World Health Organization

WHO Pharmaceuticals NEWSLETTER

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

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

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

Safety and Vigilance: Medicines,

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

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

This newsletter also includes a brief report on WHO missions to Lebanon and Ethiopia, for strengthening the national pharmacovigilance systems.

Contents

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Regulatory Matters

Safety of medicines

Signal

Baloxavir marboxil

Risk of bleeding

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for baloxavir marboxil (Xofluza®) should be revised to include bleeding as an adverse drug reaction and include a precaution on co-administration with warfarin.

Baloxavir marboxil is indicated for influenza A and B viral infections.

Patients and their families should be advised to contact their physician if bloody stool, epistaxis, haematuria or other forms of bleeding are observed, up to several days after administration of baloxavir marboxil.

A total of 25 cases of bleeding have been reported in patients treated with baloxavir marboxil in Japan during the previous three fiscal years. For 13 of the 25 cases a causal relationship with the product could not be excluded. Also, to date, three instances of patient mortality have been reported (a causal relationship with baloxavir marboxil could not be established).

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

Reference:
Revision of Precautions, MHLW/PMDA, 1 March 2019 *(www.pmda.go.jp/english/)*

Carbimazole

Risk of acute pancreatitis

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for carbimazole is being updated to include the risk of acute pancreatitis.

Carbimazole is indicated for the treatment of hyperthyroidism, preparation for thyroidectomy, and pre-and post-radioiodine treatment.

In the UK, there have been no reports of acute pancreatitis associated with carbimazole treatment in the last 55 years. However, a small number of reports were received in other countries. The mechanism of action of recurrent acute pancreatitis after re-exposure to carbimazole suggests a possible immunological mechanism.

It is advised that carbimazole is discontinued immediately and switched to an alternative therapy in patients who develop acute pancreatitis during treatment.

Re-exposure to carbimazole should be avoided in patients who have previously experienced acute pancreatitis with carbimazole or its metabolite (thiamazole).

Reference:
Drug Safety Update, MHRA, 18 February 2019 *(www.gov.uk/mhra)*

Deferiprone

Potential risk of brain and nervous system disorders in children

Canada. Health Canada will ask manufacturers to update the safety information for deferiprone (Ferriprox®) to include information on reported cases of neurological disorders in children using recommended doses of deferiprone.

A warning of the risk of neurological disorders in children taking doses 2.5 times higher than the recommended dose already exists in the product information.

Deferiprone is indicated to remove excess iron accumulated in the body from blood transfusions in the treatment of thalassemia syndromes (genetic diseases of blood production).

Health Canada assessed the potential risk of brain and nervous system (neurological) disorders, such as difficulty walking or difficulty with the coordination of movement, in children treated with deferiprone at recommended doses. Health Canada concluded that there may be a link.

Health Canada encourages consumers and health-care professionals to report any adverse drug reactions related to the use of deferiprone.

Reference:
Summary Safety Review, Health Canada, 25 February 2019 *(www.hc-sc.gc.ca)*

Eliglustat

Contraindication: Co-administration of CYP2D6 and CYP3A inhibitors

Japan. The MHLW and the PMDA have announced that the package insert for eliglustat (Cerdelga®) should be revised to state that co-administration with CYP2D6 and CYP3A inhibitors is contraindicated.

Eliglustat is indicated to improve various symptoms of Gaucher disease (anaemia, thrombocytopenia, hepatosplenomegaly and bone disease). Eliglustat is metabolized mainly by CYP2D6 and partially by CYP3A4.

There have been no reports received for the co-administration of eliglustat with CYP2D6 and CYP3A inhibitors in Japan during the previous three fiscal years.

Based on results of an investigation and in consultation with expert advisors, MHLW and PMDA have also advised that the hepatic function of patients should be considered before

prescribing eliglustat. This has also been included in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 12 February 2019 *(www.pmda.go.jp/english/)*

Febuxostat

Increased risk of death

USA. The US Food and Drug Administration (FDA) has added a boxed warning for febuxostat (Uloric®) indicating an increased risk of death compared to its alternative, allopurinol.

This conclusion was based on an in-depth review of results from a safety clinical trial that found an increased risk of heart-related death and death from all causes with febuxostat.

Febuxostat is indicated to treat gout.

It is advised that the use of febuxostat should be reserved for patients who have failed or do not tolerate allopurinol. Patients should be informed about cardiovascular risks with febuxostat and should be advised to seek immediate medical attention if they experience symptoms such as: chest pain, shortness of breath, rapid or irregular heartbeat, numbness or weakness on one side of the body, dizziness, trouble talking, and sudden severe headache.

Reference:
Safety Alerts for Human Medical Products, US FDA, 21 February 2019 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletter No.6, 2017: Potential risk of heart-related death in USA; No.3, 2016: Risk of heart failure in Canada)

Fenspiride

Potential risk of problems with heart rhythm

Europe. The European Medicines Agency (EMA) has announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended an EU-wide suspension of preparations containing fenspiride (Epistat®, Eurefin®, Eurespal® and others) due to the potential risk of problems with heart rhythm.

Fenspiride is indicated to relieve cough caused by lung diseases in children and adults.

Cases of problems with heart rhythm had been reported in patients who had taken fenspiride in the past. An exploration of animal studies show that fenspiride has the potential to prolong the QT interval in humans.

PRAC will now examine all the available evidence and make recommendations on the action to be taken by marketing authorizations on fenspiride medicines across the EU.

Health-care professionals should advise their patients to stop taking preparations containing fenspiride.

Reference:
EMA, 15 February 2019 *(www.ema.europa.eu)*

Finasteride

Potential risk of suicidal ideation

Canada. Health Canada has requested that manufacturers update the product information for finasteride (Proscar® and Propecia®) to include the potential risk of suicidal thoughts and/or behaviour (suicidal ideation).

Finasteride is used to treat prostate gland enlargement (Proscar®), and male pattern hair loss (Propecia®).

A re-assessment of initial reviews in 2012 and 2014 found that the Canadian reporting rate for finasteride and suicide/self-injury-related events increased by 2.5 times between 2012 and 2016.

To date, Health Canada has received 26 reports of suicide and/or self-injury-related events reported in patients treated with finasteride. A search in the WHO global database of Individual Case Safety Reports, Vigibase (up to September 16, 2018), found 368 international reports. Health Canada has concluded that there may be a link between finasteride use and the risk of suicidal ideation.

Reference:
Summary Safety Review, Health Canada, 26 February 2019 *(www.hc-sc.gc.ca)*

(See WHO Pharmaceuticals Newsletter No.6, 2017: Risk of depression and suicidal thoughts in France; No.4, 2017: Rare reports of depression and suicidal thoughts in UK; No.1, 2016: Risk of suicidal thoughts and behaviour in Canada)

Fingolimod

Risk of worsening multiple sclerosis symptoms

Canada. Health Canada has updated the product information for fingolimod (Gilenya®) to include the risk of worsening multiple sclerosis (MS) symptoms following withdrawal (rebound effect).

Fingolimod is indicated to treat MS, and is specifically recommended for patients who have had a poor response to, or are unable to tolerate, one or more of the other therapies for MS.

Health Canada identified 29 international reports of severe worsening of MS disease progression after fingolimod withdrawal. Also, Health Canada reviewed information from the manufacturer and the scientific literature on the risk of a rebound effect following

withdrawal of treatment with fingolimod.

Health Canada's review concluded that there may be a link between the withdrawal of fingolimod and the worsening of MS symptoms (rebound effect).

Reference:
Summary Safety Review, Health Canada, 28 February 2019 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletter No.3, 2017: Potential rebound effect after stopping or switching therapy in UK)

Glecaprevir hydrate/pibrentasvir combination

Risk of hepatic impairment and jaundice

Japan. The MHLW and the PMDA have announced that the package insert for glecaprevir hydrate/pibrentasvir (Maviret Combination®) should be revised to include hepatic impairment and jaundice as adverse drug reactions.

Glecaprevir hydrate/pibrentasvir preparation is indicated to improve viraemia in patients with chronic hepatitis C or compensated cirrhosis C. Hepatic impairment accompanied with elevation of AST, ALT, or bilirubin levels and jaundice may occur.

Eleven cases involving hepatic impairment have been reported in patients treated with glecaprevir hydrate/pibrentasvir in Japan during the previous three fiscal years. For five of the 11 cases a causal relationship with the product could not be excluded. One of the 11 cases was fatal, a causal relationship with the product could not be established.

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

Reference:
Revision of Precautions, MHLW/PMDA, 12 February 2019 *(www.pmda.go.jp/english/)*

Hydrochlorothiazide

Potential risk of non-melanoma skin cancer (NMSC)

1. Canada. Health Canada has requested manufacturers to update the product safety information for all hydrochlorothiazide-containing products to include the potential risk of non-melanoma skin cancer (NMSC).

Hydrochlorothiazide is used to treat high blood pressure and excess build-up of fluid.

