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 from the WHO global database of individual case safety reports, VigiBase.

In addition, this edition includes summaries of discussions and key recommendations of Advisory Committee on Safety of Medicinal Products (ACSoMP) Eighteenth meeting and Global Advisory Committee on Vaccine Safety (GACVS) meetings held in 2021.

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All the previous issues of the WHO Pharmaceuticals Newsletter can be accessed from our website.
Amoxicillin

Potential risk of aseptic meningitis

Canada. Health Canada has announced that the product safety information for amoxicillin-containing products will be updated to include the potential risk of aseptic meningitis.

Amoxicillin is an antibiotic indicated for the treatment or prevention of certain bacterial infections. Products may contain amoxicillin alone or in combination with other antibiotics.

Health Canada reviewed the available information by searching national and international databases, and the published literature. Twenty-one case reports of aseptic meningitis in adult patients receiving amoxicillin-containing products were obtained and all of them were found to be possibly or probably linked with the use of the amoxicillin-containing products. The review concluded that there may be a link between amoxicillin-containing products and the risk of aseptic meningitis.

Reference:
Summary Safety Review, Health Canada, 10 December 2021 (link to the source within www.hc-sc.gc.ca)

Antiepileptic drugs

Risk of major congenital malformations and neurodevelopmental disorders in children exposed in-utero

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information for antiepileptic drugs (AEDs) (including phenytoin, phenobarbital, carbamazepine, pregabalin and valproate) are to be updated based on the latest evidence of risks associated with in-utero exposure to AEDs. For some medicines in this class, use during pregnancy has been associated with major congenital malformations (MCMs) and neurodevelopmental disorders in children exposed in-utero.

AEDs are indicated for the treatment of various forms of epilepsy with some having additional indications in other therapeutic areas such as psychiatry.

A summary of the recent review includes:
• Phenytoin, phenobarbital and carbamazepine have an approximate 2-3 fold risk of MCMs compared to the general population. Study findings on the risk of neurodevelopmental disorders are contradictory and a risk cannot be excluded based on available evidence at this time.
• Pregabalin monotherapy: available data show that if used in the first trimester, it is associated with a slightly higher risk of MCMs compared to women not using pregabalin, or those using lamotrigine or duloxetine.
• Valproate: epidemiological data have demonstrated that use of valproate monotherapy during pregnancy is associated with an approximate 11% (4-5 fold) risk of MCMs and up to 30-40% for risk of neurodevelopmental disorders in children exposed in-utero.

When prescribing AEDs for a woman of childbearing potential for any indication, health-care professionals should fully consider and discuss what is known about the potential risks associated with in-utero exposure, as well as any recommendations concerning contraception and pregnancy planning, including actions to take in the event of a suspected or confirmed pregnancy.

Reference:
Newsletters and Reports, HPRA, 11 February 2022 (link to the source within www.hpra.ie)

(See also WHO Pharmaceuticals Newsletter No.1, 2021: Updated advice for the risk of congenital malformations and neurodevelopmental disorders and delay in UK)

Blonanserin or suvorexant, and posaconazole

Contraindication for co-administration

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for blonanserin (Lonasen®), suvorexant (Belsomra®), and posaconazole (Noxafil®) should be revised to include the contraindication for concomitant use of blonanserin or suvorexant with posaconazole.
**Regulatory Matters**

Blonanserin (available as an oral dosage form and as a patch) is used to treat schizophrenia; suvorexant is used for insomnia; and posaconazole (oral dosage form and intravenous injection) is indicated for fungal infections.

Posaconazole is an azole and strongly inhibits CYP3A4. Based on the prediction using a model with parameters obtained from in vivo data, it was estimated that the plasma exposure of blonanserin or suvorexant would increase to a level that causes safety concerns when either of them are co-administered with posaconazole. The risks are considered to outweigh the benefits with the increased plasma levels.

**Reference:**
Revision of Precautions, MHLW/PMDA, 17 December 2021 (link 1 and link 2 to the source within www.pmda.go.jp/english/)

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**Brolucizumab**

**Risk of intraocular inflammation and retinal vascular occlusion**

**United Kingdom.** The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for brolucizumab (Beovu®) will be updated to include advice on dosage intervals to reduce the risk of intraocular inflammation and retinal vascular occlusion. The maintenance dose of brolucizumab (after the first three doses) should not be given at intervals of less than eight weeks apart.

Brolucizumab is a monoclonal antibody indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) by intravitreal injection. Intraocular inflammation, including retinal vasculitis, and retinal vascular occlusion are adverse drug reactions known to be associated with brolucizumab.

A review was conducted on new data from a randomised study, where brolucizumab administered every four weeks was compared with aflibercept administered with the same time interval between doses. More frequent reports of intraocular inflammation, including retinal vasculitis, occurred in the brolucizumab group compared to the aflibercept group (9.3% versus 4.5%, respectively). Also in another study, the frequency of reports in the brolucizumab group with a four week dosage interval was higher than brolucizumab dosage intervals of 8 and 12 weeks.

Based on observational studies, retinal vasculitis and retinal vascular occlusion after brolucizumab treatment appear to be more frequent in female patients and in patients of Japanese ancestry.

Health-care professionals are advised to closely monitor patients treated with brolucizumab and who have a medical history of intraocular inflammation or retinal vascular occlusion.

**Reference:**
Drug Safety Update, MHRA, 18 January 2022 (link to the source within www.gov.uk/mhra)

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**Ceftriaxone**

**Potential risk of hepatitis and encephalopathy**

**Australia.** The Therapeutic Goods Administration (TGA) has announced that the product information for ceftriaxone has been updated to include a warning about hepatitis and encephalopathy as potential adverse events.

Ceftriaxone is a broad-spectrum cephalosporin antibiotic indicated for the treatment of pneumonia, skin, urinary tract, and other infections.

The TGA reviewed evidence published in the literature and international and national post-market adverse event data. There were 52 reports of hepatitis and related symptoms and three reports of encephalopathy for patients treated with ceftriaxone. Health-care professionals should be aware of reports of encephalopathy particularly in the elderly with severe renal impairment or central nervous system disorders. Suspension of treatment with ceftriaxone should be considered if encephalopathy is suspected.

**Reference:**
Medicines Safety Update, TGA, 15 December 2021 (link to the source within www.tga.gov.au)

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**Chloramphenicol**

**Recommended dose considering risk of reproductive toxicity**

**New Zealand.** The Medsafe has announced that the
product information for chloramphenicol eye drops will be updated to include dosing recommendations for children aged under two years. The recommended dose is one drop in the affected eye(s) four times daily for five days. Chloramphenicol eye drops are indicated for the treatment of infections of the eye. Some products contain boron in the excipients (boric acid and borates), which could be associated with reproductive toxicity (based on animal studies).

The Medicines Adverse Reactions Committee considered that the relevance of the animal data to humans is uncertain. Although human studies have not shown reproductive toxicity, they were not sufficiently robust to rule out this risk. The paediatric dose, reflecting the conventional dosing regimen for children, is associated with a boron exposure below the threshold of concern for reproductive toxicity.

**Reference:**
Prescriber Update, Medsafe, December 2021  [link to the source within www.medsafe.govt.nz](http://www.medsafe.govt.nz)

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**Cladribine**

**Risk of serious liver injury**

**Europe.** The European Medicines Agency (EMA) announced that the product information for cladribine (Mavenclad®) will be updated to include liver injury as an adverse drug reaction. A direct health-care professional communication (DHPC) will be issued on new recommendations for monitoring liver function.

Cladribine is indicated for the treatment of relapsing forms (repeated flare-ups of the symptoms) of multiple sclerosis in adults.

Liver injury, including serious cases and cases leading to discontinuation of treatment, has been reported in patients treated with cladribine. A recent review of available safety data has concluded that there is an increased risk of liver injury following treatment with cladribine.

