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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,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
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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 edition of the Newsletter also includes three short articles, on: the WHO Vaccine Safety Net, a working group meeting on the 'Erice call for change' and the launch of the Med Safety mobile application in Uganda.

Contents

Regulatory matters

Safety of medicines

Signal

Feature

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Regulatory Matters

Aciclovir, valaciclovir	4
Amenamavir	4
Baloxavir marboxil	4
Baricitinib	4
Cyproterone	4
Durvalumab	5
Fosfomycin	5
Ingenol mebutate	5
Leuprorelin	6
Methimazole	6
Parenteral nutrition products	6
Pegfilgrastim	7
Propylthiouracil	7
Rivaroxaban	7
SGLT2 inhibitors	8
SSRI, SNRI	8
Tofacitinib	8
Ulipristal acetate	8

Safety of medicines

Benzodiazepines, opioids	10
Fimasartan	10
Gentian violet antiseptic	10

Signal

Clozapine – Drug dose titration not performed	11
<i>Ginkgo biloba</i> L. and cardiac arrhythmias	14

Feature

The Vaccine Safety Net – WHO’s worldwide partnership to facilitate access to reliable information on vaccine safety	24
A Call for Change for the care of the unique patient	25
Launch of the Med Safety mobile application in Uganda	26

Aciclovir, valaciclovir

Risk of tubulointerstitial nephritis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for aciclovir (Zovirax®) and valaciclovir (Valtrex®) should be revised to include tubulointerstitial nephritis as an adverse drug reaction.

Aciclovir and valaciclovir are indicated to treat various conditions including herpes simplex and herpes zoster.

A total of six cases involving tubulointerstitial nephritis in patients with valaciclovir have been reported in Japan during the previous three years, including three cases for which a causal relationship between the drug and event could not be excluded. No patient mortalities have been reported. The MHLW and PMDA have concluded that a revision to the package insert for valaciclovir is necessary.

No cases involving tubulointerstitial nephritis have been reported in patients with aciclovir. However, valaciclovir is a prodrug of aciclovir, and therefore, the package insert of aciclovir is also to be revised.

Reference:

Revision of Precautions, MHLW/PMDA, 31 March 2020 (www.pmda.go.jp/english/)

Amenamevir

Risk of erythema multiforme

Japan. The MHLW and the PMDA have announced that the package insert for amenamevir (Amenalief®) should be revised to include erythema multiforme as an adverse drug reaction.

Amenamevir is indicated for

herpes zoster.

A total of 10 cases involving erythema multiforme have been reported in Japan during the previous three years, including five cases for which a causal relationship between the drug and event could not be excluded. No patient mortalities have been reported. The MHLW and PMDA have concluded that the revision is necessary.

Inclusion of toxic epidermal necrolysis and oculomucocutaneous syndrome was also considered as adverse drug reactions. Given the paucity of cases, it was concluded that it is not necessary to include them on the package insert.

Reference:

Revision of Precautions, MHLW/PMDA, 31 March 2020 (www.pmda.go.jp/english/)

Baloxavir marboxil

Risk of ischaemic colitis

Japan. The MHLW and the PMDA have announced that the package insert for baloxavir marboxil (Xofluza®) should be revised to include ischaemic colitis as an adverse drug reaction.

Baloxavir marboxil is indicated for Influenza A or B viral infections.

A total of 13 cases involving ischaemic colitis have been reported in Japan during the previous three years, including eight cases for which a causal relationship between the drug and event could not be excluded. No patient mortalities have been reported. The MHLW and PMDA have concluded that the revision is necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 31 March 2020 (www.pmda.go.jp/english/)

Baricitinib

Risk of venous thromboembolism

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has advised to discontinue baricitinib if clinical features of deep vein thrombosis or pulmonary embolism occur.

Baricitinib (Olumiant®) is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults.

Clinical trial findings showed high rates of cases of deep vein thrombosis and pulmonary embolism with baricitinib treatment compared with placebo. Consequently, it was recommended that baricitinib should be used with caution in patients with risk factors for deep vein thrombosis and pulmonary embolism, such as prior medical history of venous thromboembolism, surgery, older age and obesity.

Also, health-care professionals should advise patients undergoing treatment with baricitinib to seek urgent medical attention if they experience a painful swollen leg, chest pain or shortness of breath.

Reference:

Drug Safety Update, MHRA, 18 March 2020 (www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.6, 2019: Risk of venous thromboembolism in Japan)

Cyproterone

Restrictions in use due to risk of meningioma

Europe. The European Medicines Agency (EMA) has announced restrictions in the use of cyproterone due to reported occurrence of meningiomas (single and multiple) in association with

the use of cyproterone, primarily at doses of 25 mg/day and above.

Cyproterone is an antiandrogen medicine, indicated to treat various androgen-dependent conditions such as hirsutism, alopecia, acne, prostate cancer, and reduction of sex drive in sexual deviations in men.

EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), recommended that cyproterone 10 mg/day or more should only be used for androgen-dependent conditions such as hirsutism, alopecia, acne and seborrhoea once other treatment options have failed. Also, cyproterone should only be used for reduction of sex drive in sexual deviations in men when other treatment options are not suitable. There is no change in use of cyproterone in men for prostate cancer.

Health-care professionals should monitor patients for clinical signs and symptoms of meningioma, such as changes in vision, hearing loss, headaches, seizures or weakness in arms and legs, in line with clinical practice. If patient is diagnosed with meningioma, treatment with cyproterone must be stopped permanently.

Reference:

EMA, 27 March 2020
(www.ema.europa.eu)

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of meningioma in EU; No.4, 2019: Risk of meningioma in EU)

Durvalumab

Risk of myasthenia gravis

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the Summary of Product Characteristics (SmPC) and the Package Leaflets (PL) for durvalumab (Imfinzi®) have

been updated to reflect the risk of myasthenia gravis.

Durvalumab is a monoclonal antibody that acts as an immune checkpoint inhibitor and is indicated to treat locally advanced, unresectable non-small cell lung cancer in adults. Immune checkpoint inhibitors such as durvalumab are known to generate a wide range of immune-mediated adverse reactions.

The EMA's PRAC reviewed the risk of myasthenia gravis associated with durvalumab, considering spontaneous reports and published literature. Evidence for a potential causal relationship between the drug and event was provided including cases with a fatal outcome. Also, several literature articles describe the potential mechanism of action by which durvalumab may induce myasthenia gravis.

The PRAC concluded that there is a risk of myasthenia gravis associated with durvalumab treatment.

Patients should be monitored for signs and symptoms of myasthenia gravis and managed. If there are signs of muscular weakness or respiratory insufficiency, treatment with durvalumab should be permanently discontinued.

Reference:

Drug Safety Newsletter, HPRA, April 2020 (www.hpra.ie)

Fosfomycin

Restrictions for use

Europe. The EMA has recommended, following the advice from the Committee for Medicinal Products for Human Use (CHMP), that fosfomycin intravenous formulation should only be used to treat serious infections when other antibiotic treatments are not suitable. Also, the EMA has

recommended that fosfomycin oral formulations for children and intramuscular formulations should no longer be used, as there are insufficient data available to confirm their benefits to patients.

Fosfomycin is an antibiotic to treat a range of infections. Fosfomycin-based antibiotics first became available in the 1960s, and are available in most EU countries under names Afastural®, Fosfocin®, Urofast® etc. Generally, fosfomycin is known to cause several adverse drug reactions such as diarrhea, nausea and headache.

Intravenous formulations should only be used for the treatment of serious infections when other antibiotic treatments are not suitable, which include complicated urinary tract infections, infective endocarditis and bone and joint infections. Oral formulation can continue to be used for acute, uncomplicated cystitis in women. Intramuscular use will also be suspended as the evidence is not sufficient.

The product information for fosfomycin will be updated to take the recommendations into account.

Reference:

EMA, 27 March 2020
(www.ema.europa.eu)

Ingenol mebutate

Risks of skin cancer outweigh benefits

Europe. The EMA has completed its review of ingenol mebutate (Picato®) and concluded that the medicine may increase the risk of skin cancer and that its risks outweigh its benefits.

Ingenol mebutate is a gel applied to skin areas affected by actinic keratosis.

The review looked at results of a study comparing ingenol

mebutate with another medicine for actinic keratosis, imiquimod. A higher incidence of skin tumours, especially squamous cell carcinoma, were observed in patients treated with ingenol mebutate compared with those treated with imiquimod.

Picato® has already been taken off the market and is no longer a treatment option for actinic keratosis. Other treatment options for actinic keratosis include topical diclofenac, fluorouracil and imiquimod.

Health-care professionals should advise patients treated with ingenol mebutate to be vigilant for any skin lesions developing and to seek medical advice promptly should any occur.

Reference:

EMA, 30 April 2020
(www.ema.europa.eu)

(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of skin malignancy in UK; No.1, 2020: Use with caution in patients with a history of skin cancer in Ireland; Suspension during safety review in EU)

Leuporelin

New measures to avoid handling errors

Europe. The EMA has announced that new measures are to be taken to avoid handling errors, that result in insufficient amounts of medicines, in the preparation and administration of leuporelin depot medicines (Eligard® and Lutrate Depot®).

Depot formulations of leuporelin are given by injection under the skin or into a muscle and they release the active substance gradually over one to six months. Leuporelin is indicated to treat prostate cancer, breast cancer, conditions that affect the female reproductive system and early puberty.

The PRAC has recommended that only health-care professionals familiar with the preparation of leuporelin depot medicines should prepare and administer the medicines to patients. Patients should not inject the medicines themselves.

Product information for Eligard® is to be updated with warnings to strictly follow the instructions for preparation and administration, and to monitor patients if a handling error occurs. The MAH must replace the current device, to administer the drug, with one that is easier to handle.

Also, the PRAC recommended that instructions for Lutrate Depot® for handling the medicine be revised to make them easier to follow, and its packaging changed, so that the instructions are easier to find.

