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WHO Vision for Safety of Medicinal Products
No country left behind: worldwide pharmacovigilance for safer medicinal products, safer patients

The aim of the Newsletter is to disseminate regulatory information on the safety of medicinal 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:

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This Newsletter is also available at:
https://www.who.int/teams/regulation-prequalification

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicinal products 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.

In addition, this edition of the Newsletter includes an article on the Global Vaccine Safety Blueprint 2.0 (GVSB 2.0).

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Feature

Atezolizumab and other immune-stimulatory anti-cancer drugs

Risk of severe cutaneous adverse reactions (SCARs)

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for atezolizumab (Tecentriq®) has been updated to include information about the risk of severe cutaneous adverse reactions (SCARs), which includes Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN).

Atezolizumab is an immune-stimulatory drug indicated for cancers including those of the bladder, lung and liver. SCARs were previously known to be potentially associated with the use of atezolizumab.

A review of safety data for atezolizumab and the risk of SCARs was recently completed in Europe. Based on this review SCARs is an identified risk for atezolizumab.

Also, other products used for cancers in the same class as atezolizumab, including cemiplimab, ipilimumab, nivolumab and pembrolizumab list SCARs as possible adverse effects in the Summary of Product Characteristics (SmPC).

Health-care professionals should monitor patients for signs and symptoms for severe skin reactions and exclude other causes.

Reference:
Drug Safety Update, MHRA, 17 June 2021 (*www.gov.uk/mhra*)

(See also WHO Pharmaceuticals Newsletter No.3, 2021: Risk of severe cutaneous adverse reactions (SCAR) in Malaysia)

Bupropion

Risk of serotonin syndrome

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information (PI) for bupropion containing products (Zyban®, Contrave®) have been updated to include the risk of serotonin syndrome when co-administered with other drugs known to be associated with serotonin syndrome, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).

Bupropion is used as adjunctive therapy for smoking cessation and management of weight in adult.

Post marketing data show a possible pharmacodynamic interaction between bupropion and SSRIs or SNRIs resulting in an increased risk of serotonin syndrome.

The TGA received six cases of serotonin syndrome associated with bupropion (up to 17 June 2021).

Health-care professionals should educate patients about the signs and symptoms of serotonin syndrome, such as mental-status changes, autonomic instability, neuromuscular abnormalities and gastrointestinal symptoms. Patients should be instructed to see health-care professionals if they suspect that they are experiencing these adverse effects.

Reference:
Medicines Safety Update, TGA, 2 July 2021 (*www.tga.gov.au/*)

(See also WHO Pharmaceuticals Newsletter No.1, 2021: Increased risk of serotonin syndrome: drug interaction with other serotonergic drugs in UK; No.5, 2019: Risk of dizziness and somnolence in UK)

Cefoperazone

Risk of bleeding and hypoprothrombinemia

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has requested that health-care institutions stop supplying cefoperazone products (Cefobid®) due to the risk of bleeding, and has also advised health-care professionals to prescribe safer alternative antibiotics.

Cefoperazone is indicated for the treatment of a wide range of infections including respiratory tract infections, peritonitis and bacterial septicemia.

Results of several published studies suggest that cephalosporin antibiotics including cefoperazone is associated with the risk of bleeding via inhibiting vitamin K metabolism, which can lead to hypoprothrombinemia.

The SFDA reviewed published literature and post-marketing data to evaluate the potential risk of hypoprothrombinemia and bleeding with cefoperazone use. The SFDA found that the current evidence indicates an increased risk of hypoprothrombinemia and bleeding with the use of cefoperazone compared to other safer therapeutic alternatives that are available in Saudi Arabia for the same indications. Serious and fatal cases of bleeding have been reported with the use of cefoperazone worldwide.

The evaluation of the benefit-risk profile of products containing cefoperazone showed that the potential risks outweigh the benefits.

Reference:
Safety Alerts, SFDA, 14 June 2021 (*www.sfda.gov.sa*)

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19)

1. Risk of capillary leak syndrome (CLS)

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that people who have previously had capillary leak syndrome (CLS) must not be vaccinated with COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) and that CLS should be added to the product information as a new adverse drug reaction. CLS is a very rare, serious condition that causes fluid leakage from small blood vessels, resulting in swelling in the arms and legs, low blood pressure and low albumin level.

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) is a vaccine for preventing COVID-19 in people aged 18 years and older.

The PRAC carried out an in-depth review of six cases of CLS in people who had received the vaccine.

Health-care professionals should be aware of the signs and symptoms of CLS and of its risk of recurrence in people who have previously been diagnosed with the condition.

People who have been vaccinated with the vaccine should seek immediate medical assistance if they experience rapid swelling of the arms and legs or sudden weight gain in the days following vaccination.

Reference:
EMA, 11 June 2021 (*www.ema.europa.eu*)

2. Risk of Guillain-Barre syndrome (GBS)

Europe. The PRAC has recommended a change to the product information for COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) to include a warning on Guillain-Barre syndrome (GBS).

The PRAC has assessed all the available evidence including cases reported and data from the scientific literature, but at this stage the data neither confirms nor rules out a possible association with the vaccine.

Health-care professionals should be alert to signs and symptom of GBS to allow early diagnosis and supportive care and treatment.

People taking the vaccine are advised to seek immediate medical attention if they develop weakness and paralysis that can progress to the chest and face.

Reference:
EMA, 9 July 2021 (*www.ema.europa.eu*)

COVID-19 vaccine NRVV Ad26 (JNJ 78436735)

Risk of capillary leak syndrome (CLS)

Europe. The PRAC has recommended that people who have previously had CLS must not be vaccinated with COVID-19 vaccine NRVV Ad26 (JNJ 78436735) (COVID-19 vaccine Janssen®) and that CLS should be added to the product information as a new adverse drug reaction.

COVID-19 vaccine NRVV Ad26 (JNJ 78436735) is indicated for preventing COVID-19 in people aged 18 years and older.

The PRAC reviewed three cases of CLS in people who have had the vaccine.

Health-care professionals should be aware of the signs and symptoms of CLS and of its risk of recurrence in people who have previously been diagnosed with the condition.

Also, health-care professionals should tell people receiving the vaccine that they must seek medical attention if they experience rapid swelling of the arms and legs or sudden weight gain in the days following vaccination.

Reference:
EMA, 9 July 2021 (*www.ema.europa.eu*)

Cyclin-dependent kinases 4/6 (CDK4/6) inhibitors

Risk of interstitial lung disease and pneumonitis

United Kingdom. The MHRA has announced that the SmPCs and Patient Information Leaflets (PILs) for cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6-inhibitors) such as abemaciclib (Verzenios®), palbociclib (Ibrance®) and ribociclib (Kisqali®) have been updated to include warnings about the risk of interstitial lung disease and pneumonitis.

CDK4/6-inhibitors are indicated for some types of locally advanced or metastatic breast cancer.

Cases of interstitial lung disease and pneumonitis have been reported with the use of CDK4/6-inhibitors. Following European reviews of safety data, the product information has been updated to include this risk.

Health-care professionals should ask patients about pulmonary symptoms indicative of interstitial lung disease and pneumonitis, such as cough or dyspnea and advise them to seek advice if they occur.

Reference:
Drug Safety Update, MHRA, 17 June 2021 (*www.gov.uk/mhra*)

(See also WHO Pharmaceuticals Newsletter No.5, 2019: Rare but severe lung inflammation in USA; No.2, 2019: Risk of interstitial lung disease in Japan)

Diclofenac etalhyaluronate (injection)

Risk of serious shock and

anaphylaxis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for diclofenac etalhyaluronate (injection) (Joyclu®) should be revised to include the risk of serious shock and anaphylaxis as adverse drug reactions.

Diclofenac etalhyaluronate is indicated to treat osteoarthritis in the knee and hip joints.

A total of 10 cases of serious shock or anaphylaxis have been reported in patients treated with diclofenac etalhyaluronate in Japan (from March to May in 2021). Seven of the 10 cases were reviewed for causality and a causal relationship between the drug and event was assessed to be reasonably possible. No patient mortalities have been reported.

Sufficient preparation for emergency responses should be ensured prior to administration. Also, patients should be carefully monitored during drug administration.

Reference:
Revision of Precautions, MHLW/PMDA, 1 June 2021 (*www.pmda.go.jp/english/*)

Dienogest

Risk of venous thromboembolism

Australia. The TGA has announced that the product information (PI) for dienogest containing products have been updated to include more detailed information on the risk of venous thromboembolism (VTE).

Dienogest, a progestogen, is used in combined oral contraceptives (COCs) (Valette®, Qlaira®).

A review by the TGA in 2016 found that while the risk of VTE is generally rare, the risk is slightly increased in women using a COC containing ethinylestradiol and progestogen. Since 2016, the sponsor for both products conducted a meta-analysis of four prospective cohort studies investigating the VTE risk associated with the use of contraceptives. As a result of the analysis on VTE, the sponsor has updated the PI for dienogest containing products to include additional detail on this adverse reaction.

