

**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.

This edition of the Newsletter includes highlights from the 42nd Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring, a brief report on the Advanced Pharmacovigilance workshop organized by WHO and updates on the WHO implementation of an ADR Reporting App in countries.

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Alemtuzumab

Risk of cardiovascular disorders and immune-related disorders

Europe. The European Medicines Agency (EMA) has recommended that the use of alemtuzumab (Lemtrada®) should be restricted. It should be used to treat relapsing-remitting multiple sclerosis, only if the disease is highly active despite treatment with at least one disease-modifying therapy or if the disease is worsening rapidly. The restriction is due to reports of rare but serious cardiovascular disorders.

Alemtuzumab is indicated to treat adults with relapsing-remitting multiple sclerosis.

The EMA has also recommended updating the physician's guide and the patient information pack with advice on minimising the risk of serious cardiovascular disorders. These recommendations were issued by the Pharmacovigilance Risk Assessment Committee (PRAC) and have now been endorsed by the Committee for Medicinal Products for Human Use (CHMP).

Reference:
EMA, 15 November 2019
(www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletter No.4, 2019: Risk of serious cardiovascular and immune-mediated adverse reactions in UK; No.3, 2019: Cardiovascular and immune-mediated adverse effects in EU)

Apalutamide, Enzalutamide

Risk of interstitial lung disease

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for

apalutamide (Erleada®) and enzalutamide (Xtandi®) should be revised to include interstitial lung disease as an adverse drug reaction.

Apalutamide and enzalutamide are indicated for castration-resistant prostate cancer.

A total of four cases of interstitial lung disease occurring in patients taking apalutamide have been reported in Japan during the previous three fiscal years. One of these cases was fatal and a causal relationship could not be excluded. Additionally, 19 cases of interstitial lung disease in patients taking enzalutamide have been reported in Japan. Three of these cases were fatal and a causal relationship could not be established.

Reference:
Revision of Precautions, MHLW/PMDA, 15 November 2019 (www.pmda.go.jp/english/)

Baricitinib

Risk of venous thromboembolism

Japan. The MHLW and the PMDA have announced that the package insert for baricitinib (Olumiant®) should be revised to include venous thromboembolism as an adverse drug reaction.

Baricitinib is indicated to treat rheumatoid arthritis in patients who have had an inadequate response to conventional treatments.

A total of five cases of venous thromboembolism have been reported during the previous three fiscal years in Japan, and for one case a causal relationship between baricitinib and the event could not be excluded. No patient mortalities have been reported.

Reference:
Revision of Precautions, MHLW/PMDA, 24 September 2019 (www.pmda.go.jp/english/)

Belimumab

Risk of depression, suicidal ideation, and suicide attempt

Japan. The MHLW and the PMDA have announced that the package insert for belimumab (Benlysta®) should be revised to include depression, suicidal ideation and suicide attempt as adverse drug reactions.

Belimumab is indicated for systemic lupus erythematosus in patients who have had an inadequate response to conventional treatment.

Results of post-marketing clinical study conducted in systemic lupus erythematosus patients suggested higher incidences of depression, suicide and/or self-injury in the group administered belimumab plus standard therapy such as steroid therapy, compared with the group administered placebo and standard therapy. The MHLW and the PMDA have concluded that the revision of the package insert was necessary.

One case involving depression, suicidal ideation and suicidal attempt has been reported in Japan during the previous three fiscal years.

Reference:
Revision of Precautions, MHLW/PMDA, 29 October 2019 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.3, 2019: Risk of serious psychiatric events in UK)

Carfilzomib

Risk of reactivation of hepatitis B virus (HBV)

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that changes are being made to the Summary of Product Characteristics of carfilzomib (Kyprolis®) to recommend

screening for hepatitis B virus (HBV) before initiation of treatment.

Carfilzomib is indicated in combination with lenalidomide and dexamethasone or with only dexamethasone for the treatment of multiple myeloma.

A recent EU review has identified reports of HBV reactivation associated with carfilzomib. The review assessed cases worldwide up to 10 July 2019 and identified 23 cases of HBV reactivation from clinical studies and post-marketing information.

Health-care professionals should screen all patients for HBV before initiation of carfilzomib and consider prophylaxis with antivirals for patients with positive serology who are treated with carfilzomib. Also, health-care professionals should advise patients with a positive serology to seek medical help immediately if they experience signs and symptoms suggestive of HBV reactivation.

Reference:

Drug Safety Update, MHRA, 21 November 2019 (www.gov.uk/mhra)

Cefotaxime

Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) of Korea has updated the drug label for cefotaxime (Claforan®) to include the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Cefotaxime is an injectable third-generation cephalosporin used to treat a variety of bacterial infections.

During the evaluation process of reports of serious adverse

events (SAE), the Korea Institute of Drug Safety and Risk Management (KIDS) reviewed three SAE reports of DRESS syndrome in association with exposure to cefotaxime.

At the time of review, KIDS had received nine domestic and 24 international reports of DRESS syndrome with cefotaxime use through the Korean Adverse Event Reporting System (KAERS) since 1989. Case evaluation was performed on these reports, and a causal association could not be excluded.

This recommendation announced by MFDS was based on the results of the SAE review system, signal analysis and evaluation process at KIDS.

Reference:

Based on the communication from MFDS and KIDS, Republic of Korea, October 2019

Chloroquine

Risk of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)

India. The National Coordination Centre - Pharmacovigilance Programme of India (NCC-PvPI) has made a recommendation to the Central Drugs Standard Control Organisation (CDSCO) for the revision of the patient information leaflet (PIL) for chloroquine to incorporate Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as clinically significant adverse drug reactions.

Chloroquine is used for the treatment of malaria. Between July 2011 and April 2019, the NCC-PvPI received eight individual case safety reports (ICSRs) of chloroquine associated TEN and 10 ICSRs of SJS. The cases were reviewed by the Signal Review Panel (SRP), PvPI and IPC

which found a strong causal relationship between chloroquine associated SJS/TEN.

Reference:

Based on the communication from NCC-PvPI, IPC India (ipc.gov.in)

Dabigatran

Risk of vasculitis

New Zealand. Medsafe is placing dabigatran (Pradaxa®) on the Medicines Monitoring scheme following a report of vasculitis and rash.

Dabigatran is indicated for the prevention of stroke, systemic embolism, venous thromboembolic events, reduction of vascular mortality and treatment of acute deep vein thrombosis and/or pulmonary embolism.

In New Zealand, four reports describing suspected vasculitis or vasculitic rash with dabigatran use have been reported since 2012 until September 2019.

Reference:

Safety Communication, Medsafe, 14 November 2019 (www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.5, 2019: Risk of recurrent thrombotic events in Australia and New Zealand; No.4, 2019: Increased risk of recurrent thrombotic events in UK; No.3, 2016: Risk of thrombocytopenia in Japan; No.2, 2016: Benefit-risk balance of rivaroxaban: unchanged in EU; No.6, 2013: Apixaban, dabigatran and rivaroxaban in UK)

Epirubicin

Risk of pneumonia

Republic of Korea. The MFDS has updated the drug label for epirubicin (Pharmorubicin®) to include pneumonia as an adverse drug reaction.

Epirubicin, a derivative of doxorubicin, is an

antineoplastic agent. It is used as a component of various chemotherapy regimens to treat breast cancer, gastric cancer, Hodgkin's disease, malignant tumor of nasopharynx.

During the evaluation process of serious adverse event reports, KIDS reviewed a fatal SAE report of *Pneumocystis jirovecii* pneumonia in a patient who was receiving epirubicin-containing chemotherapy. Causal association could not be excluded between epirubicin and pneumonia in this case.

This recommendation announced by the MFDS was based on the results of the SAE review system at KIDS.

Health-care professionals should be reminded of the myelosuppressive effects of epirubicin and are advised to monitor for any signs of serious infections during use of this drug.

Reference:

Based on the communication from MFDS and KIDS, Republic of Korea, October 2019

Estradiol

Four-week limit for use of high strength estradiol creams

Europe. The EMA has announced that the PRAC has recommended limiting the use of high-strength estradiol containing creams to a single treatment period of up to four weeks.

Estradiol-containing creams are used in topical hormone replacement therapy (HRT). It is indicated to treat symptoms of vaginal atrophy in postmenopausal women. The adverse drug reactions of HRT taken orally or used transdermally include venous thromboembolism, stroke, endometrial cancer and breast cancer.

High-strength estradiol creams should not be prescribed for longer than a single treatment period of four weeks.

Reference:

EMA, 4 October 2019
(www.ema.europa.eu)

Fluoroquinolones, quinolones (oral, injectable)

Risk of tendon disorders, peripheral neuropathy and psychiatric symptoms

Japan. The MHLW and the PMDA have announced that the package inserts for fluoroquinolones and quinolones should be revised to include tendon disorders, peripheral neuropathy and psychiatric symptoms as adverse drug reactions.

Fluoroquinolones and quinolones are antibacterials, indicated for conditions such as superficial skin infections, thermal burn, tonsillitis, acute bronchitis and pneumonia. Examples of fluoroquinolones include levofloxacin (Cravit®), moxifloxacin (Avelox®), ofloxacin (Tarivid®) and piperidic acid (Dolcol®).

