggressiveness 1-1.5 hours after desloratadine intake. The patient had taken several doses and the reaction is reported to have occurred after each intake. This case also describes a positive dechallenge, with a recovery within 36 hours after drug withdrawal, as well as a positive rechallenge. No concomitant medication was reported. The patient had previously used loratadine and cetirizine without experiencing this reaction.

Literature and labelling

Psychiatric and nervous system disorder reactions, including hallucinations, dizziness, somnolence, insomnia, psychomotor hyperactivity and seizures, have been reported in association with desloratadine as adverse reactions during the post-marketing period.[1] In three placebo-controlled clinical trials, desloratadine was administered for 15 days to a total of 246 children aged 6 months to 11 years. In infants and toddlers aged 12 months to 23 months emotional lability was reported at a frequency greater than with placebo (3.1%, 0%), as was irritability in infants aged 6 to 11 months (12.1%, 11.3%).[2] Nothing is mentioned in the British National Formulary for Children about the use of desloratadine and adverse events related to aggression.[10] Aggression has been reported as an adverse event in the post-marketing period for cetirizine, another second-generation antihistamine indicated for allergic rhinitis and chronic idiopathic urticaria.[11,12]

First-generation antihistamines have more pronounced sedative properties than second-generation antihistamines, but have also been associated with agitation and irritability.[5,13] These compounds, as compared to second-generation antihistamines, have less H1 receptor selectivity and more easily enter the central nervous system (CNS).[13] It is inconclusive whether the limited penetration of second-generation antihistamines into CNS is determined by active efflux from the brain via P-glycoprotein (P-gp) or a restricted penetration through the blood-brain barrier.[13,14,15]

Cerminara et al. described seizures induced by desloratadine in four children. They speculated that susceptible patients might have a mutation in the gene coding for P-gp, causing an abnormal variant of P-gp, and thus limiting the efflux of desloratadine from the CNS.[16]

Animal studies have indicated that inactivating the histaminergic (H1) system may reduce aggression in rodents, suggestively through decreased serotonin (5-HT) activity.[17,18] However, variations in the histaminergic system and the nature of aggression among species, as well as limitations to animal models[8,19] raise uncertainty to whether these results could be fully applied to humans.

Table 1. Characteristics of paediatric reports of aggressive reaction in association with desloratadine in VigiBase®

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions*	Time to onset	Dechallenge/ Rechallenge	Outcome at time of report	Comment
1	15/M	Desloratadine (S) Risperidone, cyamemazine (both C)	Aggressiveness, behaviour disorder, excitability, titubation	2 days	Positive dechallenge (symptoms began to decline 7 days after withdrawal, however still after 14 days not fully recovered)	Recovering	Daily dose: 1 mg Medical history: Autism Use of concomitant medication for one year
2	8/F	Desloratadine (S)	Aggression, irritability	1-2 days	Positive dechallenge (drug withdrawn after six days, patient recovered within one day)	Recovered	Daily dose: 2.5 mg
3	5/M	Desloratadine (S) Brompheniramine maleate/ pseudoephedrine hydrochloride (C)	Aggression	2 days	Drug withdrawn – outcome unknown	Unknown	Daily dose: 2.5 mg Aggressive behaviour after taking amoxicillin
4	1/F	Desloratadine (S)	Aggressiveness, irritability, nightmare, drug effect lack of	"During administration"	Positive dechallenge Positive rechallenge (repeatedly)	Recovered	Desloratadine taken several times in periods of 5-7 days for about 1.5 years
5	4/M	Desloratadine (S)	Aggression, sleepiness	3 days	Positive dechallenge	Recovered	Daily dose: 2.5 mg One hour time to onset for sleepiness
6	4/M	Desloratadine, clarithromycin, montelukast** (all S)	Aggressive behaviour, stress, fever, petit mal	7 months	Negative dechallenge	Not recovered	Daily dose: 2.5 mg Chlarithromycin treatment stopped two weeks before aggressive behaviour onset
7	12/F	Desloratadine (S)	Aggressive reaction, delirium, psychotic reaction nos, hallucination auditory	5 days	Drug withdrawn and treatment with haloperidol, child's condition has improved	Not recovered	Daily dose: 5 mg
8	8/F	Desloratadine (S) Budesonide**, olopatadine (both C)	Aggressive reaction	"A few weeks"	Positive dechallenge Positive rechallenge (reintroduced with 2.5 mg)	Recovered	Daily dose: 5 mg Daily aggressiveness
9	4/M	Desloratadine (S)	Aggressiveness	3 days	Positive dechallenge (patient recovered within a week after withdrawal)	Recovered	Daily dose: 2.5 mg
10	8/M	Desloratadine (S) Fluticasone**, salbutamol (both C)	Aggressive behaviour, psychic disturbance, insomnia	-	Negative dechallenge	Not recovered	Daily dose: 2.5-5 mg Duration of desloratadine use approximately one year