Health Canada reviewed five studies that investigated the risk of NMSC with the use of hydrochlorothiazide alone or in combination with other medicines using data from thousands of patients. Health Canada's review suggests that there might be a risk of NMSC with prolonged use of hydrochlorothiazide.

Patients taking hydrochlorothiazide should be informed of potential risk factors (e.g. light-coloured skin, known personal or family history of skin cancer and ongoing immunosuppressive therapy) for NMSC and advised to regularly check their skin for new marks or growths as well as changes to existing ones.

Reference:
Summary Safety Review, Health Canada, 30 January 2019 *(www.hc-sc.gc.ca)*

2. Singapore. The Health Sciences Authority (HSA) has updated health-care professionals on the risk of NMSC with hydrochlorothiazide following the results from two recent pharmacoepidemiological studies using Danish registries.

The HSA has considered the EMA's conclusions, which suggest a biologically plausible mechanistic model supporting the increased risk of NMSC following higher cumulative doses of hydrochlorothiazide. HSA also considered Health Canada's conclusion that NMSC is a potential risk of prolonged hydrochlorothiazide treatment. However, uncertainty remains due to limitations in the studies.

HSA has not received any local reports of NMSC suspected to be associated with the use of hydrochlorothiazide.

While HSA's safety review is ongoing, health-care professionals should consider the findings from the two Danish pharmacoepidemiological studies when prescribing hydrochlorothiazide to their patients.

Reference:
Product Safety Alerts, HSA, 8 March 2019 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.1, 2019: Risk of non-melanoma skin cancer in Egypt; No. 6, 2018: Risk of non-melanoma skin cancer in UK)

Lithium

Risk of major congenital malformations

New Zealand. Medsafe has announced that it is working with manufacturers of lithium-containing medicines to provide up-to-date information on the risk of major congenital malformations with lithium use during pregnancy.

Lithium is a mood stabiliser used in the treatment of bipolar disorder.

Two recently published studies investigated the risk of congenital cardiac malformations. As a result, the risk was estimated at around 2-2.5% in both studies, while

the background rate of congenital cardiac malformations is around 1%.

Up to 1 November 2018, four cases of congenital malformations associated with the use of lithium in pregnancy had been reported to the Centre for Adverse Reaction Monitoring (CARM). Three of the cases described cardiac defects.

It is important for prescribers to discuss the benefits and risks of continuing lithium during pregnancy with women who have bipolar disorder and who are planning to, or have become pregnant.

Reference:
Prescriber Update, Vo. 40, No.1, Medsafe, March 2019 *(www.medsafe.govt.nz/)*

Macitentan

Potential risk of liver injury

Canada. Health Canada has requested that manufacturers update the safety information for macitentan (Opsumit®) to include the risk of liver injury.

Macitentan is used to treat certain types of pulmonary arterial hypertension (PAH).

Health Canada reviewed 15 Canadian reports of liver injury with macitentan. Of these reports, 14 were not found to be relevant to this review (e.g. duplicated, did not meet the definition), and it was determined that the liver injury was unlikely to be linked to the use of macitentan in the one remaining case.

Health Canada also assessed 16 relevant international reports. The link was found in one report, found to be possible in 13 reports and unlikely in one report.

Health Canada encourages consumers and health-care professionals to report any adverse drug reactions related to the use of macitentan.

Reference:
Summary Safety Review, Health Canada, 1 March 2019 *(www.hc-sc.gc.ca)*

Nivolumab (genetical recombination)

Risk of serious blood disorder

Japan. The MHLW and the PMDA have announced that the package insert for nivolumab (Opdivo®) should be revised to include haemophagocytic syndrome, haemolytic anaemia and agranulocytosis as adverse drug reactions.

Nivolumab is indicated for various kinds of cancers (e.g. malignant melanoma, unresectable advanced or recurrent non-small cell lung cancer and relapsed or refractory classical Hodgkin lymphoma).

A total of 10 cases involving haemophagocytic syndrome have been reported in patients treated with nivolumab in Japan during the previous three fiscal years. For three of the 10 cases a causal relationship with the product could not be excluded. Likewise, a total of 15 cases involving haemolytic anaemia have been reported and a causal relationship could not be excluded. One fatal case has been reported. A total of 33 cases involving neutropenia (including agranulocytosis) have been reported, and a causal relationship could not be excluded for 12 cases.

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

Reference:
Revision of Precautions, MHLW/PMDA, 12 February 2019 *(www.pmda.go.jp/english/)*

Opioids

Potential risk of opioid use disorder and related harms in children and adolescents

Canada. Health Canada has asked manufacturers to update the product safety information of opioid-containing cough and cold products to include limitations on the recommended age of use (adults only: 18 years of age and older).

Opioid-containing cough and cold products have been marketed in Canada since the 1950s. There are three prescription opioid drugs authorized to treat cough symptoms in adults and children in Canada: codeine, hydrocodone and normethadone. Low-dose codeine is also available without a prescription in most provinces. Currently, codeine products are not recommended for children under 12 years of age, and hydrocodone and normethadone products are not recommended for children under six years of age.

Health Canada reviewed the risk of opioid use disorder and related harms from these products and found limited evidence to link opioid-containing cough and cold products with opioid use disorders and related harms in children and adolescents.

Health Canada will also inform Canadians and health-care professionals about these updates.

Reference:
Summary Safety Review, Health Canada, 18 February 2019 *(www.hc-sc.gc.ca)*

(See WHO Pharmaceuticals Newsletter No.6, 2018: Life-threatening and fatal opioid toxicity from accidental exposure in UK; No.1, 2018: Limited use: Only for adults of 18 years of age and older in USA)

Oseltamivir

Risk of bleeding

Japan. The MHLW and the PMDA have announced that the package insert for oseltamivir (Tamiflu®) should be revised to include bleeding as an adverse drug reaction and include a precaution on co-administration of warfarin. Oseltamivir is indicated for treatment and prophylaxis of influenza A and B viral infections.

A total of 30 cases of bleeding have been reported in patients treated with oseltamivir in Japan during the previous three fiscal years. For three of the 30 cases, a causal relationship with the product could not be excluded. No patient mortalities have been reported to date. Also, no cases of bleeding in patients who were taking oseltamivir and warfarin together have been reported.

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

Reference:
Revision of Precautions, MHLW/PMDA, 1 March 2019 *(www.pmda.go.jp/english/)*

Palbociclib

Risk of interstitial lung disease

Japan. The MHLW and the PMDA have announced that the package insert for palbociclib (Ibrance®) should be revised to include interstitial lung disease as an adverse drug reaction.

Palbociclib is indicated for unresectable or recurrent breast cancer. When using palbociclib, patients should be carefully monitored for initial symptoms such as dyspnoea, cough and pyrexia, and by performing a chest X-ray etc.

A total of 12 cases involving interstitial lung disease have been reported in patients treated with palbociclib in Japan during the previous three fiscal years. For six of the 12 cases, a causal relationship with the product could not be excluded. Although a causal relationship with the product could not be established, out of the 12 cases, two cases of patient mortality have been reported.

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

Reference:
Revision of Precautions, MHLW/PMDA, 12 February 2019 *(www.pmda.go.jp/english/)*

Pembrolizumab

Risk of haemophagocytic syndrome and agranulocytosis

Japan. The MHLW and the PMDA have announced that the package insert for pembrolizumab (Keytruda Injection®) should be revised to include haemophagocytic syndrome and agranulocytosis as adverse drug reactions.

Pembrolizumab is indicated for malignant melanoma, unresectable advanced or recurrent non-small cell lung cancer, and relapsed or refractory classical Hodgkin lymphoma.

A total of nine cases involving haemophagocytic syndrome and seven cases involving neutropenia (including agranulocytosis) have been reported in patients treated with pembrolizumab in Japan during the previous three fiscal years. For seven of the nine cases involving haemophagocytic syndrome, a causal relationship with the product could not be ruled out. One case was fatal, and a causal relationship could not be established. In four of the seven cases reporting neutropenia, a causal relationship with the product could not be excluded.

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

Reference:
Revision of Precautions, MHLW/PMDA, 12 February 2019 *(www.pmda.go.jp/english/)*

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Risk of Fournier's gangrene

United Kingdom. The MHRA has announced that warnings about Fournier's gangrene will be added to the product information for all sodium-glucose co-transporter 2 (SGLT2) inhibitors.

SGLT2 inhibitors are indicated for the treatment of type-2 diabetes. SGLT2 inhibitors authorised in the UK include dapagliflozin (Edistride®), canagliflozin (Invokana®) and ertugliflozin (Steglatro®).

Fournier's gangrene is necrotising fasciitis of the genitalia or perineum and usually occurs almost exclusively in men.

Although diabetes mellitus is a risk factor for the development of Fournier's gangrene, some of the EU post-marketing reports were considered to possibly be related to the use of SGLT2 inhibitors.

The MHRA has received six cases (four in men and two in women) of Fournier's gangrene in association with SGLT2 inhibitors (up to January 2019).

