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

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

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

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

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

In addition, this edition of the Newsletter includes a summary of COVID-19 Subcommittee of the Global Advisory Committee on Vaccine Safety (GACVS).

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Alemtuzumab (genetic recombination)

Risk of hypothyroidism and hyperthyroidism

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for alemtuzumab (MabCampath®) should be revised to include the risk of hypothyroidism and hyperthyroidism as adverse drug reactions.

Alemtuzumab is indicated for the treatment of recurrent or refractory chronic lymphocytic leukemia and conditioning treatment prior to allogeneic haematopoietic stem cell transplant.

Cases of hypothyroidism or hyperthyroidism have been reported in patients treated with alemtuzumab overseas. Although no cases have been reported in Japan, the MHLW and the PMDA concluded that the revision of the package insert was necessary.

Reference: Revision of Precautions, MHLW/PMDA, 26 January 2021 (www.pmda.go.jp/english/)

Amiodarone and Sildenafil (co-administration)

Concomitant use no longer contraindicated

Japan. The MHLW and the PMDA have announced that the package insert for amiodarone (Ancaron®) and sildenafil (Revatio®) (when used for pulmonary arterial hypertension (PAH)) should be revised to remove the contraindication of co-administration.

Amiodarone is indicated to treat ventricular fibrillation, ventricular tachycardia and cardiac failure. Sildenafil is indicated to treat PAH or erectile dysfunction (ED).

The benefits of using amiodarone and sildenafil for the treatment of arrhythmia accompanied by right heart failure due to PAH outweigh the risks of adverse effects such as QT prolongation. To date, no clinically apparent safety problems have been observed when sildenafil (used for PAH) is co-administered with amiodarone.

It should be appropriate to maintain the current contraindications for sildenafil when used for ED, as this remains a contraindication in patients with conditions such as cardiovascular disorders in which sexual activities are considered inappropriate.

Following the above-mentioned consideration, the package inserts of sildenafil (used for PAH) and amiodarone will be updated to reflect the removal of the contraindication, although a precaution will be added.

Reference: Revision of Precautions, MHLW/PMDA, 26 January 2021 (www.pmda.go.jp/english/)

Atezolizumab

Potential risk of autoimmune hemolytic anemia

Canada. Health Canada has announced that they are working with the manufacturer of atezolizumab (Tecentriq®) to update the product safety information to include a warning for the risk of autoimmune hemolytic anemia (AIHA).

Atezolizumab is indicated to treat certain types of lung, liver, breast and bladder cancers.

Health Canada reviewed the potential risk of AIHA with the use of atezolizumab, triggered by safety information from clinical trials and from scientific literature.

Health Canada reviewed the information from the Canadian vigilance database, international databases and published literature. The review focussed on 36 case reports (one Canadian, 35 foreign).

The review concluded that there may be a link between the use of atezolizumab and AIHA.

Reference: Summary Safety Review, Health Canada, 3 February 2021 (www.hc-sc.gc.ca/)
(See also WHO Pharmaceuticals Newsletter No.1, 2020: Risk of haemophagocytic syndrome in Japan)

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

1. Risk of anaphylaxis and hypersensitivity

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the product information for COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) (Vaxzevria®) should be updated to include anaphylaxis and hypersensitivity as adverse events with an unknown frequency. Additionally, existing warnings should be updated to reflect that cases of anaphylaxis have been reported.

COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) is indicated to prevent COVID-19. Anaphylaxis is a known adverse reaction and is already included in the risk management plan for the product as a potential risk.

The update is based on a review of 41 reports of possible anaphylaxis among
approximately five million vaccinated individuals in the UK. The PRAC considered that a link to the vaccine was likely in at least some of these cases.

**Reference:**
EMA, 12 March 2021 (www.ema.europa.eu)

2. Possible link to very rare cases of unusual blood clots with low blood platelet counts

Europe. The PRAC has concluded that unusual blood clots with low blood platelets should be listed as very rare adverse effects of COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19).

Most cases have occurred in women under 60 years of age within two weeks of vaccination. Specific risk factors have not been confirmed.

The PRAC noted that the blood clots occurred in veins in the brain (cerebral venous sinus thrombosis, CVST) and the abdomen (splanchnic vein thrombosis) together with low levels of blood platelets.

The PRAC reviewed 62 cases of CVST and 24 cases of splanchnic vein thrombosis reported in EudraVigilance. The cases came mainly from the European Economic Area and UK, where around 25 million people had received the vaccine.

The combination of blood clots and low blood platelets is very rare, and the overall benefits of the vaccine in preventing COVID-19 outweigh the risks.

One plausible explanation for the combination of blood clots and low blood platelets is an immune response, leading to a condition similar to one sometimes seen in patients treated with heparin.

Health-care professionals should tell people receiving the vaccine that they must seek medical attention if they develop symptoms of blood clots, neurological symptoms or petechiae.

**Reference:**
EMA, 7 April 2021 (www.ema.europa.eu)


**Diuretics, including acetazolamide**

**Risk of eye disorders**

**Canada.** Health Canada has announced that they will work with manufacturers of diuretics (such as hydrochlorothiazide, chlorthalidone, indapamide) and acetazolamide, to update the safety information by adding a warning about the risks of choroidal effusion (CE), acute myopia (AM) and acute angle-closure glaucoma (AACG).

Diuretics are indicated to treat oedema and to lower high blood pressure. Acetazolamide has diuretic properties and indicated to treat glaucoma and certain types of seizures.

Triggered by updates made to the product safety information by the EMA, Health Canada reviewed the risks of CE, AM and AACG with the use of diuretics including acetazolamide.