**Reactions are shown as reported. Due to differences in reporting terminology some terms in the table represent WHO-ART and some MedDRA.*
***Associated with aggressive behaviour.*[5]

Discussion

VigiBase® paediatric reports on aggressive reaction and desloratadine represent six cases with a supportive temporal relationship and positive dechallenge, and of these, two reported a subsequent positive rechallenge. Four of these cases had no other medication reported while one case reported concomitant use of another antihistamine (eye drops) and a corticosteroid (nasal spray) previously associated with aggression, and another case reported concomitant use over a period of one year of antipsychotic drugs indicated for autism.

Two additional paediatric cases reported a time to onset consistent with the other cases, but negative or unknown outcome of dechallenge. One of these cases however reported that the patient was improving upon withdrawal of the drug together with treatment of haloperidol. This case described other reactions, including psychotic reaction and hallucinations, the latter a known adverse reaction

for desloratadine and which may lead to aggression.

The remaining two cases involving children were less convincing with long or missing time to onset, negative dechallenge and co-reported drugs previously associated with aggression.

The medical histories of the patients were seldom reported and identified possible confounders were few in relation to the number of paediatric reports. The neurological and behavioural development of children may be seen as a confounding factor and differentia- ting coincidental aggressiveness as a natural course of development, from a true causal association is difficult. However, a possible causal relationship is supported by a plausible temporal relationship, positive de- and rechallenge, and complementary adult cases.

The adult reports were less convincing in supporting a signal. However, one of the adult cases presented no obvious confounders, a rapid onset of the reaction, positive dechallenge as well as positive rechallenge, and thus this signal is not limited to children.

The main proportion of the cases did not indicate a serious reaction; however, aggression may have severe implications. As aggressive behaviour sometimes involves violence, both the patient him/herself and his/her surroundings may be at risk of being physically injured, and aggressive behaviour, even if only verbal, may have consequences on social interactions and the quality of life. Another implication is the legal aspect, in which it may be important to find explanations for aggressive action.

Although desloratadine is said not to readily cross the blood-brain barrier, this cannot be completely excluded and there have been reports of CNS adverse reactions from this drug.[1,2,16] One example is emotional lability, which may in a wider sense include the term discussed in this signal, found to be reported at greater frequency for desloratadine than for placebo in infants and toddlers.[2] The neurobiology of aggression is complex and is supposed to involve many different neural circuits and neurotransmitters and a mechanism can only be speculated. However, penetration into the brain and the possibility of triggering clinically relevant CNS adverse effects in susceptible patients, cannot be ruled out. Worth noting is that half of the paediatric cases had a higher than recommended daily dose, indicating a possible dose-relationship. Two of these cases also reported concomitant use of another antihistamine, which may suggest a possible additive effect.

The range of countries reporting this association strengthens the signal in the sense of being broadly observed. Also important to highlight, when this combination was assessed, VigiBase® contained in addition 108 reports (45 paediatric) of an aggressive reaction associated with loratadine, entered between 1992 and 2015 and originating from 13 different countries. This, together with the fact that aggression is described as an adverse reaction for cetirizine[11,12], another second-generation antihistamine, points to a possible class effect.