Health-care professionals are advised to perform a detailed review of history of underlying liver disorders or episodes of liver injury with other medicines before initiating treatment in patients. During treatment, liver function tests should be conducted, and repeated as necessary. In case a patient develops liver injury, treatment with cladribine should be interrupted or discontinued, as appropriate.

**Reference:**
Patients and carers, EMA, 14 January 2022  [link to the source within www.ema.europa.eu](http://www.ema.europa.eu)

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**Clindamycin**

**Potential risk of acute kidney injury**

**Australia.** The TGA has announced that the product information for clindamycin capsules and injections have been updated to include a warning about the potential risk of acute kidney injury. Clindamycin products are indicated for the treatment of serious infections caused by susceptible strains of streptococci, pneumococci, staphylococci and anaerobic bacteria. Product information for topical clindamycin products will not be updated.

The TGA reviewed five reports of renal impairment and five cases of acute kidney injury associated with systemic clindamycin.

Health-care professionals are advised to monitor the renal function during clindamycin therapy in patients with pre-existing renal dysfunction or patients taking concomitant nephrotoxic drugs. Renal function should be monitored if therapy with clindamycin is prolonged.

**Reference:**
Medicines Safety Update, TGA, 3 February 2022  [link to the source within www.tga.gov.au](http://www.tga.gov.au)

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**COVID-19 vaccine Astrazeneca (ChAdOx1-S) and COVID-19 vaccine Janssen (Ad26.COV2-S)**

**Potential risk of transverse myelitis (TM)**

**Europe.** The Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the product information for COVID-19 vaccine Astrazeneca (ChAdOx1-S, Vaxzevria®) and COVID-19 vaccine Janssen (Ad26.COV2-S, COVID-19 vaccine Janssen®) should be updated to include a warning of the potential risk of very rare
cases of transverse myelitis (TM) reported following vaccination.

TM is a rare neurological condition characterised by an inflammation of one or both sides of the spinal cord.

The PRAC has reviewed available information on cases reported globally which include cases in the European database for suspected adverse events and data from the scientific literature. The PRAC has concluded that there is a reasonable possibility of a causal relationship between the vaccines and transverse myelitis. The benefit-risk profile of the vaccines remains unchanged.

Health-care professionals should be alert to signs and symptoms of TM, allowing early diagnosis, supportive care and treatment. People receiving either of these vaccines are advised to seek immediate medical attention if they develop symptoms of the condition.

Reference:
Patients and carers, EMA, 14 January 2022 (link to the source within www.ema.europa.eu)

COVID-19 vaccine Janssen (Ad26.COV2-S)

Risk of small vessel vasculitis

Europe. The PRAC has recommended that product information for COVID-19 vaccine Janssen (Ad26.COV2-S) should be updated to include small vessel vasculitis with cutaneous manifestations as a possible adverse event of unknown frequency.

The PRAC has reviewed a total of 21 international cases provided by the latest summary safety report. Ten cases reported single organ cutaneous vasculitis (vasculitis affecting a single organ). For most of these 10 cases, other causal explanations could not be identified and in eight of the cases, the reaction occurred soon after the administration of the vaccine.

Reference:
Patients and carers, EMA, 11 March 2022 (link to the source within www.ema.europa.eu)

COVID-19 vaccine Moderna (Elasomeran)

1. Potential risk of flare-ups of capillary leak syndrome (CLS)

Europe. The PRAC has recommended that the product information for COVID-19 vaccine Moderna (elasomeran, Spikevax®) should be revised to include a warning about flare-ups of capillary leak syndrome (CLS).

CLS is an extremely rare, serious condition that causes fluid leakage from small blood vessels (capillaries), resulting in rapid swelling of the arms and legs, sudden weight gain, feeling faint, thickening of the blood, low blood levels of albumin, and low blood pressure.

The PRAC assessed all the available data as well as all the cases of CLS reported in the Eudravigilance database after the administration of Moderna and Pfizer COVID-19 vaccines (tozinameran, Comirnaty®).

The PRAC concluded that there was insufficient evidence to establish a causal association between the two vaccines and the onset of new cases of CLS.

However, the PRAC recommended that a warning in the product information for COVID-19 vaccine Moderna should be included as some of the flare-up cases pointed towards an association with COVID-19 vaccine Moderna. Such an association was not supported in cases reported after vaccination with Pfizer COVID-19 vaccines.

Health-care professionals should be aware of the signs and symptoms of CLS and of a possible risk of a flare-up in people with a history of CLS. Vaccinated individuals with a history of CLS should consult their treating physician when planning their vaccination.

Reference:
Patients and carers, EMA, 11 March 2022 (link to the source within www.ema.europa.eu)

2. Risk of paraesthesia

Europe. The PRAC has recommended that the product information for COVID-19 vaccine Moderna should be updated to include paraesthesia as an adverse event. The frequency of this paraesthesia was estimated to be rare (i.e. occurring in less than 1 in 1,000 vaccinated persons). Hypoesthesia is already included as an adverse event in the current product information.

The PRAC assessed 1,425 international reports of...
paraesthesia which were considered to be unrelated to anxiety, and possibly caused by vaccination. Additionally, results of clinical trials were reviewed, and a higher number of paraesthesia cases were reported in people who received the vaccine (2 cases) compared to those who received placebo (0 cases).

**Reference:**

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**Dexmedetomidine**

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<td><strong>Europe.</strong> The EMA has requested that the product information for dexmedetomidine is updated to include a warning of increased risk of mortality when used in patients that are in intensive care unit (ICU).</td>
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<tr>
<td>Dexmedetomidine is indicated for light sedation (a state of calm or feeling sleepy) of adult patients in ICU, to allow the patient to stay awake and respond to verbal stimulation during diagnostic or surgical procedures.</td>
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<tr>
<td>The PRAC reviewed the result of a randomised clinical trial comparing the effect of sedation with dexmedetomidine and all-cause mortality to usual standard of care in 3,904 critically adult ICU patients in need of mechanical ventilation. Dexmedetomidine was associated with an increased risk of mortality in the subgroup of patients aged 65 years and less, compared to alternative sedatives.</td>
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**Reference:**
Patients and carers, EMA, 11 March 2022 [link to the source within www.ema.europa.eu]

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<td><strong>Risk of cardiac conduction disorders</strong></td>
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<td><strong>Australia.</strong> The TGA has announced that the product information for donepezil has been updated to include a caution for use in patients with known QTc prolongation or a family history of this condition. Additionally, caution is advised in patients receiving other medicines that affect the QTc interval, or who have certain types of cardiac disease or electrolyte disturbances. Donepezil is a cholinesterase inhibitor and indicated for the treatment of mild, moderate and severe Alzheimer’s disease.</td>
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<tr>
<td>The TGA reviewed evidence published in the literature and from international and national post-market adverse event data. There were 18 cases of atrioventricular block (complete, second degree) bundle branch block, bifascicular block or Torsades de Pointes associated with donepezil use.</td>
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<tr>
<td>Health professionals should be aware of any pre-existing or family history of cardiac disease, significant electrolyte changes and relevant drug interactions when prescribing donepezil for a patient. Patients who are at risk or report a suspected cardiac adverse event should be monitored for cardiac function.</td>
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**Reference:**
Medicines Safety Update, TGA, 28 February 2022 [link to the source within www.tga.gov.au]

(See also WHO Pharmaceuticals Newsletter No.3, 2021 Potential risk of QT prolongation in Saudi Arabia)

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**Dupilumab**

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<td><strong>Saudi Arabia.</strong> The Saudi Food &amp; Drug Authority (SFDA) has announced that the product information for dupilumab (Dupixent®) will be updated to include the potential risk of psoriasis.</td>
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<td>Psoriasis is an immune-mediated disease that causes inflammation on the skin and is associated with visible signs of the inflammation such as raised plaques and scales on the skin.</td>
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<td>Dupilumab is a monoclonal antibody for interleukin 4 and interleukin 13 and is indicated for the treatment of moderate-to-severe atopic dermatitis, severe asthma and chronic rhinosinusitis.</td>
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<td>The SFDA reviewed the literature and post-marketing databases. A review of identified cases suggested a possible association between psoriasis and dupilumab use.</td>
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**Reference:**
Safety communications, SFDA, 17 March 2022 [link to the source within www.sfda.gov.sa]

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**Efavirenz**

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### Regulatory Matters

**Fingolimod**

**Risks of thrombocytopenia and severe exacerbation of disease following discontinuation**

**Japan.** The MHLW and the PMDA have announced that the product information for efavirenz (Stocrin®) should be revised to include the risk of psychoneurotic symptoms. Efavirenz is indicated for the treatment of HIV-1 infection.