Patients taking SGLT2 inhibitors are advised to seek urgent medical attention if they experience: severe pain,

tenderness, erythema, and swelling in the genital or perineal area accompanied by fever or malaise. If Fournier's gangrene is suspected, SGLT2 inhibitor treatment should be stopped and urgent alternative treatment started as appropriate.

Reference:
Drug Safety Update, MHRA, 18 February 2019 *(www.gov.uk/mhra)*

Trastuzumab (genetical recombination)

Risk of lysis syndrome

Japan. The MHLW and the PMDA have announced that the package inserts for trastuzumab products (Herceptin® and Trastuzumab BS®) should be revised to include lysis syndrome as an adverse drug reaction.

Trastuzumab is indicated for certain types of breast and gastric cancers. Patients should be carefully monitored by checking serum electrolyte levels and renal function. If any abnormalities are observed, administration of trastuzumab should be discontinued and appropriate measures such as management of hyperuricaemia should be taken.

A total of three cases involving lysis syndrome have been reported in patients treated with trastuzumab in Japan during the previous three fiscal years. For two of the three cases, a causal relationship with the product could not be excluded. Out of the three cases, one case of patient mortality has been reported, although a causal relationship with the product could not be established.

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

Reference:
Revision of Precautions, MHLW/PMDA, 12 February 2019 *(www.pmda.go.jp/english/)*

Carbimazole

Increased risk of congenital malformations

United Kingdom. The MHRA has announced that there is an increased risk of congenital malformations in babies born to women taking carbimazole during pregnancy (particularly during the first trimester and in high doses). Women of childbearing potential are advised to use effective contraception during treatment with carbimazole.

Carbimazole is indicated for the treatment of hyperthyroidism, including preparation for thyroidectomy and treatment before and after radioiodine treatment.

Carbimazole crosses the placental barrier and can cause foetal harm. An EU review concluded that there was evidence that carbimazole is associated with an increased risk of congenital malformations, especially when administered in the first trimester of pregnancy and at high doses (15 mg or more of carbimazole daily).

Reported malformations include: aplasia cutis congenita, craniofacial malformations, defects of the abdominal wall and gastrointestinal tract, and ventricular septal defect.

Carbimazole should only be used during pregnancy when clinically indicated, after a strict individual benefit-harm assessment, and only at the lowest effective dose without additional administration of thyroid hormones. The use of carbimazole during pregnancy should be preserved for situations in which a definitive therapy of the underlying disease was not suitable prior to pregnancy, and in cases of new occurrence or reoccurrence during pregnancy. If carbimazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended.

Reference:
Drug Safety Update, MHRA, 18 February 2019 (*www.gov.uk/mhra*)

Chlorhexidine digluconate

Reports of serious eye injury due to errors in administration

WHO. WHO has issued an alert about multiple reports of administration errors causing eye injuries, such as blindness, following incorrect route of administration of chlorohexidine gluconate (CHX) to the eyes instead of to the umbilical cord in newborns.

Chlorhexidine gluconate (CHX), is available as an aqueous solution or as a gel (delivering 4% chlorhexidine), and is applied to the umbilical cord stump during the first week of life for newborns who are born at home in settings with high neonatal mortality (neonatal mortality rate >30 per 1000).

Clean, dry cord care is recommended for newborns born in health facilities, and at home in low neonatal mortality settings. Use of chlorhexidine in these situations may be considered only to replace application of a harmful traditional substance such as cow dung to the cord stump. The use of CHX is being implemented in many countries (South Asia and sub-Saharan Africa) as part of a package of essential newborn interventions to reduce the incidence of omphalitis. It is also listed in the WHO Essential Medicines List.

CHX causes serious harm if mistakenly applied to the eyes, resulting in severe eye injuries. Over forty (40) cases of such incorrect administration are recorded, either as media reports, or in the literature, since 2015. Injuries associated with both the liquid and gel (ointment) formulations have been reported when CHX was mistaken for eye drops or ointments. All health-care professionals, caregivers and others involved in the distribution, use and/or administration of chlorehexidine 4% gel or solution, are advised to take all necessary measures and precautions to ensure its correct use and administration.

Suggestions to National Neonatal and Reproductive Health Programmes and/or Regulators include the following:

- Assess what products are part of the newborn package and select the optimal primary container/dosage form for CHX or modify the design of the container to distinguish the product from other medicines typically used for newborns.
- Update the product label with appropriate information on the safe use of the product.
- Develop more detailed instructions for users (flyers, posters, pictorials etc.) that are culturally appropriate and easy to understand, to ensure correct use of the product.
- Train health-care professionals who interact with mothers and/or provide the product to ensure full understanding of the indications and contraindications for use and application methods.

All stakeholders are advised to remain alert to incidents of eye injury with CHX in their settings and to report these to their National Regulatory Authority (NRA). Member States are reminded that adverse events associated with the use of any medicinal product should be reported to the NRA.

Reference:
Information Exchange System Alert No. 133, WHO,

25 February 2019
(www.who.int/medicines/regulation/medicines-safety/drugsafetyalerts/en/)

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Risk of bullous pemphigoid

New Zealand. Medsafe has warned that some medicines, including dipeptidyl peptidase-4 (DPP-4) inhibitors have been associated with bullous pemphigoid. Bullous pemphigoid is an autoimmune blistering skin disease that mainly affects the elderly.

DPP-4 inhibitors are indicated to treat type-2 diabetes mellitus. Vildagliptin, sitagliptin and saxagliptin are approved DPP-4 inhibitors in New Zealand.

Recently, DPP-4 inhibitors have been associated with bullous pemphigoid. Evidence for this association was initially based on case reports and analysis of the national pharmacovigilance database. Currently more evidence is available from controlled observational studies. The pathomechanism underlying the association between DPP-4 inhibitors and bullous pemphigoid is not yet fully understood.

It is advised that DPP-4 should be discontinued if it is suspected to be causing bullous pemphigoid. First-line treatment of bullous pemphigoid involves topical or systemic corticosteroids and supportive care.

Reference:
Prescriber Update, Vo. 40, No.1, Medsafe, March 2019
(www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.4, 2018: Risk of pemphigoid in Japan; No.3, 2018: Potential risk of a skin reaction (bullous pemphigoid) in Canada; No.6 & No. 3, 2016: Risk of pemphigoid in Japan)

Fluoroquinolones

Risk of aortic aneurysm and dissection

Singapore. The HSA has announced that there is a potential risk of aortic aneurysm and dissection associated with systemically used fluoroquinolones.

Fluoroquinolones are broad spectrum antibiotics that interfere with bacterial DNA replication and exert bactericidal activity. There are seven systemic fluoroquinolones registered in Singapore, these include ofloxacin and levofloxacin.

Across multiple epidemiological studies published between 2015 and 2018, there appears to be consistent evidence pointing to an approximately two-fold increased risk of aortic aneurysm or dissection observed with fluoroquinolone use.

Although the HSA has not received any local reports for aortic aneurysm or dissection associated with fluoroquinolones, health-care professionals are advised to take into consideration the above safety information.

Reference:
Product Safety Alerts, HSA, 8 March 2019
(*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.1, 2019: Risk of aortic aneurysm and aortic dissection in Japan; No.6, 2018: Potential risk of aortic aneurysm and dissection in UK)

Paracetamol (modified-release preparations)

Unpredictable pharmacokinetics in overdose

New Zealand. Medsafe has warned that overdoses of modified-release paracetamol medicines are difficult to treat due to prolonged absorption and unpredictable pharmacokinetics.

The Medicines Adverse Reaction Committee (MARC) reviewed the safety of modified-release paracetamol, following the suspension of these preparations in Europe.

The modified-release tablets contain both immediate-release paracetamol (31%) and slow-release paracetamol (69%). Treatment with N-acetyl cysteine in the early stage can prevent these effects but this is limited.

Overdoses of paracetamol have the potential to cause liver failure. Overdose with modified-release paracetamol results in a prolonged and unpredictable patterns of paracetamol absorption. This may lead to a delayed peak in serum paracetamol concentration.

Modified-release paracetamol has been reclassified from Pharmacy Only to Restricted Medicine, so that pharmacists can provide more information on dosing to patients.

Medsafe advises patients to contact the Poisons Centre if an overdose with modified-release paracetamol is suspected.

Reference:
Prescriber Update, Vo. 40, No.1, Medsafe, March 2019
(www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.1, 2018: Suspension in EU market: due to difficulty in managing overdose in EU; No.5, 2017: Modified- or prolonged-release preparations should be suspended from marketing in EU; No.1, 2017: Reminder of authorised dose regimen; possible need for continued treatment with NAC in UK; No.5, 2012: New guidance on treating paracetamol overdose with intravenous acetylcysteine in UK; Accidental paracetamol poisoning in Australia)

Rivaroxaban

Potential risk of bleeding by drug-drug interaction

New Zealand. Medsafe has announced that rivaroxaban (Xarelto®) could cause

bleeding as a result of a drug-drug interaction.