Based on the updated information, there is no reason for women to stop taking a dienogest containing contraceptive if they are already using it and have not experienced any problems.

Health-care professionals should consider a women's individual risk factors for thromboembolism, including smoking, obesity, increasing age and a family history of VTE.

Reference:
Medicines Safety Update, TGA, 23 June 2021 (*www.tga.gov.au/*)

Dopamine agonists

Risk of dopamine agonist withdrawal syndrome (DAWS)

Canada. Health Canada has announced that the Canadian Product Monograph (CPM) for pramipexole has been updated to include a warning on the risk of dopamine agonist withdrawal syndrome (DAWS).

Dopamine agonists are indicated to treat Parkinson's disease, restless leg syndrome and acromegaly. Apomorphine, bromocriptine, cabergoline, pergolide, pramipexole, quinagolide, ropinirole, and rotigotine containing products are available as dopamine agonists.

Health Canada has been monitoring the potential risk of DAWS since 2019, following updates made by the PMDA in Japan. In 2020, the manufacturer of pramipexole voluntarily updated the CPM to include a warning of DAWS, which triggered Health Canada's safety review for all dopamine agonists marketed in Canada.

Health Canada reviewed information from Canadian, international databases of reported adverse reactions and the scientific literature. Twenty three (23) case reports (two Canadian and 21 international) of DAWS in patients treated with dopamine agonists were evaluated.

The review has established a link between use of the dopamine agonists pramipexole, quinagolide or ropinirole and the risk of DAWS and therefore Health Canada will work with the manufacturers of quinagolide and ropinirole to update the CPMs to include a warning of the DAWS.

Although there is not enough information to establish a link between other dopamine agonists such as apomorphine, bromocriptine, cabergoline, pergolide and rotigotine and DAWS, Health Canada will work with the manufacturers of these dopamine agonists to include the potential risk of DAWS as a precaution.

Reference:
Summary Safety Review, Health Canada, 8 June 2021 (*www.hc-sc.gc.ca*)

(See also WHO Pharmaceuticals Newsletter No.5, 2019: Risk of drug withdrawal syndrome in Japan)

Ixekizumab (genetic recombination)

Risk of interstitial pneumonia

Japan. The MHLW and the PMDA have announced that the package insert for ixekizumab (Taltz®) should be revised to

include the risk of interstitial pneumonia as an adverse drug reaction.

Ixekizumab is indicated to treat certain diseases such as psoriasis vulgaris, erythrodermic psoriasis and ankylosing spondylitis.

A total of eight cases of interstitial pneumonia have been reported in patients treated with pembrolizumab in Japan in the last three years, including four cases for which a causal relationship between the drug and event was assessed to be reasonably possible. No patient mortalities have been reported.

If symptoms such as cough, dyspnea, or pyrexia, are observed, examinations such as chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial pneumonia is suspected, administration of ixekizumab should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 15 June 2021 *(www.pmda.go.jp/english/)*

Nivolumab (genetic recombination)

Risk of febrile neutropenia

Japan. The MHLW and the PMDA have announced that the package insert for nivolumab (Opdivo®) should be revised to include the risk of febrile neutropenia as an adverse drug reaction.

Nivolumab is indicated to treat certain types of cancer such as malignant melanoma, unresectable renal cell carcinoma and relapsed head and neck cancer.

After considering the results of a clinical study the MHLW and the PMDA considered that the revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 June 2021 *(www.pmda.go.jp/english/)*

(See also WHO Pharmaceuticals Newsletter No.3, 2021: Potential risk of certain blood disorders and cytokine release and tumor lysis syndromes in Canada; No.4, 2019: Potential risk of hemophagocytic lymphohistiocytosis (HLH) in Canada; No.2, 2019: Risk of serious blood disorder in Japan)

Olanzapine

Potential risk of somnambulism

Saudi Arabia. The SFDA has requested that the product information for olanzapine containing products (Olazine®, Olenza®, Zolan®) is updated to include a potential risk of somnambulism (sleepwalking) as an adverse drug reaction.

Olanzapine is indicated for treatment of schizophrenia and bipolar disorder including mixed or manic episodes.

The SFDA reviewed published literature and post marketing data on the potential risk of sleepwalking associated with olanzapine use. The SFDA identified 64 spontaneous case reports of somnambulism with olanzapine use in the WHO database, reported between 1999 and May 2021. Most reported cases were from the United States. Among these cases, 32 cases were reported as serious cases.

Reference:
Safety Alerts, SFDA, 20 June 2021 *(www.sfda.gov.sa)*

Pembrolizumab (genetic recombination)

Risk of fulminant hepatitis and hepatic failure

Japan. The MHLW and the PMDA have announced that the package insert for pembrolizumab (Keytruda®) should be revised to include the risk of fulminant hepatitis and hepatic failure as adverse drug reactions.

Pembrolizumab is indicated to treat certain types of cancers such as malignant melanoma, unresectable advanced non-small cell lung cancer and relapsed classical Hodgkin lymphoma.

A total of 29 cases of fulminant hepatitis or hepatic failure have been reported in patients treated with pembrolizumab in Japan in the last three years, including five cases for which a causal relationship between the drug and event was reasonably possible. A total of 18 patient mortalities, including three cases of which a causal relationship was assessed to be reasonably possible have been reported.

Patients should be carefully monitored through periodical hepatic function tests.

Reference:
Revision of Precautions, MHLW/PMDA, 15 June 2021 *(www.pmda.go.jp/english/)*

Remdesivir

Risk of sinus bradycardia

Europe. The PRAC has recommended a change to the product information for remdesivir (Veklury®) to include sinus bradycardia as an adverse drug reaction.

Remdesivir is indicated to treat COVID-19 in adults and adolescents with pneumonia requiring supplemental oxygen.

The PRAC reviewed available data on rare reported cases of bradycardia in patients treated with remdesivir as well as data from clinical trials and the scientific literature.

The PRAC concluded that a causal relationship between the use of remdesivir and the event is reasonably possible and recommended the revision of the product information.

The majority of the events of sinus bradycardia resolved a few days after the treatment with remdesivir was discontinued.

Reference:
EMA, 11 June 2021 *(www.ema.europa.eu)*

Sertraline

Potential risk of microscopic colitis

Australia. The TGA has announced that the PI for sertraline containing products (Zoloft® and generics) have been updated to include the potential risk of microscopic colitis.

Sertraline is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of obsessive compulsive disorder, social phobia and premenstrual dysphoric disorder.

The TGA received six cases of microscopic colitis suspected to be related sertraline (up until 20 May 2021).

Diarrhea is listed as a common adverse reaction with sertraline. If diarrhea is severe or prolonged, microscopic colitis should be considered.

Reference:
Medicines Safety Update, TGA, 23 June 2021 (www.tga.gov.au/)

Sunitinib

Potential risk of interstitial lung disease

Saudi Arabia. The SFDA has made a request to update the product information for sunitinib containing products (Renis®, Sutexa®, Sutent®) to include interstitial lung disease as an adverse event.

Sunitinib is indicated to treat gastrointestinal stromal tumor, metastatic renal cell carcinoma and pancreatic neuroendocrine tumors.

The SFDA has reviewed the published literature and post marketing data on the potential risk of interstitial lung disease with the use of sunitinib. The SFDA identified 115 spontaneous case reports of interstitial lung disease with the use of sunitinib in the WHO database.

The SFDA advised health-care professionals to discontinue sunitinib therapy if a patient developed interstitial lung disease.

Reference:
Safety Alerts, SFDA, 15 June 2021 *(www.sfda.gov.sa)*

Tamoxifen

Contraception duration extended

Australia. The TGA has announced that the duration of contraception after finishing tamoxifen treatment has been extended from two months to nine months.

Tamoxifen is a selective estrogen receptor modulator and indicated for the treatment of breast cancer.

Tamoxifen is contraindicated in pregnancy and the possibility of pregnancy should be excluded before treatment is started.

A small number of reports of spontaneous abortions, birth defects and foetal deaths have occurred following the use of tamoxifen, although no causal relationship has been established.

Women should be informed about the potential risks to the foetus if they become pregnant while taking tamoxifen or within nine months of finishing treatment.

Reference:
Medicines Safety Update, TGA, 23 June 2021 (www.tga.gov.au/)

Tofacitinib

Risk of cardiovascular events and cancer

Europe. The PRAC has recommended an update to the product information for tofacitinib (Xeljanz®) to include a new recommendation for its use due to the risk of cardiovascular events and cancer.

Tofacitinib is indicated to treat adults with moderate to severe rheumatoid arthritis.

The PRAC reviewed the data from a recent study conducted in patients who were 50 years of age or older with at least one additional cardiovascular risk factor.

The PRAC advises health-care professionals that tofacitinib should only be used in patients over 65 years old, patients who are current or past smokers, patients with other cardiovascular risk factors and patients with other malignancy risk factors, if no suitable treatment alternative is available.