Conclusion

Reports in VigiBase® primarily, but not exclusively, support a signal on aggressive reaction associated with desloratadine use in children. The paediatric reports represent a plausible temporal relationship, positive de- and rechallenges and only a few identified possible confounders. Psychiatric and neurologic adverse reactions have been reported for the drug and thus penetration into the brain and the possibility of other clinically relevant CNS effects cannot be excluded. Additional loratadine reports in VigiBase® and the fact that aggression is a known adverse reaction for cetirizine, contribute to suspicions of a possible class effect.

Thank you to the national pharmacovigilance centres contributing additional case information upon request.

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CAVEAT DOCUMENT

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

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

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

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

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

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

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

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

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

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

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

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

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

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

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

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

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

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The 38th meeting of the WHO International Working Group for Drug Statistics Methodology, Oslo, 22–23 October 2015

Medicines can provide substantial benefits, however, at the same time they have the potential to harm patients. This can result in significant costs to both high and low/middle income countries. The proportion of expenditure on medicines varies between countries and it is important to understand the patterns of use (for example, the types of medicines and their quantity). Drug Utilization Studies are essential for monitoring these patterns and trends, and understanding their impact on the efficiency with which health outcomes are gained.

The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) serve as a tool for Drug Utilization Research (DUR). DUR is undertaken to improve quality of drug use in health-care settings. DUR can also be used to compare drug consumption at international levels.

The WHO International Working Group for Drug Statistics Methodology consists of 12 members representing a wide range of geographical and professional backgrounds, including clinical pharmacology, clinical medicine, international public health, drug utilization and drug regulation. The members of the International Working Group represent different users of the ATC/DDD system and different nationalities as they represent the six WHO global regions.

The Working Group provides scientific expert advice to WHO and the WHO Collaborating Centre for Drug Statistic Methodology (WHOCC Oslo), to discuss and approve all new ATC codes, DDD assignments and alterations to existing ATC codes and DDDs. The Working Group also supports the further development of the ATC/DDD system and methods, manuals and guidelines for the practical application and appropriate use of the ATC/DDD system in drug utilization studies in a variety of settings, particularly those applicable to low and middle income countries.

The 38th meeting of the WHO International Working Group for Drug Statistics Methodology was held at the Norwegian Institute of Public Health in Oslo, Norway. The meeting started with an Open Session which provided an opportunity for anyone, including industry, to present additional information on ATC/DDD to the experts to assist them in their decision-making at the subsequent closed session.

During the Closed session, WHOCC Oslo reported on its recent activities. The Working Group intensively discussed the ATC classification and DDD items for several medicinal products, reviewed classifications, the objections and alterations of existing ATC classifications and future challenges. The Working Group discussed new DDDs for several drugs based on the available information including indications and doses used in various countries, and reviewed objections to the assigned DDDs to alter the DDDs.

The Working Group also discussed the ATC/DDD Toolkit, which is in the process of development. The purpose of the toolkit is to raise awareness and to provide guidance on how to set up and use the international ATC/DDD methodology. The ATC/DDD Toolkit will be a comprehensive online resource for anyone interested in undertaking drug utilization studies.

Decisions made during discussions by the Working Group on ATC classification or DDD assignment will be published on the website of the WHOCC Oslo and in the publication, WHO Drug Information. Decisions on a new or revised ATC classification or DDD assignment are published at first as a temporary list. Any interested party wishing to dispute this decision has the opportunity to comment within a specified period after its publication.

For more information, please see WHOCC Oslo website: http://www.whocc.no/

Pre-conference Workshop on WHO ATC/DDD Methodology and Drug Utilization Research, New Delhi, India, 2-3 November 2015.

A pre-conference workshop on WHO ATC/DDD methodology and drug utilization research was held on 2-3 November 2015 in New Delhi, India, preceding the 38th Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

This 2-day workshop on the WHO ATC/DDD methodology and drug utilization studies consisted of lectures, hands-on exercises and group discussions. The experts from the WHO Collaborating Centre for Drug Statistic Methodology (WHOCC Oslo), the Indian Council of Medical Research and the National Coordinating Centre for Pharmacovigilance Programme of India provided lectures on historical background, need for drug utilization studies, basics of the WHO Classification (ATC/DDD) system, procedures for ATC/DDD assignment, its applications, data sources, methods used for drug utilization research, current status and future prospects, in particular for low and middle income settings.