Reference:

EMA, 15 May 2020
(www.ema.europa.eu)

Methimazole

Risk of vasculitis

Canada. Health Canada has announced that it is working with the manufacturers to update product safety information of methimazole (Tapazole®) to include information about the risk of inflammation of the blood vessels (vasculitis).

Methimazole is indicated to treat hyperthyroidism and overactive thyroid gland.

Triggered by updates made by the US Food and Drug Administration (FDA) to the product safety information for methimazole related to the risk, Health Canada reviewed the potential risk of vasculitis with the use of methimazole.

Health Canada reviewed 13 international case reports of vasculitis in patients receiving methimazole, where 11 reports showed a possible link to

methimazole use. Also, Health Canada assessed 22 articles from the published literature and found that many of them suggested a potential risk of vasculitis with methimazole use although the frequency was very rare.

Health Canada concluded that there is a link between the risk of vasculitis and the use of methimazole.

Reference:

Summary Safety Review, Health Canada, 21 April 2020
(www.hc-sc.gc.ca)

(See also WHO Pharmaceuticals Newsletter No.5, 2019: Risk of inflammation of pancreas in Canada)

Parenteral nutrition products

Risk of oxidative stress when light-exposed

Singapore. The Health Sciences Authority (HSA) has announced that the use of light-exposed parenteral nutrition (PN) products containing amino acids and/or lipids might lead to adverse outcomes in neonates due to their increased susceptibility to oxidative stress arising from PN photodegradation products.

PN products are indicated for use in neonates when oral or enteral nutrition is impossible, insufficient or contraindicated.

In laboratory and clinical studies, light exposure to PN products has been shown to generate peroxides and other photodegradation products in quantifiable amounts, which can lead to oxidative stress including respiratory distress syndrome, bronchopulmonary dysplasia, periventricular leukomalacia and retinopathy of prematurity. Newborns are at a higher risk of oxidative stress compared to children and adults. Studies have shown that the formation of PN photodegradation products can be slowed down or prevented

by implementing various light protection measures.

A review of the safety issue in 2019 among premature neonates led the EMA's PRAC to recommend that light protection of PN products be extended, to neonates and children below two years of age, as a precautionary measure.

HSA has not received local reports on this problem, but is working with companies of affected products to update the local package inserts to reflect the risk.

Health-care professionals should consider the importance of the protection measures when PN products containing amino acids and/or lipids are used, in neonates and children below two years of age, to minimize the risk.

Reference:

Product Safety Alerts, HSA, 5 May 2020 (www.hsa.gov.sg)

Pegfilgrastim

Increased risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced that the package insert for pegfilgrastim (G-Lasta®) should be revised to include an increased risk of thrombocytopenia as a precaution.

Pegfilgrastim is indicated to prevent chemotherapy-induced febrile neutropenia.

Thirty cases involving thrombocytopenia in patients with pegfilgrastim have been reported in Japan during the previous three years, including one case for which a causal relationship between the drug and event could not be excluded. No patient mortalities have been reported.

A pharmacoepidemiological study on the association between pegfilgrastim and decreased platelet counts was

conducted in Japan. The relative risk of decreased platelet counts was statistically significant in patients with pegfilgrastim.

The MHLW and PMDA have concluded that precaution for thrombocytopenia should be added in the package insert.

Reference:

Revision of Precautions, MHLW/PMDA, 31 March 2020 (www.pmda.go.jp/english/)

Propylthiouracil

Potential risk of birth defects

Canada. Health Canada has announced that it is working with the manufacturers, to update product safety information for propylthiouracil (Propyl-Thyracil®), to inform health-care professionals and patients about the potential risk of birth defects.

Propylthiouracil is indicated for hyperthyroidism, several radioiodine therapies, thyroid storm and, to control an overactive thyroid gland.

Triggered by international reports of birth defects linked with propylthiouracil use in pregnant women, Health Canada reviewed the potential risk of birth defects in babies whose mothers were treated with propylthiouracil during pregnancy. The review included 12 reports of birth defects, where seven reports were found to have possible link between the use of propylthiouracil and the birth defects. Also, 22 relevant published studies were found, but the review of the studies did not find sufficient evidence.

Health Canada's reviews could not confirm or exclude a link between the risk of birth defects in babies and use of propylthiouracil in women during pregnancy.

Reference:

Summary Safety Review,

Health Canada, 3 April 2020 (www.hc-sc.gc.ca)

Rivaroxaban

Thromboprophylaxis not recommended in patients with TAVR

Ireland. The HPRA has announced that the SmPC for rivaroxaban (Xarelto®) has been updated to reflect that it should not be used for thromboprophylaxis in patients who have recently undergone transcatheter aortic valve replacement (TAVR) due to the risk of all-cause mortality, thromboembolic and bleeding events.

Rivaroxaban is an anticoagulation medicine and is indicated to treat and prevent blood clots.

The EMA's PRAC undertook a review of patients treated with rivaroxaban after TAVR. The committee considered the final results of a phase III clinical study (GALILEO), which identified an increase in all-cause mortality, thromboembolic and bleeding events in patients treated with rivaroxaban after TAVR, other randomized clinical trials and spontaneous reports.

The PRAC concluded that rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone TAVR and recommended an update of SmPCs. It also determined that the benefit-risk balance for rivaroxaban for the approved indications remains positive.

Reference:

Drug Safety Newsletter, HPRA, April 2020 (www.hpra.ie)

(See also WHO Pharmaceuticals Newsletter No.6, 2019: Risk of recurrent thrombotic events in Australia and New Zealand; No.4, 2019: Increased risk of recurrent thrombotic events in UK)

SGLT2 inhibitors

Risk of diabetic ketoacidosis

United Kingdom. The MHRA has advised health-care professionals to interrupt sodium-glucose co-transporter 2 (SGLT2) inhibitor treatment in patients who are hospitalised for major surgical procedures or acute serious medical illnesses, and to monitor ketones during the period.

SGLT2 inhibitors are indicated to treat adults with diabetes to improve glycaemic control. In UK, available SGLT2 inhibitors are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.

A detailed European review in 2016 confirmed diabetic ketoacidosis as a rare risk for the SGLT2 inhibitors.

In 2019, a new European review recommended that warnings should be updated to include routine monitoring of ketones in patients hospitalized for surgery or acute illness. Testing of ketones in blood is recommended rather than measuring ketone bodies in urine because SGLT2 inhibitors may diminish the excretion of ketone bodies in urine. The review of the evidence did not identify a specific type of surgery as being linked to an increased risk of diabetic ketoacidosis.

Health-care professionals should restart treatment with the SGLT2 inhibitor once ketone values are normal and the patient's condition has stabilized.

Reference:

Drug Safety Update, MHRA, 18 March 2020 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.1, 2020: Updated advice on monitoring ketone bodies in Ireland; No.1, 2018; Risk of non-traumatic amputations of the lower limbs, diabetic ketoacidosis and renal failure in Chile)

SSRI, SNRI

Potential risk of sexual dysfunction

Ireland. The HPRA has announced that the SmPC and the PL for medicines containing selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) will be updated to advise of the possible symptoms of sexual dysfunction which may persist following discontinuation of product.

SSRIs and SNRIs are indicated to treat major depressive disorder and anxiety disorders. SSRI containing medicinal products include citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline; SNRI containing medicinal products include duloxetine, venlafaxine, desvenlafaxine and milnacipram.

After reviewing evidence from EMA database of adverse reactions and literature, the EMA's PRAC considered that the product information for SSRI and SNRI medicinal products should be amended to warn about the possibility of sexual dysfunction, which may persist following discontinuation of the medicinal products.

Reference:

Drug Safety Newsletter, HPRA, April 2020 (www.hpra.ie)

Tofacitinib

Risk of venous thromboembolism and serious and fatal infections

United Kingdom. The MHRA has alerted health-care professionals that tofacitinib (Xeljanz®) is associated with a dose-dependent increased risk of serious venous thromboembolism; and is also known to increase the risk of serious and fatal infections

such as pneumonia, cellulitis, herpes zoster and urinary tract infections.

Tofacitinib is indicated to treat rheumatoid arthritis, psoriatic arthritis and ulcerative colitis.

In an ongoing trial to assess the use of tofacitinib in ulcerative colitis, cases of pulmonary embolism and deep vein thrombosis were also observed. As a new recommendation, maintenance treatment for ulcerative colitis at the 10mg twice-daily dose is not recommended in patients with known risk factors for venous thromboembolism such as previous venous thromboembolism, myocardial infarction, heart failure, hypertension and diabetes, unless there is no suitable alternative treatment.

Also, tofacitinib increases the risk of serious and fatal infections, with rates of infections greater in older patients. Health-care professionals should only consider use of tofacitinib in patients older than 65 years if there is no suitable alternative treatment available.

Reference:

Drug Safety Update, MHRA, 18 March 2020 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.6, 2019: Risk of blood clots in EU; No.5, 2019: Increased risk of blood clots and death with higher dose in US and Japan; No.4, 2019: Risk of pulmonary embolism in EU)

Ulipristal acetate

Licence suspension due to liver injury

United Kingdom. The MHRA has announced that the licence for ulipristal acetate (Esmya®) has been suspended due to the risk of serious liver injury, while a safety review is being conducted following a further case of liver injury requiring transplant.

Ulipristal acetate is indicated to treat moderate to severe symptoms of uterine fibroids in women who had not reached menopause.

In March 2020, EMA started a review of ulipristal acetate following a new case of liver failure requiring liver transplant that occurred despite adherence to proper risk minimization measures for liver injury.

To protect public health, marketing authorizations for ulipristal acetate 5mg products for uterine fibroids will be suspended in the UK during the review. The MHRA has received 19 suspected adverse drug reaction reports of liver disorders with the use of Esmya® in the UK.

Health-care professionals should contact patients currently being treated with ulipristal acetate as soon as possible, stop the treatment and discuss alternative treatment options for uterine fibroids as appropriate.