The MHLW and the PMDA reviewed cases of psychoneurotic symptoms reported in patients treated with efavirenz in Japan and overseas.

**Reference:**
Revision of Precautions, MHLW/PMDA, 15 March 2022 (link to the source within www.pmda.go.jp/english/)

**Hydroxychloroquine or chloroquine, and macrolide antibiotics**

**Interaction: Increased risk of cardiovascular events with co-administration**

**United Kingdom.** The MHRA has announced that the product information for hydroxychloroquine, chloroquine and macrolide antibiotics (azithromycin, erythromycin or clarithromycin) will be revised to include the increased risk of cardiovascular events and cardiovascular mortality if hydroxychloroquine or chloroquine is taken with a macrolide antibiotic.

**Hydroxychloroquine is indicated for treatment of rheumatoid arthritis, systemic lupus erythematosus, and dermatological conditions. Chloroquine is indicated for malaria prophylaxis or treatment and other indications.**

A review was conducted following the results of an observational study which shows that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events (including angina or chest pain and heart failure) and cardiovascular mortality.

Health-care professional should carefully consider the benefits and risks before prescribing macrolide antibiotics to patients being treated with hydroxychloroquine or chloroquine.

**Reference:**
Drug Safety Update, MHRA, 15 February 2022 (link to the source within www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.1, 2021: Risk of psychiatric disorders in Europe, WHO Pharmaceuticals Newsletter No.5, 2020: Risk of prolonged QT, ventricular tachycardia in Japan)

**Hydroxyethyl-starch solutions for infusion**

**Risk of kidney injury and death**

**Europe.** The PRAC has recommended that the marketing of hydroxyethyl-starch (HES) solutions for infusion should be suspended across the European Union.

HES solutions for infusion products are indicated as an addition to other treatments for plasma volume replacement following acute (sudden) blood loss.

The safety of HES solutions for infusion was reviewed in 2013 and in 2018, and a number of restrictions and measures to minimise the risk were put in place each time. Market authorization holders of HES solutions for infusion were also requested to conduct a drug utilization study to check that the restrictions were adhered to in clinical practice.
The PRAC has now reviewed the results from the study, which show that HES solutions for infusion are still being used outside the recommendations included in the product information. In view of this, the PRAC recommended that the product is suspended.

Health-care professionals should be aware that treatment alternatives are available and should be selected according to relevant clinical guidelines.

**Reference:**
Patients and carers, EMA, 25 February 2022 (link to the source within www.ema.europa.eu)

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**Ipilimumab**

**Risk of serous retinal detachment**

**Australia.** The TGA has announced that the product information for ipilimumab (Yervoy®) has been updated to include a warning about serous retinal detachment and transient vision loss.

Ipilimumab is a human monoclonal antibody that binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and boosts the response of the immune system to cancer cells. It is indicated for treatment of melanoma, renal cell carcinoma, malignant pleural mesothelioma and non-small cell lung cancer, both as monotherapy and in combination with other medicines.

The TGA reviewed evidence published in the literature with consideration for the seriousness of the adverse reaction.

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Health-care professionals are advised that the amount of photoreceptor degeneration and loss of vision can be minimised by early diagnosis and treatment.

**Reference:**
Medicines Safety Update, TGA, 18 February 2022 (link to the source within www.tga.gov.au)

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**Ivacaftor, tezacaftor, elexacaftor**

**Risk of serious liver injury**

**United Kingdom.** The MHRA has announced that the product information for the combination product of ivacaftor, elexacaftor and tezacaftor (Kaftrio®) and ivacaftor (Kalydeco®) have been revised to strengthen the existing warnings on hepatotoxicity. Additionally, the risk of drug-induced liver injury and an update on advice for liver function testing have been included.

The combination therapy is indicated for the treatment of cystic fibrosis in patients aged 6-years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

A recent review of safety data identified a case of liver failure leading to liver transplantation in an adult patient taking the combination with pre-existing cirrhosis and portal hypertension. The review also identified two other cases of serious liver injury in adult patients with no prior history of liver disease. These patients had elevations in transaminases and total bilirubin, and the patients were hospitalized with jaundice.

The existing recommendations for liver function monitoring have been strengthened to include advice to additionally measure total bilirubin. It has been advised that more frequent monitoring should be considered in patients with pre-existing liver disease.

**Reference:**
Drug Safety Update, MHRA, 15 February 2022 (link to the source within www.gov.uk/mhra)

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**Metformin**

**Permitting use in pregnancy**

**United Kingdom.** The MHRA has announced that the product information for metformin is to be updated to permit its use during pregnancy and the periconceptional phase as an addition or an alternative to insulin, if clinically needed.

Metformin is indicated for the treatment of type-2 diabetes, and good blood glucose control in pregnancy reduces the risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality.

A review was conducted using new safety data from a study investigating immediate and longer-term effects of metformin in-utero exposure on children born to pregnant women with pre-existing diabetes. The results of the study were reassuring, with no safety signals of concern identified for use of metformin.
in pregnancy relating either to those who were pregnant or their baby.

Reference:
Drug Safety Update, MHRA, 15 March 2022 ([link to the source within www.gov.uk/mhra](http://www.gov.uk/mhra))

(See WHO Pharmaceuticals Newsletter No.4, 2019: Contraindication removed in Japan)

Methadone

Potential risk of hypoglycemia

Canada. Health Canada has announced that the product safety information for methadone will be updated to include the potential risk of hypoglycemia (low blood sugar).

Methadone is indicated for the relief of severe pain in patients who have previously used opioids, or as a substitute in patients with opioid dependence.

Health Canada reviewed the available information by searching national and international databases, and the published literature. The review looked at 19 cases of hypoglycemia in adults after methadone use, of which 12 cases have a probable or possible link between methadone use and the risk of hypoglycemia. Six published studies reporting cases of hypoglycemia after methadone use were assessed and a possible link was also found.

Reference:
Summary Safety Review, Health Canada, 9 February 2022 ([link to the source within www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

Nintedanib

Risk of nephrotic syndrome

Japan. The MHLW and the PMDA have announced that the product information for nintedanib ethanesulfonate (Ofev®) should be revised to include the risk of nephrotic syndrome.

Nintedanib is indicated for the treatment of idiopathic pulmonary fibrosis and other lung diseases.

The MHLW and the PMDA reviewed cases of nephrotic syndrome reported in patients treated with nintedanib in Japan and overseas. Causality assessments concluded that a causal relationship between the drug and event was reasonably possible for all six cases reported in Japan.

Health-care professionals are advised to perform urine protein tests periodically during administration of this drug.

Reference:
Revision of Precautions, MHLW/PMDA, 15 March 2022 ([link to the source within www.pmda.go.jp/english](http://www.pmda.go.jp/english))

Non-irradiated blood preparations

Irradiation to prevent graft versus host disease (GVHD) regardless of patients’ GVHD risk level

Japan. The MHLW and the PMDA have announced that the product information for non-irradiated blood preparations should be revised to require irradiation of products prior to use to prevent graft versus host disease (GVHD) regardless of the risk level of GVHD in patients. Previously the requirement of irradiation of the products was limited to use of the products for patients considered to be at a high risk of GVHD.

Blood preparations concerned include concentrated human blood platelet, synthetic blood, and washed human red blood cells.

The MHLW and the PMDA reviewed relevant domestic guidelines on blood transfusion and blood product use and aligned requirement in the product information with the guidelines.