About 50 participants joined this session and actively participated in discussions with great enthusiasm. Several questions were raised both during and after the sessions. The workshop received positive feedback from participants.

Comments from the participants include; "Excellent organization, excellent learning", "Course was excellent and the case studies for the working groups were superb", "Very useful sharing of the rationale behind the ATC classification and the DDD", "The working group was excellent. Please add more of that in coming courses", "More frequent courses needed."

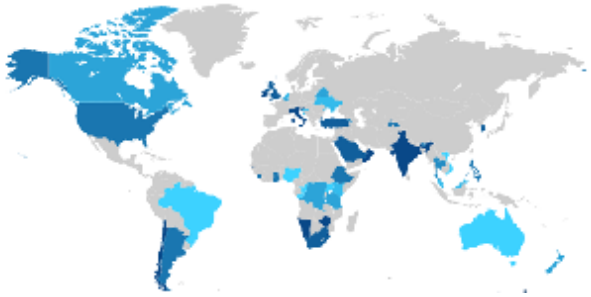
Based on the positive feedback and given the need to promote and support the use of this tool, WHO will continue to organise Workshops on ATC/DDD in collaboration with WHOCC Oslo.

The 38th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring

Indian Pharmacopoeia Commission hosts the annual meeting of representatives of the National Pharmacovigilance Centres in New Delhi, India

Minister of Health and Family Welfare, J P Nadda inaugurates the WHO meeting

The commitment of the Indian government to the cause of pharmacovigilance (PV) and medicines safety was marked by the presence of the Minister of Health and Family Welfare, Minister J P Nadda at the inauguration ceremony of the 38th Annual Meeting of Representatives of the National Pharmacovigilance Centres (NPCs) participating in the WHO Programme for International Drug Monitoring (PIDM).



Representatives from National PV Centres around the world travelled to attend

The annual meeting of representatives of the NPCs is a platform for representatives from around the world to meet and discuss PV issues. Each year an NPC hosts the meeting, and this year the Indian Pharmacopoeia Commission (IPC) welcomed delegates to the hotel Grand New Delhi, India.

Over 150 representatives from 44 countries travelled to India to attend the three-day meeting from 4 to 6 November 2015.

Opening ceremony

In Minister Nadda's opening address, he emphasized the importance of PV, and declared that *"Given the critical role that it plays in ensuring safety of medical products, it is imperative that pharmacovigilance is developed as an effective instrument for the understanding and prevention of adverse effects and any other drug related problems."*

Meeting structure

At the end of the 37th annual meeting of representatives of the NPCs participating in WHO PIDM in China 2014, participants were invited to suggest topics for the 2015 agenda by completing the questionnaire provided at the end of the meeting. The list of topics were sent electronically to all NPCs in early 2015 in the form of a second questionnaire, which requested topics to be prioritized. This set the agenda for 2015, reflecting the needs of Member States.

The meeting sessions consisted of plenaries, updates, working groups and problems of current interest. Each plenary was chaired by a panel, and delegates participated in discussions following presentations. Topics covered in the plenary sessions included, the importance of storytelling in pharmacovigilance, success stories in Oman and Chile, building a global safety culture, PV in a small country (strategies, challenges, opportunities and inspirations), signal detection, the PV programme in India: current status, integration with public health programmes, and the role of adverse drug reaction (ADR) monitoring centres. During the update sessions, presentations were made on: adverse events reporting during mass drug administration, patient reporting, using PV indicators in routine PV practice, and the WHO-UMC algorithm to detect Substandard/spurious/ falsely-labelled/falsified/counterfeit medical products (SSFFCs).

