The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicinal products and regulatory actions taken by 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 recommendations from the first joint meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), 14-16 June 2022.

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

**Risk of pulmonary arterial hypertension, dependency, and heart and psychiatric problems**

**Europe.** The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended the withdrawal of the marketing authorization for amfepramone containing products in the European Union (EU).

Amfepramone is a sympathomimetic medicine indicated for the treatment of obesity (body mass index of at least 30 kg/m²) in patients who have had no success with other weight-reduction methods. Treatment duration is for 4 to 6 weeks and amfepramone should not be used for more than 3 months.

The recommendation follows a review which found that measures to restrict the use of amfepramone have not been sufficiently effective. It found that the medicines were being used for longer than the recommended maximum period of 3 months, thereby potentially increasing the risk of serious adverse effects, such as pulmonary arterial hypertension and dependency. The medicines were also being used in patients with a history of heart disease or psychiatric disorders, further increasing the risk of heart and psychiatric problems. In addition, there were evidence of use during pregnancy, which could pose risks to the unborn baby.

The review considered all available information relating to these concerns, including data from two studies on the use of amfepramone medicines in Germany and in Denmark. In addition, the PRAC received advice from a group of experts, comprising of endocrinologists, cardiologists and a patient representative.

The PRAC considered introducing further measures to minimize the risk of adverse effects but could not identify any that would be sufficiently effective. The PRAC therefore concluded that the benefits of using amfepramone medicines do not outweigh the risks and recommended that the medicines should be removed from the EU market.

**Reference:** Patients and carers, EMA, 10 June 2022 [link to the source within www.ema.europa.eu](www.ema.europa.eu)

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**Anagrelide**

**Risk of thrombosis upon abrupt treatment discontinuation**

**Ireland.** The Health Products Regulatory Authority (HPRA) has announced that the product information for anagrelide (Xagrid®) has been updated to reflect the latest data and recommendations on the increased risk of thrombotic complications. This includes cerebral infarction upon abrupt anagrelide discontinuation.

Anagrelide is indicated for the reduction of elevated platelet counts in patients who are at risk of thrombosis and have essential thrombocythemia, are intolerant to other therapies or platelet counts are not sufficiently reduced by alternative therapy.

A cumulative analysis of the company’s safety database showed 15 events of thrombotic complications, including cerebral infarction, after a recent discontinuation of anagrelide. It was concluded that cerebral infarction, along with other thrombotic complications, while being part of the pre-existing condition/indication, may also occur upon abrupt anagrelide discontinuation, inadequate dosing, or lack of effect.

It is recommended that patients should avoid abrupt treatment discontinuation, and health-care professionals should monitor platelet counts in the event of dosage interruption or treatment withdrawal. Patients should be advised on how to recognize early signs and symptoms suggestive of thrombotic complications, and if symptoms occur to seek medical assistance.

**Reference:** Drug Safety Newsletter, HPRA, 11 April 2022 [link to the source within www.hpra.ie](www.hpra.ie)

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**Cetuximab sarotalocan**

**Risk of fistula, mucocutaneous ulceration or necrosis**

**Japan.** The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for cetuximab sarotalocan (Akalux®) should be revised to...
include the risk of fistula, mucocutaneous ulceration or necrosis at the site of laser beam irradiation.

Cetuximab sarotalocan is a chemical conjugate of dye (IR700) and cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR). It is injected intravenously to bind EGFR-expressing tumour cells in the body. Subsequently, the dye is activated locally by application of laser beam to selectively kill the EGFR-expressing tumour cells. This treatment is indicated for unresectable, locally advanced or recurrent head and neck cancer.

Japanese (4) and international (1) cases of fistula, skin ulceration or necrosis following treatment with cetuximab were evaluated. In all of the five cases, a causal relationship between the medicines and event were assessed to be reasonably possible. A caution on the risk of mucosal ulceration and mucosal necrosis was also added to the product information after reviewing these reports.

Health-care professionals are advised to check for tumour invasions into the skin or mucous membrane prior to the administration. In addition, during the treatment, the patient’s skin condition should be adequately monitored.

Reference:
Revision of Precautions, MHLW/PMDA, 14 June 2022 (link to the source within www.pmda.go.jp/english)

Clozapine

Risk of gastrointestinal hypomotility

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for clozapine has been updated to strengthen existing warnings on severe gastrointestinal adverse reactions by including the risk of hypomotility.

Clozapine is a second generation, atypical antipsychotic with potent anticholinergic effects and is indicated for treatment of resistant schizophrenia.

The updates are based on evidence published in the literature and from Australian and International post-market adverse event data. On 1 March 2022, there were 1,523 reports of gastrointestinal disorders with the use of clozapine in the TGA’s Database of Adverse Event Notifications (DAEN). This included 260 reports of constipation, 146 of intestinal obstruction, 93 of abdominal pain and 41 of small intestinal obstruction. Of the 1,023 clozapine reports with a fatal outcome, 103 were due to gastrointestinal disorders.

Health-care professionals are advised that any changes in the frequency or character of a patient’s bowel movement, as well as signs and symptoms of complications due to hypomotility should be carefully monitored; patients with evidence of constipation or gastrointestinal hypomotility should be managed promptly to prevent severe complications; clozapine should be used with caution and under careful supervision in patients with a current diagnosis or prior history of constipation; and concomitant use of clozapine with anticholinergic medicines should be avoided where possible because of the increased risk of severe gastrointestinal adverse effects or anticholinergic toxicity.

Reference:
Medicines Safety Update, TGA, 22 April 2021 (link to the source within www.tga.gov.au)

COVID-19 vaccine

Astrazeneca (ChAdOx1-S)

Risk of tinnitus, paraesthesia and hypoaesthesia

Europe. The EMA has announced that the product information for COVID-19 vaccine Astrazeneca (ChAdOx1-S, Vaxzevria®) will be updated to include the risk of tinnitus, paraesthesia (unusual feeling in the skin, such as tingling or a crawling sensation) and hypoaesthesia (decreased feeling or sensitivity, especially in the skin) as adverse effects.

Cases of tinnitus, paraesthesia and hypoaesthesia with use of Astrazeneca vaccine have been reported through routine spontaneous reporting systems. In addition, new data obtained from an ongoing clinical trial were reviewed.