The Canadian product safety information for some of the diuretics already include information on the eye disorders. Assessment of whether additional actions are required were made.

The review considered the Canada vigilance database, international databases and literature. It reviewed 49 cases (one Canadian, 38 foreign) of CE, AM or AACG reported with the use of diuretics or acetazolamide.

Health Canada’s review showed a link between the use of the diuretics including acetazolamide and the risks of CE, AM or AACG.

**Reference:**

**Hydrocortisone**

**Risk of acute adrenal insufficiency in children when switching from tablets to granules**

**United Kingdom.** The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for hydrocortisone granules (Alkindi®) will be updated following a report of an infant developing severe adrenal insufficiency when switched from hydrocortisone soluble tablets to hydrocortisone granules.

Hydrocortisone granules are indicated for replacement therapy of adrenal insufficiency in infants, children and adolescents.

Parents or carers should be advised to observe the child carefully in the first week after the switch. Also, the prescriber should instruct parents and carers what to do if the child develops any symptoms of adrenal insufficiency such as tiredness, floppiness, temperature instability, headache or vomiting.

If a child requires additional dosing during the first week after the switch, an increase in the daily dose of hydrocortisone granules should
Ifosfamide (solution)

Potential risk of encephalopathy

Europe. The EMA has announced that the PRAC has recommended that the product information for ifosfamide is revised to update the existing warning on ifosfamide-induced encephalopathy. Ifosfamide is indicated to treat several cancers, including various solid tumours and lymphomas.

Two recent studies suggested that the risk of encephalopathy with the use of ifosfamide solution is higher than with the use of the powder form. The PRAC considered all available data and concluded that an increased risk of encephalopathy with ifosfamide solution could neither be confirmed nor excluded due to limitations in the data.

The PRAC also concluded that the benefits of ifosfamide solution continue to outweigh the risks in the treatment of different types of cancers.

Patients should be closely monitored for symptoms of encephalopathy such as confusion, somnolence, coma, hallucination and blurred vision, particularly for those with an increased risk of encephalopathy. Also, co-administered medicines acting on the central nerves system such as antiemetics and sedatives must be used with particular caution or be discontinued if necessary.

Reference:
EMA, 12 March 2021
(www.ema.europa.eu)
(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of encephalopathy in Europe)

Non-steroidal anti-inflammatory Drugs (NSAIDs) that inhibit cyclooxygenase

Exposure during pregnancy: Risk of renal impairment, decreased urine output and oligohydramnios in fetus

Japan. The MHLW and the PMDA have announced that the package insert for non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase should be revised to include a precaution for pregnant women due to the risk of renal impairment, decreased urine output in foetuses and oligohydramnios in pregnant women.

NSAIDs are widely used anti-inflammatory drugs, and they include aspirin, ampiroxicam, isopropylantipyrine, ibuprofen, indometacin, etodolac, esfuribuprofen, clopidogrel, ketoprofen and salicylic acid.

The MHLW and PMDA considered the FDA’s measure to alert health-care professionals that prescribing NSAIDs in women between 20 to 30 weeks of pregnancy should be limited. Also, the MHLW and PMDA considered literature including clinical studies and observational studies and ascribed the risks to the effects of cyclooxygenase 2 inhibitors.

A total of five cases of fetal renal impairment and/or oligohydramnios have been reported in Japan in the last three years. A causal relationship between the drug and event could not be established in any of the cases. No patient mortalities have been reported.

The MHLW/PMDA concluded that the revision of the package inserts is necessary for all the NSAIDs that inhibit cyclooxygenase.

Reference:
Revision of Precautions, MHLW/PMDA, 25 February 2021
(www.pmda.go.jp/english/)
(See also WHO Pharmaceuticals Newsletter No.6, 2020: Risk of kidney problems with foetal exposure in US; No.1, 2015: Risks during pregnancy in US)

Pomalidomide

Risk of progressive multifocal leukoencephalopathy (PML)

Japan. The MHLW and the PMDA have announced that the package insert for pomalidomide (Pomalyst®) should be revised to include the risk of progressive multifocal leukoencephalopathy (PML) as an adverse drug reaction.

Pomalidomide is indicated for the treatment of relapsed or refractory multiple myeloma.

A total of three cases of PML have been reported in Japan in the last three years. A causal relationship between the drug and event was assessed to be reasonably possible for these cases. No patient mortalities have been reported.

Patients should be carefully monitored if treated with pomalidomide, for symptoms such as disturbed consciousness, cognitive disorder and paralytic symptoms imaging through MRI. If these symptoms occur, a cerebrospinal fluid test should be performed and administration should be discontinued.

Reference:
Revision of Precautions, MHLW/PMDA, 26 January 2021
(www.pmda.go.jp/english/)
**Pregabalin**

**Risk of severe respiratory depression**

**United Kingdom.** The MHRA has announced that the product information for pregabalin (Lyrica®) will be amended to include new warnings for respiratory depression.

Pregabalin is indicated for the treatment of peripheral and central neuropathic pain with partial seizures and for generalized anxiety disorder in adults.

Use of pregabalin with opioid medicines or other central nervous system (CNS) depressant medicines has been previously associated with reports of respiratory failure, coma and deaths.

A recent European review considered reports of severe respiratory depression thought to be related to the action of pregabalin alone on the CNS.

Similar warnings are already in place for gabapentin (Neurotonin®) and other gabapentinoids medicines.

Health-care professionals should consider whether adjustments are necessary for patients at higher risk of respiratory depression including those with compromised respiratory function and aged older than 65 years.