Also, health-care professionals should advise recent users to seek immediate medical attention if they develop signs and symptoms of liver injury, such as nausea, anorexia or jaundice.

Reference:

Drug Safety Update, MHRA,
18 March 2020
(www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.1, 2020: Risk of hepatic injury in EU; No.5, 2018: New measures to minimize risk of liver injury in EU and Canada; No.4, 2018: New measures to minimise the risk of liver injury in EU)

Benzodiazepines, opioids

Risk of potentially fatal respiratory depression

United Kingdom. The MHRA has reminded that benzodiazepines and opioids can both cause fatal respiratory depression, and when co-prescribed, additive effects on the central nervous system increase the risks of sedation, respiratory depression, coma and death.

Benzodiazepines and opioids are indicated to treat anxiety, insomnia, agitation, seizure, muscle spasms and pain relief.

The MHRA recently received a report of death by respiratory arrest of a man given the benzodiazepine clonazepam and among other drugs, the opioid methadone.

Health-care professionals should only prescribe benzodiazepines and opioids together if there is no alternative. If co-prescribed, the lowest doses for the shortest duration should be used and patients should be carefully monitored. Also, health-care professionals should advise patients of the symptoms of respiratory depression and sedation, and the need to seek immediate medical attention if these occur.

Reference:

Drug Safety Update, MHRA, 18 March 2020 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.5, 2016: *Serious risk of slowed or breathing difficulties and deaths in US*)

Fimasartan

Risk of liver injury

Singapore. The HSA has received reports of serious liver injury in patients treated with fimasartan (Kanarb®).

Fimasartan is an angiotensin II receptor blocker and is indicated to treat mild to moderate essential hypertension.

In 2019, HSA received four case safety reports of liver injury suspected with the use of fimasartan. All the patients were reviewed by gastroenterologists. The cases were of varying severity, including two patients with elevated alanine aminotransferase and jaundice.

From 2012 to January 2020, there were 221 case safety reports describing liver injury associated with fimasartan in the WHO global database of individual case safety reports, Vigibase.

Health-care professionals should consider the risk of fimasartan. Some signs and symptoms of liver injury include fatigue or excessive tiredness, nausea and vomiting, abdominal pain and jaundice.

Reference:

Product Safety Alerts, HSA, 5 May 2020 (www.hsa.gov.sg/)

Gentian violet antiseptic

Potential risk of carcinogenicity

Singapore. The HSA has announced its benefit-risk assessment of gentian violet antiseptic on carcinogenicity.

Gentian violet is an antiseptic with antibacterial, antifungal and antihelminthic properties. It is indicated to treat bacterial skin infections and fungal infections.

In June 2019, Health Canada issued a safety alert to warn that gentian violet containing antiseptic may potentially increase the risk of carcinogenicity. The alert was based on its review of available animal studies in the scientific

literature, suggesting carcinogenicity.

HSA has reviewed the available scientific literature and noted that current evidence on the carcinogenicity of gentian violet has mainly been observed with high-dose oral exposure to gentian violet in animal studies.

In Singapore, gentian violet is not a commonly used antiseptic, possibly due to the advent of newer and more effective antiseptics.

In light of the available data, health-care professionals are advised to be aware of the risk and be reminded that gentian violet containing antiseptic is limited to short-term external use only.

Reference:

Product Safety Alerts, HSA, 5 May 2020 (<http://www.hsa.gov.sg/>)

(See WHO Pharmaceuticals Newsletter No.4, 2019: *Risk of cancer in Canada*)

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 22 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 23). 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.

Clozapine – Drug dose titration not performed

Alem Zekarias, Uppsala Monitoring Centre

Introduction

In a screening for medication errors in the WHO global database for individual case safety reports, VigiBase, we identified a case series describing lack of dose titration when re-starting clozapine.

Clozapine is an atypical antipsychotic drug that was approved in 1956 for the indication of treatment-resistant schizophrenia (TRS) as well as for patients who have problems with extrapyramidal side effects when taking other types of antipsychotic drugs.¹ The drug has also been seen to reduce the mortality rate in patients suffering from persistent suicidal or self-injurious behaviour. Clozapine is the only available evidence-based treatment for TRS.² In 1975, almost two decades after its approval, 18 Finnish patients who had been taking clozapine developed severe blood disorders. Sixteen out of 18 patients were diagnosed with agranulocytosis, and eight of them died. This led to the withdrawal of clozapine in Finland and in several other European countries where the drug had been approved. On-going studies were stopped, and upcoming trials were forced to undertake a detailed investigation into how the drug, and potentially other antipsychotic drugs, may affect the blood. Despite withdrawal of clozapine, some psychiatrists, while closely monitoring for agranulocytosis, still had to revert to clozapine for patients who suffered relapses due to the drug's exceptional efficacy. In the late 1980s, the US FDA conducted the pivotal Clozaril study, to evaluate the efficacy and safety profile of clozapine, which found that the efficacy of the drug was higher in patients who had failed to respond to at least three previous antipsychotic

drugs, in comparison with chlorpromazine, another drug indicated for schizophrenia. The outcomes from this six-week study were the basis for the US FDA to finally approve clozapine in 1989, with the requirement that the patient should be closely monitored for white blood cells (absolute neutrophil count) before and during treatment, since the risk of developing agranulocytosis is 1% in the first year and 0.1% thereafter.¹

Schizophrenia

Schizophrenia is a chronic mental illness which affects more than 21 million people globally. Anyone can get the disease, but people in early adolescence and, generally, men appear to have a higher risk of developing it. The reason why some people contract schizophrenia is still not fully understood, but it is thought that an individual's genes, in combination with both psychosocial and environmental factors, can trigger the disease.^{3,4} Schizophrenia can manifest in different ways, and the signs are divided into positive and negative symptoms. Hallucinations and delusions, typically experienced during psychosis, are examples of positive symptoms; patients interpret the world differently by seeing things and hearing voices that are not there, often resulting in abnormal behaviour and disorganized speech. Self-neglect, apathy, social withdrawal and loss of motivation are examples of negative symptoms, as they describe behaviours which result in a loss for the individual.⁴ Among patients with schizophrenia, around 30%

are diagnosed with TRS, defined as a failure to respond to two or more anti-psychotic drugs.⁵

Dose

The recommended dose for clozapine is 300 mg per day but doses up to 900 mg are acceptable if needed. It is important that the patient is started on a low dose which is then slowly titrated, otherwise there is a higher risk of developing cardiac arrest, orthostatic hypotension, bradycardia, seizures, and syncope, all of which are dose dependent. The starting dose is 12.5 mg once or twice the first day, followed by 25 mg once or twice a day during the second day under close monitoring. If the patient tolerates the dose, it may be increased successively until a safe and optimal clinical effect is achieved, which generally takes two to three weeks. When the maximum daily dose has been achieved, it should be divided to prevent side effects. A slow dose titration is important not only at the beginning of treatment, but after an interruption lasting more than 48 hours.⁶

Mechanism of action

Clozapine, whose pharmacological mechanism is not fully established, is recommended as the second-line atypical anti-psychotic treatment (due to its difficult side effect profile) for patients who do not respond to other antipsychotic drugs, because of its action on both positive and negative symptoms. Clozapine has an absorption of between 90 to 95% when given orally, but bioavailability is only 50 to 60% due to its first-pass metabolism. The drug has a rapid antipsychotic and sedative effect on patients, as its peak concentration is achieved after approximately 2.5 hours. The agent is atypical, meaning that the likelihood of the drug causing extrapyramidal side effects, such as tardive dyskinesia, is less than the typical first-generation antipsychotic drug. Clozapine is mainly metabolized by the hepatic enzymes CYP-3A4 and 1A2 to the metabolites desmethylclozapine and clozapine N-oxide. Desmethylclozapine is the only active metabolite with similar features to clozapine but has a much weaker and shorter effect. The half-life of clozapine is dependent on the dose taken, but clinical studies have shown that the mean half-life is 12 hours.⁶

Clozapine, a multireceptorial drug, is a partial 5-HT_{1A} agonist that acts by binding to and inhibiting dopamine D₁ to D₅ and serotonin receptors. It binds more strongly to dopamine D₄ than to the other dopamine receptors, which explains its effect on the negative symptoms. Clozapine also binds to the muscarinic receptors M₁, M₂, M₃ and M₅, adrenergic (α_1 and α_2), and histaminergic receptors (H₁ to H₄). The binding to several types of receptor may account for some of the side effects clozapine can cause.^{6,7}

Adverse drug profile

Clozapine causes several serious adverse drug reactions, limiting its use. The necessity of carefully monitoring white blood cell counts is another reason for reluctance to prescribe. Beyond agranulocytosis, possible adverse reactions include myocarditis and metabolic side effects. Additional adverse effects which may increase the risk of poor treatment compliance are increased salivation, sedation, somnolence, agitation, vertigo, and weight gain. Patients treated with clozapine have also been found to have a higher risk of developing diabetes, due to the drug's inhibitory effect on the M₃ receptor. Treatment resistant schizophrenia is a serious illness, and it is of utmost importance that patients take their drug according to an established treatment schedule.^{6,7}

Reports in VigiBase

In VigiBase, as of October 2019 there were 45 case reports on the preferred term *drug dose titration not performed* in relation to clozapine. The reports have been submitted since 2015 by Australia, the United States, the United Kingdom, and Ireland, and a slight increase in the number of reports being submitted has been seen every year. The reports, from both health care professionals and patients/consumers, describe how the drug, for one reason or another, was stopped after it had been taken for several years. When the patient then started the drug again, which in all cases was more than two days after it was stopped, they resumed with the last intake dose.

Three of the 45 case reports are quoted below, showing examples of how the narratives exemplify the reported term.

"A 27-year old male had not taken his antipsychotic drug for one week because he had been on vacation. When he came back, he took his usual dose of 300 mg. Following the overdose, the patient became drowsy and altered behaviour and was admitted to hospital."