The MHLW/PMDA decision follows the European and US revisions to the package insert. It is thought that collagen tissue disorders and suppression of GABA nerves were potential mechanisms of onset of tendon disorders and psychiatric symptoms. These mechanisms and risks are common to all the antibacterials of this class.

Currently there is not enough information on the mechanism of action for peripheral neuropathy or epidemiological information to indicate that this event is a risk common to all fluoroquinolones and quinolones, but cases have been reported in Japan in patients treated

fluoroquinolones such as levofloxacin.

MHLW and PMDA have concluded that revision of the package insert was necessary to include a precaution in all fluoroquinolone and quinolone antibacterials based on the results of the investigation.

Reference:

Revision of Precautions, MHLW/PMDA, 24 September 2019 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.3, 2019: Risk of musculoskeletal and nervous systems damage in UK; No.1, 2019: Risk of tendon damage and neuropathies in Ireland; No.6, 2018: Risk of long-lasting and disabling effects in Europe; No.2, 2017: Potential risk of persistent and disabling side effects in Canada; No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in USA)

Ingenol mebutate (gel)

Increased incidence of skin tumours

United Kingdom. The MHRA has announced that the product information for ingenol mebutate gel (Picato®) is being updated to include a warning about reports of basal cell carcinoma, Bowen's disease and squamous cell carcinoma.

Ingenol mebutate gel is indicated for the treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

A European review on ingenol mebutate has begun following several studies showing an increased number of skin cancer cases in patients using ingenol mebutate gel.

A warning about the risk of keratoacanthoma was previously included in the product information, but following a separate review of safety data, the product information is being updated.

Since 2013 and up to August 2019, the MHRA received nine cases of skin malignancies with ingenol mebutate, including cutaneous squamous cell carcinoma, atypical fibroxanthoma, neuroendocrine carcinoma of the skin, Bowen's disease, and basosquamous carcinoma.

Health-care professionals should advise patients using ingenol mebutate gel to be vigilant for the development of any new skin lesions within the treatment area and to seek medical advice immediately. Also, health-care professionals should use the drug with caution in patients with a history of skin cancer.

Reference:

Drug Safety Update, MHRA, 18 October 2019 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.5, 2019: Potential risk of skin cancer in EU; No.3, 2017: Risk of hypersensitivity reactions, herpes zoster and eye injury in Australia; No.5, 2015: Risk of severe allergic reactions and herpes zoster (shingles) in the USA)

Moxifloxacin

Risk of acute generalized exanthematous pustulosis (AGEP)

Republic of Korea. The MFDS has updated the drug label for oral moxifloxacin (Avelox®) to include the risk of acute generalized exanthematous pustulosis (AGEP).

Moxifloxacin is one of fluoroquinolone antibiotics indicated for a variety of bacterial infections, including community-acquired pneumonia and tuberculosis.

AGEP is a rare cutaneous reaction that involves acute pustular eruptions, often accompanied with systemic symptoms, such as fever and leukocytosis. Current evidence suggests that this severe skin reaction is predominantly triggered by drugs.

During the evaluation process of serious adverse event reports, the KIDS reviewed one fatal SAE report of AGEP in a patient who was receiving moxifloxacin-containing tuberculosis treatment regimen.

At the time of review, KIDS had received three domestic reports of AGEP with the use of moxifloxacin through the Korean Adverse Event Reporting System KAERS since 1989. Case evaluation was performed on these reports, and a causal association could not be excluded between moxifloxacin and AGEP.

This recommendation announced by MFDS was based on the results of SAE review system and signal analysis evaluation process at KIDS.

Reference:

Based on the communication from MFDS and KIDS, Republic of Korea, October 2019

Osimertinib mesilate

Risk of TEN, Stevens-Johnson syndrome (SJS), erythema multiforme

Japan. The MHLW and the PMDA have announced that the package insert for osimertinib mesilate (Tagrisso®) should be revised to include TEN, oculomucocutaneous syndrome (Stevens-Johnson syndrome, SJS) and erythema multiforme as adverse drug reactions.

Osimertinib is indicated to treat the epidermal growth factor receptor (EGFR) gene mutation-positive inoperable or recurrent non-small cell lung cancer.

Cases of TEN, SJS or erythema multiforme have been reported in patients treated with osimertinib mesilate overseas. In Japan, five cases involving SJS and three cases involving erythema multiforme have been reported during the previous three fiscal years.

MHLW and PMDA have concluded that revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:

Revision of Precautions, MHLW/PMDA, 24 September 2019 (www.pmda.go.jp/english/)

Pentosan polysulfate sodium

Rare risk of pigmentary maculopathy

United Kingdom. The MHRA has announced that the product information for pentosan polysulfate (Elmiron®) has been updated to include rare risk of pigmentary maculopathy.

Pentosan polysulfate is indicated for the treatment of bladder pain syndrome (interstitial cystitis) with moderate to severe pain, urgency and frequency of micturition.

Health-care professionals should advise patients on pentosan polysulfate to promptly seek medical advice in case of visual changes such as reading difficulty or slow adjustment to low or reduced light environments. Also, discontinuation of the treatment should be considered in patients with pigmentary maculopathy.

Reference:

Drug Safety Update, MHRA, 19 September 2019 (www.gov.uk/mhra)

Proton pump inhibitors (PPIs)

Risk of acute kidney injury

India. The NCC-PvPI has made a recommendation to CDSCO requesting that the PIL for

proton pump inhibitors (PPIs) marketed in India should be revised to incorporate acute kidney injury as a clinically significant adverse drug reaction.

PPIs are used to treat gastric ulcers, duodenal ulcers, gastroesophageal reflux disease and Zollinger Ellison syndrome. Between July 2011 and July 2019, the NCC-PvPI has received 23 ICSRs of PPI associated acute kidney injury. The cases were carefully reviewed by SRP at NCC-PvPI, IPC, and a strong causal relationship between PPIs and acute kidney injury was concluded.

Reference:

Based on the communication from NCC-PvPI, IPC India (ipc.gov.in)

D-Sorbitol

Contraindication for patients with hereditary fructose intolerance

Japan. The MHLW and the PMDA have announced that the package inserts for D-Sorbitol, urologic irrigating solution, (UromaticS®) should be revised to include patients with hereditary fructose intolerance in the contraindications section.

D-Sorbitol is used in urologic irrigation during transurethral surgeries for prostate or bladder diseases and during or after other urological surgeries.

Although no cases involving adverse reactions related to patients with hereditary fructose intolerance have been reported in Japan during the previous three fiscal years, the MHLW and the PMDA have concluded that the revision of the package insert was necessary following the EMA's contraindication of the use of intravenous injection products containing sorbitol or fructose in patients with hereditary fructose intolerance.

Reference:

Revision of Precautions, MHLW/PMDA, 29 October 2019 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.3, 2019: Hereditary fructose intolerance in Japan)

Tocilizumab

Risk of hepatic impairment

Japan. The MHLW and the PMDA have announced that the package insert for tocilizumab (Actemra®) should be revised to include hepatic impairment as an adverse drug reaction.

Tocilizumab is indicated to treat rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, adult Still's disease, cytokine release syndrome, Takayasu's arteritis and giant cell arteritis.

Cases of hepatic impairment have been reported in patients treated with tocilizumab in Japan and overseas. In Japan, a total of 11 cases involving hepatic impairment have been reported to date. Of the 11 cases, a causal relationship between the drug and event could not be established in any of them. No patient mortalities have been reported.

MHLW/PMDA concluded that revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:

Revision of Precautions, MHLW/PMDA, 24 September 2019 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.5, 2019: Rare risk of hepatic injury in Ireland; No.4, 2019: Risk of hepatotoxicity in Australia and UK)

Tofacitinib

Risk of blood clots

Europe. The EMA has recommended that tofacitinib (Xeljanz®) should be used with caution in all patients at high risk of blood clots, as tofacitinib could increase the risk of blood clots in the lungs and in deep veins in patients who are already at high risk.

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

The recommendations follow the EMA's review of an ongoing study in patients with rheumatoid arthritis and an increased risk of cardiovascular disease, in addition to data from earlier studies and consultation with experts in the field. All data combined showed that the risk of blood clots in deep veins and lungs was higher in patients taking tofacitinib.

The recommendations were issued by the EMA's PRAC and have been endorsed by CHMP.

Patients at high risk include those who have had a heart attack or have heart failure, cancer, inherited blood clotting disorder or a history of blood clots, and those who are taking combined hormonal contraceptives, hormone replacement therapy or have recently had major surgery.

Patients should be informed about the signs and symptoms of the risk before receiving tofacitinib and be advised to seek prompt medical help if they develop these symptoms during treatment.

Reference:

EMA, 4 October 2019 (www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletter No.5, 2019: Increased risk of blood clots and death with higher dose in US and Japan; No.4, 2019: Risk of pulmonary embolism in Europe; No.3, 2019: Increased risk of blood clots in lungs and death in Europe; No.2, 2019: Increased risk of blood clots in the lungs and death in USA)

Vonoprazan

Risk of thrombocytopenia, agranulocytosis, leukopenia and pancytopenia

Japan. The MHLW and the PMDA have announced that the package inserts for preparations containing vonoprazan (Takecab®, vonoprazan/amoxicillin/clarithromycin (Vonosap®) and vonoprazan/amoxicillin/metronidazole (Vonopion®)) should be revised to include thrombocytopenia, agranulocytosis, leukopenia and pancytopenia as adverse drug reactions.