Reference:
EMA, 11 June 2021 *(www.ema.europa.eu)*

(See also WHO Pharmaceuticals Newsletter No.2, 2021: Increased risk of serious heart-related problems and cancer in USA)

Tozinameran, Elasomeran

Potential risk of myocarditis and pericarditis

1. Europe. The PRAC has concluded that very rare cases of myocarditis and pericarditis can occur following vaccination

with the COVID-19 vaccines tozinameran (Comirnaty®) and elasomeran (Spikevax®), and recommended listing myocarditis and pericarditis as adverse effects in the product information for these vaccines.

Tozinameran and elasomeran are indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus.

The review included an in-depth review of 145 cases of myocarditis and 138 cases of pericarditis following the use of tozinameran, and 19 cases of myocarditis and 19 cases following the use of elasomeran in the European Economic Area (EEA).

The PRAC concluded that the cases primarily occurred within 14 days after vaccination, more often after the second dose and in younger adult men. Also, five death cases were reported.

Health-care professionals should be alert to the signs and symptoms of myocarditis and pericarditis, such as breathlessness and palpitations.

Reference:
EMA, 9 July 2021 (*www.ema.europa.eu*)

2. Japan. The MHLW and the PMDA have announced that the package insert for tozinameran and elasomeran should be revised to include the risk of myocarditis and pericarditis as adverse drug reactions.

A total of 12 cases of myocarditis and three cases of pericarditis with the use of tozinameran have been reported in Japan, but a causal relationship was not established for any of the cases. One case of myocarditis with the use of elasomeran has been reported, but a causal relationship was not established.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2021 (*www.pmda.go.jp/english/*)

(See also WHO Pharmaceuticals Newsletter No.3, 2021: Risk of myocarditis in Europe)

WHO COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS): updated guidance regarding myocarditis and pericarditis reported with COVID-19 mRNA vaccines 9 July 2021. (*https://www.who.int/news/item/09-07-2021-gacvs-guidance-myocarditis-pericarditis-covid-19-mrna-vaccines*)

Vemurafenib

Potential risk of hyperglycemia

Saudi Arabia. The SFDA has requested that the product information for vemurafenib (Zelboraf®) is updated to include hyperglycemia as a rare adverse event.

Vemurafenib is indicated for treatment of unresectable or metastatic melanoma in adults

The SFDA reviewed published literature and post marketing data on the potential risk of hyperglycemia with vemurafenib use. The SFDA identified 131 spontaneous case reports of hyperglycemia reported with the use of vemurafenib in the WHO database.

In addition, the SFDA advised health-care professionals to inform their patients who are at increased risk of hyperglycemia about signs and symptoms of hyperglycemia and to closely monitor blood sugar levels.

Reference:
Safety Alerts, SFDA, 26 April 2021 (*www.sfda.gov.sa*)

Colchicine

Risk of fatality if overdose

New Zealand. The Medsafe has issued a warning reminding the public of the high risk of fatality with colchicine overdose and that there are no effective treatments available for severe colchicine poisoning.

Colchicine is indicated for the treatment of acute gout when nonsteroidal anti-inflammatory drugs are contraindicated, ineffective or not tolerated.

Although colchicine has a narrow therapeutic index with the well-defined separation between therapeutic and toxic doses, some clinical guidelines may refer to unapproved dosing schedules for colchicine.

From January 2016 to January 2021, the National Poisons Centre (NPC) received 56 cases related to colchicine poisoning.

The main reasons of the poisoning were child exploratory behavior, therapeutic error and intentional self-poisoning.

Health-care professionals should communicate with patients about the importance of storing medicines out of sight and reach of children and ensure patients know when and how to take colchicine.

Reference:
Prescriber Update, Medsafe, June 2021 (*www.medsafe.govt.nz/*)

Oseltamivir

Risk of hemorrhages

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has announced that they received information from Health Canada on the potential risk of hemorrhages with the use of oseltamivir.

Oseltamivir is indicated for the treatment and prophylaxis of influenza.

Health Canada had started a safety review following an update by the PMDA on the risk of hemorrhages. It concluded that there may be a link with the use of oseltamivir and the risk of lower gastrointestinal bleeding.

Health-care professionals should be alert of the risk of hemorrhages when prescribing oseltamivir to patients.

Reference:
Safety Alerts, NPRA, 8 July 2021 (*www.npra.gov.my/*)

(See also WHO Pharmaceuticals Newsletter No.1, 2021: Potential risk of haemorrhage in Canada; No.2, 2019: Risk of bleeding in Japan)

Prednisone

Risk of steroid withdrawal symptoms

New Zealand. The Medsafe has warned of cases of steroid withdrawal symptoms, such as, shaking, sweats, fatigue, puffy face and swollen legs, after taking high-dose prednisone for infective exacerbations of asthma.

Prednisone is a corticosteroid that is indicated for treatment of several conditions such as arthritis, blood disorders, breathing problems and severe allergies.

Prednisone dosing should be determined on a case by case basis taking into consideration the condition being treated and its severity. Generally, prednisone should be used at the lowest effective dose and for the shortest duration.

Prolonged use of prednisone can result in suppression of the hypothalamic-pituitary-adrenal axis. Abrupt cessation or a too-rapid withdrawal of prednisone may cause symptoms of adrenal insufficiency such as abdominal pain, nausea, diarrhea and hypotension.

Reference:
Prescriber Update, Medsafe, June 2021 (*www.medsafe.govt.nz/*)

Retinoid medicines (Oral)

Pregnancy prevention and risk of psychiatric adverse events

United Kingdom. The MHRA has announced the publication of a new guidance on remote consultations for pregnancy prevention in women of childbearing potential. The document also provides guidance on monitoring for signs of psychiatric reactions in patients taking oral retinoid medicines.

Oral forms of the retinoid medicines such as isotretinoin, alitretinoin and acitretin are indicated to treat severe dermatological diseases that are resistant or unresponsive to standard therapies.

Psychiatric adverse events have been reported in patients taking oral retinoids and they are under review.

The guidance aims to remind health-care professionals of the need to implement the pregnancy prevention programme and monitor all patients taking oral retinoids.

Remote consultations should occur with at least the same frequency as the usual clinic consultations, to allow adequate monitoring of mental health and other potential adverse events.

Reference:
Drug Safety Update, MHRA, 7 July 2021 (*www.gov.uk/mhra*)

(See also WHO Pharmaceuticals Newsletter No.2, 2018: Updated measures for pregnancy prevention and potential risk of neuropsychiatric disorders in Europe; No.1, 2015: Possible risk of psychiatric disorders in UK)

Selective serotonin

reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs)

Increased risk of postpartum hemorrhage

New Zealand. The Medsafe has announced that the results of a review of observational studies has shown that there is a small increased risk of postpartum hemorrhage when selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are used during the month up to delivery in pregnant women.

SSRIs and SNRIs are antidepressants indicated for several symptoms such as depression and anxiety disorder.

In March 2021, the Medicines Adverse Reactions Committee (MARC) reviewed the risk of postpartum hemorrhage when SSRIs (citalopram, escitalopram, fluoxetine, sertraline and paroxetine) and SNRIs (venlafaxine) are used during the month up to delivery, and considered that an increased risk of postpartum hemorrhage was biologically plausible.

Health-care professionals are reminded to continue to consider the benefits of treating depression for the pregnant women.

Reference:
Prescriber Update, Medsafe, June 2021 (www.medsafe.govt.nz/)

(See also WHO Pharmaceuticals Newsletter No.1, 2021: Increased risk of postpartum haemorrhage in UK)

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 27 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 27). 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.

Amiodarone and rivaroxaban AND gastrointestinal haemorrhage

Annette Rudolph

Summary

A signal regarding the interaction between amiodarone and rivaroxaban resulting in gastrointestinal haemorrhage was detected during a screening of VigiBase, the WHO global database of individual case safety reports (ICSRs) in autumn 2020. Up to 6 December 2020 VigiBase contained 24 unique reports of gastrointestinal haemorrhage resulting from the combined use of amiodarone and rivaroxaban. Most patients were elderly with a median age of 74 years (range 34 – 91 years). In five cases (20.8%) reduced renal function was reported, potentially influencing rivaroxaban's exposure.

The antiarrhythmic drug amiodarone and its active metabolite act as moderate inhibitors for a series of CYP enzymes as well as P-gp and therefore have the potential for PK interactions with various drugs. The oral factor Xa inhibitor rivaroxaban is metabolised hepatically via the cytochrome P450 (CYP) enzymes 3A4 and 2J2 and is eliminated renally, via P-gp-mediated secretion. Its pharmacokinetic (PK) profile carries the risk for the development of dose-dependent toxicity when administered to patients suffering from hepatic or renal impairment or to patients receiving CYP enzyme inhibiting drugs concomitantly.