**Reference:**
Drug Safety Update, MHRA, 18 February 2021
(www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.1, 2020: Risk of serious breathing problems in US; No.6, 2017: Risk of severe respiratory depression in UK; No.5, 2016: Risk of serious breathing problems (respiratory depression) in Canada)

**Salbutamol**

**Risk of shock and anaphylaxis**

**Japan.** The MHLW and the PMDA have announced that the package insert for salbutamol (Venetlin®, Sultanol®) should be revised to include the risk of shock and anaphylaxis as adverse drug reactions.

Salbutamol is indicated for relief of symptoms associated with airflow obstruction and bronchospasm.

A total of three cases of shock or anaphylaxis have been reported in Japan in the last three years, one of which was assessed to have a possible causal relationship between the drug and event. No patient mortalities have been reported.

Patients should be carefully monitored and if any abnormalities are observed, administration of salbutamol should be discontinued and appropriate measures should be taken.

**Reference:**
Revision of Precautions, MHLW/PMDA, 25 February 2021
(www.pmda.go.jp/english/)

**Sofosbuvir**

**Potential risk of severe cutaneous adverse reactions (SCAR)**

**Canada.** Health Canada has announced that they will be working with the manufacturer to update the safety information for sofosbuvir to include the risk of Stevens–Johnson syndrome (SJS).

Sofosbuvir is indicated to treat chronic hepatitis C virus infection.

Health Canada reviewed the potential risk of severe cutaneous adverse reactions (SCAR) with the use of sofosbuvir. This was triggered by an update to the product safety information made by the EMA.

The safety review focused on specific types of SCAR: SJS and toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and bullous dermatitis (BD).

Health Canada reviewed 13 foreign reports from available information in the Canada vigilance database, international databases and published literature.

The conclusion of the review was that there may be a link between the use of sofosbuvir and the risk of SJS.

**Reference:**
Summary Safety Review, Health Canada, 27 January 2021
(www.hc-sc.gc.ca)

**Ulipristal acetate**

**Further restrictions for use due to risk of serious liver injury**

**United Kingdom.** The MHRA has announced that further restrictions for use of ulipristal acetate 5mg (Esmya®) have been issued, due to the risk of serious liver injury and liver failure.

Following restrictions, ulipristal acetate can only be used for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women who have not reached menopause and when surgical procedures are not suitable or have failed.

In 2018, a safety review in Europe was conducted following four reports of severe liver injury which resulted in liver transplantation. As a result several risk minimization measures were introduced in 2018.

In 2020, a fifth case of severe liver injury resulting in liver transplantation was reported and a recent European review
recommended that the risk of severe liver injury does not justify its use for the pre-operative treatment of uterine fibroids.

Also, liver function tests must be performed before starting treatment with ulipristal acetate 5mg. If a patient shows signs or symptoms compatible with liver injury, such as fatigue, asthenia, nausea and vomiting, treatment should be stopped.

Reference:
Drug Safety Update, MHRA, 18 February 2021
(www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No.6, 2020: Risk of liver injury: restricting use recommended in Europe; No.5, 2020: Revocation of marketing authorizations recommended in Europe; No.3, 2020: Licence suspension due to liver injury in UK)
**Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence**

**Risk of liver injury**

**Europe.** The EMA has announced that autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence (Strimvelis®) could lead to genetic mutations with the potential to cause cancer. This medicine is indicated to treat severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID).

The PRAC has recommended issuing a direct health-care professional communication (DHPC) following a careful analysis of a single case of acute leukaemia (lymphoid T cell leukaemia) reported in a patient who was treated with the medicine for almost five years prior to the cancer diagnosis.

Doctors are advised to monitor patients on a long-term basis for cancerous changes through annual visits for the first eleven years and then at 13- and 15-years post treatment with the medicine.

**Reference:**
EMA, 12 February 2021 (www.ema.europa.eu)

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**Gabapentin, pregabalin**

**Risk of dizziness, somnolence, abuse and dependence**

**New Zealand.** The Medsafe has announced that gabapentin and pregabalin should not be used with central nerve system (CNS) depressant (e.g. opioids) due to the risk of dizziness, somnolence, abuse and dependence.

Gabapentin and pregabalin are indicated for the treatment of neuropathic pain. Gabapentinoids are not licensed to treat other types of pain.

Patients should not drive or operate complex machinery until it is known whether the medicines affects the ability to perform the activities. Dizziness and somnolence were the most commonly reported reasons for treatment discontinuation.

Cases of abuse and dependence have also been reported with the use of gabapentin and pregabalin in New Zealand and in other countries. Concurrent treatment with opioids and gabapentinoids increases the risk of abuse and dependence.

Up to June 2020, the Centre for Adverse Reactions Monitoring (CARM) received 50 adverse reaction reports for pregabalin (7 cases for withdrawal syndrome) and 248 reports for gabapentin (7 cases for withdrawal syndrome).

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

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**Interaction between Vildagliptin and ACE inhibitors**

**Increased risk of angioedema**

**New Zealand.** The Medsafe has announced that combined use of vildagliptin and an angiotensin-converting enzyme (ACE) inhibitor increases the risk of angioedema, compared to use of either medicine alone.

Vildagliptin is indicated for the improvement of glycemic control in type 2 diabetes. ACE inhibitors are indicated for treatment of diabetic nephropathy.

Since 2018, the CARM has received four reports of angioedema that started vildagliptin use. In two cases, the patients were already taking an ACE inhibitor when vildagliptin was initiated.

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

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**Onasemnogene abeparvovec**

**Risk of thrombotic microangiopathy**

**Europe.** The EMA has announced that the DHPC is intended to warn doctors of the risk of thrombotic microangiopathy following administration of onasemnogene abeparvovec (Zolgensma®).