Rivaroxaban is a direct-acting oral anticoagulant like dabigatran and is indicated for prevention of venous thromboembolism, stroke and systemic embolism, and deep vein thrombosis. Rivaroxaban is metabolized by both CYP3A4 and P-glycoprotein (P-gp) and therefore contraindicated in patients taking medicines that inhibit both CYP3A4 and P-gp (e.g. ritonavir and voriconazole). Also, rivaroxaban is contraindicated in patients with a creatinine clearance <15 mL/min, and in patients with significant hepatic disease.

Between January 2014 and December 2018, the CARM received 49 reports of bleeding with the use of rivaroxaban. Nineteen of these cases described events indicative of bleeding. There were also three reports of stroke.

Reference:
Prescriber Update, Vo. 40, No.1, Medsafe, March 2019 *(www.medsafe.govt.nz/)*

(See WHO Pharmaceuticals Newsletter No.3, 2016: Risk of thrombocytopenia in Japan; No.2, 2016: Benefit-risk balance of rivaroxaban: unchanged in EU; No.6, 2013: Apixaban, dabigatran and rivaroxaban in UK)

Tofacitinib

Increased risk of blood clots in the lungs and death

USA. The FDA has issued a safety alert to the public about results of a clinical trial that found an increased risk of blood clots in the lungs, and death with the use of tofacitinib (Xeljanz® and Xeljanz XR®) at higher doses of 10mg, twice a day compared to patients treated with a lower dose of tofacitinib 5mg, twice daily, or a tumor necrosis factor inhibitor.

Tofacitinib is indicated to treat rheumatoid arthritis (RA) in adult patients not responding to methotrexate. Tofacitinib works by decreasing the activity of the immune system.

FDA has not approved a 10 mg twice daily dose for RA (this dose is only approved in the dosing regimen for patients with ulcerative colitis). In the ongoing safety trial required by the FDA, the drug manufacturer is transitioning patients who were on the high 10 mg twice daily dose to the lower, currently approved dose of 5 mg twice daily. The trial is expected to be completed by the end of 2019.

Health-care professionals should follow the recommendations in the prescribing information for tofacitinib and monitor patients for signs and symptoms of pulmonary embolism. Patients should not discontinue or change the dose of tofacitinib without consulting with health-care professionals, as this may worsen the condition.

Reference:
Safety Alerts for Human Medical Products, US FDA, 25 February 2019 *(www.fda.gov)*

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

The signals in this Newsletter are based on information derived from reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 18 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC's current routine signal detection process. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 26). For information on the UMC Measures of Disproportionate reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. For more information, on the UMC Measures of Disproportionate Reporting etc., 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.

Esomeprazole and gynaecomastia in obese adults

Dr. Anthony Wong, Brazil

Summary

Gynaecomastia is the abnormal swelling of the mammary glands in males and the causes can be physiological, metabolic, idiopathic, pharmacologic or iatrogenic. About a quarter of cases can be idiopathic or secondary to pathologies affecting levels of circulating sexual hormones. A consistent proportion of cases (20%) is iatrogenic in origin, including pharmacologic, from hormone supplementation or adverse drug effects. Among these are exogenous oestrogens, anti-androgens, 5-alpha-reductase inhibitors, spironolactone and antiulcer drugs (cimetidine, proton-pump inhibitors). Gynaecomastia is stated as an adverse reaction for esomeprazole in both the United States (US) Food and Drug Administration (FDA) label and in the United Kingdom (UK) Summary of Product Characteristics (SmPC). However, obesity is not described as a risk group for this drug-induced gynaecomastia. In a screening of VigiBase, the WHO global database of individual case safety reports, esomeprazole and gynaecomastia was found to be disproportionately overreported in obese adults (BMI>30). The observed number of reports was 6 compared to 0.6 expected. For esomeprazole and gynaecomastia in general, the observed number of reports was 92 and the expected 80. The series presented here is of the six obese patients who developed breast enlargement. Five of them experienced the gynaecomastia after taking esomeprazole and one after taking ranitidine for 7 $^{1}/_{2}$ years. Only two patients reported remission of the target symptom after esomeprazole withdrawal. Among the four subjects who did not present regression of the gynaecomastia, three were very obese (BMI>36), and two whose breast enlargements regressed had BMIs of 31.6 and 31.8. Obesity is often associated with increased oestrogen due to extragonadal conversion from androgen by tissue aromatase and since esomeprazole is known to cause gynaecomastia, this can have an additive effect. There are also indications of the reaction being more difficult to reverse. However, since this is a small case series, a more extensive review is needed.

Introduction

Gynaecomastia is the abnormal swelling of the mammary glands in males and can be either physiological, metabolic, idiopathic, pharmacologic or iatrogenic in cause. Mammary glandular tissue proliferation is physiologically stimulated by oestrogens and inhibited by androgens. Gynaecomastia is usually the result of the increased ratio of free-circulating oestrogens/androgens or their altered effects on their correspondent intracellular receptors in mammary tissue.

The majority of gynaecomastia cases have physiologic causes (neonatal, pubertal and senile gynaecomastia). About a quarter can be idiopathic or secondary to pathologies affecting levels of circulating sexual hormones (i.e. testicular or adrenal neoplasias, hepatic cirrhosis, hyperthyroidism, hypogonadism, obesity, refeeding syndrome). A consistent proportion of cases (20%) is iatrogenic in origin, including pharmacologic, from hormone supplementation or adverse drug effects. Among these are exogenous oestrogens, anti-

androgens, 5-alpha-reductase inhibitors, spironolactone and antiulcer drugs (cimetidine, proton-pump inhibitors).[1]

Esomeprazole is a proton-pump inhibitor used to treat gastroesophageal reflux disease (GERD), helicobacter pylori-associated ulcers in combination with antibiotics, as well as to treat and prevent NSAID-associated ulcers. It acts by inhibiting the enzyme H+K+-ATPase and thus inhibits both basal and stimulated acid secretion.[2]

Reports in VigiBase

In a screening of VigiBase, the WHO global database of individual case safety reports, esomeprazole and gynaecomastia was found to be disproportionately overreported in obese adults (BMI>30). The observed number of reports was 6 compared to 0.6 expected. For esomeprazole and gynaecomastia in general, the observed number of reports was 92 and the expected 80. The present commentary is on the six cases reporting the possible association of esomeprazole, a proton-pump inhibitor and the occurrence of gynaecomastia in obese adults. The cases were retrieved from VigiBase on 10 January 2018, and were as follows:

1. An adult male obese patient (BMI=36.2), age not given, had taken esomeprazole for gastroesophageal reflux and diclofenac for pain during an unknown period. He presented enlargement after an unstated time. He did not smoke and reported very little alcohol consumption. There was no reference as to follow-up nor whether the breast enlargement was resolved.
2. A 77-year old slightly obese man (BMI=31.6) was taking esomeprazole (between January and August 2016) for haemorrhage of digestive tract and spironolactone for heart failure. Breast enlargement was noted in July, so both drugs were suspended in early August and the problem resolved. However, due to a recurrence of gastric symptoms, esomeprazole was reintroduced at the end of the same month. Breast enlargement did not recur. There is no mention that spironolactone was also added to his regimen.
3. A 51-year old male, very obese (BMI=41.3), received esomeprazole for two years and lercanidipine for five years, as well as hydrochlorothiazide and tramadol for unspecified periods. He developed left breast enlargement after taking the drugs for several years. A mammogram showed an apparently normal well-developed breast, without adenopathy. The enlargement persisted despite dechallenge and rechallenge of esomeprazole and lercanidipine.
4. A 61-year old slightly obese male patient (BMI=31.8), with non-Hodgkin B type lymphoma (stage 4) with multiple adenopathies and obstructive renal insufficiency (urethral infiltration), who had been a heavy smoker, was prescribed esomeprazole, amlodipine and diclofenac. He received esomeprazole 20 mg due to gastric pain and gastroesophageal reflux, and had the dose doubled to 40 mg after three days. Two days later, he developed pain and enlargement of both breasts. The gynaecomastia regressed within four weeks. Hormone levels were not checked.
5. A 60-year old male (BMI=30.4), with sarcoidosis and pyrosis, who had been taking ranitidine for over 7 $^{1}/_{2}$ years, switched to omeprazole (20 mg twice a day) for seven months and then esomeprazole (20 mg twice a day). He developed breast enlargement when on ranitidine, so one month later he began taking omeprazole and later switched to esomeprazole. Gynaecomastia persisted even after the switches.
6. A 43-year old very obese male (BMI=39.0) received esomeprazole for five months for gastroesophageal reflux. Soon after, he reported decreased libido, partial erectile difficulty and breast enlargement. After discontinuation of the drug, he recovered erection and libido, but gynaecomastia persisted.