Introduction

Amiodarone is an antiarrhythmic drug used for conversion and prevention of supraventricular arrhythmias, like atrial fibrillation (AF)[1,2]. Its antiarrhythmic effect is based on a prolongation of the heart's action potential by inhibition of voltage-gated potassium and calcium channels. Amiodarone is poorly bioavailable after oral administration. After intravenous injection it is strongly protein-bound with an extremely long plasma half-life (20-100 days). Amiodarone undergoes extensive hepatic metabolism, mainly via the CYP enzyme 3A4 and several others. In vitro experiments have shown that amiodarone and its active metabolite are moderate inhibitors for a series of CYP enzymes as well as P-gp and therefore carry the potential for PK interactions with various drugs[2,3].

Rivaroxaban is an orally bioavailable, highly selective factor Xa inhibitor, blocking the intrinsic as well as the extrinsic pathway of the blood coagulation cascade. It is indicated for prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery, treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults[4]. After oral administration, rivaroxaban reaches maximal serum concentrations (t_{max}) after two to four hours. Elimination of rivaroxaban occurs through a dual pathway: two thirds of the administered dose undergo hepatic metabolism via the CYP enzymes 3A4 and 2J2. The remaining third is eliminated renally via P-gp-mediated secretion[1,4]. Elimination half-time ($t_{1/2}$) is seven to eleven hours[4,5]. The summary of product characteristics (SmPC) advises the cautious use of rivaroxaban in patients suffering

from renal impairment as well as in patients receiving comedications inhibiting both CYP3A4 and P-gp due to potential PK interactions[4]. Due to its pharmacodynamic (PD) properties, the risk for all kinds of hemorrhages is increased under rivaroxaban therapy[4].

Reports in VigiBase

The potential signal "amiodarone – interaction with rivaroxaban causing gastrointestinal (GI) haemorrhage" was identified during a screening of VigiBase, in autumn 2020.

Up to 6 December 2020, VigiBase contained 24 unique ICSRs reporting the MedDRA preferred term (PT) "gastrointestinal haemorrhage" in patients receiving rivaroxaban and amiodarone as suspected and/or interacting drugs and these were subjected to in-depth assessment. All cases were classified as serious. In three cases (12.5%) a fatal outcome was reported. Reports were sent from five different countries (United States of America (USA), Switzerland, France, Canada, and Belgium), with most of the reports (n = 18; 75.0%) from the USA. Information on the daily dose for amiodarone and rivaroxaban was available in 19 and 12 cases, respectively. Patients received on average 19.0 mg rivaroxaban (range 15-20 mg/d) and 233.3 mg amiodarone (range 200-400 mg/d) daily. This is in line with the therapeutic doses recommended in the SmPCs[2,4]. Table 1 gives an overview of the 24 assessed case reports.

Table 1. Overview of case details

Case	Age/ Sex	Drugs	Reactions (MedDRA preferred terms)	Time-to-onset (GI haemorrhage)	Additional information
1	63/F	**Amiodarone (S)** **Rivaroxaban (I)**	Gastrointestinal haemorrhage Drug interaction	Unknown Unknown	
2	71/F	**Amiodarone (S)** **Rivaroxaban (I)** Acetylsalicylic acid (I)	Gastrointestinal haemorrhage Drug interaction	Unknown Unknown	
3	-/-	**Amiodarone (S)** **Rivaroxaban (S)** Ibrutinib (S) Acetylsalicylic acid (S) Fluconazole (S) Warfarin (S) Enoxaparin (S) Diltiazem (S) Fish oil (S) Verapamil (S) Tocopherol (S) Apixaban (S) Nicotinic acid (S) Clopidogrel (S) Ticagrelor (S)	Gastrointestinal haemorrhage Contusion Cerebral haemorrhage Haematoma Epistaxis	Unknown Unknown	
4	-/-	**Amiodarone (S)** **Rivaroxaban (S)**	Gastrointestinal bleeding	Approx. 10 days Approx. 10 days	
5	66/ M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S) Tamsulosin, Hydromorphone, Prednisone, Methocarbamole, Metoprolol, Salbutamol, Furosemide, Oxycodone, Simvastatin, Tiotropium, Lorazepam, Fluticasone/Salmeterol, Gabapentin, Clonazepam, Lisinopril (C)	Gastrointestinal haemorrhage	Approx. 2 months Approx. 2 months	
6	91/F	**Amiodarone (S)** **Rivaroxaban (S)**	Gastrointestinal haemorrhage Rectal haemorrhage Melaena Drug interaction	5 days 5 days	

Case	Age/ Sex	Drugs	Reactions (MedDRA preferred terms)	Time-to-onset (GI haemorrhage)	Additional information
			Anemia		
7	85/ M	**Amiodarone (S)** **Rivaroxaban (S)** Dabigatran (S) Acetylsalicylic acid (S) Enoxaparin (S) Furosemide, Pantoprazole, Metoprolol, Zolmitriptan (C)	Gastrointestinal haemorrhage Haematuria Fall Acute kidney injury Haemorrhage intracranial	Unknown 2 years	
8	62/ M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S)	Blood loss anemia Gastrointestinal haemorrhage	Unknown 6 months	Predisposing factors: liver cirrhosis Removal of benign colon polyp (10/12/2015)
9	73/F	**Amiodarone (S)** **Rivaroxaban (S)**	Gastrointestinal Haemorrhage Swelling (amiodarone) Weight increase (amiodarone)	Unknown 2 weeks	
10	83/F	**Amiodarone (S)** **Rivaroxaban (S)** Sertraline (S) Nadolol, Pantoprazole, Vitamin D nos, Vitamins nos, Febofibrate, Furosemide, Alprazolam, Cyanocobalamin, Fluticasone (C)	Dyspnoea Gastrointestinal haemorrhage Melaena Gastritis Haematemesis Vomiting	1 year 3 years	Predisposing factors: Solitary kidney
11	74/F	**Amiodarone (S)** **Rivaroxaban (S)** Enoxaparin (S) Dabigatran (S) Acetylsalicylic acid (S) Prednisolone, Hydrochlorothiazide, Nicotinic acid, Multivitamin, Lisinopril, Ketorolac, Atenolol, Ibuprofen (C)	Gastrointestinal haemorrhage	Unknown 20 days	
12	63/ M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S)	Gastrointestinal haemorrhage Off label use Pulse absent Acute respiratory distress syndrome Product use issue	Unknown Unknown	
13	74/F	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S) Valsartan, Diltiazem, Pravastatin (C)	Gastrointestinal haemorrhage Myocardial infarction Haemorrhagic stroke Haemoptysis Epistaxis	Unknown 5 days	
14	85/ M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S) Allopurinol, Lorazepam, Insulin, Furosemide, Ibuprofen, Acetaminophen/Hydrocodon, Nortryptilin, Omeprazole, Potassium, Sennosoid (C)	Acute kidney injury Blood blister Haemorrhage Gastrointestinal haemorrhage Petechiae Haematuria	Unknown 2 months	
15	60/ M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S)	Anaemia Gastrointestinal haemorrhage	Unknown 2 months	

Case	Age/ Sex	Drugs	Reactions (MedDRA preferred terms)	Time-to-onset (GI haemorrhage)	Additional information
16	75/F	**Amiodarone (I)** **Rivaroxaban (I)** Clopidogrel (I) Acetylsalicylic acid (I)	Overdose Gastrointestinal haemorrhage Ecchymosis	2 months 2 months	Predisponen factors: Pyelonephritis secondary to diabetes mellitus II Elevated rivaroxaban plasma concentrations at admission (500 ng/mL) Light to moderate renal insufficiency (age-dependent) (61 mL/min CKD-EPI)
17	74/ M	**Amiodarone (S)** **Rivaroxaban (S)** Acetylsalicylic acid (S) Macrogol 3350, Carvedilol, Simvastatin, Ramipril (C)	Gastrointestinal haemorrhage Blood loss anaemia	Unknown Unknown	
18	89/ M	**Amiodarone (S)** **Rivaroxaban (S)** Clopidogrel (S) Acetylsalicylic acid (S) Vitamin D, Iron, Finasterid, Nicotinic acid, Ramipril, Rosuvastatin, Tamdulosin, Trimetoprim/Sulfamethoxazole, Lycopene (C)	Gastrointestinal haemorrhage Iron defficiency anaemia Diverticulum Small intestinal haemorrhage	Unknown Unknown	
19	-/-	**Amiodarone (S)** **Rivaroxaban (S)**	Gastrointestinal haemorrhage Errosive oesophagitis	Unknown Unknown	
20	87/F	**Amiodarone (I)** **Rivaroxaban (I)** Torasemide, Enalapril, Ipratropium, Salbutamol, Spironolactone, Pramipexole, Insulin degludec, Pantoprazole (C)	Gastrointestinal haemorrhage Melaena Drug interaction	30 days 15 days	Predisposing factors: hepatic cirrhosis, renal insufficiency (GFR ca. 40 mL/min)
21	77/F	**Amiodarone (S)** **Rivaroxaban (S)** Venlafaxine (S) Oxazepam, Atrovastatin, Spironolactone, Zolpidem, Rimenidine, Furosemide, Olmesartan, Nicardipine, Macrogol 3350/Potassium/Sodium bicarbonate/Sodium sulfate (C)	Gastrointestinal haemorrhage Shock haemorrhagic	9 days 9 days	Initial creatinine clearance (52 mL/min), decreased dramatically within 10 days (21 mL/min)
22	34/F	**Amiodarone (I)** **Rivaroxaban (S)**	Gastrointestinal haemorrhage Gingival bleeding	16 days 16 days	Predisposing factors: Haemophilia A
23	72/ M	**Amiodarone (I)** **Rivaroxaban (I)** Acetylsalicylic acid (I) Metoprolol, Rosuvastatin, Loperamide, Pantoprazole, Diphenhydramine/Lorazepam (C)	Gastrointestinal haemorrhage Melaena Dyspnoea Asthenia Blood loss anemia	2 years 3 months	Predisposing factors: GI haemorrhage 6 years before event onset, chronic renal insufficiency grad III secondary to diabetes mellitus type II
24	78/F	**Amiodarone (S)** **Rivaroxaban (S)**	Optic atrophy Atrial fibrillation Haemoglobin decreased Gastrointestinal haemorrhage	1 year 2 months	