Onasemnogene abeparvovec is indicated for gene therapy for patients with spinal muscular atrophy.

The DHPC enhances awareness of this risk and advises on the need for prompt clinical management.

The DHPC for the medicine will be sent to the Committee for Advanced Therapies (CAT) and then to the Committee for Medicinal Products for Human Use (CHMP) for a final opinion.

**Reference:**
EMA, 12 February 2021 (www.ema.europa.eu)
**Propofol**

**Risk of green breast milk**

**New Zealand.** The Medsafe has announced that the CARM received a report of a patient who expressed green breast milk post-surgery after using propofol as an anesthetic agent.

Propofol is indicated for induction and maintenance of general anesthesia in adults and children. It has been reported that propofol may discolor urine.

Internationally, there are other case reports of green breast milk following administration of propofol. Health-care professionals are reminded to check the data sheet for information on breastfeeding following administration of propofol.

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

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**Tofacitinib**

**Increased risk of serious heart-related problems and cancer**

**USA.** The US Food and Drug Administration (FDA) has announced that preliminary results from a clinical trial show an increased risk of serious heart-related problems and cancer with tofacitinib (Xeljanz®) use.

Tofacitinib is indicated to treat arthritis and ulcerative colitis.

In 2019 the FDA warned that interim trial results showed an increased risk of blood clots and death. The FDA then requested that a safety trial is conducted. The clinical trial is now completed and initial results show a higher occurrence of serious heart-related events and cancer in patients with rheumatoid arthritis treated with both doses of tofacitinib compared to patients treated with a TNF inhibitor.

Health-care professionals should consider the benefits and risks of tofacitinib when deciding whether to prescribe or continue patients on the medicine.

**Reference:**
MedWatch, US FDA, 4 February 2021 (www.fda.gov)
A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 25 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 20). 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.

### Repeated capsaicin exposure leading to severe and possibly chronic hypersensitivity

**Marian Attalla and Lovisa Sandberg, Uppsala Monitoring Centre**

**Summary**

In a screening of VigiBase, the WHO global database of individual case safety reports, a case series was identified describing individuals who experienced hypersensitivity reactions due to capsaicin exposure. Many of the reported reactions are listed in product labels and prescribing information for capsaicin. However, our case series reveals that some of the experienced reactions are more severe than what is depicted in the labels. In addition, the reactions, even if starting out mild, could become more severe and even chronic with repeated exposure. Nurses and other health care professionals (HCPs) administering capsaicin treatments could be especially vulnerable, due to more frequent exposure, despite adhering to the recommended protective measures that exist for HCPs.

**Introduction**

Capsaicin is the compound found in chili peppers that causes the heat and burning sensation we feel when consuming them.\(^1\) As well as its culinary uses, capsaicin can be used to treat pain. The specific indications vary with the product but include treatment of peripheral neuropathic pain, post-herpetic neuralgia, and symptomatic management of painful diabetic peripheral polyneuropathy.\(^2,3\) Capsaicin is an agonist for the transient receptor potential vanilloid 1 (TRPV1) receptor. The initial effect of capsaicin is the activation of TRPV1-expressing cutaneous nociceptors, which can cause pain, pungency and erythema.\(^1,2\) Later effects include desensitization of cutaneous nociceptors, which is thought to underlie the pain relief.

Adverse reactions described in the label for the capsaicin patch (Qutenza), include burning sensation, dysgeusia, hypoesthesia, eye irritation, palpitations, throat irritation, cough, pruritis, nausea, increased blood pressure, and application site reactions (burning, pain, erythema, pruritis, swelling).\(^2\) For the cream formulation, runny eyes and sneezing are also listed;\(^3\) in addition, for the cream it is noted that there have been a few reports of dyspnoea, wheezing and exacerbation of asthma. In the Qutenza prescribing information, nasopharyngitis, bronchitis and sinusitis are also given.\(^4\) Hypersensitivity to capsaicin is a contraindication.\(^2,3\)

In the labels, precautions to be taken when handling the capsaicin patch, are also listed. Firstly, the patch should be administered by a physician or by a health care professional (HCP) under the supervision of a physician.\(^2\) When handling the patch, nitrile gloves should always be worn; a mask and protective glasses are recommended. Patches should not be held near eyes or mucous membranes. Removal should be done gently and slowly by rolling the patch inward to minimize the risk of aerosolization of capsaicin and thus avoid exposure through inhalation. It is also advised to
perform treatment in a well-ventilated area. The combination of capsaicin and hypersensitivity was first identified in a screening of VigiBase, the WHO global database of individual case safety reports, focusing on reports indicating severe reactions, in December 2018. In a preliminary assessment of the cases it was observed that for some reports, the reaction experienced, although often labelled, seemed more severe than what was depicted in product labels. It was also noticed that nurses experienced these reactions while giving the treatment, and that repeated exposure might worsen the reactions. It was therefore decided to also look at cases reporting the term occupational exposure to product.

Reports in VigiBase
Characteristics of reports
As of 31 January 2020, there were 42 capsaicin cases in VigiBase reporting the MedDRA preferred term (PT) Hypersensitivity, the expected number of reports being 16 (IC025 = 0.9; 17 February 2020). For the PT Occupational exposure to product there were 105 cases compared to the expected 0 (IC025 = 7.0). Seven cases reported both terms. The cases came from the United States of America and countries in Europe, including the Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Norway, Portugal, Spain, Sweden and the United Kingdom.