Reference:
COVID-19 vaccines safety update, EMA, 14 July 2022 (link to the source within www.ema.europa.eu)
Modern
(Elasomeran)

**Risk of extensive swelling of the vaccinated limb**

Europe. The EMA has announced that the product information for COVID-19 vaccine Moderna (elasomeran, Spikevax®) will be updated to include the risk of extensive swelling of the vaccinated limb as an adverse effect. In general, extensive swelling of the vaccinated limb is a condition that does not require treatment and resolves after a few days.

Up until 2 May 2022 there have been 3,200 cases of extensive swelling of the vaccinated limb with use of Moderna vaccine reported to EudraVigilance. The decision to update the product label was made following the PRAC’s assessment.

Reference:
COVID-19 vaccines safety update, EMA, 14 July 2022 (link to the source within www.ema.europa.eu)

**COVID-19 vaccines Moderna (Elasomeran) and Pfizer (Tozinameran)**

Potential risk of Guillain-Barré syndrome (GBS)

Japan. The MHLW and the PMDA assessed suspected cases of GBS reported in Japan (30 cases for Moderna vaccine and 181 cases for Pfizer vaccine). A causal association between the vaccine and event could not be excluded in 15 of the Pfizer vaccine cases (zero cases for Moderna vaccine). In the O/E (Observed-to-expected) analysis, no statistically significant difference was observed between the background (expected) rate and reported (observed) rates of GBS for both vaccines.

As a result of the assessment, the MHLW and the PMDA have decided to update the product information for mRNA COVID-19 vaccines to include a warning on GBS as a precaution, and not as an adverse effect.

In other countries and regions such as the US, UK and EU, there are no warnings for GBS following immunization in the package inserts for COVID-19 mRNA vaccines.

Vaccine recipients or their caregivers should be instructed in advance to seek medical attention immediately if a vaccine recipient experiences any symptoms that could suggest GBS (such as flaccid paralysis starting from distal limb, decreased or absent tendon reflex).

Reference:
Revision of Precautions, MHLW/PMDA, 10 June 2022 (link1 to the source within www.pmda.go.jp/english/ and link2 within www.mhlw.go.jp/)
(See also WHO Pharmaceuticals Newsletter No.3, 2021: COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19) and Risk of Guillain-Barre syndrome (GBS) in Europe)

COVID-19 vaccine Novavax

1. Risk of anaphylaxis, paraesthesia and hypoaesthesia

(1) Europe. The EMA has announced that the product information for COVID-19 vaccine Novavax (Nuvaxovid®) will be updated to include the risk of anaphylaxis, paraesthesia and hypoaesthesia as adverse effects.

Cases of anaphylaxis, paraesthesia and hypoaesthesia have been reported worldwide.

Advice for managing the risk of anaphylaxis will be updated as follows: appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine; close observation for at least 15 minutes is recommended following vaccination; and a second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Novavax vaccine.

Reference:
COVID-19 vaccines safety update, EMA, 14 July 2022 (link to the source within www.ema.europa.eu)

(2) Australia. The TGA has announced that the product information for COVID-19 vaccine Novavax has been updated to include the risk of anaphylaxis, paraesthesia and hypoaesthesia as potential adverse events.
2. Risk of myocarditis and/or pericarditis

(1) Europe. The PRAC has recommended that the product information for COVID-19 vaccine Novavax should be updated to include the risk of myocarditis and pericarditis as adverse effects together with a warning to raise awareness among health-care professionals and people receiving this vaccine.

The PRAC has concluded that myocarditis and pericarditis can occur following vaccination with Novavax vaccine. This conclusion is based on a small number of reported cases.


(2) United States. The US Food and Drug Administration (FDA) has announced that the prescribing information for COVID-19 vaccine Novavax will include the risk of myocarditis and pericarditis as adverse reactions.

Data from clinical trials provide evidence for an increased risk of myocarditis and pericarditis following administration of Novavax vaccine. Also, myocarditis and pericarditis were reported following administration of Novavax vaccine during overseas post-authorization use.


FDA News Release, US FDA, 13 July 2022 (link to the source within www.fda.gov)

(3) Australia. The TGA has announced that the product information for COVID-19 vaccine Novavax has been updated to include the risk of pericarditis as a potential adverse event.

The TGA has received a small number of reports of suspected myocarditis and/or pericarditis in people who have received Novavax vaccine. After assessing these against a set of internationally accepted criteria, three cases were likely to represent myocarditis and 12 were likely to represent pericarditis. As a result of this investigation, the product information has been updated to include pericarditis as a potential adverse event.


Crizotinib

Risk of ocular disorders in children

Europe. The EMA has announced that the product information for crizotinib (Xalkori®) has been updated to include the risk of ocular toxicity, including severe vision loss in children.

Crizotinib is a cancer medicine used to treat adults with advanced non-small cell lung cancer (NSCLC). Crizotinib use in children has been studied in those aged 6 to 18 years of age as a monotherapy for the treatment of relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) that is ALK positive or patients with unresectable, recurrent, or refractory ALK positive inflammatory myofibroblastic tumour (IMT).

Ocular disorders have been reported in 61% of paediatric patients treated with crizotinib in clinical trials for these indications. Paediatric patients should be monitored for ocular toxicity, including the risk of severe vision loss. They should receive a baseline ophthalmologic examination prior to starting crizotinib with follow-up examinations.

Health-care professionals are advised to inform patients and caregivers of symptoms related to vision and remind them to contact their doctor if any of these symptoms develop. Any ocular symptoms should be referred to an eye specialist.

Health-care professionals are also advised to consider a dose reduction of crizotinib for patients who develop Grade 2 ocular disorders. If Grade 3 and 4 ocular disorders occur, treatment with the medicine should be discontinued permanently, unless another cause is identified.

Reference: Patients and carers, EMA, 10 June 2022 (link to the source within www.ema.europa.eu)

Denosumab

Risk of hypercalcaemia in children and adolescents

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that
the product information for denosumab 60mg (Prolia®) has been updated to advise against use in children and adolescents younger than 18 years, due to the risk of serious hypercalcaemia.

Denosumab 60mg is indicated in adults for the treatment of osteoporosis in postmenopausal women and men at increased risk of fractures. Use of denosumab 60mg in children for the treatment of osteoporosis is off-label use.