Reference:
Revision of Precautions, MHLW/PMDA, 17 December 2021 ([link to the source within www.pmda.go.jp/english](http://www.pmda.go.jp/english))

Pembrolizumab

Potential risk of optic neuritis (ON)

Saudi Arabia. The SFDA has announced that the product information for pembrolizumab (Keytruda®) will be updated to include the potential risk of optic neuritis (ON).

Pembrolizumab is indicated for the treatment of advanced melanoma, metastatic non-small cell lung carcinoma and other types of cancer.

The SFDA reviewed the literature, national and global databases. Five case reports that suggested a possible association between ON and pembrolizumab use were
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identified.

Reference:
Safety communications, SFDA, 17 March 2022 (link to the source within www.sfda.gov.sa)

Tenofovir

Risk of renal adverse effects

Australia. The TGA has announced that the product information for tenofovir alafenamide will be updated to include a warning about renal adverse events.

Tenofovir is an antiviral nucleoside analogue and tenofovir containing products are indicated for the treatment of chronic hepatitis B, HIV infection and pre-exposure prophylaxis of HIV.

The TGA reviewed 14 cases of renal adverse events in people taking tenofovir as well as foreign updates to product information.

Health-care professionals are advised to assess renal function before patients start tenofovir, and then to monitor during treatment. Stopping the medicine should be considered if a decline in renal function or Fanconi syndrome is suspected.

Reference:
Medicines Safety Update, TGA, 6 January 2022 (link to the source within www.tga.gov.au)

Venetoclax

Updated recommendations on risk of tumour lysis syndrome (TLS)

United Kingdom. The MHRA has announced that the product information for venetoclax (Venclyxto®) will be updated to emphasize that all patients should be assessed for the risk of tumour lysis syndrome (TLS).

Treatment with venetoclax requires adequate risk assessment that considers comorbidities (particularly reduced renal function) and other risk factors such as splenomegaly (in chronic lymphocytic leukaemia).

Venetoclax is B-cell lymphoma-2 (BCL-2) inhibitor and is indicated for the treatment of chronic lymphocytic leukaemia and acute myeloid leukaemia. TLS is a known risk of the medicine and is associated with severe consequences including renal failure requiring dialysis and resulting in death.

A review was conducted on fatal cases of TLS which have been reported in the post-marketing setting in patients with chronic lymphocytic leukaemia treated with venetoclax. Some of these events have occurred in patients receiving a single dose of venetoclax at the lowest recommended dose for initiation, during the dose-titration phase and in patients with low-to-medium TLS risk.

It is also recommended that all patients should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics. Information on recommended dose modifications has been added in the product information.

Reference:
Drug Safety Update, MHRA, 10 December 2021 (link to the source within www.gov.uk/mhra)

Vinca alkaloids

Medication error of injection route

Australia. The TGA has announced that the product information for vinca alkaloids (vincristine sulfate, vinblastine sulfate and vinorelbine tartrate) have been updated to provide clear instructions that they should be administered by intravenous route only.

Vinca alkaloids are indicated for cancer therapy used alone or in combination. Unintended intrathecal injection of vinca alkaloids can result in fatal outcomes.

The TGA reviewed evidence published in the literature and three cases of administration errors reporting intrathecal administration of vinca alkaloids, including one death, reported to the TGA.

The updated product information mention that preparation must be by diluting in small volume intravenous bags (the "minibag" technique), rather than in a syringe, to protect against accidental administration via the spinal route. Also, any mention of 'injecting' has been replaced by 'infusing'.

Reference:
Medicines Safety Update, TGA, 24 February 2022 (link to the source within www.tga.gov.au)
**Alcohol-based hand sanitizer**

**Risk of eye injury**

**USA.** The US Food and Drug Administration (FDA) has issued a warning about exposure of hand sanitizer to the eyes (through splashing or touching the eyes after use). Exposure in the eye can result in serious injury, including severe irritation and damage to the surface of the eye.

Hand sanitizers are over-the-counter (OTC) used to reduce virus and bacteria on hands.

Eye exposure to hand sanitizer has been reported in all age groups; however, it has occurred most often in children. Such eye injuries have become much more frequent, likely due to the increased use of alcohol-based hand sanitizer during the COVID-19 pandemic.

Consumers and caregivers should avoid touching eyes after applying alcohol-based hand sanitizer to hands. Adults should always supervise young children using alcohol-based hand sanitizers, especially around some dispensers which often are at children’s eye level and can splash. If alcohol-based hand sanitizer does accidentally splash or get in the eyes, the eyes should be thoroughly rinsed under gentle running water for 15 to 20 minutes.

**Reference:** MedWatch, US FDA, 11 February 2022 (link to the source within www.fda.gov)

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**Antidepressants**

**Updated analysis on risk of suicide in young people**

**Australia.** The TGA has announced that the findings from a recent analysis investigating antidepressant use in young people and suicide rates were aligned with the previous findings. The current available evidence is not sufficient to conclude a causal relationship exists between use of antidepressant and the rates of youth suicide.

The analysis was conducted using data on the prevalence of antidepressant prescribing, mental health and other relevant conditions for young people under the age of 25 years visiting a general practice between 2011 and 2020.

Health-care professionals should pay extra attention to prescribing the optimum dose that balances the benefits and risks for individual patients, particularly if prescribing off-label in paediatric and adolescent populations.

Additionally, patients and their family members should be educated on the risk of suicidal ideation, especially in the first month of therapy, and the general benefits and risks of pharmacotherapy.

**Reference:**
Medicines Safety Update, TGA, 20 January 2022 (link to the source within www.tga.gov.au)

(See also WHO Pharmaceuticals Newsletter No.1, 2020: Risk of suicide related adverse events in children and adolescents in New Zealand)

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**Buprenorphine (buccal administration)**

**Risk of dental problems**

**USA.** The US FDA has warned that dental problems have been reported with medicines containing buprenorphine that are dissolved in the mouth.

Buprenorphine is an opioid used to treat opioid use disorder (OUD) and pain.

The dental problems, including tooth decay, cavities, oral infections, and loss of teeth have been reported, including in patients with no prior history of dental issues. The buprenorphine medicines that are associated with dental problems are tablets and films that are dissolved under the tongue or placed against the inside of the cheek.

Patients should continue taking buprenorphine medicine as prescribed. Steps to reduce risk of serious dental problems include: rinsing mouth with water, and waiting at least 1 hour before brushing teeth after buprenorphine medicines are dissolved.

Health-care professionals should be aware that the benefits of buprenorphine medicines clearly outweigh the risks in treating OUD patients and should ask patients about oral health history prior to prescribing treatment with the medicines.

**Reference:**
MedWatch, US FDA, 1 December 2021 (link to the source within www.fda.gov)
Infliximab

Risk of infection from live vaccines in infants exposed

Europe. The PRAC recommended issuing a direct health-care professional communication (DHPC) for infliximab on the need to postpone the use of live vaccines in infants who are exposed to infliximab during pregnancy or via breastfeeding.

Infliximab is an anti-inflammatory, monoclonal antibody medicine indicated for the treatment of rheumatoid arthritis, Crohn’s disease and other inflammatory diseases.

The PRAC reviewed reports that infliximab crosses the placenta following treatment during pregnancy, and it has been detected in infants up to 12 months after birth. Infliximab has also been detected at low levels in breast milk.

It is recommended that live vaccines should not be given to infants for 12 months after birth if they have been exposed to infliximab during pregnancy and those breastfed while the mother is receiving the medicine. It is also important that women treated with infliximab who become pregnant or who breastfeed their infant inform the health-care professional responsible for vaccination of their infant about their treatment with infliximab.

Reference:
Patients and carers, EMA, 11 February 2022 (link to the source within www.ema.europa.eu).

Kratom

Risk of acute liver injury

New Zealand. The Medsafe has announced that patients taking natural health products containing kratom may be at risk of serious adverse reactions, such as acute liver injury.