"36-year old patient that has been taking the drug for more than 15 years forgot to pick up the prescription and therefore didn't take the drug for three days. When he then took the drug again, he continued his normal dose and experienced sedation due to this overdose"

"A male patient stopped taking clozapine for eight days due to a bug he was suffering from. When he then re-started the treatment, he started with 100 mg which lead to mild tachycardia."

It is known that if a patient stops taking clozapine for more than 48 hours, a gradual re-introduction is required until the therapeutic dose is reached, to minimise the risk of patients experiencing sedation, seizure, orthostatic hypotension and cramps. A slow dose titration is also important since otherwise an overdose reaction may be triggered in the patient.⁶

Additional added terms

VigiBase contains reports with clozapine and the preferred term “drug dose titration not performed” since 2015, the year the term was included in the MedDRA terminology. To capture reports that may have been entered in the database before 2015 for the same problem in relation to clozapine, an expansion of the search to nearby preferred terms including “product dose omission”, “product dispensing error”, “therapy cessation” and “treatment noncompliance” was made. Reports that included the medical terms orthostatic hypotension, bradycardia, and syncope, terms that the patient had a higher likelihood to get with a rapid dose increase, were included. The search resulted in 154 cases in total, of which three described how the patient had stopped the drug and then re-started without dose titration, which led to confusion, disorientation and feeling unwell. Several of the cases did mention that the patient was re-initiated/re-titrated, but the strengths were not given. The cases demonstrated the importance of involving the patient themselves (which might be challenging in this patient group) or someone close

to the patient who knows and understands why the drug should be dose titrated under close monitoring when there has been a treatment break of more than 48 hours.

Labelling

The summary of product characteristics for clozapine states that if the patient has stopped taking the drug for more than two days, “treatment should be re-initiated with 12.5 mg given once or twice on the first day”. A faster dose titration up to the optimal therapeutic level is acceptable if the dose is well-tolerated by the patient.⁶ In the patient information leaflet however (Figure 1), the first sentence states that if a patient has forgotten to take his dose, he should take it as soon as he remembers. However, further down the same section, it is mentioned that the patient should contact his doctor if they haven’t taken the drug for over 48 hours. By setting it out in this way, there is a risk that the patient might not read further and resume his normal dose as soon as possible.⁸

If you forget to take Clozaril

If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, leave out the forgotten tablets and take the next dose at the right time. Do not take a double dose to make up for a forgotten dose. Contact your doctor as soon as possible if you have not taken any Clozaril for more than 48 hours.

Figure 1: Quote from Clozapine (Clozarils®) Product Information Leaflet.

Conclusion

An update in the patient information leaflet for clozapine, explaining the importance of re-titration if it has been more than 48 hours since the last dose, might increase the treatment compliance within this vulnerable patient group.

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***Ginkgo biloba* L. and cardiac arrhythmias**

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Summary

This analysis considered 162 reports identified using the Standardised MedDRA Queries - SMQ (broad) for cardiac arrhythmias (dataset: 11 September 2019) and the substance *Ginkgo biloba* (Gb) in VigiBase, the WHO global database of individual case safety reports. For all reports where Gb was the sole suspect drug (n=92), there were 46 cases with dechallenge information, and of those, 39 had a positive dechallenge. Among the 25 reports with a high completeness score (≥ 0.75), Gb was the sole suspect drug for 20 reports; dechallenge information was given for 14 of these cases, all of which provided some documentation of positive dechallenge. For most of this subset of 14 reports, the specified time to onset of the reactions was within days. Pre-existing arrhythmias may cause a wide range of symptoms, including tinnitus (which was the indication for use of ginkgo in 18 of the 162 reports), so confounding by indication cannot be excluded. A mechanism by which *Ginkgo biloba* could induce cardiac arrhythmias is not clear; however, the number, nature and diversity (geographical origin, range of products implicated) of the reports and published cases indicate a signal between *Ginkgo biloba* and cardiac arrhythmias.

Introduction

Ginkgo (*Ginkgo biloba* L.; Ginkgoaceae) is a dioecious plant that has been used in medicine for around 5,000 years.¹ Traditional Chinese medicine (TCM) uses the seeds (kernel/nuts) and leaves of ginkgo trees for therapeutic purposes.² The chemical constituents of the leaves and seeds of *G. biloba* (Gb) are quite different, although both parts contain ginkgolic acids.² Today, standardised concentrated extracts and other formulations of Gb leaves are marketed worldwide, and used in cognitive deficiency, intermittent claudication (generally resulting from peripheral arterial occlusive disease), and vertigo and tinnitus of vascular origin.²

Internationally, there are substantial differences in the ways in which herbal medicines and other 'natural health' products/complementary medicines' and 'dietary/food supplements' are regulated, or whether they are regulated at all. Gb-containing products are available under different regulatory regimes; in many countries they are marketed as a 'dietary/food supplement', 'natural health product', and, in some countries, as a herbal medicinal product. Under Health Canada's Natural Health Product Regulations, the monograph for Gb leaf allows product licence applications for Gb-containing products for the following uses/purposes: "helps to enhance cognitive function in adults"; "helps to enhance memory in adults";

"helps to support peripheral circulation"; "helps to enhance cognitive function and memory in adults".³

In the European Union (EU), Gb-containing traditional herbal medicinal products granted a Traditional Herbal Registration (THR) may be indicated for "the relief of heaviness of legs and the sensation of cold hands and feet associated with minor circulatory disorders".⁴ In the UK, several Gb leaf products have been granted Traditional Herbal Registrations (THR) for relieving "symptoms of Raynaud's syndrome and tinnitus, based on traditional use only".⁵ There are some Gb-containing products that have 'regular' marketing authorisations. This is possible in the EU under the regulatory provisions for 'well-established use', which allow Gb-containing herbal medicinal products authorised under this system to be indicated for "the improvement of (age-associated) cognitive impairment and of quality of life in mild dementia".⁴ Oral doses typically comprise 120–240 mg dry extract in two or three divided doses.²

British Pharmacopoeial (BP) standard refined and quantified *Ginkgo biloba* L. leaf dry extract contains: flavonoids, expressed as flavone glycosides (Mr 756.7), 22–27% (dried extract); sesquiterpene lactones: bilobalide 2.6–3.2% (dried extract), ginkgolides A, B and C 2.8–3.4% (dried extract); ginkgolic acids: maximum 5 ppm (dried extract).⁶ As with other herbal medicinal products, there is variation in the qualitative and quantitative composition of ginkgo leaf crude plant material and commercial ginkgo leaf products;⁷ further, products containing different Gb leaf extracts have different *in-vitro* dissolution rates, resulting in differences in bioavailability in humans.⁸ There may be substantial differences between the pharmaceutical quality of authorised herbal medicinal products containing *Ginkgo biloba* L. leaf extracts, and that of Gb-containing products sold as 'dietary supplements', and they may lack pre-market assessment of quality, effectiveness (typically based on evidence of 'traditional use') or efficacy, and safety.⁹

Cardiac arrhythmias are disorders of heart rhythm; they can consist of abnormalities in rate, regularity, or site of origin (e.g. supraventricular or ventricular) of the cardiac impulse, or conduction disturbances resulting in abnormal sequences of activation.¹⁰ Cardiac arrhythmias can cause a diverse range of symptoms, including cardiac symptoms, such as tachycardia, bradycardia, or palpitations, as well as other symptoms, such as dyspnoea, weakness, dizziness, light-headedness, and syncope; they can also lead to cardiac arrest and sudden death. Some cardiac arrhythmias are asymptomatic. Cardiac arrhythmias can be supraventricular or ventricular, and slow (bradyarrhythmia) or fast (tachyarrhythmia). Supraventricular arrhythmias include atrial

fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia; ventricular arrhythmias include ventricular tachycardia, ventricular fibrillation and long QT syndrome. Ventricular tachycardia may appear similar to supraventricular tachycardia on an ECG trace yet is treated very differently.¹⁰ Causes and risk factors for cardiac arrhythmias include electrolyte disturbances, congenital channelopathies, hypertension, myocardial infarction, thyroid disease, diabetes, cardiomyopathy, other heart damage and previous heart surgery. Certain types of arrhythmias can also be drug- (e.g. in digoxin toxicity) or substance-induced (use of caffeine, nicotine, excess alcohol, or 'recreational' drugs, such as amphetamines). Most antiarrhythmic agents can have proarrhythmic effects, and some medicines or non-prescription products can have cardiac adverse effects.¹¹

This assessment involved a data extract from VigiBase, the WHO global database of individual case safety reports, for *Ginkgo biloba* (substance) and Cardiac arrhythmias (MedDRA SMQ broad). The search included only single-ingredient *Ginkgo biloba* products; of note is that the Cardiac arrhythmias (MedDRA SMQ broad) standardised query includes the preferred term (PT) syncope and loss of consciousness, but not dizziness. The observed number of reports for the SMQ was roughly as expected. Case narratives, if present, were not translated except where the authors had some knowledge of the language in which the narrative was written (French, German).

Reports in VigiBase

This analysis was undertaken at the request of UMC subsequent to a 2016 joint Lareb/UMC (unpublished) analysis that concluded that the 123 VigiBase cases and literature reports available at that time suggested a signal relating to use of *Ginkgo biloba* and cardiac arrhythmias. In the current analysis (September 2019), 164 case

reports were identified in the data extracted from VigiBase. Two reports appeared to be duplicates and, for these, the most recent report only was included in the analysis. Thus, this analysis comprised 162 reports containing adverse drug reaction (ADR) terms identified using the SMQ (broad) for cardiac arrhythmias for the (herbal) substance *Ginkgo biloba*. The reaction start date was recorded for around 80% of the 162 reports and, for around 40% of these, was during the last five years.