Cases of serious and life-threatening hypercalcaemia requiring hospitalization and complications due to acute renal injury have been reported in children and adolescents younger than 18 years receiving denosumab 60mg in clinical trials, investigating the treatment of osteogenesis imperfecta. Worldwide, 20 cases of hypercalcaemia were reported, during off-label treatment with denosumab 60mg in children and adolescents younger than 18 years. There were also a small number of reports of hypercalcaemia in patients younger than 18 years after stopping treatment (rebound hypercalcaemia). A recent European review assessed the cases of severe hypercalcaemia and recommended stronger warnings against use of denosumab 60mg in children and adolescents younger than 18 years. The MHRA has considered this review together with the safety data and agreed that the product information should be updated.

Reference:
Drug Safety Update, MHRA, 19 April 2022 (link to the source)

within www.gov.uk/mhra)

(* Another denosumab product, denosumab 120mg (Xgeva®) remains authorised for adults and skeletally mature teenagers with giant cell tumour of bone.)

Dexamethasone, betamethasone

Risk of phaeochromocytoma crisis

Japan. The MHLW and the PMDA have announced that the product information for dexamethasone and betamethasone containing products should be revised to include the risk of phaeochromocytoma crisis.

Dexamethasone and betamethasone are steroids, that are available in various formulations. Products for oral use, injections and suppositories are subject to this revision.

Cases of phaeochromocytoma crisis reported with the use of dexamethasone (oral dosage form and injections) and betamethasone (injections) in Japan and overseas were evaluated. Several cases were assessed to have a possible causal relationship between the drug and event. There were no case reports of phaeochromocytoma with the use of betamethasone, but the same update to the safety information was made as a precaution.

If a marked elevation in blood pressure is observed following administration of these drugs, health-care professionals should consider the possible occurrence of phaeochromocytoma crisis and take appropriate measures.

Reference:
Revision of Precautions, MHLW/PMDA, 13 May 2022 (link to the source within www.pmda.go.jp/english)

Interferon beta

Removal of contraindication in pregnant women

Japan. The MHLW and the PMDA have announced that the product information for interferon beta-1a (Avonex®) and interferon beta-1b (Betaferon®) (hereafter referred as “IFNβ”) should be revised to remove the contraindication in pregnant women and replaced with a precaution on the use in pregnancy.

IFNβ is used to prevent relapse of multiple sclerosis. In Japan, administration of IFNβ to pregnant women has been contraindicated from the time of initial approval in 2000.

The MHLW and the PMDA reassessed the risk of foetal death or spontaneous abortions that were observed in reproductive toxicity studies in monkeys, and concluded that there is no need for a blanket contraindication of IFNβ in pregnant women based on these studies.

European, Scandinavian, and US registry studies in pregnant women with multiple sclerosis administered with IFNβ, as well as other epidemiological studies and literature reports did not necessarily suggest the possibility of an increase in the risk of spontaneous abortions and congenital anomalies.

Package inserts in other countries vary with regards to the status of contraindications.
In the EU, the contraindication was removed in 2019; in the US the contraindication is not included; and in Australia IFNβ-1a is contraindicated while IFNβ-1b is not. Clinical benefits of continuing IFNβ treatment during pregnancy was taken into consideration.

Instead of a contraindication, a precaution has been added to limit the use during pregnancy only when the potential therapeutic benefits are considered to outweigh the potential risk.

Reference: Revision of Precautions, MHLW/PMDA, 4 April 2022
(link1 and link2 to the source within www.pmda.go.jp/english)

Iodine-containing contrast media (ICM)

Risk of hypothyroidism

USA. The US FDA has announced that the prescribing information for all iodinated contrast media (ICM) injections will be updated to include a new warning on the risk of undertactive thyroid or a temporary decrease in thyroid hormone levels as well as new monitoring recommendations for use in children 3 years or younger.

ICM injections are drugs containing iodine which is used to enhance the ability to see blood vessels, organs, and tissues on medical images such as X-rays or computed tomography scans.

The US FDA reviewed research studies published in the medical literature evaluating the risk of hypothyroidism.

Most cases of decreased thyroid hormone levels were temporary and did not require treatment. The reported rate ranged from 1 to 15 percent and tended to be higher in newborns, particularly those who were preterm.

It is recommended that Health-care professionals monitor patients from birth through to 3 years of age for the possibility of hypothyroidism or a temporary decrease in thyroid hormone levels following exposure to ICM.

Certain pediatric patients are at an increased risk, including newborns, babies with a of low birth weight, premature babies, or those that have a condition (including cardiac complications) that requires care in neonatal or pediatric intensive care units.

Reference: MedWatch, US FDA, 30 March 2022 (link to the source within www.fda.gov)

(See WHO Pharmaceuticals Newsletters No.5, 2018: Risk of hypothyroidism in Singapore. No.1, 2018: Possible risk of hypothyroidism in infants in New Zealand and No. 6, 2015: Rare cases of undertactive thyroid in infants in the USA)

Levothyroxine and ciprofloxacin

Possible interaction:
Increased risk of hypothyroidism

New Zealand. The Medsafe has announced that the product information for levothyroxine and ciprofloxacin are being updated to include information on the drug-drug interaction between levothyroxine and ciprofloxacin and the risk of hypothyroidism.

Levothyroxine is indicated for the treatment of hypothyroidism. Ciprofloxacin is a fluoroquinolone antibiotic indicated in adults for infections caused by ciprofloxacin-sensitive pathogens.

The Centre for Adverse Reactions Monitoring (CARM) received a report of hypothyroidism symptoms in a patient taking levothyroxine and a course of ciprofloxacin. The symptoms improved upon stopping ciprofloxacin and increasing the levothyroxine dose temporarily. In addition, a search in the literature identified a case report and study that reported or suggested this interaction.

It is recommended that health-care professionals should instruct patients to separate the administration times of these two concomitant medicines by leaving at least a six-hour gap between administration of both medicines. Patients should be informed about this potential interaction, advised on what signs and symptoms to look out for (e.g., fatigue, lethargy or feeling cold), and should be monitored them for any changes in thyroid function.

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

Mefenamic acid, doxycycline

Risk of fixed drug eruption

India. The Central Drugs Standard Control Organization
(CDSCO) has approved the recommendation to revise the prescribing information leaflet (PIL) for mefenamic acid and doxycycline to include fixed drug eruption as an adverse drug reaction. Mefenamic acid is indicated for the treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhea, mild to moderate pain, inflammation, fever and dental pain. Doxycycline is used as a broad-spectrum antibiotic.