O Abiri from Sierra Leone presenting during the update session

The session on problems of current interest consisted of short presentations based on pre-selected abstracts that were submitted prior to the meeting. There was a range of topics, some focused on particular ADRs of concern, for example dimethyl fumarate and progressive multifocal leukoencephalopathy. Others discussed PV systems and country experiences, for example strengthening PV systems in South Africa. Delegates were given the opportunity to share their experiences, interact and help find solutions.

Success story: database linking and transition to E2B in Chile

Chile is a South American country occupying a long narrow strip of land bordering the South Pacific Ocean. It is estimated that there are currently over 17 million inhabitants in Chile. The NPC in Chile was initially formed in 1995 and joined the WHO PIDM in 1996.

The NPC is situated in the National Drugs Regulatory Authority. Currently, Individual Case Safety Reports (ICSRs) are compiled in an excel spreadsheet database. Initially reports were received as an email or as paper form and were manually imputed into the database. This process is very time consuming, however was manageable with relatively small number of reports. However reporting rates increased substantially (~ 10000 reports /year) after it became mandatory for health-care professionals and the pharmaceutical industry to report adverse drug reactions in 2010. Hence, processing reports into the database was no longer timely. In addition to this, three separate parallel reporting systems existed: 1) the initial excel database held at the NPC; 2) an online database for adverse events following immunization (AEFIs): 3) an online database for reporting suspected adverse effects (created by the institution's Information Technology unit). The use of three databases made analysis of ICSRs difficult. In 2013, the NPC took steps to consolidate data from the three databases and transfer data to the WHO global database of ICSRs, VigiBase using the internationally recommended format, ICH-E2B. E2B is a standardized format for transferring data between databases of different structure. It works by defining the type of information as well as the format of the information (using XML document Extendable Markup Language) to be transferred. Chile initially transferred data to VigiBase® using the INTDIS format in excel.

The NPC in Chile plan to approach this by identifying and implementing changes in the database needed to comply with E2B standards, developing data bridges to transmit information between the three databases to form a single pool of data, and to develop tools to transmit data to VigiBase (under E2B standards).

Measures taken to consolidate data included developing a computer programme in Excel to facilitate data entry. This used standardized terminology and made data entry of reports partially automatic. Secondly, custom filters were added to the Excel database to help with data analysis. The transition is still in process, and the next step is to ensure all AFEI reports received online are transferred to the Excel database. Tools are being developed for this. In the meantime the International Vaccine Institute in South Korea is working with the NPC to implement a tool to generate E2B messages from vaccine reports in the Excel database. The national immunization programme is adapting their system in terms of coding and data fields to become compatible with the NPC database, this is expected to be ready in January 2016.

Finally, the WHO Collaborating Centre (CC) for International Drug Monitoring in Uppsala will support Chile to make the E2B message in a format that can be imported to VigiBase® by email initially, with the plan to switch data transfer from NPC computer to VigiBase® directly (server to server).

Summary of presentation by J R Saelzer from Chile

Adverse event reporting during mass drug administration and reducing the spread of Ebola in Sierra Leone

Sierra Leone is situated in west coast of Africa and has a population of about 9 to 10 million people. The country is comprised of four geopolitical regions and 12 districts. In May 2014, health officials confirmed the presence of a case of Ebola in the eastern part of Sierra Leone. By August 2014, the disease spread to all but one district in the country. Ebola, formally known as Ebola haemorrhagic fever is a virus disease that can be transmitted to people from wild animals and spreads in the human population through human to human transmission. Mortality rate is high and up until November 1st, there have been over 3500 deaths related to Ebola in Sierra Leone. Ebola is characterized by fever, diarrhoea, headache, vomiting muscular pain, and in some instances bleeding. Most of these symptoms occur in other common health conditions, such as malaria and typhoid. The signs and symptoms usually manifest between 2-21 days after contact with the virus. The risk of the virus spreading was increased in Sierra Leone due to many factors, such as: poor socioeconomic status, weak health-care infrastructures, limited knowledge of the disease, lack of manpower, delay in effective coordinated response mechanisms to outbreaks (nationally and internationally), traditional and cultural practices, (e.g. washing of dead bodies, caring for the sick at home, hand shaking, and hugging). Of particular risk, was the potential confusion between symptoms of Ebola and malaria. As symptoms are similar, people with malaria often presented themselves at Ebola treatment centres, hence non-infected persons were at risk of exposure.