Kratom is a herbal substance made from the leaves of a tropical evergreen tree (Mitragyna speciosa or kratom tree), which is indigenous to South East Asia, the Philippines, New Guinea and parts of Africa but also cultivated elsewhere. Extracts from the leaves of the kratom tree have shown psychotropic (mind-altering) and opioid-like activity. In New Zealand, Mitragyna speciosa is classified as a prescription medicine to control use.

A case has been reported to the Centre for Adverse Reactions Monitoring (CARM) where the individual developed a hepatic reaction in relation to use of kratom.

Reference:
Prescriber Update, Medsafe, December 2021 (link to the source within www.medsafe.govt.nz/).

Omalizumab

Potential risk of thromboembolic events

New Zealand. The Medsafe has announced that health-care professionals should be observant of thromboembolic events in patients being treated with omalizumab.

Omalizumab (Xolair®) is a recombinant monoclonal antibody that binds to free human immunoglobulin E (IgE) and is indicated for the treatment of allergic asthma and chronic idiopathic urticaria.

Thromboembolic events associated with omalizumab treatment have been observed in clinical trials and reported in the post-marketing setting including a case of fatal ischaemic bowel.

Reference:
Prescriber Update, Medsafe, December 2021 (link to the source within www.medsafe.govt.nz/).

Paclitaxel

Caution for medication error

United Kingdom. The MHRA has requested health-care professionals to take caution not to confuse Paclitaxel formulations with nab-paclitaxel.

Nab-paclitaxel indicated for the treatment of certain cancers of the breast, pancreas, and lung. Paclitaxel is indicated for the treatment of cancers of the ovary, breast, and lung, and advanced AIDS-related Kaposi’s sarcoma. They have different indications, pharmacokinetics, dosages, and preparation and administration instructions; therefore, they are not interchangeable.

Although the UK has not received a case report to suggest harm has occurred in the countries due to a mix-up of these paclitaxel formulations, errors in dosing or administration could have
potential consequences for clinical response and increased toxicity or adverse reactions.

Health-care professionals should make a clear distinction between paclitaxel formulations when prescribing, dispensing, administering, and communicating about these medicines. The use of brand names is advised for nab-paclitaxel formulations.

Reference:
Drug Safety Update, MHRA, 18 January 2022 (link to the source within www.gov.uk/mhra)

Triptans

Risk of Takotsubo cardiomyopathy (TCM)

New Zealand. The Medsafe has informed health-care professionals of the potential risk of triptan-associated Takotsubo cardiomyopathy (TCM).

Takotsubo cardiomyopathy is a reversible form of cardiomyopathy characterised by transient systolic dysfunction and apical ballooning of the left ventricle.

Triptans (rizatriptan and sumatriptan) are indicated for the treatment of migraines.

The CARM has received one case report of TCM with rizatriptan use. Also, reports of serious coronary events have been associated with triptan medicines. Internationally, there are a few case reports associating triptan use (mostly sumatriptan) and TCM.

Health-care professionals are advised to initiate supportive therapy in hospital if triptan-associated TCM is suspected in patients.

Reference:
Prescriber Update, Medsafe, 3 March 2022 (link to the source within www.medsafe.govt.nz)

Umbralisib

Possible increased risk of death with lymphoma investigated

USA. The US FDA is investigating the risk of death in patients treated with umbralisib (Ukoniq®). Enrollment of new patients in ongoing clinical trials of umbralisib has been suspended until the review is complete.

Umbralisib is PI3 kinase inhibitor used to treat adults with marginal zone lymphoma (MZL) and follicular lymphoma (FL) when the disease has returned or it did not respond to prior treatment(s).

Initial findings from a clinical trial evaluating umbralisib used for the treatment of chronic lymphocytic leukemia (CLL) indicate a possible increased risk of death and serious adverse events in patients taking umbralisib.

Health-care professionals should review patients’ progress on umbralisib and discuss with them the risks and benefits of continuing the treatment in the context of other available treatments.

Reference:
MedWatch, US FDA, 2 March 2022 (link to the source within www.fda.gov)
A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on 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 30 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is maintained by the Uppsala Monitoring Centre (UMC) on behalf of WHO 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 22). 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.

Acenocoumarol and semaglutide – Drug interaction

Summary

A preliminary signal with the MedDRA Preferred Term (PT) ‘Drug interaction’ in association with concomitant use of acenocoumarol and semaglutide was highlighted during a signal detection activity at Uppsala Monitoring Centre in October 2020. Acenocoumarol is a vitamin K antagonist used as an anticoagulant drug, and semaglutide is a glucagon-like peptide-1 (GLP-1) analogue used in the treatment of type 2 diabetes mellitus. In eight of the cases with concomitant use there was at least one PT indicating changes of anticoagulation drug levels, decreased International Normalised Ratio (INR), or a possible clotting disorder complication. This led to the hypothesis that semaglutide may decrease the effect of acenocoumarol, resulting in an increased risk of clotting. The time from starting treatment with semaglutide to the onset of the reaction ranged between one day and one month in seven of the cases, which is consistent with semaglutide’s pharmacokinetic properties. In two cases there was a strongly suggestive temporal relationship, where semaglutide was added to ongoing long-term treatment with acenocoumarol and the onset of the reaction occurred shortly after semaglutide initiation. One of the patients experienced two such episodes, with a positive rechallenge. Five of the cases gave INR values, which clearly showed a decrease in INR compared to the reported therapeutic range. A drug interaction between acenocoumarol and semaglutide is not described in the UK SmPC nor in the FDA product label for either of the drugs, but other GLP-1 analogues have shown some effect on the vitamin K antagonist warfarin during concomitant use. There are at least three pathways that could potentially be involved in an interaction between acenocoumarol and semaglutide. Semaglutide is a new drug, and it may still be too early to say that no serious complications will occur. Acenocoumarol has a narrow therapeutic range and is susceptible to clinically relevant drug interactions, and any suspicions of altered drug effects should be taken seriously, especially when patients at risk of coagulation disorders, such as type 2 diabetes mellitus patients, or COVID-19 patients, are concerned.

Introduction

A preliminary signal with the MedDRA Preferred Term (PT) ‘Drug interaction’, in association with concomitant use of the drugs acenocoumarol and semaglutide, was highlighted during a signal detection activity at Uppsala Monitoring Centre in October 2020. The focus of the signal detection was to identify signals for drugs used during the treatment of SARS-CoV-2 (COVID-19) infection (although none of the patients in this case series were being treated for COVID-19).

Besides the PT ‘Drug interaction’, the reports of interest also included the terms ‘Anticoagulation drug level below therapeutic’ and/or ‘International normalised ratio decreased’. These findings led to the hypothesis that semaglutide may decrease the effect of acenocoumarol, resulting in an increased risk of clotting. It was decided to further investigate the reports in VigiBase and whether literature findings would support this hypothesis.
Acenocoumarol is an anticoagulant drug that was first approved in 1957. It is widely used in Europe but is not approved in the United States. It is used for the treatment and prevention of thromboembolic diseases, e.g. deep vein thrombosis and myocardial infarction.¹

The drug is a coumarin derivative and a vitamin K antagonist. It exerts its anticoagulant effect by inhibiting the formation of coagulation factors II (prothrombin), VII, IX, and X and of protein C or its cofactor protein S. The drug is taken orally and is rapidly absorbed; at least 60% of the administered dose is systemically available, and peak plasma concentrations are achieved within one to three hours. Over 98% of acenocoumarol is protein-bound, mainly to albumin. The elimination half-life of acenocoumarol from the plasma is relatively short; 8 to 11 hours. Haemorrhage is a common side-effect.²

Acenocoumarol has the same mechanism of action as warfarin, which is more widely used because of its longer half-life.³

Semaglutide is a new antidiabetic drug that was approved in 2017 in the United States and in 2018 in Europe.⁴,⁵ It is used in the treatment of adults with insufficiently controlled type 2 diabetes mellitus,⁶ to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease,⁶,⁷ but is also indicated for chronic weight management.⁸