The National Coordination Centre – Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopoeia Commission (IPC) reviewed 23 case reports of fixed drug eruption with use of mefenamic acid and 94 case cases with the use of doxycycline, and found a strong causal relationship between each of the two drugs and the event.

Reference:
Based on the communication from IPC, India, June 2022
(link1 and link2 to the source within cdsco.gov.in)

Metformin

Risk of reduced vitamin B12 levels

United Kingdom. The MHRA has announced that the product information for metformin containing medicines have been updated to state that vitamin B12 deficiency is a common adverse drug reaction of metformin and may affect up to 1 in 10 people who take it.

Metformin is indicated for the treatment of type 2 diabetes mellitus and prevention of type 2 diabetes in patients with a high risk of developing it.

Vitamin B12 deficiency is a known adverse drug reaction of metformin, and the current literature has suggested that the frequency of this adverse drug reaction is higher than previously thought.

The product information has also been updated to note that the risk of this adverse reaction increases with an increase in metformin dose and treatment duration, and in patients with risk factors known to cause vitamin B12 deficiency. Health-care professionals are advised to test vitamin B12 levels in those presenting with anaemia or neuropathy, and that periodic vitamin B12 monitoring should be considered in patients with risk factors for vitamin B12 deficiency.

Reference:
Drug Safety Update, MHRA, 20 June 2022
(link to the source within www.gov.uk/mhra)

Metronidazole

Risk of prolonged QT and ventricular tachycardia

Japan. The MHLW and the PMDA have announced that the product information for metronidazole containing products should be revised to include the risk of prolonged QT and ventricular tachycardia (including torsade de pointes).

Cases involving prolonged QT and/or ventricular tachycardia (including torsade de pointes) reported in Japan and overseas were evaluated. In one case reported overseas, a causal relationship between the drug and event was assessed to be reasonably possible.

Reference:
Revision of Precautions, MHLW/PMDA, 14 June 2022
(link to the source within www.pmda.go.jp/english)

Molnupiravir, nirmatrelvir/ritonavir

1. Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the product information for molnupiravir (Lagevrio®) and nirmatrelvir/ritonavir (Paxlovid®) should be revised to include the risk of anaphylaxis.

Molnupiravir and nirmatrelvir/ritonavir are antivirals indicated for the treatment of disease caused by SARS-CoV-2 infection (Covid-19).

Japanese and international cases of anaphylaxis following the treatment of Covid-19 with these medicines, were evaluated. For molnupiravir, a causal relationship between the drug and event was assessed to be reasonably possible in two out of eight cases reported in Japan and one out of 11 cases reported overseas. For nirmatrelvir/ritonavir, a causal relationship was reasonably possible in all cases of which one case was reported in Japan and three cases were reported overseas.

Reference:
Regulatory Matters

Revision of Precautions, MHLW/PMDA, 14 June 2022 (link1 and link 2 to the source within www.pmda.go.jp/english/)

2. Risk of hypersensitivity

Australia. The TGA has announced that the product information for molnupiravir and nirmatrelvir/ritonavir have been updated to add information about the risk of hypersensitivity.

Molnupiravir and nirmatrelvir/ritonavir are contraindicated in patients with a history of clinically significant hypersensitivity reactions to the active ingredients or any other components of the products listed in the package inserts. Post-market experiences of hypersensitivity have been reported for both medicines.

Health-care professionals are advised to immediately discontinue treatment and initiate appropriate medications and/or supportive care if signs or symptoms of a clinically significant hypersensitivity reaction occur.

Reference: Medicines Safety Update, TGA, 10 June 2022 (link to the source within www.tga.gov.au)

Nivolumab, pembrolizumab

Risk of severe gastritis

Japan. The MHLW and the PMDA have announced that the product information for nivolumab (Opdivo®) and pembrolizumab (Keytruda®) should be revised to include the risk of severe gastritis.

Nivolumab and pembrolizumab are indicated for cancer treatment, including malignant melanoma.

Cases of severe gastritis reported in Japan were evaluated (nivolumab: 11 cases and pembrolizumab: 12 cases). A causal relationship between the medicines and event was assessed to be possible in three of the nivolumab cases and in three of the pembrolizumab cases. The gastritis were considered to be caused by immune reactions.

Reference: Revision of Precautions, MHLW/PMDA, 14 June 2022 (link to the source within www.pmda.go.jp/english/)

Nomegestrol, chlormadinone

Risk of meningioma

Europe. The PRAC has recommended that the product information for medicines containing nomegestrol or chlormadinone should be updated to include meningioma as a rare adverse effect and advise on new measures to minimize the risk.

Meningioma is a tumour of the membranes covering the brain and spinal cord. It is usually benign and is not considered to be a cancer, but due to their location in and around the brain and spinal cord, meningiomas can in rare cases cause serious problems.

Nomegestrol or chlormadinone containing medicines are indicated for gynaecological and menstrual disorders, hormone replacement therapy and, at lower doses, as hormonal contraceptives (birth control).

The PRAC reviewed available data, including post market safety data and results from two recent epidemiological studies. These data showed that the risk of meningioma increases with an increase in dose and duration of treatment.

The PRAC has recommended that medicines containing high-dose chlormadinone (5 – 10 mg) or high-dose nomegestrol (3.75 – 5 mg) should be used at the lowest effective dose and for the shortest duration possible, and only when other interventions are not appropriate; low- and high-dose nomegestrol or chlormadinone medicines must not be used in patients who have, or have had, meningioma; and patients should be monitored for symptoms of meningioma during treatment with these medicines.

Reference: Patients and carers, EMA, 8 July 2022 (link to the source within www.ema.europa.eu)

Pregabalin

Risk of major congenital malformations in children exposed in-utero

United Kingdom. The MHRA has announced that the product information for pregabalin will be updated to include information from a new study which has suggested pregabalin may slightly increase the risk of major congenital malformations if used in pregnancy.

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Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy in adults with partial seizures with or without secondary generalization, and for generalized anxiety disorder in adults.

The MHRA reviewed the results of a Nordic observational study that consisted of 2,700 pregnancies exposed to pregabalin in the first trimester, alongside a recent European review which had the same conclusions. The study showed a higher prevalence of major congenital malformations in the babies (live or stillborn) exposed to pregabalin in the first trimester of pregnancy compared with those not exposed to pregabalin or any other antiepileptic drug. The review concluded that pregabalin use during the first trimester of pregnancy may cause a slight increase in risk of major congenital malformations in the unborn child.