Patient characteristics for these 162 reports are summarised in Table 1. Two-thirds of the cases concerned females, and over 70% of patients involved were 45 years or over. The indication, or reason for use, of Gb was given for fewer than 40% of cases; the most common indications were tinnitus/'ear noises' (n=18), Alzheimer's disease, dementia, cognitive disorder, memory impairment (n=10), perfusion/circulatory disorders (n=6), hearing disorders other than tinnitus, hearing loss (n=5), vertigo, vestibular disorders (n=4), unspecified prophylaxis (n=3). In one case, the indication for use of Gb was palpitations.

There were around 30 different proprietary Gb product names for the reported medication; these products were labelled as containing Gb leaf or leaf extracts. Around 17% of reports stated only the generic, common or binomial name for Gb, i.e. ginkgo, *Ginkgo biloba*, including incorrect spellings (e.g. *Ginkgo biloba*), without specifying a product, type of preparation or plant part. In one report (from the Republic of Korea), the medication was described as 'Ginkgonis semen', meaning the seed of Gb. In most instances, Gb was taken as an oral formulation, although there were two cases where Gb had been administered intramuscularly, and six cases where Gb was administered intravenously. The indications for use of parenteral Gb preparations were typically poorly described and included tinnitus, or unspecified heart, cerebrovascular, peripheral, or psychotic disorders, or prophylaxis (not further specified).

Table 1. Characteristics of patients described in VigiBase reports identified using the SMQ (broad) for cardiac arrhythmias and substance *Ginkgo biloba* (dataset date: 11 September 2019) for all reports (n=162) and for the subset of reports with a completeness score of ≥ 0.75 (n=25)

Characteristic		All reports (n=162) n (%)	Reports with completeness score ^a ≥ 0.75 (n=25) n (%)
Sex	Female	107 (66%)	17 (68%)
	Male	52 (32.7%)	8 (32%)
	Not stated	3	-
Age	< 18 years	2*	-
	18 – 44 years	25	5
	45 – 64 years	41	6
	65 – 74 years	39	9
	> 75 years	37	5
	Not stated	18**	-

* one participant was stated to be '0 years', the other '12 months'

** one was stated to be an adult

a) The completeness score is a multidimensional measure of the quantity of information provided on each individual case safety report (ICSR) with respect to certain pre-selected data entry fields on the report; each of these fields is given a score if it contains information, each field score is weighted, and then the scores are combined into one overall score for the whole ICSR. The maximum total score is 1.0

The reports came from 18 countries, with Germany and the Republic of Korea contributing the highest number; these two countries collectively contributed more than half (56%) of the reports. All other countries had contributed between 1 and 10 reports, with the exception of France (n=16). Geographically, most countries were in Europe (n=13) and contributed two-thirds of the reports; 25% of the reports came from Asia (n=one country: Republic of Korea), 8% were from North America (n=two countries), and the remainder (1.2%) were from South America and Africa (n=two countries).

Overall, 55 cases (34%) met the definition for serious ADR outcomes; of these, there were five deaths, and four cases were classed as life-threatening; the remainder (n=45; one not stated) were classed as serious because they resulted in/prolonged hospitalisation, were disabling/incapacitating, or otherwise medically significant. There were a further two deaths among cases not coded as serious ADRs; in both these cases, it was stated that the reaction may have contributed to the death.

Gb was the sole suspect drug in 92 (57%) cases. Dechallenge (mostly through drug withdrawal, rather than dose reduction) was documented for 46

of these cases; the dechallenge outcomes were: recovered (n=37; 80%); recovering (n=2); not recovered (n=1); unknown (6; 13%).

One case report can comprise multiple reported ADRs. For these 162 reports, the ADRs within the SMQ cardiac arrhythmias consisted of 26 MedDRA Preferred Terms (PTs). The five most frequently reported were: palpitations (n=67), tachycardia (n=24), loss of consciousness (n=14), syncope (n=13) and bradycardia (n=10). See Table 2 for all SMQ cardiac arrhythmias MedDRA PTs.

The ten most frequently co-reported ADRs by MedDRA PT were: dizziness (n=22), headache (n=14), nausea (n=13), hyperhidrosis (n=8), paraesthesia (n=8), dyspnoea (n=7), tinnitus (n=7), vomiting (n=7), anxiety (n=6), tremor (n=6). It is notable that tinnitus is one of the indications for use of Gb.

Other medicines most frequently co-reported, including where stated as an active ingredient of a multi-ingredient medicinal product, were acetylsalicylic acid (n=11), ascorbic acid (n=11), levothyroxine (n=9), and tocopherol (n=8).

Table 2. Characteristics of case reports (n=162) in VigiBase by MedDRA PT-level*

Reaction (PT)	All reports (n=162)	Reports with completeness score of ≥ 0.75 and Gb as sole suspect and positive dechallenge (n=14)
Palpitations	67	6
Tachycardia	24	1
Loss of consciousness	14	-
Syncope	13	2
Bradycardia	10	1
Arrhythmia	9	1
Atrial fibrillation	8	1
Heart rate increased	7	-
Heart rate irregular	4	-
Electrocardiogram abnormal	3	-
Extrasystoles	3	-
Atrioventricular block first degree	1	-
Cardiac arrest	4	-
Heart rate decreased	3	-
Supraventricular tachycardia	2	-
Torsade de pointes	2	-
Ventricular fibrillation	2	-
Ventricular tachycardia	2	1
Adams-Stokes syndrome	1	-
Arrhythmia supraventricular	1	-
Cardiac fibrillation	1	1
Cardio-respiratory arrest	1	-
Electrocardiogram QT prolonged	1	-
Sinus bradycardia	1	-
Sudden death	1	-
Supraventricular extrasystoles	1	-

* Each case report may comprise one or more ADR PT

VigiBase reports with high completeness score

Among the 162 reports, 25 (15%) had a completeness score of ≥ 0.75 . As for the full set

of reports, two-thirds of the 'high completeness score' subset cases concerned females, and over 70% of patients were aged 45 years or over. For these reports, the indication for use of Gb was

given in all but one case; among these cases, the most common indications for use of Gb were tinnitus (n=6), cognitive disorder, memory impairment (n=3), perfusion/circulatory disorders (n=3), hearing disorders other than tinnitus, hearing loss (n=3), unspecified prophylaxis (n=3). In one case, the indication for use of Gb was 'vitamin supplementation'. There were nine different proprietary Gb product names described as the reported medication; these products are labelled as containing Gb leaf or leaf extracts; three reports stated only the generic, common or binomial name for Gb, i.e. ginkgo, *Ginkgo biloba*, including incorrect spellings (e.g. *Gingko biloba*), without specifying a product, type of preparation or plant part.

In over 80% of these cases, Gb was taken as an oral formulation; there were two cases where Gb had been administered intramuscularly, and one case where it was administered parenterally (not further specified). The indications for use of parenteral Gb preparations were typically poorly described and included tinnitus (n=1), or peripheral vascular disorders, or prophylaxis (not further specified).

This subset of reports originated from 10 countries, with Germany and the Republic of Korea contributing the highest numbers of reports; collectively contributing more than half (56%). All other countries contributed one or two reports. Geographically, most countries (n=7) were in Europe and contributed 68% of the reports; 24% of the reports came from Asia (n=one country: Republic of Korea), and the remainder (8%) were from South America and Australia (n=two countries; one report each).

Overall, 10 cases (40%) met the definition for serious ADR outcomes; of these, there was one death, one case was classed as life-threatening, five cases resulted in/prolonged hospitalisation, and three were otherwise medically significant.

Gb was the sole suspect drug in 20 (80%) cases. Dechallenge (drug withdrawal, n=13; dose reduction, n=1) was documented for 14 (70%) of these cases; the dechallenge outcomes were: recovered (n=12; 86%); recovering (n=1); for a further report the information on dechallenge outcome was conflicting (n=1). These 14 cases are detailed in Table 3. All these cases referred to oral administration of Gb, although one listed an IV/IM injectable formulation of Gb as the suspected medicine. Five of these reports were considered 'serious', and none were fatal; seven had occurred from 2016 to the date of the data extract (September 2019).

For these 14 reports, the ADRs within the SMQ cardiac arrhythmias consisted of eight MedDRA Preferred Terms (PTs); the most frequently reported being palpitations (n=6). Table 2 shows all SMQ cardiac arrhythmias MedDRA PTs for these 14 reports. The most frequently co-reported ADR by MedDRA PT was dizziness (n=6); headache (n=2),

nausea (n=2), and blood pressure decreased (n=2) were the only other co-reported ADR PTs reported more than once. For ten of these 14 reports, no other medicines were co-reported. However, for one of them, the case narrative revealed that the patient was taking a 'dietary supplement' sourced from the USA that contained Gb leaf extract and vinpocetine 5mg.

Two other reports of the 20 in which Gb was the sole suspect drug concerned patients who had received parenteral formulations of Gb on one day for tinnitus and unspecified peripheral vascular disease. Patient 1, female, 65 years, took 87.5mg, parenteral route not stated; patient 2, female 61 years, took 5mL, intramuscularly. Both patients experienced reactions within one day of receiving the treatment (patient 1: skin discolouration, bradycardia, hypotension, nausea, shock; patient 2: tachycardia, dyspnoea, hypertonia); the reactions resulted in hospitalisation for patient 1 and thus were described as serious; both patients were reported to have recovered. Aspects of patient 1's reaction are consistent with symptoms of an anaphylactic reaction; anaphylaxis was not indicated by the reporter.