Vonoprazan is indicated to treat several conditions including gastric ulcer, duodenal ulcer and used in the adjunct therapy to *Helicobacter pylori* eradication.

A total of 19 cases of thrombocytopenia, 15 cases of agranulocytosis and leukopenia and 17 cases of pancytopenia have been reported in Japan during the previous three fiscal years. Of the cases, two mortalities in patient with thrombocytopenia have been reported, but a causal relationship between the drug and event could be established for none of them.

Reference:

Revision of Precautions, MHLW/PMDA, 29 October 2019 (www.pmda.go.jp/english/)

Yellow fever vaccine

Strengthened recommendation for people with weakened immunity

United Kingdom. The MHRA has issued a safety bulletin informing health-care professionals of the UK's Commission on Human Medicines recommendations for yellow fever vaccine (Stramaryl®). It is recommended that further precautions should be taken in

people with weakened immunity and in those aged 60 years and older taking the yellow fever vaccine. Yellow fever is a life-threatening viral infection and the yellow fever vaccine is highly effective in protecting those at risk of the disease during travel to an area where there is a risk of infection. Because the vaccine contains a live, weakened strain of the yellow fever virus, strict adherence to contraindications and precautions is essential to reduce the risk of serious adverse effects in those who may have a weaker immune system. Two risks to yellow fever vaccine are viscerotropic disease and neurotropic disease, very rare but can be fatal. The risks are more likely to occur in certain groups, particularly people with a weakened immune system, people without a thymus, and people aged 60 years or older.

Every vaccinee should be advised to seek emergency medical attention if they develop signs or symptoms of viscerotropic disease and neurotropic disease.

Reference:

Drug Safety Update, MHRA, 21 November 2019 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.3, 2019: Risk of fatal adverse reactions in UK)

Fingolimod

Increased risk of congenital malformations

United Kingdom. The MHRA has announced that fingolimod (Gilenya®) is associated with an increased risk of major congenital malformations including cardiac, renal and musculoskeletal defects when used during pregnancy.

Fingolimod is indicated to treat highly active relapsing-remitting multiple sclerosis in patients aged 10 years and older.

A recent EU review concluded that fingolimod exposure in pregnancy is associated with a two-fold increase in the risk of congenital malformations compared with the observed rate of 2 to 3% in the general population.

Fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before starting fingolimod, women of childbearing potential must be informed of the risk of teratogenicity and have a negative pregnancy test. If a woman on fingolimod becomes pregnant, fingolimod should be stopped immediately and a referral to an obstetrician for close monitoring during pregnancy and an ultrasound should be made.

Highly active disease has been reported in a small number of patients for up to six months after discontinuing fingolimod. Physicians should monitor patients discontinuing fingolimod for any return of disease activity.

Reference:

Drug Safety Update, MHRA, 19 September 2019
(www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.5, 2019: Risk of congenital malformations in EU)

Montelukast

Risk of neuropsychiatric reactions

United Kingdom. The MHRA has announced that prescribers should be alert for neuropsychiatric reactions in patients taking montelukast (Singulair®), and careful consideration of the benefits and risks of continuing treatment should be taken if these reactions occur.

Montelukast is an oral leukotriene receptor antagonist and is indicated to treat asthma and symptomatic relief of seasonal allergic rhinitis.

A recent EU review confirmed the known risks of neuropsychiatric reactions and found that the magnitude of risk was unchanged. However, the review identified some cases in which there had been a delay in neuropsychiatric reactions being recognised as a possible adverse drug reaction.

A range of neuropsychiatric reactions has been reported in association with montelukast, including sleep disturbances, depression, agitation, disturbances of attention or memory, and very rarely, hallucinations and suicidal behaviour.

In the UK, MHRA received 219 reports of suspected adverse neuropsychiatric reactions such as nightmares, night terrors, depression, insomnia, aggression, anxiety and abnormal behaviour, to the Yellow Card Scheme between 2014 and 2018.

Reference:

Drug Safety Update, MHRA, 19 September 2019
(www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.3, 2013: Neuropsychiatric risks in Australia)

Nivolumab

Risk of colitis

United Kingdom. The MHRA has announced that patients on nivolumab (Opdivo®) who present with colitis, and those who do not respond to steroid treatment for immune-related colitis, should be investigated to exclude other causes such as cytomegalovirus (CMV) infections.

Nivolumab is an immune checkpoint inhibitor used in the treatment of various cancers. It is indicated as monotherapy or in combination with ipilimumab (Yervoy®), which has also been associated with CMV gastrointestinal infection or reactivation.

An European review identified 20 serious cases worldwide suggestive of CMV infection or reactivation with nivolumab monotherapy, and a further eight cases were reported of either CMV infection or CMV hepatitis associated with nivolumab and ipilimumab combination therapy. Of a total of 28 serious cases, 18 were suspected to be gastrointestinal CMV infection (10 cases for nivolumab and eight cases for nivolumab plus ipilimumab).

Health-care professionals should advise patients to contact them immediately at the onset of symptoms of colitis including diarrhoea, blood in stools or abdominal pain. If patients on nivolumab present with colitis, possible causes should be investigated, including infections.

Reference:

Drug Safety Update, MHRA, 18 October 2019
(www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.4, 2019: Risk of enteritis in Japan)

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 21 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 24). 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.

Levonorgestrel-releasing intrauterine device and panic attacks: a signal raised in patient reporting

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Summary

As of November 2018, more than 600 reports in VigiBase, the WHO global database of individual case safety reports, describe a relationship between a levonorgestrel-releasing intrauterine device (LNG-IUD) and panic attacks. These reports were highlighted during a signal detection screening focusing on patient reports. In many cases, the reporter presented evidence of the significant impact on quality of life for many women during LNG-IUD use. Panic attacks may occur as a symptom in various somatic and psychiatric illnesses, but also occur in individuals without a comorbidity, as described in many of these cases. In 98% of the cases LNG-IUD was the only suspected drug and 62% of these were considered as serious. The LNG-IUD was removed in 46% of the cases. In 51% of these cases, the patient improved upon removal and two cases reported a recurrence after the second or fourth insertion. The summary of product characteristics and patient information leaflets for LNG-IUD mention, among other adverse drug reactions, depressed mood/depression – but not panic attacks. We strongly believe that the collected information in these spontaneous reports support the relationship between LNG-IUDs and panic attacks. Prescribers and patients need to be aware that panic attacks, while on an LNG-IUD, could be related to the medication and could require discontinuation of the LNG-IUD in some cases.

Introduction

Levonorgestrel is a hormonal contraceptive progestin drug used in gynaecology for different indications. It can be used as a single substance or as the progestogen component in oral contraceptives and hormonal replacement therapy.^{1,2} Levonorgestrel as single substance is the active ingredient in emergency birth control pills, intrauterine devices, and birth control implants.

This assessment focusses on the reports in VigiBase, the WHO global database of individual case safety reports (ICSRs), for levonorgestrel (LNG)-releasing intrauterine devices (IUD), hereafter referred to as LNG-IUD. LNG-IUD are used by fertile women to prevent pregnancy, to reduce bleeding in idiopathic menorrhagia, and in combination with oestrogens for hormonal replacement therapy.^{1, 2}

LNG-IUDs emit a low and constant hormonal dose released directly into the uterus and its endometrium. LNG-IUDs are marketed around the world and available in several strengths (52 mg, 19.5 mg and 13.5 mg levonorgestrel).^{1, 2}

The contraceptive effect of LNG-IUDs is achieved through changes in cervical mucus inhibiting the passage of sperm, suppressed proliferation of the endometrium, and, in some women, suppression of ovulation.¹⁻³

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a panic attack is a discrete period of intense fear or discomfort, often accompanied by physical symptoms such as palpitations and trembling. Experiencing repeated, consistent panic attacks that hinder everyday activity is defined as a symptom of panic disorder.⁴

Panic attacks may occur in a variety of somatic and psychiatric illnesses, particularly depression, but also in individuals without other morbidity. Panic disorder may present significant obstacles in everyday life.^{5, 6}

Reports in Vigibase

As of November 2018, there were 602 reports for the MedDRA preferred term 'panic attack' associated with LNG-IUDs in Vigibase. There were an additional nine reports that were excluded as they concerned levonorgestrel in the form of an emergency contraceptive pill. The reports were from the United States of America, Germany, France, Canada, Netherlands, Switzerland, Sweden, Belgium, Norway, Croatia, Slovenia, the Czech Republic, Portugal, Lithuania, Australia, Ireland, Cyprus, Slovenia, Malta, Luxembourg, Hungary and Ireland.