The product information continues to advise that effective contraception should be used during treatment and that use in pregnancy should be avoided unless it is clearly necessary.

Reference:
Drug Safety Update, MHRA, 19 April 2022  (link to the source within www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletters No.2, 2022 Risk of major congenital malformations and neurodevelopmental disorders in children exposed in-utero in Ireland)

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**Somatropin**

**Removal of contraindication to diabetes mellitus**

**Japan.** The MHLW and the PMDA have announced that the product information for somatropin preparations (Genotropin®, Growject®, Humatrope® and Norditropin®) should be revised to remove the contraindication in patients with diabetes mellitus.

Somatropin is a recombinant human growth hormone and is indicated for growth hormone-deficient short stature without epiphyseal closure. In Japan, administration of all somatropin preparations to patients with diabetes mellitus was a contraindication from the time of initial approval in 1988.

The MHLW and the PMDA reviewed overseas (the US, EU, Canadian, and Australian) package inserts, clinical practice guidelines and standard textbooks, which do not contraindicate somatropin in patients with diabetes mellitus, but provide a special caution instead. In the serious Japanese cases reporting changes in glucose metabolism following somatropin administration, the reactions eventually improved and were adequately controlled by the temporal discontinuation of somatropin or initiation of antidiabetic drugs. Published literature and post-marketing surveillance studies (Japanese and overseas) reported several cases of patients with concurrent diabetes mellitus in which exacerbation of diabetes mellitus was not observed following administration of somatropin.

While removing the contraindication, some precautions should be added for use of somatropin in patients with diabetes mellitus, glucose intolerance, or diabetes mellitus risk factors. Close monitoring of blood glucose and HbA1c is required during administration of somatropin, as well as dosage adjustment of antidiabetic drugs if needed.

Reference:
Revision of Precautions, MHLW/PMDA, 4 April 2022  (link1 and link2 to the source within www.pmda.go.jp/english)

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**Teicoplanin**

**Risk of acute generalised exanthematous pustulosis (AGEP)**

**Japan.** The MHLW and the PMDA have announced that the product information for teicoplanin (Targocid® and generics) should be revised to include the risk of acute generalised exanthematous pustulosis (AGEP).

Teicoplanin is indicated for teicoplanin-susceptible strains of methicillin-resistant Staphylococcus aureus (MRSA).

The MHLW and the PMDA reviewed a total of two cases reported overseas, and in one case a causal relationship between the drug and event was assessed to be reasonably possible.

Reference:
Revision of Precautions, MHLW/PMDA, 13 May 2022  (link to the source within www.pmda.go.jp/english)
**Regulatory Matters**

### Umbralisib

**Possible increased risk of death**

**USA.** The US FDA has announced that approval for the cancer medicine umbralisib (Ukoniq®) has been withdrawn due to safety concerns.

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

Updated findings from the clinical trial (evaluating umbralisib to treat chronic lymphocytic leukemia (CLL)) continued to show a possible increase in the risk of death in patients receiving umbralisib. As a result, it was concluded that the risks of treatment with umbralisib outweigh its benefits.

Health-care professionals should stop prescribing umbralisib and switch patients to alternative treatments. In limited circumstances in which a patient may be receiving benefit from umbralisib, the marketing authorization holder plans to make it available under expanded access.

**Reference:**
MedWatch, US FDA, 1 June 2022 *(link to the source within www.fda.gov)*

(See WHO Pharmaceuticals Newsletters No.2, 2022 Possible increased risk of death with lymphoma investigated in the USA)

### Valacyclovir

**Potential risk of drug reaction with eosinophilia and systemic symptoms (DRESS)**

**Canada.** Health Canada has announced that the product safety information for valacyclovir containing products will be updated to include the potential risk of drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS is a rare, but serious, and potentially life-threatening drug reaction that includes fever, rash, elevated white blood cell count, and can affect one or more organs.

Valacyclovir is indicated for the treatment of cold sores (herpes labialis), shingles (herpes zoster) and treatment, suppression or reduction of the transmission of genital herpes.

Health Canada reviewed information provided by the manufacturer of Valtrex®, data from the Canada Vigilance database, and the published literature. Health Canada reviewed 115 cases (three Canadian, 112 international) of DRESS in patients taking valacyclovir, of which 26 cases (international) met the criteria for further assessment. Of the 26 case reports, four cases, including three published in the scientific literature, were assessed to be "probably" linked to the use of valacyclovir. Twenty-one cases, including one death, were found to be possibly linked, and one case was unlikely to be linked to the use of valacyclovir. In 25 of the 26 cases, patients were also taking other medications known to cause DRESS. Health Canada's review concluded that there may be a link between the use of valacyclovir-containing products and the potential risk of DRESS.

**Reference:**
Summary Safety Review, Health Canada, 24 May 2022 *(link to the source within www.hc-sc.gc.ca)*
Benzodiazepines

Potential risk of abuse, dependence and withdrawal

New Zealand. The Medsafe has reminded prescribers of the recent update to the product information for benzodiazepines regarding the potential risks of abuse, dependence and withdrawal, even when taken at recommended dosages.

New Zealand dispensing data shows that diazepam and lorazepam are the most dispensed benzodiazepines. The total amount of these medicines that were dispensed for all indications has increased in the period between 2016 and 2020 which may suggest frequent and/or long-term use.

Between August 1969 and March 2022, the CARM received 23 case reports of withdrawal and/or dependence with the use of benzodiazepines. Clonazepam (nine cases) was the most frequently reported benzodiazepine, followed by lorazepam (five), diazepam (three) and triazolam (three).

Health-care professionals are advised to counsel patients about the risks of benzodiazepines when initiating treatment, regularly review the ongoing need for treatment, and gradually taper benzodiazepines following continuous or high-dose use to reduce the risk of withdrawal reactions.