Literature and Labelling

Gynaecomastia is stated as an adverse reaction for esomeprazole in both the United States (US) Food and Drug Administration (FDA) label and in the United Kingdom (UK) Summary of Product Characteristics (SmPC). However, obesity is not described as a risk group for this drug-induced gynaecomastia in either source.[2,3]

Discussion

The series presented here is of six patients who developed breast enlargement. Five of them developed the gynaecomastia after taking esomeprazole and one after taking ranitidine for 7 $^{1}/_{2}$ years (he also received omeprazole and esomeprazole after gynaecomastia). Only two patients reported remission of the target symptom after esomeprazole withdrawal. The series is too small for statistical analysis, but an interesting factor is that esomeprazole and gynaecomastia was disproportionately overreported for obese adults but not for esomeprazole and gynaecomastia in general. Among the four subjects who did not present regression of the gynaecomastia, three were very obese (BMI>36), and two whose breast enlargements regressed had BMIs of 31.6 and 31.8.

Male obesity can often be associated with true gynaecomastia as this condition is caused by an imbalance between oestrogen action relative to

androgen action at the breast tissue level. Increased extragonadal conversion of androgens to oestrogens by tissue aromatase, as occurs in obesity.[4] However, sometimes adipose tissue accumulation at breast level can be mistaken for real gynaecomastia. This condition, particularly frequent in overweight subjects, takes the name of pseudo-gynaecomastia. Often gynaecomastia and pseudo-gynaecomastia are both present in the same subject at the same time.[5]

Patient 2 also received spironolactone, which has strongly been associated with gynaecomastia. Upon withdrawal of both drugs, the mammary enlargement regressed and did not recur, even when esomeprazole was re-introduced, but not spironolactone. It appears that spironolactone promotes gynaecomastia through the inhibition of 17-β hydroxysteroid dehydrogenase.[6]

Patient 5, with the lowest BMI (30.4), who had persistent enlarged breasts, had been taking ranitidine for over 7 $^{1}/_{2}$ years. Ranitidine, like cimetidine, is a H2 histamine receptor blocker and one of the drug classes that has been implicated with gynaecomastia, with relative risk >7 for treated patients, and strongly dose-dependent.[5]

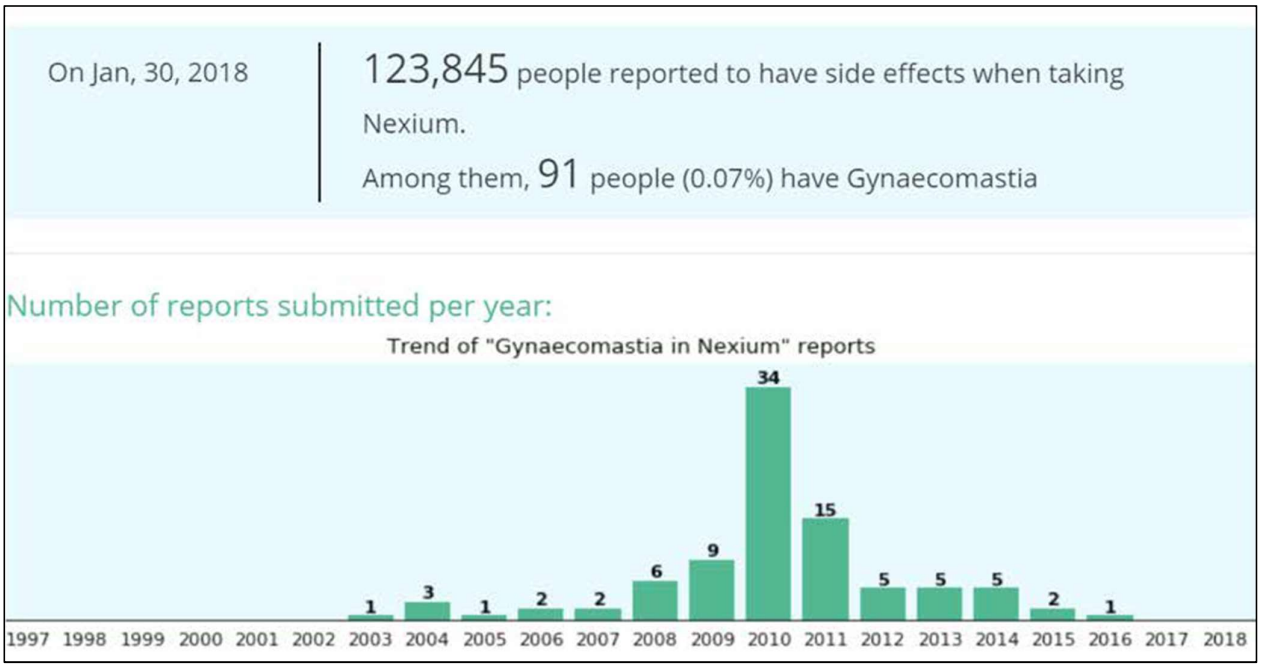
Omeprazole and its S-enantiomer esomeprazole at high concentrations appear to inhibit cytochrome P450 (CYP) 3A4 – which strongly catalyses the oxidation of estradiol, its major catabolic pathway – giving rise to an increase in estradiol levels.[7] Omeprazole is extensively metabolised by CYP2C19, for which >15 variant alleles associated with a decreased metabolism have been identified (the frequency of poor metabolisers among Europeans ranges from 1% to 6% [8,9]) and it is possible that such patients, when treated for long periods with higher doses of omeprazole, would be at particular risk for the development of gynaecomastia. For anti-histamines such as cimetidine, a similar mechanism mediated by CYP3A4, in combination with an androgenic receptor blockage, has been proposed.[10]

In VigiBase, the association of gynaecomastia and proton-pump inhibitors is disproportionately overreported for lansoprazole and omeprazole. Furthermore, the association of esomeprazole and gynaecomastia appears to be quite significant, according to recent pharmacovigilance statistics presented in the United States (figure 1).[11]

Conclusion

Esomeprazole is known to cause gynaecomastia, as stated in the label. Their metabolic pathway appears to catalyse oxidation of estradiol, thereby increasing estradiol levels, and is strongly dose dependent. In this particular series, all six patients with gynaecomastia were obese, whereas the breast enlargement regressed upon removal of esomeprazole in the two mildly obese patients, but not in the remaining four very obese patients. Obesity is often associated with increased oestrogen due to extragonadal conversion from androgen by tissue aromatase and since esomeprazole is known to cause gynaecomastia, this can have an additive effect. There are also indications of the reaction being more difficult to reverse. However, since this is a small case series, a more extensive review is needed.

Figure 1. Report statistics on Nexium and gynaecomastia (from FDA reports)[11]



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Glibenclamide/glyburide and palpitations in the Asian population

Raquel Herrera Comoglio, Argentina

Summary

Glibenclamide (glyburide in the US) is an oral blood glucose lowering drug (BGLD), a second-generation, long-acting sulfonylurea (SU) approved for use in the US in 1984, following its introduction in Europe by several years; in other countries it was approved later (in Singapore in 1990). SUs are currently first-line agents or an add-on therapy to other oral hypoglycaemic agents (OHAs), usually metformin. About a quarter of newly-diagnosed patients initiate therapy with SUs.

Sulfonylureas stimulate insulin release by binding to specific sites on the beta cells (insulin secretagogue agent). As other SUs, glibenclamide is metabolized in the liver and excreted by the kidney. The genetically polymorphic cytochrome P450 (CYP), enzyme CYP2C9 is mainly responsible for the hepatic metabolism of sulfonylureas (SUs). It has been found that pharmacokinetics of glibenclamide depends significantly on CYP2C9 genotypes. CYP2C9 pharmacogenetic variants are more frequent in South-Asian populations (10-25%) than in Caucasian ones (2%–6%).

Hypoglycaemia, a very well-known type A adverse effect of glibenclamide and other BGLDs, can manifest through a variety of symptoms. Palpitations are an unspecific symptom that can be the expression of the adrenergic counter-regulation to hypoglycaemia.

One hundred individual case safety reports (ICSRs) with the combination glibenclamide and palpitations were retrieved from VigiBase, the WHO global database of ICSRs on 15 January 2018. Many also mention other related terms, including

hypoglycaemia, sweating and blurred vision. Half of the set came from South-Asian countries. In the 59 reports in which time to onset (TTO) could be calculated, it ranged from 0 days to 20 years, with the majority (30 reports) in the 0 to 10 days group. Of these 30 reports, 21 originated from South-Asian countries.

To the best of our knowledge, for glibenclamide there is no regulatory labelling or warning that refers to an increased risk of hypoglycaemia in patients with defective isoenzyme genetics.

ICSRs contain limited information, and a patient's pharmacogenetic status is usually never stated. In spite of these known limitations, we have identified characteristics of ICSRs mentioning glibenclamide as a suspected drug, and palpitations as an early hypoglycaemic symptom that could be suggestive of a defective metabolism (short time-to-onset, geographic region). We hypothesize that patients presenting with hypoglycaemia and with a short TTO could have defective genetic variants, and therefore this is considered a signal.