Sixty-two percent of the cases were considered as serious. Two cases were fatal due to the patient committing suicide, and in one case the patient died after a cardiac arrest. In 31% of the cases there was no indication for the treatment reported. In total, 69% of the reports included a specific indication for treatment. Among these, the indication was contraception in 89% of the cases, in 7% of the cases it was used to reduce bleeding and in 4% it was used for various indications such as endometriosis, oestrogen replacement therapy, etc. The patients were aged between 17 and 60 (median 33 years) for the reports that included this information. Other psychiatric terms were co-reported, such as depression (246 cases), anxiety (303), mood swings (80), depressed mood (54), suicidal ideation (42). Six percent of the cases lacked reporter qualification information. Of the 94% of the reports that did include this, 80% were from patients, 12% from physicians and 8% from pharmacists, other health care professionals and a lawyer.

Based on the overall reporting of adverse drug reactions (ADRs) for levonorgestrel and the ICSRs including panic attack in Vigibase, the association has been highlighted as significantly disproportionately reported, by IC analysis, since 2009.⁷ On 8 March 2019, the observed number of reports was 633 compared to the expected 204 (IC025: 1.51).

The median time to onset was five months, for the reports that included this information. In 46% of the 602 cases the drug was withdrawn. In 51% of these cases, the patient improved upon removal,

and two cases reported a recurrence after the second or fourth insertion. In 98% of the reports levonorgestrel was the only suspected drug; in the remaining 2%, other drugs were also reported as co-suspected in causing the reaction. In one of these cases the co-suspected drug was levetiracetam, used to treat generalised tonic-clonic seizure, and this drug does have panic attack listed in the product information.⁸ In another case, venlafaxine was the co-suspected drug, but it was used to treat the panic attacks. In other cases, the co-suspected drugs were cyproterone/ethinylestradiol, etonogestrel, ethinylestradiol/etonogestrel, drospirenone/ethinylestradiol, ethinylestradiol/levonorgestrel, lamotrigine, sumatriptan, prednisone, ciprofloxacin, levofloxacin, and moxifloxacin. None of these have panic attack listed as an ADR in the EU product information.⁹⁻¹⁹ In 16% of 602 cases concomitant medication was also reported and those most frequently mentioned were levothyroxine (12 cases), sertraline (9 cases), and ibuprofen (8 cases). It is possible that some concomitant or bystander drugs may have contributed to the event.

In one of the reports with rechallenge, a woman of 34 experienced aggression, anhedonia, depression and panic attacks about two months after having the LNG-IUD inserted. At first, they are cyclical, peaking in the luteal phase of my cycle, but as the intensity increases, they affect me more of the time. From 6-7 months after having the coil inserted, they are very debilitating and affect my ability to work, socialise, and conduct relationships. From 9 months onwards, it becomes unbearable. I have used the Mirena coil [LNG-IUD] 4 times (each time for endometriosis) and have experienced the same pattern each time. Each time, I need to have it reinserted after a break, to control my endometriosis. Other interventions didn't work.

Some cases noted that women with a history of panic attacks and other disorders experienced a recurrence or exacerbation after insertion of LNG-IUD. In one case the reporter herself describes that she experienced a panic attack seven years prior when using an oral contraceptive, Cerazette (desogestrel). Twelve days after the insertion of the LNG-IUD she experienced severe panic attacks, along with difficulty breathing. The symptoms ended after discontinuation of the treatment. She had told her gynaecologist about the side effects. He was surprised and said that the patient was the first in 20 years to have these side effects. The device was removed at the patient's request and she has been feeling better since.

Several reports describe a positive dechallenge, where the panic attacks stopped after the LNG-IUD was removed.

- A woman of 22 with no past medical history or prescription drug use experienced depressed mood, panic attacks, nervousness and palpitations following administration of LNG-IUD for contraception. Time to onset was three

weeks. She mentioned that “*the symptoms appeared gradually and those were treated with a few visits to a psychologist, without effect*” After the LNG-IUD was removed the patient recovered within two and a half months.

- A 38-year-old woman reported that, a week after insertion, she started to experience states of restlessness/agitation, which worsened and intensified to states of anxiety and panic attacks. Since she was not taking any other medication and did not experience any other stressful circumstances, she “knew” that her state must have been caused by the IUD. She removed the IUD and had recovered within a month.

The following examples illustrates the severe impact on quality of life for many of the women affected.

- A 23-year-old woman explains that she has suffered from crippling anxiety and depression and has had numerous panic attacks since having the LNG-IUD fitted. *It has affected my personal and academic life, and as a fourth-year student this has been an already stressful time and has been made worse from the anxiety and depression I have been feeling. I was not warned, neither was it stated in the pamphlet that was given to me after insertion, nor was it stated in the video I was asked to watch before considering the LNG-IUD.*
- A woman of 37 experienced panic attacks and other psychiatric disorders around one month after the insertion of an LNG-IUD. When the attending gynecologist told her that the events were not associated with her LNG-IUD use, the patient trusted that. Consequently, for more than one year the patient underwent psychiatric treatment for her condition. After LNG-IUD was removed the patient “*feels better every day*”. The patient stated that her marriage had almost failed. The antidepressant drugs were no longer needed and were discontinued.
- Another compelling case concerns a woman of 29, with depressed mood, anxiety and panic attacks following insertion of LNG-IUD with a latency of two weeks. The LNG-IUD was withdrawn after two years and the patient recovered within two weeks. The reporter mentioned that the symptoms had been diagnosed as ‘burn-out’. Due to her condition, the patient was unable to work for two years, but after removal of the LNG-IUD she fully recovered and was able to work again.

Literature and labelling

The Summary of Product Characteristics (SmPC) and Patient Information Leaflet for LNG-IUD from the EU include psychiatric disorders; depressed mood/depression and nervousness, and the one from the USA include depression/depressed mood, as acknowledged side effects, but do not mention

panic attacks. Other systemic side effects include acne, hirsutism, chloasma, migraine, etc.^{1, 2}

A signal was published in the WHO Pharmaceuticals Newsletter describing severe psychiatric disorders such as panic attacks, suicidal ideation and self-injurious behaviour with desogestrel, a hormonal contraceptive in the same therapeutic group as levonorgestrel.²⁰ This signal cites two documented cases retrieved from PubMed where a levonorgestrel sub-dermal implant system was associated with depression and panic disorders.²¹

Between January 2017 and October 2017, the European Pharmacovigilance Risk Assessment Committee (PRAC) made an extensive review of data provided by Market Authorization Holders (MAHs) and data from studies performed by EMA regarding LNG-IUDs and panic attacks, anxiety, sleep disorder and restlessness. The decision by PRAC was to not include the association of LNG-IUDs and panic attack and the previous mentioned psychiatric disorders in the label as the evidence was not considered to be strong enough yet, but they encouraged the MAHs to continue to monitor these events.²²

Discussion and Conclusion

Panic attack is not listed as an ADR in the EU and US patient information leaflet for LNG-IUD while some other psychiatric events are, such as depressed mood, depression, and nervousness.^{1,2} Even though LNG-IUD has mainly local progestogenic effects in the uterine cavity, this suggests that the substance might cross the blood-brain barrier in small concentrations and hence potentially be able to cause panic attacks. As of November 2018, there were 602 reports in VigiBase from patients and doctors of a suspected causal link between panic attacks and LNG-IUD use. In 98% of these reports LNG-IUD was the only suspect drug and in 51% the reaction subsided when the IUD was removed. Predisposing factors such as depression or a history of panic attacks was present in some cases.

In the literature, no cases of LNG-IUD and panic attacks have been published, but there are two documented cases where an LNG sub-dermal implant system is associated with depression and panic disorders. Furthermore, a signal on desogestrel, another hormonal contraceptive progestin, has been associated with panic attacks and other psychiatric disorders. This suggests that a relationship between LNG-IUDs and panic attacks might be expected. The PRAC has also discussed this combination, but the decision was not to include the ADR in the SmPC at this stage, instead recommending continued monitoring of the combinations. The cases discussed in our assessment originated from 22 countries, including within the EU, the Americas and Australia, and therefore give a broader perspective of the problem.

The reporter in many cases relates a significant impact on quality of life, which many women have had during LNG-IUD use. In one case the patient expressed the stressful situation she experienced as there was nothing in the label or introduction video she saw before choosing to insert the device. In many cases the patients improved upon removal of the LNG-IUD and two cases mentioned recurrence after the second or fourth insertion.

While clinical pre- and post-marketing studies have not been able to firmly establish a causal relation between LNG-IUDs and panic attacks this does not exclude the possibility that individual women in rare cases may be more sensitive or predisposed to the reaction. We believe that the collected information in these spontaneous reports support a relationship between LNG-IUDs and panic attacks and that patients and prescribers may need to be made aware of the association.