Reference:
Prescriber Update, Medsafe, June 2022  (link to the source within www.medsafe.govt.nz)
(See also WHO Pharmaceuticals Newsletter No.6, 2020: Boxed warning updated to improve safe use in the US)

Duvelisib

Possible increased risk of death and serious adverse effects

USA. The US FDA has warned that results from a clinical trial show a possible increased risk of death with duvelisib (Copiktra®) compared to alternative medicines to treat leukemia and a lymphoma. The trial also found duvelisib was associated with a higher risk of serious adverse effects, including infections, diarrhea, inflammation of the intestines and lungs, skin reactions, and high liver enzyme levels in the blood.

Duvelisib is indicated for the treatment of adults with chronic lymphocytic leukemia or small lymphocytic lymphoma who have received at least two prior therapies that did not work or stopped working.

The US FDA is notifying the public of these risks and is continuing to evaluate the safety of duvelisib.

It is recommended that Health-care professionals should consider the risks and benefits of continuing duvelisib in the context of other available treatments, and to advise patients receiving duvelisib of the possible increased risk of death and higher risk of serious adverse events.

Reference:
MedWatch, US FDA, 30 June 2022 (link to the source within www.fda.gov)

First-generation oral sedating antihistamines

Risk of serious harm in children

Australia. The TGA has warned that first-generation oral sedating antihistamines, including those available over-the-counter (OTC), should not be used for the treatment of cough, cold and flu symptoms in children under six years and for any indication in children under two years of age.

First-generation oral sedating antihistamines include products containing diphenhydramine and pheniramine. These medicines can cause children serious harm, or even death, and there is little if any evidence that they are effective in treating cough, cold and flu symptoms. Warnings on use in children have been introduced in the labelling since 2020.

Up until 24 May 2022, 226 cases reporting the use of first-generation oral sedating antihistamines in newborns, infants and children were received by TGA. The reports included a range of adverse events, including hypersensitivity reactions, vomiting, hallucination, tremor and abnormal movement. Of the 226 cases, 20 related to off-label use, misuse or overdose in children four years and under.

The TGA’s independent Advisory Committee on Medicines (ACM) reinforced the importance of health professionals providing thoughtful diagnosis, advice and treatment of allergy, cold
and flu symptoms in children. They also reiterated that it is inappropriate to use antihistamines for sleep and behaviour disturbance, especially in children and adolescents.

**Reference:**
Medicines Safety Update, TGA, 13 July 2022 ([link to the source within www.tga.gov.au](http://www.tga.gov.au))

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## Olaparib

### Potential risk of Pneumocystis Jirovecii Pneumonia (PJP)

**Saudi Arabia.** The Saudi Food & Drug Authority (SFDA) has released a safety signal concerning olaparib (Lynparza®) and the potential risk of Pneumocystis Jirovecii Pneumonia (PJP). PJP (formerly Pneumocystis carinii) is a lung infection caused by the fungal organism Pneumocystis jirovecii.

Olaparib is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (BRCAm) and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, who have previously been treated with chemotherapy.

In 2021, the SFDA detected the signal and reviewed all the evidence available. SFDA has examined the local and WHO global databases, which resulted in identifying four ICSRs. The SFDA used the WHO causality assessment criteria, and one ICSR was supportive of the association. The disproportionality of the number of observed and expected ICSRs (IC=1.1) together with one case report published in the literature were supportive for an association, too.

Health-care professionals should be aware of this potential risk, and it is advisable to monitor any signs or symptoms of PJP in treated patients.

**Reference:**
Safety Alert, SFDA, 28 March 2022 ([link to the source within www.sfda.gov.sa](http://www.sfda.gov.sa))

## Pembrolizumab

### Potential risk of cholestasis

**Saudi Arabia.** The SFDA has identified a safety signal for pembrolizumab (Keytruda®) and the potential risk of cholestasis.

In 2021, the SFDA detected the signal by reviewing the medical literature. The SFDA extracted and reviewed ICSRs that were most complete (completeness score of >0.8) from the local and WHO global databases. WHO causality assessment criteria were applied on the extracted cases and most of cases were assessed to have a positive association (out of 33 ICSRs: one case was assessed to be certain, 10 probable, and seven possible cases). The investigation concluded that the current available evidence is sufficient to support the relationship between pembrolizumab and cholestasis.

This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.

**Reference:**
Safety Alert, SFDA, 28 March 2022 ([link to the source within www.sfda.gov.sa](http://www.sfda.gov.sa))

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## Safety of Medicines

**Olaparib**

### Potential risk of Pneumocystis Jirovecii Pneumonia (PJP)

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Olaparib is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-risk, and health-care professionals should be aware of this potential adverse reaction.

**Reference:**
Safety Alert, SFDA, 28 March 2022 ([link to the source within www.sfda.gov.sa](http://www.sfda.gov.sa))

## Secukinumab

### Potential risk of erectile dysfunction (ED)

**Saudi Arabia.** The SFDA has identified a safety signal for secukinumab (Cosentyx®) and the potential risk of erectile dysfunction (ED).

Secukinumab is a recombinant human immunoglobulin G1κ monoclonal antibody that selectively binds and neutralizes interleukin-17A and is indicated for the treatment of plaque psoriasis, psoriatic arthritis and ankylosing spondylitis.

In 2021, the SFDA detected the signal and reviewed all the evidence available on the association. SFDA has reviewed the local and WHO global databases, which identified 37 ICSRs. Causality assessment using the WHO criteria was performed in cases that were more complete (nine cases). Seven of the ICSRs were assessed to be supportive of an association, with two being probable and five being possible. A positive dechallenge was reported in two cases.

Health-care professionals should be aware of this potential risk, and are advised to monitor any signs or symptoms of ED in patients treated with secukinumab.

**Reference:**
Safety Alert, SFDA, 28 March 2022 ([link to the source within www.sfda.gov.sa](http://www.sfda.gov.sa))
Topiramate

Potential risk of neurodevelopmental disorders in children exposed in-utero

Europe. The EMA has started a review to assess new data on a potential risk of neurodevelopmental disorders in children who have been exposed to topiramate during pregnancy.

Topiramate is indicated for the treatment of epilepsy as well as for the prevention of migraine. The use of topiramate in pregnant women is already known to increase the risk of birth defects; safety measures have been introduced including some advice for women with epilepsy to avoid becoming pregnant whilst being treated with topiramate.

Recently, a study based on data from a Nordic registry that investigated the risk of neurodevelopmental disorders associated with several anti-epileptic drugs, including topiramate was published. The study conclusions suggest a possible increase in the risk of autism spectrum disorders, intellectual disability and child neurodevelopmental disorders with the exposure to topiramate during pregnancy.