Introduction

Glibenclamide is an oral blood glucose lowering drug (BGLD), a second-generation sulfonylurea (SU). SUs induce glucose-independent insulin release from the pancreatic β-cells by binding to the ATP-sensitive potassium (KATP) channel. The polymorphic enzyme cytochrome P450 (CYP) 2C9 is the main enzyme catalysing the biotransformation of SUs.

Hypoglycaemia is a pharmacological, dose-dependent (type A) adverse effect of blood glucose lowering agents, especially insulin and insulin secretagogues. Mild hypoglycaemia is associated with adrenergic and neurogenic symptoms, such as tremor, palpitations and perspiration. Severe hypoglycaemia is characterized by symptoms related to reduced glucose to the brain, such as weakness, poor concentration, slurred speech, confusion or even seizure or coma.

In normal individuals, hypoglycaemic counter regulation is a multifactorial process that involves reduction of insulin secretion, increasing glucagon secretion, adrenergic activation, increased growth hormone and cortisol secretion. Hypoglycaemia increases plasma levels of both epinephrine and norepinephrine, released primarily from the adrenal medulla. Recovery from hypoglycaemia is dependent on the adrenergic response. Individuals with preserved autonomic neurological response manifest these higher levels of catecholamines through palpitations, increased heart rate, piloerection, etc.[1]

A number of factors can increase the possibility of hypoglycaemic events: over-prescribing, inappropriate dosing, changes in exercise or diet, pharmacodynamic (PD) interactions (other blood glucose lowering agents),[2] pharmacokinetic (PK) interactions (agents with high protein-binding), antibiotics, substandard or fake medicines, comorbidities (infection, pancreatic cancer, cancer, renal, hepatic and cardiovascular disease) and patient characteristics (elderly, BMI, poor nutrition).[2,3] In addition, published case reports and case series have highlighted the association between CYP2C9 genetic polymorphisms and hypoglycaemic events.

Glibenclamide's daily dosage is between 1.25 and 20 mg. The usual starting dose of glibenclamide tablets is 2.5 to 5 mg daily.[4] The defined daily dose (DDD) is 7 mg or 10 mg (micronized and non-micronized, respectively).[5] Glibenclamide is not recommended in the elderly or in individuals with a glomerular filtration rate (GFR)<50 mL/min. The combination of glibenclamide and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different, but complementary mechanisms.[4]

Several studies which evaluated the safety of SUs consistently showed that glibenclamide is associated with a higher risk of hypoglycaemia when compared to other SUs, including glipizide, gliclazide and glimepiride.[6-9] Glibenclamide was associated with a 52% greater risk of experiencing at least one episode of hypoglycaemia compared with other secretagogues (relative risk 1.52 [95% CI 1.21-1.92]) and with an 83% greater risk compared with other sulfonylureas (1.83 [1.35-2.49]).[10]

According to the National List of Essential Medicines (NLEMs), glibenclamide (2.5 and 5.0 mg) is an essential SU in five countries, India, Pakistan, Nepal, Sri Lanka and Bangladesh. In Sri Lanka, glibenclamide is the most commonly prescribed SU by GPs.[11]

The polymorphic CYP2C9 isoenzyme catalyses the biotransformation of SUs in the liver. The mutant alleles CYP2C9*2 and CYP2C9*3 are known to have a reduced drug-metabolizing activity than the wildtype CYP2C9*1, the decrease in catalysing activity of the *3 allele being more pronounced. The *3 variant is most common in Asians with a frequency of 10%–25% compared to that of 2%–6% in Caucasians. Involvement of CYP2C19 in the metabolism of SUs is also reported. CYP2C19*2 and CYP2C19*3 are variants that encode a non-functional CYP2C19 enzyme. Individuals with either of the variants are labelled as poor metabolizers.[12]

In Asian populations, genetic variability of CYP2C9 is dominated by the less functioning allele *3 (3.4% in East Asians and 11.3% in South Asians) while in Europeans, genetic variability expresses mainly the *2 variant (Europeans 11.7% and admixed Americans 6.6%), Other allelic variants are also present in South Asian and African populations. [13]

Reports in VigiBase

A total of 100 Individual Case Safety Reports (ICSRs), with the combination glibenclamide and palpitations were retrieved from VigiBase, the WHO global database of ICSRs, on 15 January 2018, and were reviewed case by case. Four repeated reports were identified, and there was a likely duplicate from the US, therefore only 95 cases were considered. Of these, 47 reports were from Asian countries and 48 reports from non-Asian countries. Most reports included hypoglycaemic symptoms (dizziness, sweating, vision blurred, etc.), and 18 explicitly reported hypoglycaemia. Most of the Asian ICSRs (34/47, 72%) had a completeness score (level of documentation) >0.50. Case series distribution of gender, region and completeness score is set out in Table 1.

Table 1. Case series characteristics: gender, region and completeness score

Gender			
Total		**n (%)**	
Female		60 (63.16)	
Male		30 (31.6)	
Unknown		5 (5.3)	
Number of reports (%)			
Asian countries n 47 (49.5%)		**Other countries n 48 (50.5%)**	
Thailand	26 (27.3%)	US	29 (30.5%)
India	8 (8.4%)	Germany	4 (4.2%)
Singapore	6 (6.3%)	Peru	3 (3.2%)
China, Malaysia	6 (6.3%) 3 each	Canada, Sweden	4 (4.2%) 2 each
Japan	1 (1.1%)	Australia, Italy, Denmark, Eritrea, Namibia, Oman, Spain and United Kingdom	8 (8.4%) 1 each
Completeness Score			
Total		**n (%)**	
≥ 0.70		23 (24.2)	
0.31 - 0.69		43 (45.3)	
0.1 - 0.28		29 (30.5)	

In Asian ICSRs, the reporter is given in 35 reports (74.5%), and all but one were physicians, the remaining one, a pharmacist. In 32 ICSRs, the sender's comment highlighted the Asian origin.

Patients were relatively younger in Asia than in the other countries: 36/47 (76.6%) were ≤ 64 years old. The age distribution is described in Table 2.

Table 2. Age distribution

Age	**Asian countries n/n total (%)**	**Other countries n/n total (%)**	**N Total (%)**
Reported	47/47 (100%)	39/48 (81%)	
6 years	0	1/48 (2%)	1 (1.1%)
24-44 years	11/47 (23%)	0	11 (11.6%)
45-64 years	25/47 (53%)	22/48 (46%)	47 (49.5%)
65-74 years	6/47 (13%)	7/48 (15%)	13 (13.7%)
above 75 years	5/47 (11%)	9/48 (19%)	14 (14.7%)
Unknown	0	9 (19%)	9 (9.5%)
Total ≥65 years	11/47 (23%)	16/48 (31%)	26/95 (27.4%)
Total ≤ 64 years	36/47 (77%)	23/48 (52%)	61/95 (64.2%)

Onset date and at least start date of glibenclamide therapy were stated in 59 out of 95 ICSRs (57.9%); so it was possible to calculate time-to-onset (TTO) in this subset of reports. In three ICSRs, the onset date was stated as previous to the reported start of drug administration.

In 28 Asian reports, TTO ranged from 0 to 60 days, and in 21 reports, TTO was up to 10 days. In six ICSRs symptoms manifested the same day, and in 11 ICSRs TTO was 1 day. Time to onset is set out in Table 3.

Table 3. Time to onset

Time to onset (TTO)	**n (total)**	**n (Asia)**
0-10 days	30	21
12-28 days	4	4
Within a month*	4	2
33-36 days	2	1
43-61 days	3	2
90-270 days	9	4
1-20 years	7	2
Total	59	36

** Reports with the same year and month reported for drug start and reaction onset*

The dose for glibenclamide was reported in 65 cases (68.4%) and ranged from 1.8 mg to 20 mg daily. Fifty ICSRs reported low doses: one 1.8 mg, 13 cases between 2-2.5 mg, 33 a dose of 5 mg, two with 3.5 mg and one with 7.5 mg. Nine patients were treated with 10 mg, three with 15 mg and another three patients with 20 mg. The percentage of patients with doses ≤ 5 mg was similar in Asian countries and in non-Asian countries (77% and 76% respectively).

Thirteen reports (14%) were classed as serious, two of them were fatal, and 18 (19%) were classed as non-serious. In the two fatal cases, other BGLDs

were suspected (ipragliflozin and sitagliptin); glibenclamide is reported as not withdrawn. Two ICSRs reported syncope as an adverse reaction, which indicates a more serious state.

Alternative causes of hypoglycaemia

Possible interactions: An ICSR from a non-Asian country reports hypoglycaemia in a 78-year-old woman treated with hydroxychloroquine because of a rheumatoid arthritis. Three Asian country reports mention drugs possibly interacting: one of a 75-year-old woman, who started a triple therapy with metformin 1 g, pioglitazone 30 mg and glibenclamide 5 mg, and presented with palpitations and dizziness on the seventh day; another one mentions phenytoin administration with confusing TTO dates; another report mentions hypoglycaemic symptoms the same day that amoxicillin was administered, and 10 days after the therapy with glibenclamide was started.