References

- Electronic Medicine compendium: Summary of Product Characteristics for Levonorgestrel. Available from <https://www.medicines.org.uk/emc/product/1132/smpc>. Accessed: 04 November 2018.
- US DailyMed: Summary of Product Characteristics for levonorgestrel (Mirena). Available from <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=dcdb6aa2-b3fa-479a-a676-56ea742962fc&audience=consumer>. Accessed 04 November 2018.
- Encyclopedia Britannica. Levonorgestrel Last updated 2014. <https://www.britannica.com/science/levonorgestrel>. Accessed December 14, 2018
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
- The epidemiology of panic disorder and agoraphobia in Europe, R.D. Goodwin, C. Faravellib, S. Rosib, F. Coscib, E. Trugliab, R. de Graaf c, H.U. Wittchen, European Neuropsychopharmacology 15 (2005) 435-443.
- Medscape, Clinical reference for health care professionals: <https://emedicine.medscape.com/article/287913-overview>. Accessed 15 November 2018.
- G Niklas Norén, Johan Hopstadius, Andrew Bate. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. Stat Methods Med Res. 2013 Feb;22(1):57-69.
- Electronic Medicine compendium: Summary of Product Characteristics for levetiracetam. Available from <https://www.medicines.org.uk/emc/product/2883/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Cyproterone/Ethinylestradiol. Available from <https://www.medicines.org.uk/emc/product/1122/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Etonogestrel. Available from <https://www.medicines.org.uk/emc/product/5720/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Ethinylestradiol/Etonogestrel. Available from <https://www.medicines.org.uk/emc/product/6449>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Drospirenone/Ethinylestradiol. Available from <https://www.medicines.org.uk/emc/product/1607/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for ethinylestradiol/levonorgestrel. Available from <https://www.medicines.org.uk/emc/product/1127/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Lamotrigine. Available from <https://www.medicines.org.uk/emc/product/8052/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Sumatriptan. Available from <https://www.medicines.org.uk/emc/product/707/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Prednisone, Available from <https://www.medicines.org.uk/emc/product/5714/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Ciprofloxacin. Available from <https://www.medicines.org.uk/emc/product/7256/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Levofloxacin. Available from <https://www.medicines.org.uk/emc/product/6130/smpc>. Accessed: 14 January 2019.
- Electronic Medicine compendium: Summary of Product Characteristics for Moxifloxacin. Available from <https://www.medicines.org.uk/emc/product/3273/smpc>. Accessed: 14 January 2019.

20. WHO Pharmaceuticals Newsletter No.5, 2018: World Health Organization; 2018. Desogestrel and severe psychiatric disorders: panic attack, suicidal ideation and self-injurious behaviour.
21. Wagner KD, Berenson AB. J Clin Psychiatry. 1994 Nov;55(11):478-80. Norplant-associated major depression and panic disorder.
22. Pharmacovigilance Risk Assessment Committee (PRAC), 30 November 2017. Levonorgestrel and anxiety, panic attacks, mood changes, sleep disorders and restlessness
https://www.ema.europa.eu/documents/minutes/minutes-prac-meeting-23-26-october-2017_en.pdf.

Response from Bayer

Hormonal fluctuations during the natural cycle, as well as progestins used for hormonal contraception, can exert effects on mood especially in vulnerable women [1]. LNG-IUDs release low amounts of levonorgestrel into the uterine cavity which then reach the blood circulation [2]. In women sensitive to levonorgestrel side effects, this can lead to e.g. mood disturbance. Based on the finding that mood changes in terms of depression/depressive mood were more often observed in study subjects using LNG-IUDs compared to (non-hormonal) comparators, "Depressed mood/depression" is included in the undesirable effects section of the product information of Bayer's LNG-IUDs. These side effects of levonorgestrel are expected to occur soon after insertion of an LNG-IUD. Likewise, they are expected to resolve after removal of LNG-IUD.

Acknowledging that effects on mood are described in the LNG-IUD labels, the signal investigation performed by the PRAC in 2017 concluded that "the available evidence does not support an association between the use of levonorgestrel-releasing intrauterine systems with isolated anxiety disorder, panic disorder, sleep disorder or restlessness". This conclusion was based on a thorough review of data provided by the MAHs and studies performed by EMA. EMA had conducted a study in The Health Improvement Network (THIN) database (large UK primary care electronic medical records database), comparing women using LNG-IUDs with those using copper IUDs [3], and a comparative analysis between LNG-IUD users and users of implantable etonogestrel in the European Union Drug Regulating Authorities Pharmacovigilance (EudraVigilance) database. Within their respective limitations owing to their data source and observational studies in general, neither of these studies showed an association between LNG-IUD and panic attacks.

In accordance with the PRAC conclusion, Bayer continues to monitor events of panic attacks as part of routine safety surveillance. In addition, as agreed with PRAC, neuropsychiatric disorders (including panic attacks) have been added as secondary outcomes in Bayer's large post-authorization safety study including users of different IUDs (LNG-IUDs and copper IUD) that is currently running in ten European countries [4]. Bayer is consistently

updating the regulatory authorities around the world as new data become available regarding LNG-IUDs, and has worked with the agencies to make label updates when appropriate.

The PRAC review comprised the case reports from global sources in the safety databases of the MAHs and regulatory authorities and therefore likely included the cases reported to VigiBase until 2017. In this procedure Bayer provided a cumulative review of available data including a detailed analysis of the single cases recorded in the Bayer Pharmacovigilance safety database, a review of the clinical trial data and a review of information available from published literature regarding psychiatric reactions and LNG-IUD.

At the time of the analysis performed in 2017, more than 500 reports mentioning, among other events, panic attacks in Mirena users had been received by Bayer globally. The EMA/PRAC signal investigation was associated with considerable media attention, resulting in stimulated reporting of psychiatric (perceived and actual) side effects in women using LNG-IUDs. Consequently, after analysis in 2017 until end of 2018, Bayer has additionally received 280 reports mentioning panic attacks in Mirena users.

The absolute number of case reports received for a product needs to be put into relation to the product's market exposure. For Mirena, the total cumulative post-marketing experience since launch in 1990 until end of 2018 is estimated to be over 166 million woman-years. With 795 cases received for Mirena since launch, the cumulative reporting rate for panic attacks for Mirena is low with 0.5 per 100,000 woman-years of exposure. Due to stimulated reporting, the reporting rate is not constant over time: It was 0.6 per 100,000 woman-years in the two years before the PRAC signal investigation (2015-2016), and 0.9 per 100,000 in 2017-2018.

The characteristics of the case reports of panic attacks in LNG-IUD users have not changed since the signal investigation performed in 2017. An investigation of the newly registered case reports in Bayer's safety database confirms the previous results and shows a pattern similar to the cases investigated by the UMC. The vast majority of

reports are not-medically confirmed consumer reports. Evaluation of cases mentioning panic attack is frequently hampered by the limited information provided. The diagnostic accuracy is unclear in many cases and there is a high overlap with symptoms referring to depression/depressed mood. Often, the described events reportedly affected general well-being. The majority of the events classified as serious, however, do not meet unequivocal seriousness criteria (such as hospitalization); additionally, in almost half of the serious cases the seriousness was determined by other co-reported events, and the event "panic attack" was non-serious. The described changes of the patient's mental and/or emotional state are often difficult to interpret and due to their unspecific nature, a conclusive medical assessment of a causal association is frequently not possible. Many reports describe mood changes that are part of the spectrum of "Depression/Depressed mood", reactions which (as pointed out by the PRAC) are already reflected in the product information of Bayer's LNG-IUDs.

Interpretation of disproportionate reporting of panic attacks for LNG-IUD needs to take into account that the user population of LNG-IUD (women of fertile age) is at higher risk of developing of panic attacks (compared to men or the elderly population [5]). Additionally, the aforementioned stimulated reporting triggered by the signal investigation on psychiatric side effects of LNG-IUD has led to a further increase of reports of panic attacks in LNG-IUD users, likely contributing to the disproportionality observed in the WHO VigiBase.

The choice of a LNG-IUD is made on an individual benefit/risk assessment after careful discussion between a woman and her health care professional. The effectiveness of LNG-IUD in preventing

pregnancy as well as other positive effects must be considered when weighing the benefits against possible adverse effects. In the context of general contraceptive counseling, health care professionals should consider pre-existing psychological symptoms or any history of sensitivity to levonorgestrel. An LNG-IUD should only be prescribed after a full discussion and an evaluation of all contraceptive options has been made.

References

1. Merki-Feld, G.S., et al., *ESC expert statement on the effects on mood of the natural cycle and progestin-only contraceptives*. Eur J Contracept Reprod Health Care, 2017: p. 1-3.
2. Reinecke, I., et al., *An Integrated Population Pharmacokinetic Analysis to Characterize Levonorgestrel Pharmacokinetics After Different Administration Routes*. J Clin Pharmacol, 2018. 58(12): p. 1639-1654.
3. Slattery, J., et al., *Cohort Study of Psychiatric Adverse Events Following Exposure to Levonorgestrel-Containing Intrauterine Devices in UK General Practice*. Drug Saf, 2018. 41(10): p. 951-958.
4. *European Network of Centers for Pharmacoepidemiology and Pharmacovigilance*. <http://www.encepp.eu/encepp/viewResource.htm?id=27388>. Last accessed 09 April 2019.
5. APA, American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-V)*. Arlington, VA, American Psychiatric Association 2013. Chapter Anxiety Disorders page 189-233. 2013.