Of the hypersensitivity cases, women comprised 76% of them and men 12%; the rest were unknown. The age ranged between 27 and 84 years, the median being 54 years. The capsaicin patch was the most commonly used formulation (62%). Serious cases constituted 52% of the reports. The top 10 co-reported reactions were cough (10 cases), throat irritation (9), occupational exposure to product (7), dyspnoea (5), pruritis (5), application site pain (4), eye pain (4), urticaria (4), application site erythema (3), and blister (3).

Of the occupational exposure cases, women made up 93% while men only accounted for 4%, which might reflect a higher number of female nurses. The sex was unknown for the rest. The age ranged between 27 and 65 years, with the median being 47 years. The capsaicin patch was also the most used formulation (96%) among these cases. Serious cases made up 12% of the reports. The top 10 co-reported reactions were throat irritation (44 cases), cough (35), dyspnoea (23), eye irritation (14), eye pain (9), wrong technique in product usage process (8), glossitis (7), hypersensitivity (7), rhinorhoea (7), and rhinalgia (7).

The co-reported reactions for both terms overlap and mainly describe symptoms of hypersensitivity of which many are known for capsaicin. However, in some cases the reactions seemed more severe than what was set out in the product labels. In other cases, which mostly concerned nurses who administered the treatments, the reactions, which at first were mild and manageable, became worse and lasted longer with repeated exposure. A few cases also described nurses who experienced adverse reactions even though they took the protective measures that were recommended in the labels and prescribing information, including wearing a mask, nitrile gloves and protective glasses.

Case examples
Here follow some cases that illustrate reactions that became worse and/or lasted longer with repeated exposure:

- A 42-year-old nurse had administered the Qutenza patch once or twice per week using nitrile gloves, mask, glasses and gown. At first, she had rhinitis and runny eyes which would disappear after 3 to 5 hours. A year later, she experienced dyspnoea and chest tightness which would disappear one hour after handling a patch. At the time of reporting, the nurse no longer administered patches.

- Three cases concerned nurses working at the same clinic and who treated patients with Qutenza. Over previous years there had been an increase in the number of treatments performed and the exposure to the substance had become more intense. The nurses had always felt the allergic symptoms, but they would disappear “up until a month ago” when they worsened and did not resolve. One of the nurses had never previously reacted to chili, but after eating chili-flavoured chocolate she reacted with a burning mouth and throat for 24 hours, as well as blisters in the mouth. She often had to use eye drops and lip balm to relieve dry and irritated eyes and lips. Occasionally, she also used over-the-counter analgesics. Another nurse, who started administering treatments in 2010, experienced irritated lips, eyes and mouth, as well as blisters in the mouth and a cough which would disappear initially. In 2016, her symptoms worsened and lasted longer, and as the symptoms in the eyes were present every day, she felt she had bad eyesight. It was also reported that previously the symptoms would disappear when off duty, but not anymore.

- A woman in her 60s had been treated four times with Qutenza with good effect. After each treatment with the patch, the patient's symptoms, including reduced taste, white tongue, coughing from throat irritation, and sore eyes, increased gradually. After the first two treatments she had so few side effects that she did not mention them at control visits. Following the fourth treatment, the symptoms “became a substantial problem”. After the third, and especially the fourth, treatment she experienced adverse effects that persisted for four weeks. Symptoms were relieved by...
treatment with antihistamines. Some other cases described reactions which seemed more severe than those set out in the product labels, especially for symptoms affecting the airways:

- A 52-year-old female HCP experienced irritated airways and severe persistent cough when applying a Qutenza patch. It was reported that her lung function was decreased, but initially improved with bronchodilators. Asthma was also reported, but treatment for that did not seem to improve her condition. Oral cortisone was also given, and the cough improved slowly but was triggered easily. The reporter described seriousness as a permanent disability.

- A nurse had received proper instructions on handling Qutenza for one patient. Upon opening the patch to treat a patient, she coughed severely and had to be treated with cortisone and anti-allergy medications, left the clinic/workplace and went home. The next day she returned to work and felt fine, but on entering the room where she had opened the patch, she started coughing severely again and had to be treated. At the time of reporting the nurse was recovering but still had a hoarse voice.

Another interesting case described a sales representative who experienced severe reactions just from being in the room where capsaicin was administered to a patient:

- A 58-year-old female sales representative experienced numbness and swelling of the tongue, cough, severe pruritis, and burning/irritation of the eyes during administration of the capsaicin patch to a patient. She was not in direct contact with the patch but was near it and did not wear any protection. She was treated with antihistamines and all events resolved on the same day except for numbness and swelling of the tongue, which resolved three days later. The swollen tongue event was described as a “very heavy reaction” according to the physician. It was reported that, ever since experiencing these reactions, the sales representative would wear protection and did not have any more problems.

Discussion and conclusion

Although many of the reactions reported in the case series are described in product labels and prescribing information, the severity of some reactions is not reflected there, and the reactions, even if starting out mild, could become more severe and even chronic with repeated exposure. Our case series also indicates that nurses and other HCPs administering Qutenza could be especially vulnerable to the increased severity of reactions, probably due to more frequent exposure. Although protective measures and other recommendations exist for HCPs, despite adhering to them individuals can still experience capsaicin-related symptoms, and as some of the cases demonstrated, the reactions may become worse and even chronic with repeated exposure. It would therefore be wise to review the risk minimization guidelines, and to consider including recommendations for HCPs to stop giving capsaicin treatments if they have reacted once before, to avoid further complications. In addition, it could also be prudent to consider protective equipment for anyone who is in a room where capsaicin is being administered, even if they themselves do not handle the product.