Among the 24 cases, 12 patients were female and nine male with a median age of 74 years (range 34 – 91 years). In three cases information on patients' sex and age was missing. In five cases (20.8%) the MedDRA PT "Drug interaction" was specifically co-reported. In eight cases (33.3%) rivaroxaban and

amiodarone were the only two reported drugs (including one case with concomitant hepatic and renal impairment, and one case with underlying haemophilia). In five cases (20.8%) reduced renal function was reported, potentially influencing rivaroxaban's plasma concentrations (see Table 1).

Patients received a median of three suspected/interacting drugs (range two to 19). Fourteen reports included co-medications that, in addition to rivaroxaban, had anticoagulant or antiplatelet activity. Acetylsalicylic acid was listed in all fourteen reports and in five of these one or more other antiplatelet agents (clopidogrel, ticagrelor) or anticoagulants (warfarin, enoxaparin, apixaban, dabigatran) were also listed as shown in Table 1.

Analysing the concomitant drugs, in total 12 substances had PD interaction potential, another four substances had PK interaction potential and one substance (ticagrelor) had PK as well as PD interaction potential with rivaroxaban[6,7]. A data-driven exploration of the reports pinpointing features using vigiPoint[8] revealed an unexpectedly frequent reporting of nicotinic acid as a concomitantly administered drug (12.9% (three ICSRs) in cases reporting GI haemorrhage with rivaroxaban and amiodarone in combinations (foreground) vs 0.3% in cases reporting GI haemorrhage with rivaroxaban (background 1) and 0.0% in cases reporting GI haemorrhage with amiodarone (background2)).

An overview of the 18 potentially interacting substances is given in table 2.

Table 2. Potentially interacting co-medication in the 24 assessed ICSRs

Substance (WHODrug AI)	No. of ICSRs	PK/PD interaction*	Comment**
Acetylsalicylic acid	15	PD	Haemorrhagic risk
Clopidogrel	4	PD	Haemorrhagic risk
Enoxaparin	4	PD	Haemorrhagic risk
Nicotinic acid	4	PD	Dose-dependent risk for coagulopathy
Diltiazem	3	PK	Moderate CYP3A4 inhibitor
Apixaban	2	PD	Haemorrhagic risk
Dabigatran	2	PD	Haemorrhagic risk
Fluconazole	2	PK	Moderate CYP3A4 inhibitor
Ibrutinib	2	PD	Haemorrhagic risk
Ibuprofen	2	PD	Haemorrhagic risk
Ticagrelor	2	PK/PD	Weak CYP3A4 inhibitor Weak P-gp inhibitor Haemorrhagic potential
Verapamil	2	PK	Moderate CYP3A4 inhibitor P-gp inhibitor
Warfarin	2	PD	Haemorrhagic risk
Venlafaxin	2	PD	Haemorrhagic risk
Carvedilol	1	PK	P-gp inhibitor
Ketorolac	1	PD	Haemorrhagic risk
Sertralin	1	PD	Haemorrhagic risk

* CYP-/PgP-interaction as labelled in the Flockhart table/DrugBank

** Haemorrhagic risk as labelled in substance's SmPC

In one case (Table 1, case 16) it was noted that the plasma concentrations of rivaroxaban were elevated (500 ng/mL, ref. ≤ 249 ng/mL) at admission in a patient suffering from a mild to moderate renal insufficiency who was concomitantly treated with clopidogrel and acetylsalicylic acid. In addition, 13 suspected drugs were reported for another patient with both GI and cerebral haemorrhages (Table 1, case 3). In 11 cases, there were at least four co-existing risk factors present increasing the bleeding risk with rivaroxaban, including concomitant drugs and/or organ diseases or dysfunction (Table 1, cases 3, 5, 7, 8, 11, 13, 14, 16, 17, 18, and 23).

These findings suggest that the reasons for the occurrence of GI haemorrhage with rivaroxaban could be multifactorial, for example increased pharmacological effect through PK and/or PD mechanisms, or increased susceptibility through underlying diseases (e.g. previous GI haemorrhage, and haemophilia A).

Literature and Labelling

Labelling

Rivaroxaban:

According to the Summary of Product Characteristics (SmPC) of Xarelto® (rivaroxaban), limited clinical data suggest that rivaroxaban plasma concentrations are significantly increased (approximately 44-64%) in patients suffering from severe renal impairment (creatinine clearance 15-29 mL/min), resulting in increased PD effects[4,9]. The FDA's SmPC of rivaroxaban therefore advises to regularly assess patient's renal function and possibly adjust the dose accordingly[9]. Furthermore, a formal contraindication for the use of rivaroxaban in patients suffering from hepatic disease is imposed, as it has been associated with a clinically relevant bleeding risk[4].

The SmPC advises also against the use of rivaroxaban in patients being concomitantly treated with azole-antimycotics or HIV protease inhibitors, since substances that are strong inhibitors of both CYP3A4 and P-gp may increase rivaroxaban plasma concentrations to a clinically significant degree resulting in an increased risk for bleeding. Inhibitors of only one of the rivaroxaban elimination pathways – either CYP3A4 or P-gp – are expected to increase rivaroxaban plasma concentrations to a lesser extent. Advice on the use of weak to moderate inhibitors of CYP3A4 and P-gp, such as amiodarone, is absent. The SmPC warns, however, specifically against co-treatment with dronedarone, a less lipophilic successor substance of amiodarone, in patients receiving rivaroxaban therapy, due to limited available clinical data[4].

The SmPC labels bleeding as the most reported adverse reaction in patients treated with rivaroxaban. Amongst bleeding events, gastrointestinal tract haemorrhages were observed most frequently occurring in 3.8% of cases in one study[10]. Due to its pharmacological properties, rivaroxaban can cause an increased risk of occult or overt bleeding from any tissue or organ[4].

Amiodarone:

Amiodarone and its active metabolite, desethylamiodarone, act as inhibitors of various CYP enzymes as well as the P-gp, resulting in increased exposure to their substrates[1,2]. Though only a limited number of in vivo DDI have been reported, a potential for other interactions should be anticipated in relation to amiodarone[11]. Importantly to consider is amiodarone's long half-life. Therefore, effects resulting from PK interactions may be observed months after discontinuation of amiodarone therapy[1].

According to the SmPC of amiodarone, thrombocytopenia, potentially increasing the risk of haemorrhagic events, is labelled as a very rare adverse reaction[2].

Literature

A series of four published case reports describes patients experiencing increased anticoagulation parameters and/or haemorrhagic events after co-treatment with rivaroxaban and amiodarone, in one case even weeks after amiodarone cessation[1].

The four case reports describe three male and one female patient, aged 71 to 88 years old, who were admitted to the hospital due to experiencing haemorrhagic events (pulmonary haemorrhage, intracerebral mass bleeding, and cardiac tamponade)[12–14] or elevated INR [1]. In two cases the adverse reactions resolved after withdrawal of rivaroxaban[1,12], in one case rivaroxaban as well as amiodarone were withdrawn and the patient recovered[14], and in one case the patient's death was reported as outcome[13]. In one case the patient's renal function was reported to be impaired (eGFR = 50 mL/min)[1].

Discussion

In the 24 assessed ICSRs reporting GI haemorrhage in combination with amiodarone and rivaroxaban as suspected or interacting drugs, amongst the 79 reported concomitant drugs, 17 substances were found to have PK and/or PD interaction potential[6]. The potential DDI between amiodarone and rivaroxaban was identified and labelled by the reporter in only five cases. A possible reason for this circumstance might be missing awareness/labelling. Furthermore, amiodarone's long half-life might impede recognition of the potential DDI.