Literature and Labelling

As many products containing *Ginkgo biloba* are sold and marketed as 'dietary supplements', such products will not have an official Summary of Product Characteristics (SmPC) against which to check whether arrhythmias are labelled. However, Gb-containing products that have 'regular' marketing authorisations, such as those authorised in the EU under the provisions for 'well-established use', do have official product information. It is beyond the scope of this signal review to identify and assess the SmPC for every Gb-containing product on the global market. However, as an example, the SmPC for a Gb-containing product marketed in Ireland does not list undesirable effects relating to cardiac arrhythmias.¹² In the EU, SmPCs for herbal medicinal products are based on the respective EU herbal monographs (formerly known as the Community herbal monographs). The EU herbal monograph produced by the European Medicines Agency (EMA) Committee on Herbal Medicinal Products (HMPC) for *Ginkgo biloba* L. folium (ginkgo leaf) lists dizziness as a common undesirable effect under 'nervous system disorders',⁴ but does not list any effects relating to cardiac arrhythmias. The monograph also refers to a clinical study indicating that the C_{max} of nifedipine may be increased by *G. biloba* leaf: increases in C_{max} of up to 100% occurred in several participants, who then experienced dizziness and worsening of hot flushes.⁴

Further, the EMA's final assessment report on *Ginkgo biloba* L. folium (ginkgo leaf) includes information that is relevant to this signal. The report compiled information on Gb-containing products marketed in the EU, and products

marketed in several countries were described as listing palpitation [sic], palpitations and/or arrhythmia(s) as risks.¹³ Also, product information from one country included the statement that “concomitant intake of ginkgo leaf and nifedipine has caused an increased heart frequency of 5-10% in well beings [volunteers?]”, but this may be due to the Gb-related increase in C_{max} of nifedipine discussed above; the EMA assessment also included statements from several countries regarding the need to use ginkgo with caution with vasodilators, antiarrhythmics, and medicines causing bradycardia.

There is little information in the scientific literature relating to an association between ginkgo and arrhythmias. The earliest reference identified for this assessment is from a book summarising research literature and sponsor data on a specific Gb extract, EGb-761 (Tebonin® forte, developed by Willmar Schwabe) that has been extensively researched in clinical and preclinical studies. This text summarises spontaneous reports received by the sponsor (Schwabe) for Tebonin® forte from 1982 to 1988,¹⁴ which include “palpitation” [sic] among other reported adverse reactions (including dizziness). It is possible that these data are the source of the “palpitation(s)” listings on Gb-containing products that are referred to in the EMA final assessment report (reference 10) on *Ginkgo biloba* L. folium discussed above.

Several published case reports describe arrhythmia-type adverse reactions; at least one (reference 17) is included in the VigiBase reports described above. One report describes a 35-year-old woman who experienced frequent nocturnal palpitations lasting several minutes after taking a *Ginkgo biloba* leaf extract (240mg/day) as a general tonic.¹⁵ The woman had no previous medical history, clear chest X-ray, and no physical abnormalities; electrocardiographic (ECG) examination showed a sinus rhythm of 80 beats/minute without conduction abnormalities or ST-T changes, and Doppler echocardiography did not reveal any cardiac structural or functional abnormalities. However, a 24-hour Holter ECG monitoring showed four nocturnal episodes of paroxysmal atrial fibrillation. The woman stopping taking Gb and her symptoms resolved within days; a repeated 24-hour ECG Holter did not show any arrhythmias over the following 12 months.¹⁵

Another report describes episodes of ventricular arrhythmia in a generally healthy 49-year-old man who had been taking Gb (40mg three times daily) for two weeks to improve his cognitive function. The man described experiencing palpitations and ECG showed sinus rhythm with frequent ventricular premature beats.¹⁶ The palpitations stopped within two days of discontinuing Gb, but returned two days after the man resumed ginkgo treatment two weeks later. ECG again showed frequent ventricular ectopic beats similar to those of the first episode. These resolved within one day of stopping ginkgo. A further case describes an electrical storm in a 72-

year-old man with ischaemic cardiomyopathy and who had an implantable cardioverter defibrillator (ICD).¹⁷ The man had been taking a standardised Gb extract (120mg daily) for tinnitus for three weeks and experienced several episodes of dizziness. His ICD device revealed that he had experienced 1,440 episodes of sustained ventricular tachycardia over the previous four months, with a substantial proportion occurring in the previous ten days. The man stopped taking Gb and his condition improved markedly within days. Ventricular premature contractions have also been reported in a 37-year-old woman who had been taking Gb 180mg/day (no further product details given) for 5 months and who had undergone a surgical procedure.¹⁸

Systematic reviews (e.g. Birks et al, 2009¹⁹) of randomised clinical trials of Gb extracts typically report that there is no difference in the overall frequency of reported adverse reactions among participants receiving ginkgo preparations versus placebo. Interestingly, the Cochrane systematic review and meta-analysis of ginkgo preparations for cognitive impairment and dementia found that the adverse event dizziness was reported significantly *less* frequently for high doses (>200mg special extract daily) of *Ginkgo biloba* than for placebo, although this analysis was based on data from only two randomised clinical trials.¹⁹

Preclinical studies give conflicting results regarding the effects of *Ginkgo biloba* and its constituents on cardiac rhythm: both pro- and anti-arrhythmic effects have been reported in different animal models. For example, several experimental studies describe effects of *Ginkgo biloba* and/or its constituents on action potential duration and cationic currents in rodent ventricular myocytes.^{20,21} Other studies have reported positive chronotropic and inotropic effects for Gb extract and certain constituents in rat-isolated atria, suggesting the potential to induce atrial arrhythmias.²² Anti-arrhythmic effects have been described in studies in isolated guinea-pig ventricular myocytes, which showed that Gb extract and the constituent ginkgolide can prevent ischaemic arrhythmias and have an antiarrhythmic effect via inhibition of potassium and calcium ion currents.²³ Earlier studies reported a concentration-dependent antiarrhythmic effect for the Gb extract EGb-761 on reperfusion-induced arrhythmias in isolated rat hearts.²⁴

Discussion and Conclusion

A total of 162 reports of cardiac arrhythmias associated with *Ginkgo biloba* use was identified in VigiBase for this signal review. The reaction start date was during the last five years for at least one third of the reports. The few published case reports appeared between 2002 and 2013, and the signal has not otherwise been published, so the possibility of notoriety or publicity bias (a type of selection bias relating to the greater likelihood of a case

being reported if the person had been exposed to a drug known, thought, or likely to cause the adverse event of interest²⁵) is likely to be small.

The 162 reports came from 18 countries. Where reports are received from several countries, this can strengthen the likelihood of there being a causal association. Of note is that this extract from VigiBase did not contain any reports from China; this is unusual given the use of *Ginkgo biloba* in traditional Chinese medicine for thousands of years.¹ The absence of reports from China could, in part, reflect different indications and patterns of use of Gb there, or different susceptibility to this particular type of ADR, but is likely to be due to differences in identifying and/or reporting ADRs in China for this category of products/preparations.²⁶

It is important to note that this combination (*Ginkgo biloba* and cardiac arrhythmia) was initially identified as a *potential* signal during a joint signal detection sprint involving the UMC and the Netherlands Pharmacovigilance Centre Lareb, with a focus on finding safety concerns reported by patients.²⁷ The assessment described here was a manual review of cases, and focussed particularly on those with a higher (≥ 0.75) completeness score.

Disproportionality analysis conducted using VigiLyze indicates that there are *fewer* reports than expected, based on the overall reporting for *Ginkgo biloba* and the overall reporting for cardiac arrhythmias. Subgroup analyses in VigiLyze do not reveal disproportionalities for any individual countries or age groups or other variables (for individuals aged 18-44 years, there are 26 reports versus 15 expected, but this is not statistically significant and could reflect random variability). However, disproportionality analysis for *Ginkgo biloba* and 'palpitations', the most commonly reported PT (Preferred Term) for ginkgo in the cardiac arrhythmias SMQ, revealed 67 reports on palpitations compared to 38 expected and thus gives a (marginally) positive IC₀₂₅ (information component; IC₀₂₅ is the lower end of the 95% credibility interval for the IC) value (0.4; analysis conducted 17 January 2020).

It is not known what impact the under-reporting of any ADRs associated with *Ginkgo biloba* from China (and, possibly, some other countries) has had on the disproportionality analyses. However, unless a substantial proportion of these 'missing' ADRs for *Ginkgo biloba* relate to cardiac arrhythmias, accounting for a large number of 'missing' ADRs associated with *Ginkgo biloba* would likely result in this combination having *even fewer* reports than expected. Nevertheless, disproportionality analysis based solely on aggregated numbers of reports can overlook possible signals.²⁸

The 162 reports related to around 30 different proprietary Gb products, and 17% of the reports did not identify a specific manufacturer's product, describing ginkgo in generic terms only. At least some of the proprietary product names may relate

to the same extract of *Ginkgo biloba* marketed under different names in different countries. Nevertheless, the range of products implicated strengthens the likelihood that this is, indeed, a signal. Similarly, dose and dosage information was often incomplete, or unclear; where provided, doses and dosages were typically within, or lower than, the recommended range for Gb leaf extracts.

Several of the proprietary products have a well-established use or other marketing authorisations and, therefore, are required to comply with pharmaceutical quality standards. As a substantial proportion of the reports relate to these 'authorised' Gb products, this *may* strengthen the likelihood that, if there is a causal relationship, the reaction is related to the phytochemical constituents of *Ginkgo biloba*, rather than to constituents that are present because of adulteration in the supply chain. However, poor quality, including adulteration, of Gb-containing products marketed as 'food/dietary supplements' sold on European and other markets is well documented,^{9,29,30} and the possibility that this problem is relevant to some of the cases discussed here cannot be excluded.