The PRAC decided that further assessment is warranted to determine the scope and the best regulatory procedure to assess these potential risks. The EMA will communicate further as soon as more information becomes available.

Reference:

Patients and carers, EMA, 8 July 2022 (link to the source within www.ema.europa.eu)

(See also WHO Pharmaceuticals Newsletters No.2, 2022 Risk of major congenital malformations and neurodevelopmental disorders in children exposed in-utero in Ireland)
WHO convened the first joint meeting (virtual) of the **WHO Global Advisory Committee on Vaccine Safety (GACVS)** and the **WHO Advisory Committee on Safety of Medicinal Products (ACSOMP)** from 14 to 16 June 2022.

An integrated WHO Pharmacovigilance team was established in 2020, to combine work related to the safety of medicines and vaccines within the Department of Regulation and Prequalification (RPQ). Following this transformation, WHO convened a joint meeting of the Advisory Committee on Safety of Medicinal Products (ACSoMP) and the Global Advisory Committee on Vaccine Safety (GACVS) for the first time on 14–16 June 2022. A summary of the presentations and recommendations from the medicines-specific sessions and from the sessions of common interest for the pharmacovigilance of medicines and vaccines is provided below.

The medicines-specific sessions were co-chaired by Dr June Raine from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and Dr Gerald Dal Pan from the United States Food and Drug Administration (US FDA) and sessions common to both vaccines and medicines were co-chaired by Dr Dure Samin Akram from the Health, Education and Literacy Program in Pakistan and Dr Gerald Dal Pan.

### Survey on sodium valproate

Valproate containing products are known teratogens, and the risk of congenital malformations, developmental disorders are well documented. WHO has added a cautionary note on the use of valproate in pregnant women and women of childbearing potential in the Essential Medicines List (EML) and has amended the WHO mental health gap action programme (mhGAP) intervention guide to include warnings against the use of valproate in pregnant women and women of childbearing potential. Many high-income countries (HICs) have taken regulatory measures such as introducing pregnancy prevention programmes to minimize the risks, and the impact of these interventions are being assessed. However, there is very little information on the usage of valproate products or risk minimization measures in low- and middle-income countries (LMICs). To bridge this gap in knowledge WHO plans to design a survey to investigate valproate usage in LMICs. The WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services, the Indian Pharmacopoeia Commission (IPC) and Pharmacovigilance Programme of India (PvPI), have already conducted a survey in India. This survey will be a starting point, from which the WHO survey will be designed. IPC were invited to present their experiences and lessons learned. The main objectives of the survey were to assess the impact of the awareness campaign on the teratogenic risks of valproate containing medicines and understand the knowledge, attitude and practices of healthcare providers towards the use of valproate containing medicines.

### Recommendations:

Based on lessons learned, ACSoMP recommends that WHO consider the following when designing their survey:

- Consider including interviews as well as a survey to maximise responses and when analysing data, stratify by speciality of responders to understand potential confounders and biases.
- Information on alternative treatment should be collected to understand the context of valproate prescribing, additionally there is value in targeting questions to ask about potential obstacles to using alternatives (e.g., cost, access, awareness).
- It would be useful to follow-up children exposed during pregnancy, to assess any long-term effects, particularly in young males who have been exposed to valproate products. The use of pregnancy or disease-specific registries could be useful to assess the impact of sensitization following an awareness campaign over time.
- The Committee also recommended that paediatricians should be included in awareness campaigns since they can prescribe valproate-containing treatments and as children progress to adolescence and adulthood, they may already be taking the drug and be unaware of the risk should pregnancy occur.

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The Committee requested that the next ACSoMP meeting will include a session to review any updates from the Essential Medicines List (EML).

Update on eye disorders during leishmaniasis treatment with miltefosine
Miltefosine is an oral anti-infective that was authorized in India in 2002 for the treatment of some forms of leishmaniasis, including post-kala-azar dermal leishmaniasis (PKDL). PKDL presents as a skin rash that occurs after successful treatment of visceral leishmaniasis that occurs in all Leishmania donovani endemic areas. Miltefosine was included in the Essential medicines list (EML) in 2011 and was authorized in USA and Germany in 2014. Since 2016, 60 cases of ocular disorders, including permanent blindness, following miltefosine treatment have been reported in India, although causality has not been established to date. In February 2022 WHO published a statement that included recommendations for health professionals, and this was actively shared globally with all WHO regions, with a particular focus on countries in the South-East Asia region, especially Bangladesh and Nepal where miltefosine has also been used. In April 2022, the South-East Asia Regional Technical Advisory Group on visceral leishmaniasis (kala-azar) shared ACSoMP’s concerns, and they sought prompt responses from WHO and Member States. Further, WHO is setting up a multistakeholder expert group to advise WHO on the causal relationship, provide recommendations on the need to update risk minimization measures, and for further studies to address remaining uncertainties.

Recommendations:
- The Committee requested the opportunity to comment on the developed terms of reference (ToR) for the multistakeholder expert group.
- It was highlighted that all available evidence, including quality, non-clinical and clinical data should be considered, and it was recommended that safety data from other products from the same therapeutic class should also be explored. To facilitate future benefit-risk reviews, the number needed to harm and number needed to treat should be calculated.
- WHO should ensure adequate awareness of the current published recommendations in all countries where miltefosine is used. A standard operating procedure (SOPs) for pre-treatment ophthalmic examination and examinations every two weeks, once treatment with miltefosine is started, has been developed in India and this could be shared to facilitate implementation in other countries.
- A multi-country active pharmacovigilance study should be conducted to improve both data collection and awareness, building on existing disease programmes.
- ACSoMP expressed interest in a proposal from the WHO Country Office in India to lead a pharmacogenomic / molecular study in India to provide quick results, in accordance with recommendations made by the multidisciplinary group.

Safety of COVID-19 therapeutics updates
An update of the latest published recommendations for COVID-19 therapeutics and an outline of the process used to develop the recommendations by the WHO COVID-19 guideline development group were shared. WHO has published the 11th version of the ‘Therapeutics and COVID-19’ living guidance and the 4th version of the ‘Clinical management of COVID-19’ guidance. The assessment pipeline for COVID-19 therapeutics is updated weekly.