Nicotinic acid was co-reported with an unexpected frequency in cases of GI haemorrhage following concomitant use of amiodarone and rivaroxaban. In the SmPC of nicotinic acid as well as in published case reports the potential to cause decreased platelet counts and coagulopathy are discussed, mentioning that the exact mechanism of action of nicotinic acid is not yet explored[15–20].

The assessed reports also raise awareness of concomitant prescribing of anticoagulant and antiplatelet medicines as there are few indications for their combined use. In 15 cases patients received additional substances with antithrombotic activity. Most were "elderly patients" (≥ 65 years old). Advanced age is a known risk factor for bleeding events associated with anticoagulation. Furthermore, it is known that renal function decreases with advancing age. For five patients impaired renal function was specifically reported. A series of four published literature case reports indicates that the potential DDI in real-world clinical practice warrants attention[1,12–14].

According to the European public assessment report (EPAR) Risk Management Plan (RMP) from 2018[21], potential risks of rivaroxaban treatment of patients with severe renal impairment (creatinine clearance < 30 mL/min) as well as patients being co-treated with systemic inhibitors of CYP3A4 or P-gp - other than azole antimycotics and HIV-protease inhibitors - were identified as "missing information". In 2013, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended an updating of

the European SmPC of rivaroxaban regarding the sections "Contraindications" and "Interactions"[22]. It was recommended to include a series of potential DDI, amongst them amiodarone, to be mentioned for cautious concomitant use. Based on preclinical and clinical data that did not show a significantly increased clinical risk the market authorisation holder did not consider including amiodarone in section 4.5.

Haemorrhage being a known risk associated with rivaroxaban, the identification of a possible interaction with another medicine, such as amiodarone, resulting in an increased risk of haemorrhagic events is inevitably confounded. However, although several of the assessed cases as well as the published case reports include confounding factors, such as the use of concomitant medications and underlying organ dysfunctions, the case series supports the hypothesis of a clinically relevant potential interaction between amiodarone and rivaroxaban and suggests particular caution for co-prescription in patients predisposed to rivaroxaban-related haemorrhage through age, co-morbidities and other medicines that also increase the risk through PK or PD mechanisms. . The decision to consider co-prescribing amiodarone and rivaroxaban is an opportunity to review the patient's medicines especially where multiple antithrombotic medicines are being prescribed. There are clinical indications for dual antiplatelet/anticoagulant therapy but de-prescribing of an unnecessary antiplatelet medicine may be appropriate in some cases[23].

Conclusion

Due to their overlapping indication field and their clinical significance, amiodarone and rivaroxaban could commonly be used concomitantly or close in time in clinical practice. The observed concomitant treatment of patients with multiple drugs potentially increasing the risk for haemorrhagic events via PK and/or PD interactions with rivaroxaban and amiodarone constitutes a concern for their use in real-world clinical practice. Caution when attempting concomitant use of amiodarone and rivaroxaban should be advised, recommending benefit/risk exploration on an individual patient basis, particularly in vulnerable patients.

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Myocarditis and the COVID-19 vaccines

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Summary

The vaccines being used against the SARS-CoV-2 virus include the first mRNA-based vaccines approved for use in humans (Pfizer-BioNTech and Moderna) and continuous evaluation of their safety is critical. An assessment of the reports in VigiBase, the WHO global database of individual case safety reports, regarding myocarditis following administration of one of the COVID-19 vaccines was performed. As of 5 May 2021, there were 214 cases reporting the preferred term "Myocarditis" for all COVID-19 vaccines. There was no statistically significant disproportionate reporting across all COVID-19 vaccines, but when stratified by vaccine manufacturer there was a statistically significant increase in observed reports compared to a calculated expected number of reports for the Moderna and Pfizer-BioNTech vaccines. The 214 cases went through manual clinical evaluation and 141 were included in the final analysis. The cases were generally serious (n=132, 94%) and, in keeping with disease epidemiology, more common in males (n=87, 62%) and in younger adults, with 95 (67%) reports for those between 18 and 44 years old. The median time-to-onset (TTO) was three days (range 0 to 34 days). There were more cases after the second dose, a finding driven completely by the mRNA vaccines, and there seemed to be a more rapid onset of symptoms after the second dose. A relationship has been proposed for COVID-19 disease and myocarditis as well as myocarditis following smallpox vaccination. The mechanism of any association is unclear, but they could include the interaction of the spike protein used in the vaccine with myocardial cells, and an inflammatory response to the vaccine. It is not possible to estimate the incidence of myocarditis from this case series and there are other factors such as geographic distribution of use of each vaccine that will affect the results. However, from the available evidence there does appear to be a possible association with the mRNA vaccines and myocarditis that requires further investigation.

Introduction

A global vaccination campaign is currently in progress, protecting against infection with the virus SARS-CoV-2. These vaccines include the first mRNA-based vaccines approved for use in humans.

Myocarditis, an inflammation of the myocardium can be caused by many agents, but most commonly by viral infections, including coronaviruses[1,2]. However, it is associated with several causes, such as the smallpox vaccine[2,3]. Myocarditis can range from asymptomatic to a life-threatening disease and often presents with chest pain, arrhythmia, or heart failure[4,5]. The gold-standard for diagnosis is biopsy, but this is rarely performed. Cardiac MRI has recently become a preferred diagnostic tool, as it is more specific than other investigations such as ECG or echocardiography[5].

Reports in VigiBase

VigiBase, the WHO global database of individual case safety reports (ICSRs), was used to explore the combination of COVID-19 vaccines and myocarditis. As of 5 May 2021, there were 678,607 ICSRs related to the COVID-19 vaccines, 214 of which with the preferred term "Myocarditis". Disproportionality calculations were non-significant (observed 214 versus expected 222). However, when stratified by vaccine manufacturer, the disproportionality calculations of Pfizer-BioNTech and Moderna were found to be statistically significant (see Table 1). The Pfizer-BioNTech and Moderna vaccines also represented the vaccines with the most recorded cases, 105 and 51 respectively.

Upon manual clinical review of the ICSRs, four were duplicates; a further 69 were excluded based on pre-determined exclusion criteria, which were:

- that the case did not meet any of the diagnostic criteria for possible, probable or confirmed myocarditis,
- there were other possible diagnoses,

  or
- the onset of symptoms occurred prior to the first vaccination dose.

All included ICSRs (n=141) were adjudged to be a possible, probable or confirmed myocarditis case, with adjusted diagnostic certainty criteria, based on previous study protocols (see Table 2)[2,3]. The most frequently used, more specific, lower-level terms (LLTs) were "Myocarditis" (n=97, 69%), "Myopericarditis" (n=15, 11%), "Perimyocarditis" (n=14, 10%) and "Acute myocarditis" (n=10, 7.1%). The reports came from 20 countries, the main contributors being the United States of America (n=50, 35%), the United Kingdom (n=23, 16%), and Germany (n=9, 6.4%).

The included cases were mostly serious (n=132, 94%) and were more often seen in patients aged between 18 and 44 years (n=95, 67%, overall median age = 34) and in males (n=87, 62%). See Table 3 and 4 for an overview of cases by diagnostic certainty and vaccine manufacturer. More were seen after the second dose (n=57, 40%), although this was driven by the mRNA vaccines (Pfizer-BioNTech and Moderna) as no other cases following use of the other vaccines occurred after the second vaccine dose. This will be affected by the different vaccine programmes, for example, the AstraZeneca vaccine typically has a longer interval between doses and the Janssen vaccine is a one-dose only vaccine. There also seemed to be a shorter time-to-onset (TTO) for cases following the second vaccine dose (median = 3 days, range = 0 to 22 days) compared to the first dose (median = 4 days, range = 0-34 days). This remained true when comparing across categories of diagnostic certainty (see Table 3). The overall TTO for mRNA vaccines seemed to be shorter than that of the other vaccines (Pfizer-BioNTech median = 3 days, and Moderna median = 2 days, compared to AstraZeneca median = 4 days, and Janssen, Sinopharm and Sinovac median = 6 days). The COVID-19 vaccines were the only suspect medication in all cases, and no concomitant medication was reported more than three times.