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a hormone with multiple actions in glucose and appetite regulation, and in the cardiovascular system. Semaglutide reduces blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high.⁶

Maximum concentration is reached within one to three days and steady state exposure achieved after four to five weeks of once weekly administration. It has an elimination half-life of approximately one week. Semaglutide is extensively bound to plasma albumin (>99%). The mechanism of blood glucose lowering also involves a minor delay in gastric emptying.⁶ It may be administered either subcutaneously or orally.⁵,⁹ Gastro-intestinal disorders, such as diarrhoea, vomiting and constipation are frequent side-effects for semaglutide.⁶

For patients who are not on anticoagulation, the international normalised ratio (INR) is usually 1.0. For patients who are on anticoagulant therapy, the therapeutic INR ranges between 2.0 and 3.0.¹⁰

There is no clear consensus on what constitutes a ‘significant’ subtherapeutic INR. Some health-care professionals class an INR of <1.7 as significant, while others consider <1.5 as significant. Acute diarrhoea and/or vomiting can result in a low INR due to reduced or incomplete absorption of anticoagulant from the gastrointestinal tract. Disease states that are known to decrease INR include hypothyroidism, diabetes mellitus, oedema, hyperlipidaemia, and visceral carcinoma.¹¹

Reports in VigiBase

There were 15 cases where acenocoumarol and semaglutide were co-reported, and where at least one of the two drugs was noted as the suspect or interacting drug. Of these, eight had at least one PT that indicated changes of anticoagulation drug levels, decreased INR, or a possible clotting disorder complication. The eight selected cases with concomitant use of acenocoumarol and semaglutide are presented in Table 1.

The remaining seven cases reported various PTs, such as ‘Diarrhoea’ (four cases), ‘Dizziness’ (two), ‘Urinary tract infection’ (two), ‘Asthenia’, ‘Diabetes mellitus inadequate control’, ‘Diabetic nephropathy’, ‘Dyspnoea’, ‘Erectile dysfunction’, and ‘Vomiting’ (all in one case each). There were no cases with bleeding or increased INR. Semaglutide was the only suspect drug in five cases and in two both drugs were suspect along with several others.

In the eight selected cases, there were five males and three females. The patients’ ages ranged between 53 and 75 years, with a median/mean of 71/68.

The countries which submitted these ICSRs were the Netherlands (seven) and Switzerland (one). The co-reported PTs of interest were: ‘Anticoagulation drug level below therapeutic’, ‘Coagulopathy’, ‘Drug interaction’, ‘International normalised ratio decreased’, ‘Myocardial infarction’, and ‘Therapeutic product effect decreased’. There was one serious case (with myocardial infarction) but with no fatal outcome.

The subcutaneous route for semaglutide was used in all cases. Narratives in VigiBase were sparse in all but one, and the original reports were requested, which provided additional valuable information. The patients’ INR values were reported in five cases; during co-treatment of acenocoumarol and semaglutide, INR decreased to between 1.0 and 1.5 (reported therapeutic range 2.0 to 3.0).

In two cases (2 and 6), there was a well-documented suggestive temporal relationship.
Acenocoumarol had been taken as long-term treatment for around six years in both cases when semaglutide was added. Time-to-onset from starting with semaglutide was one month in both patients. In case 2, semaglutide was withdrawn, the dose of acenocoumarol was increased, and the patient recovered. In case 6, both drugs were continued, and the patient had not recovered at the time of reporting.

In four other cases, there was a start date for semaglutide but not for acenocoumarol. The time-to-onset for semaglutide in these four were one day, eight days, 14 days and one month. It is possible that semaglutide was added to long-term treatment of acenocoumarol in these cases. In one, both drugs had the same start date (14 days), and in the last case there were no start dates given for either drug.

In two cases (2 and 5) the patient recovered after semaglutide dechallenge. In case 2, the patient was rechallenged with semaglutide twice and the reaction recurred on both occasions.

A suspected drug interaction was reported in six of the eight cases. A potential complication to clotting; ‘Myocardial infarction’, was reported in one (case 5) eight days after semaglutide was started.

**Literature and labelling**

A drug interaction between acenocoumarol and semaglutide is not described in the UK SmPC nor in the FDA product label for either of the drugs. There is no published clinical trial regarding drug interactions between acenocoumarol and semaglutide. Clinical trials with warfarin and semaglutide have been performed, and in those semaglutide did not change the effect of warfarin to a clinically relevant degree. Even so, frequent monitoring of INR is recommended upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives.6,12,13

Other GLP-1 analogues have shown some effect on warfarin during concomitant use:

i) During dulaglutide treatment, the time of INR response was delayed by six hours, but not considered clinically relevant.14

ii) A delay in t\text{max} of about two hours was observed when warfarin was administered 35 minutes after immediate release exenatide. No clinically relevant effects on C\text{max} or the area under the curve (AUC) were observed. Increased INR, sometimes associated with bleeding, has been spontaneously reported during concomitant use of warfarin and prolonged-release exenatide.15

iii) After concomitant administration of warfarin with repeated dosing of lixisenatide, there were no effects on AUC or INR, while C\text{max} was reduced by 19% and t\text{max} was delayed by seven hours.16

**Discussion and conclusion**

There are case reports in VigiBase that support a drug interaction between acenocoumarol and semaglutide. In two cases there was a strong suggestive temporal relationship, where semaglutide was clearly added to long-term treatment of acenocoumarol for around six years and the onset of the reaction first occurred one month after semaglutide initiation. In one of these two cases (case 2) there were also two positive rechallenges, i.e. the INR decreased after semaglutide was re-introduced. Decreased INR values compared to the reference therapeutic range were also reported in four of the other cases, which further strengthens the signal.

The time-to-onset of one day to one month in seven of the cases is consistent with semaglutide’s pharmacokinetic properties; since semaglutide reaches steady state after four to five weeks, it is worth considering that semaglutide could make the INR unsteady especially during the first month after treatment initiation.

There are at least three pathways that could potentially be involved in an interaction between acenocoumarol and semaglutide:

i) Semaglutide inhibits gastric emptying and has the potential to change the rate of absorption of oral medicines, which could impact the effect of medications where rapid uptake is important.6 This means that the uptake of acenocoumarol could be affected, and the anticoagulant effect decreased. Semaglutide also causes gastrointestinal adverse reactions, e.g. vomiting, diarrhoea and constipation, which may impair the absorption of oral medicines.5 These were not reported in the eight cases, although they may have been omitted.

ii) Over 98% of acenocoumarol is protein-bound, mainly to albumin, and >99% of semaglutide is bound to plasma albumin.2,6 This could cause fluctuations in INR.

iii) Semaglutide inhibits glucagon secretion.6 It is known that the anticoagulant effect of acenocoumarol and warfarin may be
potentiated by concomitant administration of glucagon.\textsuperscript{2,17,18} The mechanism is not known, but it has been speculated that glucagon may act synergistically with the anticoagulant to depress hepatic synthesis of vitamin K-sensitive clotting proteins, or by increasing the affinity of warfarin for its receptor site.\textsuperscript{18}

One limitation of the current assessment is that none of the reports included information on diabetic control at the time of the reaction. Diabetes mellitus is one of the conditions that may decrease INR, so this could be a potential confounder.

A drug interaction between acenocoumarol and semaglutide is not described in the UK SmPC or the FDA product label for either of the drugs, and no clinical trial to study this association has been published. There are published clinical trials which investigate interactions between warfarin and semaglutide, as well as with other GLP-1 analogues. In the two clinical trials of warfarin and semaglutide, there were no clinically relevant effects on warfarin exposure or INR.\textsuperscript{12,13} However, the number of subjects in the clinical trials was only 23 and 52 respectively, and only healthy subjects were included. The mean age of the subjects was also lower (44 and 54 years respectively) than the mean age of the VigiBase case series.

Even if warfarin is not affected by semaglutide to a clinically relevant degree, this does not necessarily mean that another vitamin K antagonist is unaffected. Acenocoumarol has a more rapid uptake and a shorter half-life than warfarin, which could perhaps make it more susceptible to clinically relevant drug interactions than warfarin.