As mentioned, the labels do not seem to reflect the severity of some reactions, which are often described as mild. In our case series, this seems especially true for symptoms related to the airways. For example, the reaction ‘cough’ is labelled, which sounds mild, but in one case the cough was so severe that the affected nurse had to be treated with cortisone and anti-allergy medications. In another case, the nurse experienced a decreased lung function. In addition, 26 cases of dyspnoea were noted. Dyspnoea is not listed in capsaicin labels. However, for the cream formulation, it is described that there have been few reports of dyspnoea. Considering this, it could be worth also to clarify in the labels that it is possible to experience more severe reactions than those currently given.

References
Signal

Sarilumab, tocilizumab and Pneumothorax
Rebecca E Chandler, MD. Uppsala Monitoring Centre

Summary
Sarilumab and tocilizumab are human monoclonal antibodies which block the cytokine interleukin-6 (IL-6) receptor. Licensed for the treatment of moderate to severe rheumatoid arthritis in combination with methotrexate (MTX), both were “repurposed” for use in the treatment of COVID-19 disease when IL-6 was considered to play an important role in the pathophysiology of severe forms of the disease. A screening of VigiBase with a focus on drugs used in the COVID-19 indication identified a statistical signal for sarilumab and pneumothorax; the signal was strengthened by disproportionate reporting with tocilizumab used in labelled indications. A case series of 72 reports of pneumothorax for sarilumab (5 reports) and tocilizumab (67 reports), was identified and reviewed. Signal assessment has suggested a plausible causal relationship between therapies which antagonise the actions of IL-6 and pneumothorax, specifically in patients with underlying lung inflammation or injury.

Drugs
Sarilumab and tocilizumab are human monoclonal antibodies which block the cytokine interleukin-6 (IL-6) receptor. Both were licensed for the treatment of moderate to severe rheumatoid arthritis in combination with methotrexate (MTX) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Tocilizumab has subsequently been approved also for use in active systemic or polyarticular juvenile idiopathic arthritis, giant cell arteritis and cytokine release syndrome, a side effect of Chimeric Antigen Receptor-T cell (CAR-T) therapy. Sarilumab was approved by both the US FDA and the EMA in 2017, and tocilizumab received its first approval in 2009. The class of anti-IL-6 agents (e.g. sarilumab, tocilizumab and siltuximab) have been used in the treatment of COVID-19 disease based upon favourable results from a single-arm 21-person trial in China. The hypothesis is that IL-6 may have an important role in the inflammatory response in the lungs of severely ill COVID-19 patients. Various trials with anti-IL-6 agents have been initiated, completed and/or halted; results appear to suggest some marginal benefit in hospitalised patients; however, there is no evidence of a decreased risk of mortality.

Event
Pneumothorax is the presence of air or gas in the pleural cavity between the visceral and parietal pleura of the lung. Clinically it can manifest as collapse of the lung on the affected side or even a shift of the entire mediastinum resulting in hemodynamic compromise. Primary, or spontaneous, pneumothorax (PSP) occurs in the absence of either pre-existing lung disease or of an inciting event. Secondary pneumothorax (SPS) occurs in the context of underlying lung parenchymal disease or due to trauma. PSP typically occurs in persons between the ages of 20-30 years, while PSP typically occurs in persons 60-65 years of age; there is a male predominance in both types and an association with cigarette use. Common causes of SPS are chronic obstructive pulmonary disease and iatrogenic causes in intensive care units such as positive pressure ventilation and central venous catheter placement. Pneumothorax has been reported in the context of COVID-19 disease. Published case reports and case series have described the occurrence of pneumothorax in various stages of COVID-19 pneumonia, even in patients without underlying pulmonary disease and not associated with positive pressure ventilation. It has been speculated that bulla formation secondary to COVID-19 induced alveolar damage result in pneumothorax.

Reports from VigiBase
As of 13 November 2020, there were 72 cases of pneumothorax reported for sarilumab (5 reports) and tocilizumab (67 reports). 39 of them concerned females, 30 concerned males, and three had the sex unreported. Ages ranged between 9 to 86 years, 18 reports had age unreported. Reports originated from the United States (21 reports, 29.1%), Japan (15, 20.8%), Canada (12, 16.7%), the United Kingdom (11, 15.3%), Australia (7, 9.7%), France (3, 4.2%), Germany (2, 2.8%), and Egypt (1, 1.4%).

68 reports were "serious" and the remaining four had no information on "seriousness"; 18 reports (25%) had a fatal outcome.

The most common drugs reported as "concomitant" were methotrexate (17 reports, 23.6%), prednisolone (13, 18.1%), folic acid and hydroxychloroquine (each with 11 reports, 15.3%), and paracetamol and prednisone (each with 9 reports, 12.5%). The most common drugs reported as "interacting" were methotrexate (6 reports, 8.3%), prednisolone (4, 5.6%), methylprednisolone and tacrolimus (each with 2 reports, 2.8%), and leflunomide (1, 1.4%).

In all the sarilumab reports, the indication for use...
was "COVID-19". In the large majority of the tocilizumab reports, the indications for use were labelled indications such as "rheumatoid arthritis", "temporal arteritis", and "juvenile rheumatoid arthritis"; concomitantly reported ADRs included several terms indicating lung inflammation or injury, including pneumonia (16 reports, 23.9%), interstitial lung disease (8, 11.9%), rib fracture (7, 10.4%), lower respiratory tract infection (5, 7.5%), pleural effusion (5, 7.5%).

It was possible to calculate the time to onset of the event for pneumothorax in 20 of the 72 reports, where it ranged from 0 to 2,608 days. The median time to onset was 586 days. In three cases where the TTO was long, the dose was increased during treatment, and onset date from the dose increase was shorter (2 to 6 months).