Nintedanib and ischaemic colitis

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Summary

Nintedanib is a small molecule protein kinase inhibitor approved for the treatment of idiopathic pulmonary fibrosis, a rare and progressive disease with a median survival of only several years after diagnosis. Statistical screening of VigiBase, the WHO global database of individual case safety reports, identified disproportional reporting of the MedDRA Preferred Term (PT) "colitis" with nintedanib. Review of published literature and further exploration allowed for refinement of the signal from the non-specific term of "colitis" to the more specific clinical scenario of ischaemic colitis. A number of Bradford Hill criteria, including strength of association, specificity, consistency, analogy and plausibility, are discussed to support the hypothesis of a causal relationship between nintedanib and ischaemic colitis. Communication of this signal is considered warranted, as early identification of ischaemia may prevent progression to the serious, life-threatening event of gastrointestinal perforation. Given that the most commonly occurring gastrointestinal adverse reaction for nintedanib is diarrhoea, which can be a symptom of ischaemic colitis, it could be important to inform health care providers to rule out ischaemia prior to the recommended symptomatic treatment of diarrhoea with loperamide.

Introduction

The drug

Nintedanib is a small molecule receptor tyrosine kinase inhibitor (TKI) blocking vascular endothelial growth factor receptors (VEGFR 1-3), fibroblast growth factor receptors (FGFR 1-3) and platelet-derived growth factor receptors (PDGFR) α and β kinase activity. In pre-clinical studies, nintedanib was found to inhibit the proliferation and transformation of human lung fibroblasts and showed antifibrotic and anti-inflammatory activity in two animal models of pulmonary fibrosis.¹

Idiopathic pulmonary fibrosis (IPF) is a rare disease of unknown aetiology that is characterized by an excess of fibroblasts, leading to fibrosis of the interstitium of the lung. The fibrosis is a progressive process, leading to decreased lung volume and ultimately, respiratory failure. Median survival, as described across a range of studies, is only two to five years after diagnosis. IPF is an uncommon disease with a prevalence of 3 per 10,000, and it is most prevalent in middle-aged and elderly patients.¹

Nintedanib was licensed for use in the treatment of IPF by both the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) in 2014. In two pivotal clinical trials,

benefit with nintedanib was measured by a reduction in the decline of a measure of lung function, the forced vital capacity (FVC), by approximately 94 mL/year and 125 mL/year respectively. It has also been licensed by the EMA for use in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.¹ Additionally, given its anti-angiogenic effects as a VEGFR-inhibitor, it is being tested in clinical trials for other oncology indications.

Ischaemic colitis

Ischaemic colitis is a condition caused by insufficient blood flow to the large intestine which results in mucosal ulceration, inflammation and haemorrhage. Causes can be either physiological (hypotension, secondary to embolus/thrombosis) or iatrogenic (secondary to medicines, surgery). Ischaemic colitis clinically manifests with diarrhoea, colicky abdominal pain, and rectal bleeding. It can be difficult for clinicians to differentiate ischaemic colitis from infective and inflammatory colitis. With its high mortality rate, patients with ischaemic colitis should be recognised quickly, as colonoscopic evaluation is recommended within 48 hours of symptom onset. Colonoscopy can distinguish those cases that may be treated with conservative management from those that require emergency resection. The complications which can arise from ischaemic colitis include obstruction, necrosis, and perforation.²

Reports in VigiBase

The drug-ADR combination of nintedanib-colitis was identified as a statistical signal during a screening of VigiBase, the WHO global database of individual case safety reports, performed in December 2018. The original case series included 25 cases which, upon review, described either different specific types of colitis, such as ischaemic or inflammatory, or were unspecified. Given that nintedanib acts upon the VEGF-receptor, a decision was taken to explore the association between nintedanib and the more specific clinical concept of "ischaemic colitis".

One case with the original MedDRA Preferred Term (PT) "colitis" was considered to have information sufficient to be considered as "ischaemic colitis" (colonoscopy results were provided). Subsequent exploration within VigiBase used the MedDRA Standardised Medical Query (SMQ), "ischaemic colitis (narrow)". Nine additional cases were identified through this search strategy. The final case series consists of 10 cases: five reporting

colitis ischaemic, two reporting intestinal ischaemia, one with both colitis ischemic and intestinal ischaemia, one intestinal infarction and one colitis.

Table 1. Disproportionality analysis (VigiBase data up to 5 May 2019)

Substance	Reaction	N _{observed}	N _{expected}	IC	IC ₀₂₅
Nintedanib	Colitis (PT)	30	9.23	1.65	1.09
Nintedanib	Ischaemic colitis SMQ (narrow)			1.77	1.14
	Colitis ischaemic (PT)	6	1.56	1.65	0.28
	Intestinal ischaemia (PT)	3	1.10	1.13	-0.92
	Intestinal infarction (PT)	1	0.21	1.07	-2.72

Illustrative case report

A 56-year-old female with a medical history of bronchial carcinoma and hypothyroidism. Therapy for bronchial carcinoma was initiated with nintedanib at 400 mg per day, and the patient was treated for 20 days. Twenty-five days after initiation of nintedanib, the patient experienced intestinal ischemia and gastrointestinal necrosis. She underwent surgical resection of the descending portion of the large intestine. Pathology revealed: "from the colon descendens, sigmoideum and upper rectum with intense and distinct ischemic necrosis of gut wall, inclusion of max. 2.3 cm polyp, without evidence of vital mucosa. Beside a 0.9 cm tubular adenoma with slight intraepithelial neoplasia (low-grade adenoma following WHO-classification)". Transmural hemorrhagic necrosis (reaching out up to the resection area) of gut wall without inflammation, as appropriate for ischemia. Tumour-free resection of vessels and gut sections. The patient was subsequently initiated on docetaxel about one month after the event of gastrointestinal ischaemia.

Case series

Of the 10 reports in the case series, there was a predominance of males: seven reports compared to reports for females (table 2). Ages ranged between 53 and 78; age was not given in one report. Reports originated from five countries (one country in the Americas, three in Europe, one in Asia). Time to onset ranged from three days to five months. In seven cases, the indication for use of nintedanib was idiopathic pulmonary fibrosis; in the three other cases, non-small cell lung cancer, bronchial carcinoma and glioblastoma. Diagnostic results were given in three cases (6, 8, and 10). Fatal outcomes were reported in four cases. Very limited information regarding the individual cases was available for most cases given that narratives had not been entered into VigiBase. Potential confounding factors/risk factors for ischaemic colitis was advanced age for many of the cases, concomitant use of corticosteroids in two cases (1

and 5) and the medical history of hyperlipidaemia in two cases (2 and 5).

Labelling and literature

Product labelling for nintedanib includes warnings for diarrhoea and gastrointestinal perforation in section 4.4 of the Summary of Product Characteristics. There is also information regarding management options for serious cases of diarrhoea including hydration, anti-diarrhoeal products, and dose reduction and information regarding potential risk factors for gastrointestinal perforation, such as previous abdominal surgery or peptic ulceration, and diverticular disease and concomitant use of corticosteroids or NSAIDs. Included in the list of ADRs in section 4.8 are nausea, vomiting, diarrhoea, abdominal pain and pancreatitis.³

Within the risk management plan were the identified risks of diarrhoea and liver function abnormalities as important identified risks and "perforation" as an important potential risk; there were no planned post-authorisation safety studies to further characterise any risks for the gastrointestinal system.⁴

Discussion

The aim of this signal assessment is to argue for a potential causal relationship between nintedanib and ischaemic colitis. Five of the Bradford Hill criteria can be used to support this causal hypothesis, including strength of association, specificity, consistency, biological plausibility, and analogy.⁵

The strength of association has been explored with various approaches to analysing disproportionality in VigiBase. The initial drug-ADR combination identified by statistical screening of the database using the vigiRank algorithm for combination prioritisation was nintedanib-colitis. Colitis, being a general term meaning "inflammation of the colon", provides no specificity as to the cause of the pathology. Within the MedDRA hierarchy, the PT colitis is located within an HLT colitis (excluding

infectious); other PTs included within this HLT reflect the diversity of etiology of colitis: examples include autoimmune colitis, colitis ulcerative, necrotizing colitis, colitis ischaemic, colitis microscopic. Within this HLT, only two PTs were noted to exhibit significant disproportionality, colitis (IC₀₂₅ 0.89) and colitis ischaemic (IC₀₂₅ 0.32). To explore the potential to improve the specificity of the association, a subsequent search was performed utilising the SMQ ischaemic colitis (narrow); disproportionality analysis at this drug-SMQ level revealed an IC₀₂₅ 1.14. PTs included within this SMQ exhibiting increased disproportionality (observed > expected, although not all significantly enough to result in IC₀₂₅ > 0) were large intestine perforation (IC₀₂₅ 1.48), large intestinal haemorrhage (IC₀₂₅ -0.34), colitis ischemic (IC₀₂₅ 0.28), intestinal ischaemia (IC₀₂₅ -0.92), gastrointestinal necrosis (IC₀₂₅ -1.50), and intestinal infarction (IC₀₂₅ -2.72). The clinical concepts of perforation and haemorrhage are already included as warnings in the product labelling.

Consistency of the association is exhibited in the case series in the description of the clinical scenario of ischemic colitis, albeit being coded to various MedDRA PTs, from several countries throughout the world.