The recommendations are graded as strong or conditional, based on the strength of the evidence and provide information on target population and populations who should not be treated, as well as specific conditions to be respected during treatment, including duration, and warning about potential drug-drug interactions. Guidance on information for patients and what, if any, safety monitoring should be done is provided. Derivatives, such as webinars, toolkits and treatment algorithms, based on the guidelines have been developed to disseminate the information.

Discussions/conclusions:
The general approach used, and the use of network meta-analyses for assessment of comparison treatments were discussed. Most studies that have been reviewed were performed in high income countries (HICs), although some have included patients in LMICs. While the relative risk from the studies may not differ with location the absolute risk may vary. This can affect the generalizability of the guidance. Generalizability is

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discussed in the guidance, and the locations of the studies are noted, but they are not taken into account in analyses.

**Active surveillance: methods and data management tools**

Molnupiravir, the first oral treatment for non-severe COVID-19 disease, received a WHO conditional recommendation for use on 3 March 2022. One of the conditions is that there should be a robust, active pharmacovigilance programme in countries using this product. To respond to this requirement, on 11 March 2022, WHO published a protocol for cohort event monitoring (CEM) studies on molnupiravir in LMICs. The plan for the implementation of the protocol in 6 to 12 countries was shared with the Committees. This plan consists of developing a training programme, and data collection, management and transfer tools. WHO has started developing the data collection and management tools, these will be useable in studies assessing other treatments and vaccines, even in clinical trials. Data will come from diverse sources, and at various times throughout the monitoring period. IT solutions are needed for both study participants and study-site staff as well as principal investigators. In addition, as the study will be carried out in numerous countries, the IT solutions need to be available in different languages and with flexibility to adapt to the local context.

**Recommendations:**

- The joint Committees recommended that case report forms (CRFs) should be adapted to pick up gestational age at time of exposure for the baby, when following pregnant women who were inadvertently exposed to the medicine, particularly since the exposure time is short.
- CRFs should be adapted to prompt participants to report concomitant over-the-counter medications.
- Different countries have different data privacy laws for collection and sharing of data. When a final list of countries that will implement the protocol is available, a strategy for respecting these laws should be developed.

**Monitoring safety in pregnancy**

WHO has three ongoing initiatives to improve safety monitoring during pregnancy. The first is a collaborative project between the Pharmacovigilance team and PATH (formerly known as the Program for Appropriate Technology in Health) aiming to map and assess the strengths and limitations of pregnancy exposure registries available in LMICs. The second is an internal WHO project, to map various WHO initiatives to assess the availability of minimal data elements to study pregnancy and neonatal outcomes in LMICs and to propose methods to harmonize these data elements. The third project is the monitoring of the safety of COVID-19 vaccines during pregnancy, which is a collaboration with the WHO Sexual and Reproductive Health and Research team.

An Expert Steering Committee (ESC), set up to oversee the first two projects, will provide independent, authoritative, and scientific advice to WHO on the safety of health interventions in pregnancy, and for the implementation of pregnancy exposure registries and other methods for monitoring the safety in pregnancy in LMICs. This will be critical for the preparation of LMICs for the safe introduction and use of health products in pregnant women. The ESC will also provide best practice guidance on the safety monitoring of health interventions in pregnancy.

The third initiative, the WHO COVID-19 pregnancy cohort study, is a longitudinal cohort study that comprises about 21,000 consecutively recruited pregnant women who will be followed every 4 to 6 weeks up to 6 weeks postpartum, to capture information on maternal, pregnancy, perinatal, neonatal and postpartum outcomes as well as non-pregnancy related outcomes. Information on COVID-19 vaccination status, when and which vaccine was administered will also be collected. Consistency between countries and study sites for outcome definitions, such as gestational age, and the data collected will be maximized by the use of standardized case report forms and standardized training provided to the investigators.

As of June 2022, over 10,000 women have been recruited in eight countries, including about 4500 vaccinated women, of whom about 1700 and 1300 were exposed and unexposed, respectively, to SARS-CoV-2 infection. This study is very labour, time and resource intensive and the rapidly evolving pandemic adds to the challenges for running this type of study, but it is hoped that this initiative will help to strengthen the existing infrastructure for the future.

**Discussions and conclusions:**

The committee discussed collection of comorbidity data and controlling for confounding factors, sample size, consistency between countries and complexities around the determination of SARS-CoV-2 infections during pregnancy. The Committee encouraged the continuation of the cohorts and the use of the existing
infrastructure after this study, so that important data on maternal and neonatal outcomes can continue to be collected.

**Updates on the framework for WHO Listed Authorities**
The framework and specifications for WHO listed authorities (WLAs) were developed in response to changes to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) structure in 2015 which had an impact on the definition of stringent regulatory authorities (SRAs). The definition of WLA, to be used to replace the concept of SRA, was adopted by the Expert Committee for Specifications for Pharmaceutical Products (ECSSP) in October 2020 (WHO TRS 1033), and corresponds to a regulatory authority or a regional regulatory system that has been documented to comply with all the relevant indicators and requirements specified by WHO for the requested scope of listing, based on an established benchmarking and a performance evaluation process. The objectives are to build capacity consistent with good regulatory practices in Member States as well as to promote regulatory cooperation, convergence and transparency through networking, work sharing and reliance. In 2021 a policy document describing the purpose, definitions and high-level operating principles related to the evaluation and public listing of authorities was published.³

The WLA was launched on 31 March 2022.⁶ The voluntary process is initiated following a request from a Member State for a national or regional regulatory authority (RA) that must have a maturity level 3 to be eligible for performance evaluation. To be publicly listed as a WLA the RA will undergo a performance evaluation process, which differs from benchmarking processes as it is more like an inspection and audit and is not intended to help build capacity. The approach is based on the established global benchmarking tool (GBT) and a performance evaluation framework (PEF), which is a series of new indicators and tools for performance evaluation. The PEF has seven performance evaluation indicators (PEIs) which are assessed during a field trip. These are described in a specific manual that also has checklists. The PEF is being piloted in two to four countries. Based on these experiences the PEF manual will be updated and the WLA operational guidance will be published by the end of 2022.

**Discussions and conclusions:**
The promotion of reliance by the WLA initiative was discussed. The benefits of the WLA process and recognition of regulatory decisions made by WLAs to manufactures and procurement agencies were highlighted. Overall WLA will contribute to facilitating access to good quality medicinal products and vaccines.

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