Changes in physical activity: An ICSR from a non-Asian country reports the case of a 62-year-old woman under therapy with glibenclamide and metformin who developed bouts of palpitations, confusion, and chest discomfort, particularly at times of unpredicted physical activity.

Incident comorbidities and incident concomitant therapies: An ICSR from an Asian country reports hypoglycaemia in a 52-year-old woman who was started on dual therapy with metformin 1 g daily and glibenclamide 5 mg; the TTO was 10 days. On day 8, a prescription of 2 g of amoxicillin is reported (only one-day of treatment), and doxycycline 200 mg daily, given for three days, because of an acute upper respiratory infection. Some anti-infective agents may enhance the hypoglycaemic effect of glibenclamide and infection itself can trigger hypoglycaemia.

An ICSR from a non-Asian country reports hypoglycaemia and palpitations in a 59-year-old woman treated with glibenclamide 5 mg over nine months. Two days before the hypoglycaemic event occurred, the patient had received medication for a cardiac event (morphine, nifedipine, isosorbide dinitrate, furosemide, enalapril).

Other alternative causes: In two reports from a non-Asian country (TTO 170 days and 215 days), palpitations are more likely related with other morbidities (atrial fibrillation, reduced left ventricular ejection fraction). In another ICSR from an Asian country (TTO 270 days), other medications suggesting an acute coronary syndrome are reported.

Literature and labelling

The US FDA label only mentions CYP2C9 as induced by rifampicin, and potentially reducing glibenclamide plasma levels as a consequence. There is no mention of poor metabolizers.[4] The Health Sciences Authority of Singapore issued a warning about glibenclamide in older patients and renal impairment. However, there is no mention of pharmacogenetic variability.[14]

A statement from the Royal Dutch Pharmacists Association Working Group concluded that there are no dose recommendations based on patients' pharmacogenetic status to give at this time (2011).[15]

"Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement", an initiative of the South Asian Federation of Endocrine Societies (SAFES), developed in accordance with the American Association of Clinical Endocrinologists/ American College of Endocrinology (AACE/ACE) doesn't mention pharmacogenetic variability as a cause of sulfonylurea intolerance.[11]

According to a paper published in 2014, gefitinib product information is the only EMA label containing a warning about CYP2C9 metabolization.[16]

SUs Metabolism and isoenzymes genetic polymorphisms

A PK study performed in healthy male volunteers showed that in homozygous carriers of the genotype *3/*3, total oral clearance was less than half of that of the wildtype genotype *1/*1 (P <.001). Correspondingly, insulin secretion measured within 12 hours after glyburide ingestion was higher in carriers of the genotype *3/*3 compared with the other genotypes (P =.028), with no clinical effects.[17]

In a case-control study of 20 diabetic patients admitted to the emergency department with severe hypoglycaemia during SU drug treatment, it was found that the CYP2C9 genotypes *3/*3 and *2/*3 that are predictive of low enzyme activity were more common in the hypoglycaemic group than in the comparison groups (10% vs < 2%, respectively). Other factors in the group with severe hypoglycaemia were lower body mass indexes, higher rates of renal failure, older age, and higher doses of glibenclamide.[18]

In a study assessing the frequency of CYP2C9 genetic variants in Type 2 diabetes mellitus (T2DM) patients receiving sulfonylureas (92 reporting drug-associated hypoglycaemia, and 84 having never experienced hypoglycaemia), it was found that the presence of the allele CYP2C9*3 increased the risk of hypoglycaemia (OR: 1.687, adjusted for age, BMI, mean daily dose of SU, duration of T2DM and renal function; p = 0.011).[19]

A study performed in Chinese healthy male volunteers found that CYP2C9 polymorphism appears to exert a dominant influence on glibenclamide pharmacokinetics and pharmacodynamics in vivo; hypoglycaemia developed in 3 of 6 CYP2C9*1/*3 carriers and 2 of 12 CYP2C9*1/*1 carriers.[20]

A prospective population-based study did not observe over-representation of the CYP2C9 slow metabolizer genotypes in the hypoglycaemic patients group. However, in the control group, patients with CYP2C9 genotypes predicting slower metabolism of SU drugs were treated with significantly lower doses than were extensive metabolizers.[21]

A study performed in Turkey with 108 diabetic patients treated for ≥ 3 months with SUs (glimepiride, gliclazide, glipizide) found that heterozygosity and homozygosity for CYP2C9 variant alleles (*2 or *3) tended to be more frequent among patients who reported hypoglycaemic attacks.[22]

Interactions: Several published cases report hypoglycaemia induced by hydroxychloroquine, and observational studies suggest a dose-dependent protective effect of hydroxychloroquine on drug-induced diabetes in rheumatic patients treated with corticosteroids.[23-26] Co-administration of anti-infective agents that are CYP2C9 inhibitors can increase the risk of hypoglycaemia in glipizide and glyburide users.[26] Therefore, co-administration of other CYP2C9 inhibitors might also increase the risk of hypoglycaemia, although an increased risk of hypoglycaemia might not be present with less strong (non-clinically-relevant) CYP2C9 inhibitors. P-Glycoprotein inhibitors might also increase the risk of hypoglycaemia.[26] A few ICSRs of this set mentioned suspected or concomitant drugs that could interact with glibenclamide. It is worth noting that an interacting agent can theoretically exert additive effects on an isoenzyme with genetically reduced functionality.

Discussion and conclusion

Hypoglycaemia is a sulfonylureas dose-related type A adverse effect. In subjects with preserved autonomic function, the fall in blood glucose levels triggers the adrenergic counter regulation, which manifests through palpitations. Glibenclamide is metabolized by CYP2C9 isoenzyme, which is highly polymorphic. The frequency of polymorphism of defective CYP2C9 alleles (CYP2C9*2 and CYP2C9*3 variants) in South-Asian populations is reported to be 10-25% of a total population; defective isoforms are also present – but much less frequently - in Caucasian populations. Poor metabolizers (CYP2C9*2 and CYP2C9*3 alleles carriers) can show higher plasmatic levels of glibenclamide, leading to low blood glucose levels and triggering counter regulation mechanisms, such as adrenergic response.

Even though observational studies have not shown conclusive results, a literature review supports a relationship between clinical effects and CYP2C9 polymorphic variants. A PK study conducted in Caucasian volunteers saw no clinical effects of the difference in metabolization, but hypoglycaemia was more frequent in one conducted with Chinese volunteers.

To date, no regulatory labelling or warning has highlighted the contribution of poor metabolizer status on higher frequency or severity of hypoglycaemia in patients treated with glibenclamide.

Even though ICSRs provide no information on the pharmacogenetic status of patients, short TTO and, to a lesser extent source countries may suggest a pharmacogenetic cause. This can also be a class characteristic.

In this set of VigiBase reports, the proportion of cases with short TTO, and the number of good quality reports coming from Asian countries in relatively young patients might be considered as a signal of the potential association of an increased frequency of palpitations as symptoms of hypoglycaemia in patients treated with glibenclamide who are poor metabolisers. Also, in 32 ICSRs, the sender's comments highlighted the Asian origin. This hypothesis would need specific pharmacogenetic studies in patients treated with glibenclamide and experiencing hypoglycaemia with short TTO or interacting medications.

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Phenprocoumon – Accidental overdose

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Phenprocoumon is a long-acting vitamin K antagonist approved to treat and prevent thromboembolic disease. The oral anticoagulant is also indicated in patients diagnosed with atrial fibrillation for the prevention of ischemic stroke. Phenprocoumon and any other drugs in the anti-coagulant family act by preventing further extension of a formed clot thus preventing secondary thromboembolic consequences which may lead to serious, sometimes fatal outcomes.[1]

In VigiBase, the WHO global database of individual case safety reports (ICSRs), there are, as of February 2018, 19 cases with the drug phenprocoumon and the preferred term accidental overdose. The cases involve patients of 63 to 89 years of age, ten females and nine males.

The majority of the reports describe how phenprocoumon had been switched at a pharmacy to a generic brand with similar drug name, appearance and dosing, causing the patient to misunderstand the new dose regime, leading to overdose and internal haemorrhage. Twelve cases described patients taking two anticoagulants at the same time, the original one prescribed plus the generic, instead of only one of them, or taking a higher dose than prescribed of one of the drugs because of a mix-up of medications, causing a synergistic effect leading to a higher risk for haemorrhage.

An 80-year-old female developed a massive urinary tract haemorrhage after an accidental intake of three tablets of the generic medicine at the same time as she continued taking the medicine she had been on for the last eight years. This confusion caused a life-threatening situation.

A further, 88-year-old female patient, whose therapy was changed from her regular medicine to a generic substitute, left her confused and she mixed up the package design with that of her concomitant medications. The error was noticed during a check-up with a coagulation screen corrected accordingly.