The biologic plausibility of an association between nintedanib and ischaemic colitis is based upon its inhibitory action of the VEGF-receptor. VEGF is a protein which mediates multiple functions within the vascular system, including endothelial cell proliferation as well as vascular permeability and vasodilation.⁶ A mouse model has shown that inhibition of VEGF signalling resulted in regression of capillaries of intestinal villi⁷ and it has been hypothesized that VEGF inhibition contributes directly to GI perforation by inducing regression of normal blood vessels in the GI tract⁸ (presumably via an intermediate step of ischaemia). Furthermore, VEGF mediates release of nitric oxide, and its inhibition causes vasoconstriction⁶; indeed, hypertension is a well-characterised ADR for all anti-VEGF agents. Additionally, the labelling for anti-VEGF agents include a warning for arterial thromboembolism; the label for nintedanib specifically cautions for acute myocardial ischaemia in the treatment in patients at higher cardiovascular risk including known coronary artery disease.³

Given its inhibitory effect on the VEGF receptor, the ADR profile for nintedanib can be considered analogous to other anti-angiogenic agents which antagonise VEGF (aflibercept, bevacizumab) or inhibit the VEGF-receptor (regorafenib, sorafenib). Indeed, the labels for all products contained harmonised wording regarding the risk of gastrointestinal perforation, and all also lack the inclusion of ischaemic colitis. However, literature review reveals case reports of ischaemic colitis with other VEGF-receptor antagonists, specifically, aflibercept (intravitreal administration)⁹ and bevacizumab,¹⁰ both of which were administered

intravitreally. Data mining within VigiBase reveals evidence of disproportional reporting of MedDRA PT within the "ischaemic colitis" SMQ for a number of other anti-angiogenic agents (bevacizumab: intestinal ischaemia IC₀₂₅ 2.23; colitis ischaemic IC₀₂₅ 2.24; aflibercept: colitis ischaemic IC₀₂₅ 0.62; midostaurin: intestinal ischaemia IC₀₂₅ 0.38; ranibizumab: intestinal ischaemia IC₀₂₅ 0.36; sunitinib: intestinal ischaemia IC₀₂₅ 0.22; sorafenib: colitis ischaemia IC₀₂₅ 0.18).

Given that both diarrhoea and gastrointestinal perforation are included in the label, it is relevant to consider the possibility that gastrointestinal ischaemia is the underlying pathology for each of these "known" ADRs. Small perturbations of blood flow by VEGF inhibition can lead to rapid metabolic changes in the intestinal mucosa characteristic of hypoxia and ischaemia.¹¹ Epithelial hypoxia is clinically associated with diarrhoea,¹² and changes in the bowel mucosa are consistent with ischaemic colitis.¹³ A small study of 10 patients aimed to examine the underlying pathophysiologic mechanism of diarrhoea. Sigmoidoscopy revealed no evidence of ischaemia in any of the 10 subjects; however, gastroduodenoscopy revealed mucosal abnormalities in 8 patients.¹⁴ There is better knowledge on the role of ischaemia in gastrointestinal perforation, as perforation is a known complication of gastrointestinal ischaemia. However, the labelling currently describes other risk factors for perforation such as concomitant corticosteroid use and prior history of abdominal surgery without mention of gastrointestinal ischaemia.

Taking all of the presented evidence together, it is considered that there is a reasonable possibility that nintedanib can cause ischaemic colitis.

Conclusions

Screening of VigiBase has identified a signal of disproportional reporting of colitis with nintedanib, a small molecule tyrosine-kinase inhibitor. Given that nintedanib blocks VEGF receptors, the initial signal was further explored in VigiBase and refined to the more specific clinical phenomenon of "ischaemic colitis". The case series supporting this signal consists of 10 cases, captured under several MedDRA PTs including "colitis", "colitis ischaemic", "intestinal ischaemia" and "intestinal infarction". Assessment of the signal demonstrated the data support of the Bradford Hill criteria has resulted in a conclusion of a reasonable possibility of a causal relationship between nintedanib and ischaemic colitis.

It appears prudent to consider the addition of ischaemic colitis to the product labelling for nintedanib. Furthermore, given that the most commonly occurring gastrointestinal adverse reaction is diarrhoea, which can be a symptom of ischaemic colitis, it could be important to inform health care providers to rule out ischaemia prior to

the recommended symptomatic treatment of diarrhoea with loperamide.

References

1. European Medicines Agency. Assessment report Ofev Procedure No. EMEA/H/C/003821/0000. London: European Medicines Agency; 2015. Available from: https://www.ema.europa.eu/en/documents/assessment-report/ofev-epar-public-assessment-report_en.pdf. Accessed March 2019
2. Trotter JM, Hunt L, Peter MB. Ischaemic colitis. *BMJ* 2016;355:i6600
3. European Medicines Agency. Ofev: EPAR Product information. Available from: https://www.ema.europa.eu/en/documents/product-information/ofev-epar-product-information_en.pdf. Accessed March 2019.
4. European Medicines Agency. Ofev: EPAR Risk management plan summary. Available from: https://www.ema.europa.eu/en/documents/rmp-summary/ofev-epar-risk-management-plan-summary_en.pdf. Accessed March 2019.
5. Perrio M, Voss S, Shakir SA. Application of the Bradford Hill Criteria to Assess the Causality Cisapride-Induced Arrhythmia. *Drug Safety*. 2007;30(4):333-46.
6. Ellis LM, Hicklin DL. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nature Reviews Cancer*. 2008;8:579-91.
7. Kamba T, Tam BY, Hashizume H, et al. VEGF-dependent plasticity of fenestrated capillaries

in the normal adult microvasculature. *Am J Physiol*. 2006;290(2):H560-H5766.

8. Saif MW, Elfiky A, Salem RR. Gastrointestinal perforation due to bevacizumab in colorectal cancer. *Ann Surg Oncol*. 2007;14:1860-9.
9. Batteux B, Gras V, Mahboud Y, Liabeuf S, Bennis Y, Masmoudi K. Ischemic colitis associated with intravitreal administration of aflibercept: a first case report. *Br J Clin Pharmacol*. 2019 April;85(4):845-8.
10. Onoda Y, Shiba T, Hori Y, Maeno T, Takahashi M. Two cases of acute abdomen after an intravitreal injection of bevacizumab. *Case Rep Ophthalmol*. 2015;6(1):110-4.
11. Zheng W, Kuhlicke J, Jackel K. Hypoxia inducible factor-1 (HIF-1)-mediated repression of cystic fibrosis transmembrane conductance regulator (CFTR) in the intestinal epithelium. *FASEB J*. 2009;23:204-13.
12. Sreenarasimhaiah J. Diagnosis and management of ischemic colitis. *Curr Gastroenterol Rep*. 2005;7:421-6.
13. Lordick F, Geinitz H, Theisen J, Sendler A, Sarbia M. Increased risk of ischemic bowel complications during treatment with bevacizumab after pelvic irradiation: report of three cases. *Int J Radiat Oncol Biol Phys*. 2006;64:1295-8.
14. Boers-Sonderen M, Mulder S, Nagtegaal ID, Derikx L, Wanten G, Mulders P, et al. A biopsy-guided analysis of diarrhea in patients treated with tyrosine kinase inhibitors of the vascular endothelial growth factor receptor. *Journal of Clinical Oncology*. 2015;33(15) Suppl:e15596.

Table 2. Cases identified as representing the clinical scenario of "ischaemic colitis". The cases within this table have been identified from VigiBase review of number MedDRA PTs, including colitis ischaemic, intestinal ischaemia, intestinal infarction, and the originally signalled PT, colitis.

Case	Age/Sex	Drugs	Indication	ADR	Dosage	TTO	Outcome	Notes
1	78y/M	Nintedanib (S) Prednisolone (S) Acetylcysteine (C) Dimemorfan (C) Drug not accepted in WHODrug (C)	Idiopathic pulmonary fibrosis	Ischaemic enterocolitis	300 mg qd x 2 months, followed by 200 mg qd (duration unknown)	15 days	Recovered	55 kg, 159 cm Report from study
2	74y/M	Nintedanib (S) Vonoprazan (C) Irbesartan; Trichlormethiazide (C) Atorvastatin (C) Acetylsalicylic acid (C)	Idiopathic pulmonary fibrosis	Colitis ischaemic Pneumonia bacterial	300 mg qd x 11 months 200 mg x qd x 2 months	3 days	Recovered	62.9 kg, 165 cm Report from study
3	65y/F	Nintedanib (S) Alfacalcidol (C) Levothyroxine (C) Ascorbic acid; pantothenic acid (C)	Idiopathic pulmonary fibrosis	Colitis ischaemic	300 mg qd x 10 months	4 months	Not recovered	50.5 kg, 161 cm Report from study