Mass drug administration (MDA) of malaria chemoprevention was introduced as an intervention to reduce the spread of Ebola. Hence, a combination of amodiaquine and artesunate (AS-AQ) was distributed and administered to communities with the aim of controlling malaria. By reducing the number of febrile cases due to malaria in the community, the number of suspected Ebola episodes that would otherwise require screening and isolation in Ebola treatment centres would be reduced, reducing the risk of Ebola transmission among malaria patients. During the MDA campaign it was imperative to monitor for suspected ADRs, to ensure that the drug combination is safe when administrating on a large scale, and to learn more about the drug safety profile when used in this population. The PV objectives were: to quantify previously recognized ADRs, identify unknown ADRs, evaluate effectiveness, and to decrease mortality and morbidity related to adverse events. In addition, the PV initiative built the trust of the community. For example, the misconception that the anti-malaria tablets caused Ebola was managed through effective advocacy and communication.

Prior to MDA, the community and health workers were sensitized on the need for the MDA, monitoring the safety of medicines and reporting ADRs. This involved TV and radio programmes, media, social media and pre-conferences/meetings. Both active and passive PV methods were employed during the MDA. For active surveillance, monitoring was managed at four levels: community, health facility, district and national levels. A total of 33 PV monitors and supervisors were assigned at national and district levels, and over 8000 drug distributers were involved. Independent monitors in the community were also employed. Community monitors visited communal areas, health facilities and made door to door visits. In addition a 24 hour toll-free call centre was set up to answer queries during the campaign. Reports of ADRs were received at all levels. The district PV supervisors would check for completeness before forwarding reports to the NPC. At the NPC ICSRs were collated, assessed for completeness, assigned severity grading, screened for unknown events and subjected to causality assessments.

Reports were evaluated to identify unknown ADRs, and the range of ADRs to expect, so that health workers can counsel patients and health facilities can know what to monitor. In addition, parameters of non-compliance could be identified. It was found that some patients were not fully compliant, and may have not completed the full three day course or split the doses (e.g. take one tablet twice a day instead of two together). In some circumstances it may have been beneficial to provide incentives, for example, food and water with doses to reduce adverse events. On reflection, it was highlighted that there needs to be better provision of rescue medications. During this campaign the NPC successfully managed information by being available in person at the distribution sites during mass administration, where they built trust and awareness resulting in acceptance of the programme amongst the community.

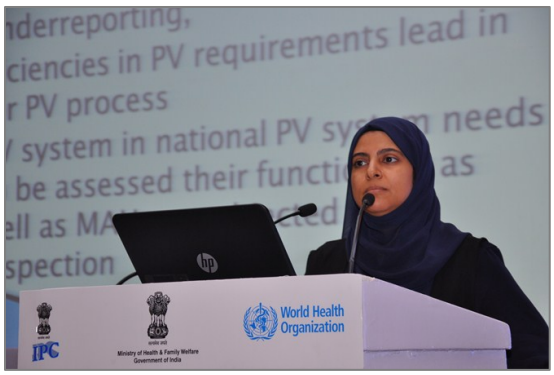
Summary of presentation by O Abiri from Sierra Leone

Eight working groups took place over the first two days of the meeting. Delegates had the opportunity to select and attend two. During the working groups participants took part in discussions and worked together to formulate recommendations for NPCs, WHO and WHO CCs. The recommendations were presented to all participants on day 3 of the meeting. The recommendations will be published in the WHO Pharmaceuticals Newsletter No.1, 2016.

Working Group on PV in Pregnancy

Future meeting

The Sultanate of Oman has offered to host the 39th annual meeting of representatives of the NPCs participating in the WHO PIDM, from 14 to 17 November 2016.



M Juma from the Sultanate of Oman presenting in the updates session