Acenocoumarol has a narrow therapeutic range, its dose management is very difficult, and there are significant inter-individual differences in stabilising dosages. Acenocoumarol is therefore susceptible to clinically relevant drug interactions,\textsuperscript{19} and any suspicions of altered drug effects should be taken seriously, especially when those at risk of coagulation disorders, such as type 2 diabetes mellitus patients,\textsuperscript{20} or COVID-19 patients,\textsuperscript{21} are concerned.

This is an early signal of a possible drug interaction between acenocoumarol and semaglutide. Although very few serious potential consequences were reported, it is advisable to keep this potential drug interaction in mind and take frequent measurements of INR, especially when beginning concomitant administration.

### Table 1. Selected cases with concomitant use of acenocoumarol and semaglutide

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Suspect (S), interacting (I) or concomitant (C) drugs</th>
<th>MedDRA Preferred Terms</th>
<th>Time-to-onset</th>
<th>Action drug and outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56/M</td>
<td>Semaglutide (S) Acenocoumarol (C)</td>
<td>Coagulopathy</td>
<td>-</td>
<td>Rechallenge: Unknown</td>
<td>Rechallenge done but outcome unknown.</td>
</tr>
<tr>
<td>2</td>
<td>53/M</td>
<td>Acenocoumarol (I) Semaglutide (I)</td>
<td>Anticoagulation drug level below therapeutic, drug interaction, international normalised ratio decreased</td>
<td>6 years 1 month</td>
<td>Dose increased Drug withdrawn 2 positive rechallenges</td>
<td>Outcome: Recovered</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Semaglutide was added to long-term treatment of acenocoumarol. INR was lowered to 1.6 therapeutic 2-3. INR returned to therapeutic level after dechallenge of semaglutide and increased dose of acenocoumarol. Semaglutide was rechallenged twice and the reaction recurred on both occasions (INR 1.5).</td>
</tr>
<tr>
<td>3</td>
<td>70/F</td>
<td>Acenocoumarol (I) Semaglutide (I) Insulin (C)</td>
<td>Drug interaction, international normalised ratio decreased, therapeutic product effect decreased</td>
<td>- 14 days</td>
<td>Dose not changed</td>
<td>Start date acenocoumarol missing. The decreased INR value was not reported.</td>
</tr>
<tr>
<td>No.</td>
<td>ID</td>
<td>Gender</td>
<td>Drug 1</td>
<td>Drug 2</td>
<td>Event Description</td>
<td>Outcome</td>
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<td>4</td>
<td>74/M</td>
<td>M</td>
<td>Acenocoumarol (I)</td>
<td>Semaglutide (I)</td>
<td>Drug interaction, international normalised ratio decreased</td>
<td>- 1 day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Digoxin, furosemide, glitazide, losartan, metoprolol, pantoprazole, spironolactone (C)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>72/M</td>
<td>M</td>
<td>Semaglutide (S)</td>
<td>Acenocoumarol (C)</td>
<td>Myocardial infarction</td>
<td>8 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gliclazide, metformin, metoprolol, omeprazole (C)</td>
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<tr>
<td>6</td>
<td>75/F</td>
<td>F</td>
<td>Acenocoumarol (I)</td>
<td>Semaglutide (I)</td>
<td>International normalised ratio decreased, drug interaction</td>
<td>5.5 years 1 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allopurinol, atorvastatin, beclometasone/formoterol, clopidogrel, digoxin, furosemide, glimepride, isosorbide, losartan, macrogl, metformin, metoprolol, nifedipine, nitroglycerin, pantoprazole, risedronic acid, solifenacin, spironolactone, tiotropium, tramadol/paracetamol, zopiclone (C)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>75/F</td>
<td>F</td>
<td>Acenocoumarol (I)</td>
<td>Semaglutide (I)</td>
<td>International normalised ratio decreased, drug interaction</td>
<td>14 days 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Atorvastatin, colecalciferol, hydrochlorothiazide, irbesartan, isosorbide, levothyroxine, metformin, metoprolol, pantoprazole (C)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>70/M</td>
<td>M</td>
<td>Acenocoumarol (I)</td>
<td>Semaglutide (I)</td>
<td>Anticoagulation drug level below therapeutic, drug interaction</td>
<td>- 1 month</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

**Notes:**
- Drug interaction
- International normalised ratio decreased
- Outcome: Recovering
- Outcome: Not recovered
- Start date
- Dose not changed
- INR decreased
- Anticoagulation drug level below therapeutic
- Other possible causes were excluded.
- Type 2 diabetes mellitus since 14 years
- Atrial fibrillation
- Incipient neuropathy
- Heartburn
- Obesity
- Hypertension
- Sporadic alcohol user
- Ex-smoker.

**Case 4:**
- The patient required a double dose of acenocoumarol to reach the therapeutic range of 2-3.

**Case 5:**
- Serious case. Start date acenocoumarol missing. Rechallenge done but outcome unknown. Type 2 diabetes mellitus (since 14 years), atrial fibrillation, incipient neuropathy, heartburn, obese, hypertension, sporadic alcohol user, ex-smoker.

**Case 6:**
- Semaglutide was added to long-term treatment of acenocoumarol. INR decreased to 1.1-1.7, despite a dose increase of acenocoumarol from 2.64 mg to 4.71 mg. The INR was stable before the start of the semaglutide (2-3).

**Case 7:**
- The INR decreased from therapeutic range (not included) to 1.0-1.1. Other possible causes were excluded. The dose of acenocoumarol was increased by 240% to reach the required therapeutic INR range.

**Case 8:**
- Start date acenocoumarol missing. INR was lowered to 1.1-2.0 (therapeutic 2-3).
Reference


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 WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003, to provide advice to WHO, including its Collaborating Centre for International Drug Monitoring (the UMC), and through it, to the Member States of WHO, on safety issues relating to medicinal products.

A summary of discussions and key recommendations from the 18th meeting of ACSoMP is provided below.

**An integrated approach to pharmacovigilance and vaccine safety monitoring**

Reorganization in WHO led to the formation of a Medicines and Health Products (MHP) Division with two departments – one on Health Product Policy and Standards (HPS) and one on Regulation and Prequalification (RPQ). During the transformation, former medicines and vaccines safety teams merged into one team dealing with pharmacovigilance and the safety of medicinal products in the RPQ department. The Committee noted that the combined focus would facilitate future work on the safety of medicines and vaccines globally and this new arrangement in WHO reflected the systems in operation in many countries.

**Dolutegravir and data review of neural tube defects, September 30, 2021**

Dolutegravir (DTG) has been regularly discussed by members of ACSoMP in recent years. DTG is a widely used and highly effective antiretroviral medication recommended for treatment of people with HIV/AIDS, but the confidence in this medicine was shaken in 2018, when preliminary results from a nationwide birth surveillance programme in Botswana found a potential association between periconceptional DTG exposure with the development of neural tube defects (NTDS) in a setting without folate fortification. However, as the cohort expanded over subsequent years, there was a significant decline in the strength of the signal, with the prevalence of NTDs with preconception exposure to DTG no longer being significantly different than observed with non-DTG preconception antiretroviral treatment exposures. Studies in other settings have supported these subsequent findings. Although the results of the Tspamo study is showing a very positive balance of benefit to risk of a very effective medicine, there is a concern that some countries remain hesitant to use DTG despite its effectiveness.

**Recommendations:** ACSoMP recommends that this misconception is corrected because it limits regimen harmonization across populations, and, in turn, impedes DTG-based ART scale up efforts. Models such as Tspamo study are recommended to be used in future to study all medicines and vaccines given during pregnancy. Pregnancy exposure registries and birth defect surveillance systems in LMIC settings would support the assessment of therapeutic and preventive interventions on maternal and birth outcomes.