It is also notable, and of concern, that one case narrative revealed that the patient was taking a 'dietary supplement' sourced from the USA that contained Gb leaf extract and vinpocetine 5 mg; this information was only evident from the case narrative and vinpocetine was not listed on the case report as a drug of exposure. Vinpocetine is a synthetic derivative of apovincamine, a vinca alkaloid obtained from the leaves of the lesser periwinkle *Vinca minor* L. Products containing vinpocetine, with or without ginkgo, are promoted as dietary supplements for, e.g. "*supporting healthy brain function*", but there is a lack of robust clinical evidence to support these claims.³¹

For all reports where Gb was the sole suspect drug (n=92), there were 46 cases with dechallenge information and, of those, 39 had a positive dechallenge. Among the 25 reports with a high completeness score (≥ 0.75), Gb was the sole suspect drug for 20 reports; dechallenge information was documented for 14 of these cases and, all information considered, there was evidence that dechallenge was positive. For most of this subset of reports, the specified time to onset of the reactions was within days. Two of the reports (both from non-health-professionals) provided some rechallenge information. For one, the case narrative states that the patient reported a positive rechallenge four times. The other report indicates rechallenge within a month of stopping Gb and after the reaction (palpitations) had resolved; the outcome is not entirely clear on the report, but appears to indicate that the reactions were resolved/resolving. Three other reports state that rechallenge was performed, but the outcome is stated as unknown.

Although positive dechallenge (and, more so, positive rechallenge) can indicate a causal relationship, in some cases, concomitantly used

drugs are indicative of a pre-existing cardiac disorder, and for some cases, information on medical history is lacking. Pre-existing arrhythmias may cause a wide range of symptoms, including tinnitus (which was the reason for use of ginkgo in 18 of the 162 reports), so confounding by indication cannot be excluded. For example, with reference to the total number of reports, other medicines most frequently co-reported included acetylsalicylic acid, which could be being taken for prophylaxis of cardiac events in patients at risk, and levothyroxine, indicating thyroid disease, which can be a risk factor for cardiac arrhythmias. Also, one of the 14 reports (Table 4, case 4) stated that the patient concerned was taking acenocoumarol for atrial fibrillation (start date not given), began taking Gb leaf extract for tinnitus, and experienced tachycardia, nausea and vomiting within 6-7 days.

Literature on the association between *Ginkgo biloba* and cardiac arrhythmias in humans comprises a small number of case reports, at least one of which is included in the VigiBase reports. There is limited and, in part, conflicting information from preclinical studies, in that different studies have described pro- and, more usually, anti-arrhythmic effects for Gb extracts.²⁰⁻²⁴ In general terms, however, some medicines with anti-arrhythmic effects can have pro-arrhythmic complications;¹¹ whether this applies to *Ginkgo biloba* requires investigation. Like other herbal medicines, ginkgo extracts are complex chemical mixtures. Two important groups of compounds found in ginkgo leaf extracts are the ginkgo flavonoid glycosides and the terpene lactones, but other chemical constituents may contribute to the pharmacological (and toxicological) effects of ginkgo preparations.

The key limitation of this analysis relates to the possibility of confounding by indication and the contribution(s) of possible underlying co-morbidities to the adverse reactions experienced. Another limitation is that the search in VigiBase using the substance *Ginkgo biloba* identified reports relating to single-ingredient Gb preparations only; therefore, reports of cardiac arrhythmias occurring in patients who took multi-ingredient products containing ginkgo have not been identified and assessed. Also, it is possible that patients could have described non-cardiac symptoms, such as dizziness, the PT for which is not included in the MedDRA SMQ (broad) for cardiac arrhythmias. Analysis of VigiBase reports for the PT dizziness and substance *Ginkgo biloba* could be part of further investigation in association with this signal.

In conclusion, although a mechanism by which *Ginkgo biloba* could induce cardiac arrhythmias is not fully elucidated, the number and nature of the cases in VigiBase and the additional published case reports suggest a signal between *Ginkgo biloba* and cardiac arrhythmias.

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Table 3. Characteristics of VigiBase reports identified using the SMQ (broad) for cardiac arrhythmias and substance *Ginkgo biloba* (dataset date: 11 September 2019) with a completeness score of ≥ 0.75 , *Ginkgo biloba* as sole suspect drug, and a positive dechallenge (n=14)

Case	Sex, age	Serious	Year of Gb use and ADR	Gb product** and daily dose	Reason for use of Gb	Concomitant medicines	Treatment duration	Reactions (MedDRA preferred term)	Time to onset (from start of medication)	Outcome
1	m, 74	Yes	2015	Gb P1 120mg	Memory impairment	amlodipine simvastatin	8 days	Syncope Dizziness Nausea	8 days	Recovered
2	f, 75	Yes	2015-16	Gb P2 60mg and vinpocetine 5mg	Vitamin supplementation		NK	Atrial fibrillation Off label use	11 months	Recovered Unknown
3	f, 67	Yes	2018-18	Gb P3a 120mg daily	Light headedness		NK	Dizziness Circulatory collapse Syncope	unclear, but < 4 weeks	Recovered Recovered Recovered
4	f, 85	Yes	2014	Gb P4 3mL	Tinnitus	acenocoumarol	7 days	Tachycardia Vomiting Nausea	6 days for N&V; 7 days for tachycardia	Recovered Recovered Recovered
5	m, 72	Yes	2006-07	Gb P5 (n/s) 120mg	Tinnitus	acetylsalicylic acid bisoprolol ramipril simvastatin torasemide molsidomine	21 days stated in ICSR but does not match start/end dates	Ventricular tachycardia Dizziness Epigastric discomfort	NK	Recovered Recovered Recovered
6	m, 37	No	2017	Gb P3b 240mg	Prophylaxis	<i>Hypericum perforatum</i> (St John's wort) dry extract	3 days	Arrhythmia	NK	Recovering
7	m, 76	No	2018-19	Gb P6 120mg	Cognitive disorder		2 months	Chills Heart rate decreased Blood pressure decreased	NK	Recovered Recovered Recovered
8	f, 45	No	2015	Gb P7a two ampoules (17.5mg/5mL IV/IM)	Sensorineural hearing loss, unspecified		one day	Palpitations Dizziness Anxiety	within one day	Recovered Recovered Recovered
9	f, 80	No	2019	Gb P8 unclear	Tinnitus		one day	Dizziness Blood pressure decreased Palpitations	within one day	Recovered Recovered Recovered
10	f, 41	No	2010	Gb P9 160mg	Raynaud's syndrome		NK	Palpitations Headache	within one day	Recovered Recovered
11	m, 62	No	2014	Gb P9 120mg	Claudication intermittent		8 days	Bradycardia	8 days	Recovered
12	f, 62	No	2017	Gb P7b 80mg	Sudden idiopathic hearing loss		4 days	Palpitations	one day	Recovered
13	m, 36	No	2018	Gb P3a 240mg	Tinnitus Tinnitus		11 days	Palpitations	8 days	Recovered
14	f, 65	n/s	2002	Gb P3a 120mg	Heat stroke and sunstroke		49 days	Somnolence Insomnia Palpitations Cardiac fibrillation Headache Tremor	21 days	Not recovered* Not recovered* Not recovered* Not recovered* Not recovered* Not recovered*

> Case 7: ICSR states rechallenge was done, but no rechallenge outcome is stated.

> Case 8: ICSR states oral administration for Gb, but the Gb product listed is an injectable formulation in ampoules; ICSR states rechallenge was done, but no rechallenge outcome is given.

> Case 9: Dose is stated as half a tablet, but formulation is film tablets, which are not intended for breaking.

> Case 10: Patient report; the summary of the case narrative states that the dose was reduced and that the patient reported a positive rechallenge on four occasions.

> Case 11: Case narrative states that the patient's medical history indicates type-2 diabetes mellitus and femoral arterial occlusion.

* The ICSR dechallenge information states that the dechallenge outcome was resolved/resolving.

** Each number relates to a different proprietary product name, or a generic name where no specific product was given in the report.

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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The Vaccine Safety Net – WHO's worldwide partnership to facilitate access to reliable information on vaccine safety

The Vaccine Safety Net (VSN) is a worldwide network of websites, verified by the World Health Organization, that provide reliable information on vaccine safety and vaccines more generally. The Network was initiated in 2003 to tackle the problem of websites with misleading and alarming information on the safety of vaccines. The VSN websites are verified against strict criteria that were developed by the WHO Global Advisory Committee on Vaccine Safety (GACVS).

The VSN has two main goals: the first goal is to facilitate access to trustworthy and science-based information about the safety of vaccines for internet users, regardless of their geographic location, cultural background, languages and health literacy. The second goal of the VSN is to collaborate, not only within the Network, but also with other international initiatives, to increase awareness about vaccines, contribute to reducing vaccine hesitancy and strengthen confidence in vaccines.

The VSN's greatest asset is the diversity of its websites. Trusted information is generated from different parts of the world and in multiple languages. This allows for culturally sensitive material, tailored to local context, that takes into consideration the audience's health literacy. The Network includes websites owned by governments, professional associations, academia, information platforms, fact-checking websites, as well as community owned websites, from high-income and low-income countries. To date, VSN boasts of 88 websites, from 39 countries, providing information in 35 languages. It is estimated that two million new users are accessing information made available by VSN members every month and that last year, some 72 million pages were viewed on VSN websites.



There are two ways by which a website can apply for VSN membership. Either a website owner requests WHO for site evaluation against GACVS criteria for good information practices, or WHO scouts for promising candidate-websites according to a predefined outreach strategy. Corporate websites and sites that seem to be irregularly updated are not considered. Once screened, the website undergoes a thorough evaluation of its content, with a focus on the scientific accuracy. At least 50 variables are assessed, in four main categories that include the website's credibility, content, accessibility and design. Once the assessor's recommendations are implemented to satisfaction, the websites are listed on the WHO website and can be accessed from [the VSN portal](#).



To signal their membership to the VSN, newly qualified websites are authorized to host the VSN visual identity on their website. This VSN logo has two purposes: 1. it signals to visitors that the information they are accessing meets the good information practices criteria and, 2. it serves to promote the entire network as a place for trusted vaccine information. While the VSN is a network established and coordinated by WHO, this does not imply an affiliation with, or endorsement of that organization by WHO, beyond a recognition by WHO that its website meets VSN criteria.

[The VSN portal](#) serves as the VSN hub on the internet. It provides central access, to the public and health care professionals, to resources and information presented by the Network's members. At the same time, it also offers members a password-protected area to share information, exchange best practices and help break isolation. The search menu on the portal's homepage has been customized to search across VSN websites ONLY. Therefore, the results page obtained after typing a specific keyword in the search field will only display information from credible sources.