Patients typically presented with chest pain, sometimes with accompanying fever and shortness of breath after vaccination. The terms "Chest pain" (n=53, 38%), "Troponin increase" (n=35, 25%) and "Pyrexia" (n=34, 24%) were the most common to be co-reported. Thirty-two patients (23%) explained in the narrative that they felt generally unwell with flu-like symptoms post vaccination before developing chest pain a few days later. Fifty-two cases (37%) reported perimyocarditis or myopericarditis, either as a LLT included in the preferred term of myocarditis, described in the narrative, or had both of the two preferred terms (PTs) of pericarditis and myocarditis. There were no clear differences in the case demographics or case descriptions of those reporting myopericarditis or perimyocarditis (Table 3). Two of the confirmed cases were diagnosed via biopsy during coronary angiography. One patient presented 12 days after vaccination (dose 1, Pfizer-BioNTech) after suffering nausea, diarrhoea and vomiting, and was found to have a troponin increase with biopsy findings of myocyte damage and mixed inflammatory infiltrate. Another confirmed case presented with myalgia and fever after the AstraZeneca vaccine (TTO and dose unknown), and was found to have ST elevation on ECG, and a biopsy showed an acute neutrophilic myocarditis. The other confirmed case was part of an autopsy where myocarditis and pericarditis were listed as the cause of death in an 81-year-old patient who had been vaccinated with the Pfizer-BioNTech vaccine (dose unknown) two days prior to the onset of myocarditis.

Two patients reported having previous myocarditis and one patient reported three episodes of prior pericarditis. There was also one case that occurred alongside a flare of dermatomyositis after vaccination. There were six other patients who had a medical history of autoimmune or inflammatory conditions (Sjögren syndrome, tubulointerstitial nephritis, Crohn's disease, Hashimoto's thyroiditis alongside an undiagnosed possible rheumatological disorder, a possible undiagnosed disorder, and a patient under investigation for possible multiple sclerosis with a positive antinuclear antibodies). Three cases mentioned positive infectious tests (COVID-19, histoplasma and mycoplasma). Sixteen cases (11%) reported previous confirmed or suspected COVID-19 infections, and 20 (14%) had a negative COVID-19 test at the time of symptoms. Eighteen cases (13%) had negative screening for other causes that included viral, bacterial, autoimmune and rheumatological screens, and two further cases were awaiting a screening for other causes. Several cases reported treatment with anti-inflammatories such as colchicine and ibuprofen. There were 69 cases (49%) given as recovered or recovering from myocarditis, 29 (21%) were not recovered, four had a fatal outcome (2.8%), and 41 (29%) had an unknown outcome.

Literature and labelling

Myocarditis was initially not mentioned in the product information or literature for any COVID-19 vaccine[6–13]. However, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) has recommended to update the product information for both the Pfizer-BioNTech and Moderna vaccines, listing myocarditis and pericarditis as very rare side effects together with a warning to raise awareness among health-care professionals and people taking these vaccines[14]. Similarly, the FDA has added a warning for both vaccines for myocarditis and

pericarditis[15].There is also an increasing number of cases reported in the literature regarding myocarditis after COVID-19 vaccination[16–19]. There have also been reports of smallpox vaccine-related myocarditis[2,3] and this is noted as an adverse event in the product information[20]. There are also a few cases of myocarditis following influenza vaccination[21-23], but this is less frequently reported[22].

Discussion and conclusion

Myocarditis is more common in males and is typically seen more frequently in young individuals without underlying medical conditions[24,25]. This is in line with our case series, where most cases were male, young, and of presumed good health due to lack of recorded concomitant medications. However, in some reporting platforms there is limited opportunity to note concomitant medication. Of interest, 61% of reports in VigiBase giving the patient's gender were for females, and this increased to 74% for all reports regarding the COVID-19 vaccines.

The exact pathophysiology of myocarditis is not fully understood, but it is suggested to have three stages of disease: The first stage, lasting a few days, occurs when the causative agent enters the cardiomyocytes causing cell damage and triggering an innate immune response. The second stage is dominated by an acquired immune response, and in the third stage patients recover or develop a persistent cardiomyopathy[26]. The inflammation can occur directly due to cell damage or caused by the immune response[26]. With regard to COVID-19, it has been hypothesised that myocarditis can occur due to direct cell invasion via the spike protein interacting with the angiotensin-converting enzyme 2 (ACE2), which is widely expressed and prevalent in cardiomyocytes[1,27,28]. However, in cases of COVID-19 related myocarditis, SARS-CoV-2 has not been found in cardiomyocytes, but only in the remaining myocardium, thus the cell injury was thought to be due to the generalised inflammatory response to COVID-19, part of which is Th1 activation[29,30]. Studies of myocarditis associated with smallpox vaccination, as well as the case report of myocarditis following the Pfizer-BioNTech vaccination[31], have proposed cytokine related inflammation as the mechanism[3]. Both mechanisms are unproven but could be plausible for COVID-19 vaccines as they are based on viral spike proteins and stimulate a strong Th1 response[32–34].

The incidence of myocarditis is estimated to be between 10 and 20 per 100,000 persons per year, which is likely to be an under-representation due to sub-clinical cases[25] and there has been a surge of patients presenting with COVID-19 related myocarditis[1]. The COVID-19 pandemic has also changed healthcare seeking behaviour[35,36], therefore it is difficult to estimate the current background incidence. The limitations of spontaneous reporting mean it is not possible to estimate the incidence of myocarditis following COVID-19 vaccination. From previous studies of vaccine-associated myocarditis it has been suggested that myocarditis cases following vaccination monitoring through passive surveillance is significantly underestimated[3]. The number of reports is highest for the Pfizer-BioNTech and Moderna vaccines and these two vaccines are the only COVID-19 vaccines with statistically significant disproportionate reporting. This strengthens the possibility of an association for these two vaccines but does not confirm it. Interestingly, these two vaccines are the only ones reported here that have reports after the second vaccine dose, with a shorter TTO after the second dose. This suggests a possible dose–response relationship, although the results will be affected by the different vaccine schedules and possibly by geographical variation of vaccine usage. The various vaccination programmes use different vaccines and may have different reporting patterns. As disproportionality varied between countries, the geographical distribution of reporting also requires further investigation, even when stratified by vaccine manufacturer. The cases with a very short TTO were not excluded because of inconsistencies in TTO reporting. In some reporting platforms, for example, it is not possible to record different TTOs for different adverse events.

In conclusion, this case series highlights a potential serious adverse event following vaccination with the COVID-19 vaccines. This association is better defined with the two mRNA vaccines of Pfizer-BioNTech and Moderna, with disproportionate reporting and a possible dose–response relationship. There are also plausible mechanisms and a temporal relationship, with similar reactions seen during COVID-19 disease and after smallpox vaccination. This case series does not prove causality of myocarditis by the mRNA vaccines, but it does highlight an area that requires longitudinal follow-up.

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Table 1. Observed and expected calculations for cases, by vaccine manufacturer, in VigiBase, as of 5 May 2021

	All reports (n=687,607) (%)	*Observed myocarditis cases*	*Expected myocarditis cases*	
Moderna	62,782 (9.1)	51	17	*
Pfizer-BioNTech	249,769 (36)	106	83	*
Janssen	26,965 (3.9)	7	9	
AstraZeneca	317,638 (46)	47	106	
Sinopharm	3,627 (0.5)	1	1	
Sinovac	12,436 (1.8)	1	4	

* Statistically significant. N.B. One case with an unspecified COVID-19 vaccine is not included in this table.

Table 2. Adapted diagnostic certainty criteria[2,3]

Possible (n=76)	Probable (n=62)	Confirmed (n=3)
Two of the following criteria*: • ECG changes in line with myocarditis. • Troponin or other cardiac biomarker increased • Echocardiogram suggestive of myocarditis or decreased myocardial function of any age OR Report from physician where only diagnosis is myocarditis, myopericarditis or perimyocarditis.*	Same criteria as "possible" but with confirmed new changes on Echocardiogram. OR MRI findings in keeping with acute myocarditis.* OR Report or diagnosis is from cardiologist.*	Biopsy or autopsy confirmation of myocarditis.

*Adapted by the assessor

Table 3. Overview of case demographics of the included cases and by diagnostic certainty