**Sodium valproate and pregnancy**

The WHO Expert Committee on the Selection and Use of Essential Medicines at its 23rd meeting in June–July 2021 added a cautionary note with the listings of sodium valproate to indicate that its use should be avoided in pregnant women and women of childbearing potential. Current WHO guidelines include recommendations for use of valproate in patients with epilepsy and bipolar disorder. However, because the use of valproate in women of childbearing age during the preconception phase leads to a high risk of birth defects and developmental disorders in infants, WHO’s recommendations on valproate for epilepsy and bipolar disorders in pregnant or breast-feeding women state that: 1) women with epilepsy should have seizures controlled as well as possible with the minimum dose of antiepileptic drug taken in monotherapy, wherever possible, and that valproate should be avoided in women of childbearing age; and that 2) in women, with bipolar mania planning...
Features

a pregnancy or, in women who are pregnant or breastfeeding, valproate should be avoided due to risk of birth defects. It was noted that newer medicines need to be made more available in LMICs and that WHO is reviewing the current evidence for valproate and other medications in women of childbearing age and is updating the recommendations for their use in epilepsy and bipolar disorders.

Recommendations: Concerns about the continued inappropriate and dangerous use of valproate in women of childbearing age should be advocated as it is known that this drug causes a certain proportion of children to be born with malformations every year. Although educational material has increased awareness of these dangers amongst health-care professionals in some settings, sodium valproate is still being prescribed. More work is needed to understand why practices do not coincide with increased awareness. Monitoring safety of medicines during pregnancy should be revisited in future ACSoMP meetings.

Monitoring the safety of medicines used in leprosy

WHO’s leprosy team requested advice from ACSoMP on the monitoring of leprosy medicines, most of which are old and have known adverse effects. There is basically little data on adverse drug reactions collected through reporting systems with leprosy medicines.

Recommendations include:

- Developing a pharmacovigilance package containing a watch list of adverse reactions of concern together with advice on their management and prevention to help minimize risk, as many of the medicines used in leprosy are older drugs with a known safety profile. The package should also contain advice on studies to be carried out. Further investigations into the effectiveness of thalidomide for treatment of erythema nodosum leprosum reactions in leprosy and follow up cohort studies to monitor harms and quantify risks were suggested.

- National leprosy programmes could usefully learn from the experience of tuberculosis programmes with regard to active surveillance and IT solutions for data sharing.

- The upcoming consultation by the WHO leprosy programme in November 2021 should focus on the development of a future programme of work that would include a range of pharmacovigilance priorities that would form the basis of global activities and help build stakeholder ownership of the leprosy programme and its work.

Tuberculosis signal on hallucinations with delamanid in children

Delamanid has been recommended for use in treating multidrug-resistant tuberculosis (MDR-TB) or rifampicin-resistant tuberculosis (RR-TB). In May-June 2021 WHO convened a Guideline Development Group (GDG) meeting on the management of TB in children and adolescents. Among the data reviewed was information from the manufacturer (Otsuka Pharmaceuticals) on a safety signal of hallucinations. WHO recommended that delamanid may be used as part of longer regimens in children with MDR-/RR-TB aged below 3 years. Children of all ages treated with delamanid need to be closely monitored throughout the duration of treatment. The signal of hallucinations was discussed during the ACSOmp meeting.

Recommendations: The signal of hallucinations should be evaluated further and a specialist in childhood psychology and sleep disorders should be requested to consider the evidence. An in-depth investigation of this signal should be facilitated by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre in collaboration with other relevant experts. Additionally, reporting of adverse events with delamanid directly to VigiBase should be encouraged.

Visceral leishmaniasis: ocular adverse events with miltefosine

The advice of ACSOmp was requested for managing the signal of eye disorders during the treatment of leishmaniasis with miltefosine. Miltefosine is the first and only oral antileishmanial medicine and is listed in
WHO’s Essential Medicines List (EML). Depending upon the parasite species and endemic areas of its presence, miltefosine is one of the medicines indicated (either as monotherapy or combined with other leishmaniasis medicines) for all four clinical forms of leishmaniasis, i.e. cutaneous, mucocutaneous, visceral (VL) and post-kala-azar dermal leishmaniasis. In South-East Asia miltefosine has been used in VL patients for 28 days per oral daily treatment and currently for 12 weeks per oral daily treatment for PKDL.

In India, between 2004-2014, more than 200,000 VL patients have been treated with miltefosine and during the period 2016 and 2020, some 6322 post-kala-azar dermal leishmaniasis (PKDL) patients were treated. Of these, since 2019, 48 patients (age range 8–72 years) have reported an ocular adverse event following the use of miltefosine.

**Recommendations:**

- Risk management regarding the use of miltefosine is needed. At the same time, there is a need for further information. Early communication, detection and management of ocular events is extremely important since early withdrawal could reduce the problem. A statement from WHO to raise awareness should be issued as soon as possible.

- Eye examinations are essential in order to find out exactly what is causing the problem and there is a need to study the safety of miltefosine beyond 28 days therapy.

- Laboratory tests should be conducted to investigate potential impurities, and quantities of the drug in each capsule.

- A multistakeholder subgroup of ACSoMP on miltefosine will be established to get a clearer understanding of this issue.

- Pharmacovigilance for Kala-azar elimination programme should be strengthened.

**African trypanosomiasis – update on fexinidazole**

Human African Trypanosomiasis (HAT), or sleeping sickness is lethal without treatment, tends to be found in poor rural areas, often on the borders of countries and remote from urban centres. Fexinidazole was obtained a positive scientific opinion through Article 58 by the EMA for treatment of HAT, after considering the benefits and risks of the medicine in November 2018. As one of the conditions for the positive approval, EMA asked Sanofi to conduct a phase 3 post-authorization safety study of fexinidazole.

An update on a planned post-authorization safety study of fexinidazole in the treatment of HAT was presented during the ACSoMP meeting. So far, there have been reports on 126 patients receiving fexinidazole, – far fewer than expected – partly due to the fact that the disease is becoming rarer and also because there are long delays in receiving data. Eighty eight of the 126 patients experienced some kind of adverse event. Two patients died – one most likely from an unrelated cause and one from suicide. The same drug was evaluated in South America for Chagas disease and several cases of depression were reported, including one case of suicide. Suicidal ideation has now been added to the formal description (SmPC) of fexinidazole. The issue of suicidal ideation is important since several medicines are known to be associated with this.

**Recommendations:** A suggestion for proactive data collection in this particular context was made. ACSoMP acknowledged the progress made so far and recommended that the safety data from the EMA is made available to the Advisory Committee in future.
The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to provide independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern. The following four meetings were held in 2021 via online. The reports of the meetings, including the summary of sessions, recommendations and conclusions, are published in the weekly epidemiological record (WER) available online at the links below.

45th meeting on 15 December 2021
GACVS addressed the work achieved on the safety of COVID-19 vaccines, and the latest evidence on case management for thrombosis with thrombocytopenia syndrome (TTS). They also reviewed the guidance on vaccine-associated enhanced disease (VAED) as an adverse event of special interest (AESI) and the evaluation criteria 2.0 for Vaccine Safety Net (VSN).
https://www.who.int/publications/i/item/who-wer9710-81-96

Full meeting on 17 September 2021
GACVS addressed the GACVS nOPV2 Sub-committee, safety and genetic stability data of the novel type-2 monovalent oral poliovirus (nOPV2) vaccine implemented under WHO Emergency Use Listing (EUL) in 4 countries.
https://www.who.int/publications/i/item/WHO-WER-9704-17-24

Special meeting on 10 August 2021
GACVS addressed the RTS,S/AS01 malaria vaccine, collected through the Malaria Vaccine Pilot Evaluation (MVPE), which is the evaluation component of the Malaria vaccine implementation programme (MVIP).
Report is published on the same record as 45th meeting.

44th meeting on 8-9 June 2021
GACVS addressed the GACVS COVID-19 Sub-committee, COVID-19 vaccine-related events early warning system and Safety profile of nOPV2 vaccine.
https://www.who.int/publications/i/item/wer29-2021-96-321-328