The rapidly evolving digital information and communication landscape requires the Network to increase its visibility through social media space. In August 2019, Pinterest teamed up with leading public health organizations, including the WHO, the CDC, the American Academy of Pediatrics and the VSN to facilitate the access to reliable information about immunization to its audience. Future plans of the VSN social media strategy include growing the followers base, expanding the reach and diversifying platforms, continuing to

document learnings and insights gained from interactions, analyzing patterns of successful publications and interactions, and further developing collaborations with Facebook, Twitter and Google, as well as with social media influencers around the globe.

In a world where information competes for attention and misinformation proliferates, understanding the root causes for not vaccinating, monitoring behaviors, responding to the needs of those who hesitate to vaccinate, and maintaining the public health gain of vaccination are crucial.

Analyses detailing the Network's visitors' profile and interests, geographic outreach, visibility on Google search have stimulated participating institutions to review their online visibility. During February 2018 to February 2019, 20 million user visits ("sessions") were recorded from a subset of 30 participating websites, with 34 million pages viewed. A total of 10.5 million new users were documented.



The scope of the VSN web analytics will be expanded to integrate social media listening and audience analysis. The results are expected to inform each VSN member about their respective information strategies. This should also help the Network test global information campaigns and measure their impact.

The Network is exploring the use of Artificial intelligence and machine learning as tools to continuously improve the delivery of tailored messaging, and testing new ways of interaction such as employing chatbots. VSN members contributed to the content development of a Minimum Viable Product (MVP) for a Vaccine Safety Chatbot to address the most common concerns that the public has around issues related to vaccine safety. Next steps would determine whether the tool could be integrated in VSN member website's homepage. The VSN network could then make use of the chatbot to capture behavioral interactions, document information needs and identify potential vaccine safety information signals. The chatbot would generate its own analytics that would guide the Network to respond with tailored information in a timely manner. Additionally, chatbot's qualitative data could be analyzed in conjunction with the quantitative data captured by the VSN listening project. A multidisciplinary group consisting of medical anthropologists, clinical researchers, epidemiologists, behavioral scientists and communication specialists would analyze the behavioral interactions and information needs and provide answers using the latest science, tailored to the literacy level and sentiment expressed. VSN would partner with key digital communication and social media players such as Pinterest, YouTube, Google, etc. to broaden the audience outreach.

In conclusion, the WHO Vaccine Safety Net is a global good that serves to promote true knowledge and information about vaccine safety and immunization programmes.

A Call for Change for the care of the unique patient

Elena Rocca and Rani Lill Anjum, research fellows, CauseHealth Risk and Safety project, Centre for Applied Philosophy of Science, Norwegian University of Life Sciences, Norway

What type of observations must medical science include as a basis of knowledge expansion and decision making? Is there still a place for causal reasoning at the side of statistical correlations at population level? And what is the role of patient-produced evidence in medical care?

In the open access document '[Erice Call for Change: Utilising Patient Experiences to Enhance the Quality and Safety of Healthcare](#)', a multi-disciplinary group of eighteen researchers and stakeholders including clinicians, patients and patient representatives, as well as experts from academia, regulatory agencies and pharmaceutical industry, discuss new perspectives in the conceptualisation of causal evidence for clinical decision-making.

The document was drafted in September 2019, during a meeting in which the group was invited to discuss the role of rich narratives and individual experiences of patients for improving clinical practice and research. The

meeting took place in Erice, Sicily, and was organised by the International School of Pharmacology at the Ettore Majorana Foundation, in collaboration with Uppsala Monitoring Centre, Sweden, and the NMBU Centre for Applied Philosophy of Science, Norway.

The 'Erice Call for Change' focuses on two main questions:

'– How should clinical practice and research gather and utilise rich narratives of patients' individual experiences to improve general medical and therapeutic knowledge and patient safety?

– How can such narratives help inform and improve treatment decisions for each individual and for others?'

The working group identified and discussed the potential and the challenges of using patient-produced evidence both for improving general medical knowledge and for making better clinical decisions.

'While there is already some drive in the profession towards some of the changes proposed', states the document, 'the potential for improvement is still vast. This call for change sets out the direction in which healthcare should be moving'.

The participants and the promoters called for a maximum distribution and discussion of the practical and conceptual issues listed in the document among all the arenas in which evidence-based decisions are made, which affect the quality and effectiveness of medical care.

The participants were: Rani Lill Anjum, Norway; Jean-Christophe Delumeau, Singapore; Ivor Ralph Edwards, Sweden; Birgitta Grundmark, Sweden; Kai Brynjar Hagen, Norway; François Houÿez, France; Bruce Hugman, UK; Tobias Gustum Lindstad, Norway; Marie Lindquist, Sweden; Matthew Low, UK; Ugo Moretti, Italy; Eugenio Paci, Italy; Christine Price, UK; Elena Rocca, Norway; Lovisa Sandberg, Sweden; Ruth Savage, New Zealand; Penny Sawell, UK and Anders Sundström, Sweden.

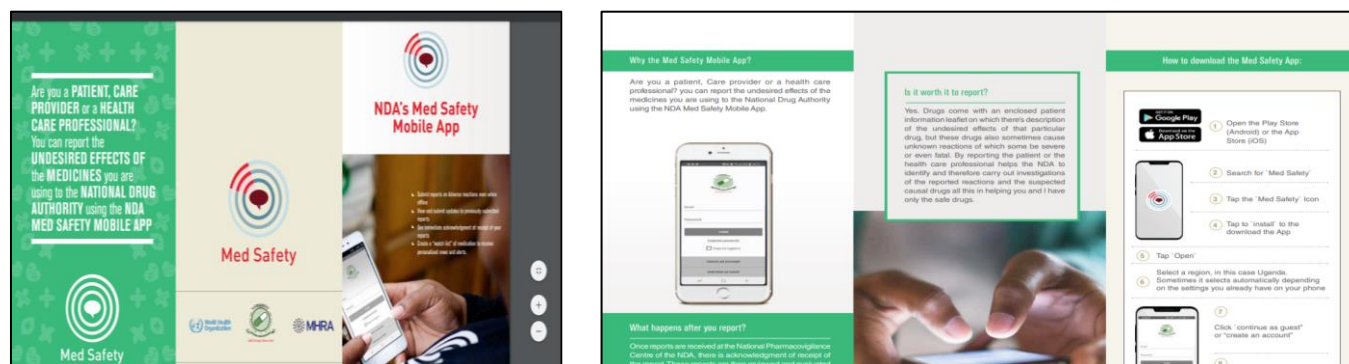


Reference: Rocca, E., Anjum, R.L. Erice Call for Change: Utilising Patient Experiences to Enhance the Quality and Safety of Healthcare. *Drug Saf* (2020). <https://doi.org/10.1007/s40264-020-00919-2>

Launch of the Med Safety mobile application in Uganda

Dr Helen Byomire Ndagije, Director Product Safety and Ms Victoria Nambasa, Manager Pharmacovigilance, National Drug Authority (NDA), Uganda

The Med Safety mobile application for reporting suspected adverse drug reactions (ADR) on both iOS and Android devices is a welcome addition to the electronic platforms that NDA has instituted. The mobile application that was launched on 26th February 2020 during the eighth annual pharmacovigilance stakeholder



meeting is believed to bring mobility and convenience to ADR reporting by both health workers and the public. Prior to this, reports have been submitted to NDA mainly using the paper form and other electronic reporting platforms including a toll-free line, WhatsApp, email, and a web portal.

One month of intensive mass media campaigns on the television, radio, local newspapers and a press conference on the eve of the launch were held. The launch attracted 200 stakeholders from the Ministry of Health (MoH) Uganda, health professional associations, hospitals, health centres, patient representatives' organisations, academia, local governments and the pharmaceutical industry. The event was officiated by the Commissioner of Pharmacy department, MoH Dr Neville Okuna Oteba, the National Drug Authority head Dr David Nahamya and WHO country representative Dr Yonas Tegegn Woldemariam.

Dr David Nahamya welcomed guests, highlighted the contributions of stakeholders and appreciated WHO for its technical and financial support and Medicines and Healthcare Products Agency (MHRA) for supporting the development and customization of the Application for Uganda. In his speech Dr Yonas Tegegn Woldemariam, emphasized that the Med Safety App is meant to improve the quality & quantity of adverse drug event reporting in countries.

Dr Helen Ndagije, the Director of Product Safety presented an overview of pharmacovigilance activities in Uganda, in which she also reported on the progress of implementation of stakeholder recommendations from the previous annual meeting. The demonstration of the application was made by Miss Victoria Nambasa. Dr Oteba reiterated the MoH's commitment to support pharmacovigilance.

The launch ended on a high note when 20 health workers and over 10 health institutions were recognized and awarded with certificates or plaques of excellence. The recognition was based on commitment to reporting ADRs consistently, not only in terms of quantity, but also of quality of reports.



Dr Helen Ndagije at a radio talk-show a week before the launch of the Med Safety application



L-R Dr David Nahamya, Dr Yonas Tegegn Woldemariam, Dr Neville Okuna Oteba and Dr Fred Sebisubi listening to the Director Product Safety at the Med Safety app launch event.

A number of activities following the launch have been undertaken, including sensitization and training of 118 health facilities on how to use the Application. Between 26 February and 11 May 2020, 27 reports were received via the App, with one case being submitted by a patient and the rest by health-care workers who had never submitted reports before.

A randomized trial is planned starting July 2020 to assess the feasibility and acceptability of implementing a mobile App for the reporting of ADRs associated with dolutegravir and IPT at selected ART-sites in Uganda. The research will also help determine if the use of the Med Safety App increases ADR-reporting by at least 25% during a year of follow-up, in comparison to existing methods using paper-form and web-form.