		*All cases (N=210)**	*Included cases (n=141)***	*Possible cases (N=76)*	*Probable cases (n=62)*	*Confirmed cases (n=3)*	*Perimyocarditis/ Myopericarditis**** *(n=52)*
Vaccine (%)	Pfizer-BioNTech	105 (50)	72 (51)	33 (43)	37 (60)	2 (66)	24 (46)
	Moderna	49 (23)	36 (26)	23 (30)	13 (21)	0 (0.0)	14 (27)
	AstraZeneca	47 (22)	29 (21)	18 (24)	10 (16)	1 (33)	11 (21)
	Janssen	5 (2.3)	2 (1.4)	0 (0.0)	2 (3.2)	0 (0.0)	2 (3.8)
	Sinopharm	1 (0.5)	1 (0.7)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
	Sinovac	1 (0.5)	1 (0.7)	1 (1.3)	0 (0.0)	0 (0.0)	1 (1.9)
	Unknown	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age Years (%)	18-44	136 (65)	95 (67)	52 (68)	42 (68)	1 (33)	36 (69)
	45-64	47 (22)	28 (20)	15 (20)	13 (21)	0 (0.0)	11 (21)
	65-74	13 (6.2)	9 (6.4)	6 (7.9)	3 (4.8)	0 (0.0)	3 (5.8)
	75+	5 (2.4)	3 (2.1)	0 (0.0)	1 (1.6)	2 (67)	1 (1.9)
	Unknown	9 (4.3)	6 (4.3)	3 (3.9)	3 (4.8)	0 (0.0)	1 (1.9)
Median age (years) (range)		35 (18-90)	34 (18-81)	32 (18-74)	35 (19-81)	80 (39-81)	32 (19–81)
Sex (%)	Male	128 (61)	87 (62)	44 (58)	42 (68)	1 (33)	35 (67)
	Female	80 (38)	52 (37)	31 (41)	19 (31)	2 (67)	17 (33)
	Unknown	2 (0.9)	2 (1.4)	1 (1.3)	1 (1.6)	0 (0.0)	0 (0)
Dose number (%)	1ST	68 (32)	40 (28)	18 (24)	21 (34)	1 (33)	11 (21)
	2ND	71 (34)	57 (40)	28 (37)	29 (47)	0 (0.0)	21 (40)
	Unknown	71 (34)	44 (31)	30 (39)	12 (19)	2 (67)	20 (38)
Median TTO (days) (range)		3 (-5–49)	3 (0–34)	3 (0-27)	3 (0-34)	7 (2-12)	3 (0–34)
Median TTO (days) per dose (range)	1ST	4 (0-37)	4 (0–34)	5 (0–27)	3.5 (1-34)	12 (N/A)	4 (1-34)
	2ND	3 (0-22)	3 (0-22)	3 (1–22)	3 (0-13)	N/A	3 (0-10)
	Unknown	3 (-5–49)	2.5 (0–20)	2 (0-20)	4 (0-20)	2 (N/A)	2 (0-13)
Mean TTO (days) per dose (S.D.)	1ST	6.9 (8.1)	6.6 (7.5)	6.1 (6.9)	6.8 (8.1)	12 (N/A)	8.2 (9.6)
	2ND	3.6 (3.6)	3.5 (3.6)	3.9 (4.3)	3.1 (2.8)	N/A	3.2 (2.3)
	Unknown	5.3 (7.8)	4.6 (5.3)	3.9 (4.9)	6.5 (5.8)	2 (N/A)	3.2 (3.4)
Serious (%)	Serious	195 (93)	132 (94)	69 (91)	60 (97)	3 (100)	49 (94)
Fatal (%)	Fatal	4 (1.9)	3 (2.1)	2 (2.6)	0 (0.0)	1 (33)	2 (3.8)
Geographical region (%)	PAHO	84 (40)	51 (36)	28 (37)	22 (35)	1 (33)	17 (33)
	Europe	122 (58)	88 (62)	47 (62)	40 (65)	1 (33)	35 (67)
	WPR	3 (1.4)	1 (0.7)	0 (0.0)	0 (0.0)	1 (33)	0 (0.0)
	EMR	1 (0.5)	1 (0.7)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: TTO – Time-to-onset, SD – Standard deviation, PAHO - Pan American Health Organization, WPR – Western Pacific Region, EMR – Eastern Mediterranean Region

**All cases in VigiBase with duplicates excluded.*

***Included cases are all cases after the exclusion criteria were applied, they were then further categorised to possible, probable or confirmed cases according to the adapted diagnostic certainty criteria.*

**** Cases where perimyocarditis or myopericarditis was used as a lower-level term included in the preferred term of myocarditis, described in the narrative, or had both of the two preferred terms of pericarditis and myocarditis. These cases are taken from the included cases and include possible, probable and confirmed cases.*

Table 4. Overview of case demographics of the included cases by vaccine manufacturer

		Pfizer-BioNTech (N=72)	*Moderna (N=36)*	*AstraZeneca (N=29)*	*Janssen (N=2)*	*Sinopharm (N=1)*	*Sinovac (N=1)*
Age (years) (%)	18-44	50 (69)	30 (83)	12 (41)	2 (100)	0 (0.0)	1 (100)
	45-64	15 (21)	3 (8.3)	10 (34)	0 (0.0)	0 (0.0)	0 (0.0)
	65-74	2 (2.8)	2 (5.6)	4 (14)	0 (0.0)	1 (100)	0 (0.0)
	75+	3 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Unknown	2 (2.8)	1 (2.8)	3 (10)	0(0.0)	0 (0.0)	0 (0.0)
Sex (%)	Male	41 (57)	28 (78)	15 (52)	2 (100)	1 (100)	0 (0.0)
	Female	30 (42)	8 (22)	13 (45)	0 (0.0)	0 (0.0)	1 (100)
	Unknown	1 (1.4)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dose (%)	1ST	15 (21)	7 (19)	15 (52)	2 (100)	1 (100)	0 (0.0)
	2ND	32 (44)	25 (69)	0 (0.0)	N/A	0 (0.0)	0 (0.0)
	Unknown	25 (35)	4 (11)	14 (48)	0 (0.0)	0 (0.0)	1 (100)
Median TTO (range)		3 (0-34)	2 (0–23)	4 (1-20)	6 (1-11)	6	6
Serious (%)	Serious	68 (94)	33 (92)	28 (97)	2 (100)	0 (0.0)	1 (100)
Fatal (%)	Fatal	1 (1.4)	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Geographical region (%)	PAHO	19 (26)	29 (81)	0 (0.0)	2 (100)	0 (0.0)	1 (100)
	Europe	53 (74)	7 (19)	28 (97)	0 (0.0)	0 (0.0)	0 (0.0)
	WPR	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
	EMR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)

Abbreviations: TTO – Time to onset, PAHO - Pan American Health Organization, WPR – Western Pacific Region, EMR – Eastern Mediterranean Region

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.
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Moving towards a WHO Global Overarching Pharmacovigilance Strategy

WHO is preparing to launch the Global Vaccine Safety Blueprint 2.0 (GVSB 2.0) during its First WHO Global pharmacovigilance meeting scheduled on 16-18 November 2021. The GVSB 2.0 has been developed through a step-wise consensus process to define the strategic priorities and objectives in the area of vaccines safety for the coming years. It aligns with the WHO's five-year plan to help build effective and efficient regulatory systems for delivering quality assured Medical Products for All (2019-2023)[1], and the Immunisation agenda 2030[2].

The GVSB 2.0 expands upon the dichotomous minimal and enhanced capacity concept by incorporating the concept of maturity levels (ML), from the WHO Global Benchmarking Tool (GBT)[3] to evaluate national regulatory systems, that uses a scale from 1 to 4. Based on the maturity level, gaps and challenges can be identified to drive the improvement of the system, that then leads to a more solid framework for public health interventions. It also promotes better collaboration and reliance from more advanced countries. The GVSB 2.0 implementation has already been initiated through the development and roll out of the WHO manual for COVID-19 vaccine safety surveillance and PV capacity strengthening in countries using the WHO GBT tool.

It is acknowledged that there are more commonalities than differences in how vigilance for vaccines and medicines is carried out, and most regulatory authorities do not have separate systems or processes for monitoring the safety of vaccines and medicines. The overall vision, goals and operating principles for a vaccine safety monitoring system described in the GVSB 2.0 are equally relevant for medicines and for building product-agnostic pharmacovigilance systems in countries. With many competing priorities and limited resources, there is value in building common systems and approaches that are smart, product-agnostic, address common needs and product specificities, and advance the principles of work-sharing and reliance.

To better support the overall concept of an integrated pharmacovigilance system, the learnings from the implementation of the GVSB 2.0 over 2021-2023 and the fast-paced innovation during the pandemic will inform the development of an overarching WHO pharmacovigilance strategy for medicines and vaccines for post 2023. The Global Vaccine Safety initiative[4], the WHO framework to convene its member states and partners to implement the Blueprint strategy will be reorganized from the present single steering group to specific task forces to drive and learn from the blueprint implementation to inform the Global PV strategy.

[1] World Health Organization. (2019). Delivering quality-assured medical products for all 2019-2023: WHO's five-year plan to help build effective and efficient regulatory systems. World Health Organization. https://apps.who.int/iris/handle/10665/332461. License: CC BY-NC-SA 3.0 IGO

[2] Immunization Agenda 2030 (who.int)

[3] available from: https://www.who.int/tools/global-benchmarking-tools

[4] The Global Vaccine Safety Initiative: enhancing vaccine pharmacovigilance capacity at country level *Bull World Health Organ* 2014;92:695–696 | doi: http://dx.doi.org/10.2471/BLT.14.138875

Going Green

The WHO Pharmaceuticals Newsletter has been published online and in paper for many years. However, going forward, we will stop issuing paper copies of the newsletter and make it available only in electronic format, our small contribution to a green planet. Thank you for your understanding and support.

All the previous issues of the newsletter can be accessed from our website at:

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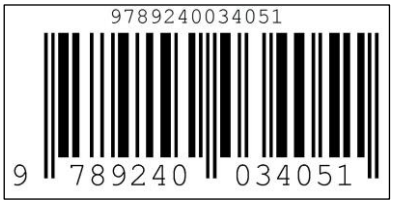
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