**Product labelling**

The Summary of Product Characteristics (SmPC) for both sarilumab and tocilizumab contain only a warning for tuberculosis and list pneumonia as a potential infection. There are no ADRs from the Respiratory system SOC included in the "tabulated list of adverse reactions" in either label.1,2

Interstitial lung disease is mentioned in the "description of selected adverse reactions" following the table in the SmPC for tocilizumab.

Appraisal of the publicly available list of signals reviewed by the Pharmacovigilance Risk Assessment Committee of the EMA found that "pneumothorax" has not been previously signalled for either tocilizumab or sarilumab.17

**Discussion**

Investigations were made within VigiBase for both sarilumab and tocilizumab contained only a warning for tuberculosis and list pneumonia as a potential infection. There are no ADRs from the Respiratory system SOC included in the "tabulated list of adverse reactions" in either label.1,2

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**Conclusion**

The causality criterion of consistency can be suggested by the reports included in VigiBase submitted from multiple countries.

Regarding the hypothesis of a causal relationship between IL-6 blockade and pneumothorax, the link between these agents and gastrointestinal perforation, specifically in the setting of the underlying inflammatory conditions of diverticulitis, could be considered as being analogous and supportive. "Gastrointestinal perforation" is a known risk with the use of sarilumab and tocilizumab and in the labelling of both products1,2; for sarilumab it is specifically named in section 4.8 and for tocilizumab it is described as a "complication of diverticulitis". The risk management plans similarly name "gastrointestinal perforation" (sarilumab) and "complications of diverticulitis" (tocilizumab) as "important identified risks".21,22

The biological plausibility of this relationship has been shown in mouse models of bowel injury. IL-6 has been demonstrated to be induced at the site of intestinal inflammatory injury by intraepithelial lymphocytes, and the inhibition of IL-6 resulted in decreased epithelial proliferation and subsequent impaired wound healing.23
Alveolar macrophages, lung fibroblasts, endothelial cells and bronchial epithelial cells have been demonstrated to generate IL-6 in vitro upon stimulation, and alveolar macrophages recovered from pathologic specimens have been found to express IL-6 mRNA. Inhibition of IL-6 localised to the lung could therefore impair healing at the site of pneumonia or inflammation, thereby increasing the risk of perforation of the lung parenchyma.

Key to the argument for biological plausibility is the inherent disposition of the patients for pneumothorax, such as pneumonia. A source of the inflammation or other type of injury in the lung tissue is the “wound” whose repair is impaired by the absence of IL-6. An assessment of the temporal link between the use of tocilizumab or sarilumab and pneumothorax is therefore less dependent on the relationship of the occurrence of the event to the initial date of taking the medication. Instead, it is more dependent on the occurrence of lung pathology, such as pneumonia, while taking one of these drugs. Where the information was available in 15 cases, the TTOs from the pulmonary events to pneumothorax were 0 days in 8 cases, and 1, 9, 10, >11, > 19, >45 and 86 days in one case each.

**Conclusion**

Statistical screening of VigiBase with a focus on drugs used in the COVID-19 indication has identified a signal of pneumothorax associated with two IL-6 receptor blockers, sarilumab and tocilizumab. The signal was identified by disproportionate reporting of the event with sarilumab used in COVID-19 patients and was strengthened with the disproportionate reporting with tocilizumab used in labelled indications. The reported disproportionality, reports from a wide spread of countries, analogy to other known reactions, and biological plausibility, suggested a possible causal relationship between the anti-IL-6 agents sarilumab and tocilizumab and the occurrence of pneumothorax. Further studies are needed to more thoroughly investigate this relationship with all anti-IL-6 agents in patients with underlying lung inflammation or pathology.

**References**

5. Available at: [https://www.roche.com/media/releases/medcor-2020-09-18.htm](https://www.roche.com/media/releases/medcor-2020-09-18.htm)
7. Pneumothorax. Available at: [https://emedicine.medscape.com/article/424547-overview#a1](https://emedicine.medscape.com/article/424547-overview#a1)


Response from Sanofi

March 8th, 2021

Reference: Invitation to Comment on Draft WHO Signal on Sarilumab and Pneumothorax

Thank you for the opportunity to comment on the WHO UMC draft signal text with a patient safety concern on Sarilumab and Pneumothorax.

Background

Sanofi is the market authorization holder (MAH) of Kevzara® (sarilumab).

Sanofi has not previously identified a safety signal for pneumothorax with sarilumab.

In response to this invitation to comment, Sanofi performed a search in the Global Pharmacovigilance (GPV) database.

Results

PV database

A search from 01 January 1900 to 31 January 2021 was performed in the Sanofi global PV database. This search was performed to identify all solicited and unsolicited cases, both medically confirmed and non-medically confirmed, reported with sarilumab as a suspect drug including diagnosis and symptoms using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1, coded with the following Preferred Terms (PT): Pneumothorax; Pneumothorax spontaneous; Pneumothorax traumatic; Procedural pneumothorax; Pyopneumothorax.

A total of 36 cases were retrieved, including 30 cases in patients treated with sarilumab for COVID-19 and 6 patients treated with sarilumab for RA.

COVID-19 indication:

A total of 30 cases were reported in patients treated with sarilumab for COVID-19, including 27 cases from 6R88-COV-2040, 2 cases from EFC16844, and 1 case from APHP200375.

Among these 30 cases, 8 were reported in female patients and 22 in male patients. Cases were reported in 18 adults and 12 elderly patients.

Outcome was reported as fatal in 16 cases, recovered in 12 cases, and not recovered in 2 cases.

Time to onset was within 1 day in 3 cases, between 2 days and 7 days in 9 cases, between 7 days and 1 month in 15 cases, more than 1 month in 2 cases,
unknown in 1 case.