Anticoagulated patients are a vulnerable group requiring coagulation monitoring by health-care professionals to achieve the optimal pharmacological effect without causing bleeding. The population treated is generally elderly and takes these drugs in combination with other medication, thus increasing the risk of confusion and medication error. Switching products at the pharmacy level requires adequate information and reassurance that the patient has fully understood the dosing and monitoring instructions essential to prevent harm, including life-threatening events.

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Selegiline and hypoglycaemia in underweight adults

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Summary

Hypoglycaemia has been described in association with non-selective monoamine oxidase inhibitors, and there have been isolated published case reports of hypoglycaemia in association with selective inhibitors of MAO-B. A signal for hypoglycaemia in association with the use of selegiline in underweight patients was detected in VigiBase. A review of all reports of hypoglycaemia suggests this may represent a true association, based additionally on the presence of positive dechallenges, a published case report, and a possible mechanism for the adverse reaction.

Introduction

Selegiline is an irreversible inhibitor of monoamine oxidase (MAO), indicated for the treatment of Parkinson's disease, either as monotherapy or in combination with levodopa. The recommended dose of the conventional tablet formulation is 5-10 mg daily. Selegiline is a selective inhibitor of MAO-B at doses up to around 20 mg daily; at higher doses,

there is increased inhibition of MAO-A.[1] The bioavailability of selegiline is low (around 10% of an oral dose reaches the systemic circulation), and may be increased up to threefold when administered with a high-fat meal.

Hypoglycaemia, defined as a blood glucose concentration below 3.0 mmol/L, is relatively common in people with diabetes. Less common causes of hypoglycaemia include endocrine causes (adrenal or pituitary insufficiency), critical illness (including sepsis, renal failure, and hepatic failure), starvation, alcohol excess, and insulinoma.[2]

The medicines most commonly causing hypoglycaemia are antidiabetic agents, particularly insulin and sulfonylureas. Many other medicines have been associated with hypoglycaemia, such as quinine, beta blockers, and SSRIs, but the evidence for the association is generally poor.[3,4]

Reports in VigiBase

This drug-ADR combination was detected in VigiBase, the WHO global database of individual case safety reports (ICSRs), when screening for potential signals associated with underweight or overweight patients. The combination of selegiline-hypoglycaemia was highlighted in the underweight (low BMI) group, however the reports in this case series were all from Japan. For this reason, the screening was expanded to also include reports where BMI data was unavailable.

Of 2,926 reports for selegiline there were 16 of hypoglycaemia (IC=0.71; IC_{025}=-0.09): seven from Japan, seven from USA, and one each from Canada and the UK. There were nine males and seven females. Ages ranged from 50 to 88 years, with a median of 75 years.

Thirteen patients were taking other medicines used in the treatment of Parkinson's disease: all of these were taking levodopa (10 with carbidopa; 3 with benserazide); other anti-Parkinsonian medications included amantadine, pramipexole, entacapone, and ropinirole (three patients each).

There was limited information on potential confounding factors; one patient was taking sertraline, a medicine also associated with the occurrence of hypoglycaemia. Two patients were taking insulin, indicating a clear alternate cause for hypoglycaemia.

Time to onset was stated in ten reports. In four, the onset was within one month of starting the drug; in three of these cases the reaction abated on stopping the drug, and in the fourth the outcome was unknown. In the remaining six reports for which time to onset was given, it varied from two months to six years. In four of these reports, the reaction abated on stopping the drug; withdrawal had no effect in one; and the outcome was not known in the remaining report. One other report with unknown time to onset describes a positive dechallenge.

Five of the seven patients from Japan were underweight (BMI range 14.2-17.9); BMI is unknown for the remaining patients. The formulation of selegiline used in Japan is an orally-disintegrating tablet, compared to a conventional tablet in most other countries. Two of the US reports involved a transdermal patch. No additional information was available from the report narratives.

For the related medicine rasagiline, of the 2,565 reports, seven mentioned hypoglycaemia (IC=-0.25; IC_{025}=-1.51).

Literature and Labelling

Hyperglycaemia and hypoglycaemia are listed as very rare adverse events in the "post-marketing surveillance data" section of the Australian Product Information for Eldepryl (selegiline), as well as in the Japanese labelling (as frequency unknown).[1] Hypoglycaemia is not mentioned in the UK, US, or Canadian labelling for selegiline products.

Hypoglycaemia has been reported rarely in association with non-selective MAO inhibitors such as phenelzine and tranylcypromine.[5] Single case reports have been published of hypoglycaemia in association with the use of both selegiline and rasagiline.[4,5]

Non-selective MAO inhibitors are responsible for the breakdown of dopamine, serotonin, and norepinephrine. A possible mechanism for hypoglycaemia with MAO inhibitors is that increased serotonin increases insulin sensitivity and insulin release,[4] and decreases gluconeogenesis. Selective MAO-B inhibitors are responsible for the breakdown of dopamine only, at the doses normally prescribed, but can also inhibit MAO-A at higher doses.

The orally-disintegrating selegiline tablet has a recommended dose of 1.25-2.5 mg daily. The Cmax (3.34 ng/mL for a 1.25 mg dose) is higher than for the conventional tablet formulation (1.12 ng/mL for a 5 mg dose), as is the dose-adjusted bioavailability.[6]

Discussion and Conclusion

Although hypoglycaemia has been described in association with use of a number of medicines, the evidence to support this is not strong, other than for antidiabetic agents. A mechanism has been proposed for the development of hypoglycaemia in association with the use of medicines that increase serotonin. In this case series of 16 reports, BMI data was available for five patients (all from Japan), indicating that all five were underweight; unfortunately, BMI data is not available for the remaining patients. It is possible that in underweight patients, a normal dose of selegiline may result in higher blood concentrations, and therefore loss of MAO-B selectivity. This may be exacerbated by the formulation used: the Japanese

patients all received an orally disintegrating tablet formulation of selegiline, which has a higher Cmax and bioavailability than the conventional tablet formulation. Other contributing factors may be the variable bioavailability of selegiline when administered with food, and the fact that starvation, which may be the reason for being underweight, is itself a risk factor for hypoglycaemia. The variable time-to-onset data is consistent with the adverse reaction being dependent on patient weight, which may change during a course of treatment. Also in support of a signal, nearly half of the reports describe resolution of hypoglycaemia upon withdrawal of selegiline. The association has also been described for rasagiline, another selective MAO-B inhibitor.

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CAVEAT DOCUMENT

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs).
Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

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

Tentative and variable nature of the data

Uncertainty: 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 is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: 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 adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

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

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

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

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

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Strengthening Pharmacovigilance in Lebanon and Ethiopia

(1) Lebanon

The National Pharmacovigilance Centre (NPC) in Lebanon has been a member of the WHO Programme for International Drug Monitoring (PIDM) since July 2018. The Ministry of Public Health and the NPC in Lebanon invited WHO to support a baseline assessment of pharmacovigilance (PV) functions and develop a road map for strengthening PV in the country. A delegation from WHO Headquarters and the WHO Eastern-Mediterranean Regional Office attended a three-day meeting in Beirut, Lebanon from 19 to 21 March 2019.

The NPC is part of the Lebanese Food, Drug and Chemical Administration (LFDCA) which is based in the Pharmacy Faculty at the Lebanese University in Hadath. The monitoring of the safety of medicines started in 2002 in the pharmacy faculty as an academic activity. Following an agreement with the Ministry of Public Health (MoPH) in 2016, the LFDCA continues to work towards developing the PV system in the country to collect and analyze data, carry-out benefit-harm evaluations, and make recommendations to the MoPH through a technical committee to inform guidelines and policies for the safe and effective use of medicinal products for patients.

The first two days (19-20 March) of the meeting consisted of discussions on the current PV situation in Lebanon, PV gaps and future plans. Following this, on 21 March 2019, the delegation met with his Excellency Dr Jamil Jabak, the Minister of Public Health. The importance of PV was advocated, and the Minister expressed his support. In the upcoming months the NPC will finalize a PV roadmap, and work with the MoPH to campaign and promote PV to health-care professionals.

(2) Ethiopia, using the 3S approach, Addis Ababa, 19-21 February 2019

Access to priority medicines and vaccines in low- and middle-income countries (LMICs) has improved significantly in the last few years. The World Health Organization, (WHO) and the Bill and Melinda Gates Foundation (BMGF) have launched the Project Smart Safety Surveillance (also known as Project 3S) in 2016, to help LMICs identify, assess and adequately manage the risks with new medicines and vaccines.

Ethiopia is potentially a country for 3S PV interventions, to help strengthen PV capacity for an existing product bedaquiline (BDQ) and to prepare the PV system to proactively put measures in place to monitor the safety of potential products such as Tafenoquine (TFQ).

WHO delegates from the country office, Regional Office for Africa, and Headquarters met with the Ethiopian Food and Drug Administration (EFDA), and managers from the National TB and malaria programmes to discuss strengthening and integrating PV activities in Addis Ababa from 19-21 February 2019. Through various discussions WHO gained an understanding of legislations, plans for reformation, integration of PV with public health programmes and current processes. WHO will be working with the country to finalize and implement a PV work plan and roadmap.