From the review of these 30 cases, all were confounded by mechanical ventilation, known to cause iatrogenic pneumothorax. In all cases, pneumothorax was assessed as not related to sarilumab by the reporter. The underlying COVID-19 and related pneumonia/respiratory failure is a more likely explanation for the occurrence of pneumothorax in all these cases.

**RA indication:**

A total of 6 cases were reported in patients treated with sarilumab for RA.

Among these 6 cases, 5 were reported in female patients and 1 in a male patient. Cases were reported in 4 adults and 2 elderly patients.

Outcome was reported as fatal in 1 case, recovered in 4 cases, and unknown in 1 case.

Time to onset was more than 2 years in 3 cases, unknown in 3 cases.

In 1 case, the reporter assessed the event of pneumothorax as not related to sarilumab. The case was confounded by the patient’s medical history of heavy smoking.

Three cases were reported from a consumer in the scope of a PSP and were not medically confirmed. In all these cases limited information was provided for a proper causality assessment:

- In 1 case, pneumothorax occurred in context of pneumonia and bronchitis.
- In 1 case, pneumothorax occurred after a lumbar vertebral fracture.
- In 1 case, pneumothorax was probably related to the biopsy procedure on a lung nodule.

In 2 cases, the reporter assessed the event of pneumothorax as related to sarilumab.

- In the first case, the patient, with medical history of dyspnea and interstitial lung disease, climbed a mountain and experienced worsening of dyspnea after climbing, 941 days after the first IP intake and 3 days after the most recent dose. The patient was diagnosed with right side hydropneumothorax. Sarilumab was permanently discontinued. The patient recovered from right side hydropneumothorax with corrective treatment. About 967 days after the first IP intake and 29 days since the most recent, the patient was diagnosed with recurrent pneumothorax right. The patient recovered from recurrent pneumothorax with corrective treatments. About five years after initiation of sarilumab, and 2 years after permanent discontinuation, the patient died of pneumonia. No autopsy was performed.
- In the second case, the patient with no

Discussion

A total of 36 cases with event of pneumothorax were reported with sarilumab.

Among these 36 cases, 30 patients were treated with sarilumab for COVID-19. All cases were confounded by mechanical ventilation, known to cause iatrogenic pneumothorax. In all cases, pneumothorax was assessed as not related to sarilumab by the reporter. The underlying COVID-19 and related pneumonia/respiratory failure is a more likely explanation for the occurrence of pneumothorax in all these cases.

Among these 36 cases, 6 patients were treated with sarilumab for RA. One case was assessed as not related to sarilumab and was confounded by patient’s medical history of heavy smoking. Three cases were not medically confirmed, had limited information and were confounded by context of pneumonia and bronchitis, lumbar vertebral fracture, and biopsy procedure on a lung nodule. In the 2 remaining cases, reporter assessed pneumothorax as related to sarilumab. However, in the first case, patient had concurrent dyspnea and ILD and pneumothorax occurred after high altitude walking. In the second case, patient experienced small pneumothorax (alveolar rupture) in the context of severe pneumonia 1.5 months after sarilumab was discontinued. Both high altitude and pneumonia are known causes of pneumothorax.
Conclusion
A comprehensive review of the available data in the Sanofi PV database is not suggestive of a causal relationship between sarilumab and pneumothorax.

As a result, Sanofi considers that there is no further action required at this stage and continue to monitor this event through routine pharmacovigilance activities.
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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COVID-19 Subcommittee of the Global Advisory Committee on Vaccine Safety (GACVS)

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance, provides scientific recommendations for policy-making by WHO, the WHO Strategic Advisory Group of Experts (SAGE) on immunization, national governments and international organizations, recommends the creation of ad hoc task forces for methodological and empirical research into potential adverse events and prioritizes aspects of vaccine safety to be monitored during their use. The 43rd GACVS meeting on 1–3 December 2020, held online, addressed pharmacovigilance of COVID-19 vaccines, safety in pregnancy with the Global Vaccine Safety Multi-country Collaboration Project, a new vaccine safety indicator for the immunization agenda 2030, and the safety of RTS,S malaria vaccine.1

The GACVS agreed that a subcommittee be established to review, evaluate and interpret post-introduction data on COVID-19 vaccine safety, as these become available from different sources, to:

- advise WHO on the safety of the different COVID-19 vaccines;
- provide recommendations on safety studies, to investigate and/or validate emerging safety signals; and
- guide the development of COVID-19 vaccines safety advisories and communiques on vaccine safety for Member States.

Since its inception, the COVID-19 GACVS subcommittee has been holding regular virtual meetings to review emerging safety data with the COVID-19 vaccines. The Subcommittee has reviewed and issued advice on:

- Reports of deaths of very frail elderly individuals vaccinated with Pfizer BioNTech COVID-19 vaccine, BNT162b2* (22 January 2021)2
- Reports of influenza-like illness in individuals vaccinated with COVID-19 vaccines (8 March 2021)3
- Safety of AstraZeneca COVID-19 vaccines** (19 March 2021)4,5,6

WHO is carefully monitoring the rollout of all COVID-19 vaccines and will continue to work closely with countries to manage potential risks, and to use science and data to drive response and recommendations. The COVID-19 GACVS subcommittee highly recommends that all countries conduct safety surveillance on all COVID-19 vaccines and provide data to their local authorities and to the WHO global database of individual case safety reports. This is urgently needed to support evidence-based recommendations on these life-saving vaccines.

* WHO PQ EUL (31 December 2020), approved by US FDA and EMA
** WHO PQ EUL (15 February 2021), approved by EMA

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3 https://www.who.int/news/item/08-03-2021-gacvs-covid-19-review-influenza-like-illness