Case	Age/Sex	Drugs	Indication	ADR	Dosage	TTO	Outcome	Notes
		Minodronic acid (C) Drug not accepted in WHODrug (C)						
4	77y/M	Nintedanib (S) Insulin (C)	Idiopathic pulmonary fibrosis	Colitis ischaemic Abnormal loss of weight Septic shock Decreased appetite Vomiting Nausea Diarrhoea	150 mg 2 per day		Died	
5	77y/F	Nintedanib (S) Tacrolimus (C) Prednisolone (C) Trimethoprim /sulfamethaxazole (C) Warfarin (C) Alfacalcidol (C) Rabeprazole (C) Loperamide (C) Drug not accepted in WHODrug (C) Drug not accepted in WHODrug (C) Drug not accepted in WHODrug (C) Drug not accepted in WHODrug (C)	Idiopathic pulmonary fibrosis	Ischaemic enterocolitis	200 mg qd x 5 months	5 months	Died secondary to ischaemic enterocolitis and lower gastrointestinal perforation	36 kg, 153 cm Report from study. History of hyperlipidemia, osteoporosis, gastroesophageal reflux disease, venous thrombosis, constipation, insomnia, chronic gastritis, breast cancer
6	53y/M	Nintedanib (S)	Glioblastoma	Mesenteric ischaemia Colitis ischaemic Obstipation Stomach pain Thromboembolic event Ischaemia peripheral Wound healing delayed Wound infection	400 mg per day	27 days	Died	185 cm Report from study. Patient presented with abdominal pain 27 days after initiation on nintedanib. Admitted to hospital, diagnosed with ischaemic colitis (grade 2), and treated with mesalazin. Five days later, the patient experienced obstipation. Ten days later, the patient had stomach pain (grade 3), acute mesenteric ischemia (grade 4), thromboembolic event (grade 4), and peripheral ischemia (grade 3). Had thrombectomy of arteria mesenterica superior, explorative laparotomy and small intestinal segment resection. Hospitalisation complicated by wound healing disorder which led to cardiovascular failure, sepsis and death.
7	-/M	Nintedanib (S) Omeprazole (S) Indacaterol (C) Olmesartan (C) Salbutamol (C) Lercanidipine (C)	Fibrosis lung	Bowel ischemia Vein thrombosis mesenteric	2 DF per day		Recovering	
8	56y/F	Nintedanib (S) Docetaxel (S) Zoledronic acid (C) Levothyroxine (C)	Bronchial carcinoma	Intestinal ischaemia Bowel ischaemia Gastrointestinal necrosis Necrosis bowel	400 mg per day	25 days	Unknown	Surgery preparation of colon descendens, sigmoideum and upper rectum with intense and distinct ischemic necrosis of gut wall, inclusion of max. 2.3 cm polyp, without evidence of vital mucosa. Beside a 0.9 cm in sano resected tubular adenoma with slight intraepithelial neoplasia (low-grade adenoma)

Case	Age/Sex	Drugs	Indication	ADR	Dosage	TTO	Outcome	Notes
								following WHO-classification). Transmural hemorrhagic necrosis (reaching out up to the resection area) of gut wall without inflammation, as appropriate for ischemia.
9	74y/M	Nintedanib (S) Lansoprazole (C)	Idiopathic pulmonary fibrosis	Intestinal infarction			Died	69 kg
10	57y/M	Nintedanib (S) Ipratropium (C) Acetylsalicylic acid (C) Glyceryl trinitrate (C) Fluvastatin (C) Torasemide (C) Lometazepam (C) Metamizole (C) Omeprazole (C)	Non-small cell lung cancer	Colitis Diarrhoea Vomiting Nausea Mucositis Anorexia Respiratory failure	400 mg once per day	9 days		Serious. Clinical trial patient. Died, cause of death "respiratory failure" Medical history: Idiopathic cardiomyopathy Bronchial disorder Insomnia Pain Smoker Alcohol abuse Patient experienced diarrhoea and vomiting which required hospitalisation 10 days after initiation of drug. CT scan of abdomen on day of admission with probably stenosis lesion of the sigmoid colon and proximal colonic dilation and loops of small bowel. Colonoscopy 11 days after discontinuation of drug revealed ischemic colitis. Repeat CT 16 days after discontinuation revealed no evidence of obstruction. Investigator considered that there is a causal relationship between the drug and GI symptoms and signs.

Response from Boehringer Ingelheim AB

The opportunity to comment on the signal of 'ischaemic colitis' for nintedanib identified by the Uppsala Monitoring Center (UMC) is acknowledged.

Nintedanib is authorised in 2 indications:

- treatment of Idiopathic Pulmonary Fibrosis (IPF) and to slow disease progression (Ofev)
- treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy (Vargatef)

In the indication IPF, nintedanib is administered as monotherapy (starting dose 150 mg bid). In the indication NSCLC nintedanib is administered in combination with docetaxel (starting dose of 200 mg bid). The dose of nintedanib can be reduced for the management of adverse reactions.

Diarrhoea, vomiting, nausea, abdominal pain, pancreatitis and bleeding are included in the list of ADRs of nintedanib. Diarrhoea and bleeding are

important identified risks. For Vargatef perforation, mucositis and venous thromboembolism (VTE) are also ADRs. Perforation is an important identified risk. Arterial thromboembolism is an important potential risk of nintedanib and perforation and VTE are important potential risks for Ofev. These conditions are regularly monitored.

Stomatitis, diarrhoea, nausea, vomiting, constipation as well as enterocolitis, colitis, ischaemic colitis, and neutropenic enterocolitis are known ADRs of docetaxel.

The signal of 'colitis' has been evaluated for nintedanib with DLP 15 Oct 2018 based on HLT 'colitis, excluding infective'. In the next version of the EU SmPC 'colitis' will be included as ADR of nintedanib.

In order to appropriately address all comments by the UMC, it has been decided to evaluate data from all sources with regard to ischaemic colitis under treatment with nintedanib.

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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42nd Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring

Bogotá, Colombia, 29 October – 1 November 2019

The WHO annual meeting of National Pharmacovigilance Centres (NPCs) is a platform for countries from around the world to meet and discuss pharmacovigilance issues. Each year one Member State participating in the WHO Programme for International Drug Monitoring (PIDM) hosts the meeting. The region in which the host country is placed rotates each year allowing greater accessibility to countries within its proximity. In 2019, the Colombian National Institute of Food and Drug Surveillance (INVIMA) welcomed delegates to Bogotá, Colombia. It has been seven years (2012) since the last National Pharmacovigilance Centres meeting was held in the region of the Americas, in Brazil. More than 150 participants from 65 Member States travelled to attend the meeting, which took place from 29 October to 1 November 2019.

The meeting consisted of an open and closed session. Non-state actors such as the International Society of Pharmacovigilance were invited to attend the open session. The closed session was by invitation only, and only included government nominated representatives.

Pre-meeting training and open session

Prior to the start of the meeting two training sessions (28-29 October) on Pharmacovigilance tools (Vigiflow and Vigilyze) were held by the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre. The open session took place on the afternoon of 29 October 2019 and consisted of pharmacovigilance success stories shared by NPCs from Eritrea, Canada, Norway, Thailand and Zambia.



Closed session

The closed meeting session consisted of plenaries, working groups, and signals of current interest. The choice of topics covered in the 42nd annual meeting stemmed from the requests of Member States made in the 41st annual meeting.

The Honourable Minister of Health and Social Protection in Colombia, Mr Juan Pablo Uribe Restrepo opened the meeting, with a speech highlighting the importance and leadership of INVIMA and the valuable contribution of PV to public health at a national and international level.

Plenary sessions

The plenary sessions started with a report on progress and achievements that WHO and WHO Collaborating Centres have made on the recommendations of the previous Annual Meeting in Geneva, Switzerland 2018.

A variety of other topics were presented during the plenary sessions. These included: Pharmacovigilance and artificial Intelligence, PV of anti-TB and anti-malarial medicines (learnings from Brazil and Peru), the concept of WHO Listed Authorities (WLA), research updates from the Uppsala Monitoring Centre and proposed updates on WHO data accessibility.

Signals of Current interest

This session consisted of short presentations based on abstracts that were submitted prior to the meeting. Participants from Albania, Brazil, Eritrea, Ghana, Iraq, Japan, Morocco, the Netherlands, Pakistan, Uganda, Vietnam, Zambia and Zimbabwe took the opportunity to present PV issues. A variety of subjects were discussed which ranged from examples of medication errors, therapeutic failures, new previously unknown ADRs, and innovative methods.

Working Groups

Four working groups were offered over a period of two days. Prior to the workshop, delegates were provided with a list of objectives and outcomes and had the opportunity to attend two workshops of preference. During each workshop, moderated discussions were held, and attendees formulated and agreed on a list of recommendations that were specifically targeted at WHO, WHO CCs and/or the NPCs. A rapporteur from amongst the workshop participants presented the recommendations to the whole delegation during the plenary session on the last day of the meeting. Working groups consisted of: 1) Making ADR reporting “easy like Sunday morning”; 2) Smart Safety Surveillance: what does this mean, how do we implement it?; 3) Signal detection methodology and application and 4) Using the WHO Global Benchmarking Tool (GBT) for improving National PV Systems. The recommendations from the working groups will be available in the next issue of the WHO Pharmaceuticals Newsletter.

Future meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring

The annual meeting of representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring will now occur every two years. ICDRA will be used as the platform for discussions on pharmacovigilance every other year in lieu of the national centres meeting. The next ICDRA meeting will take place in 2020 in New Delhi, India.

Advanced Pharmacovigilance workshop on Causality assessment, signal detection and benefit risk analysis

Geneva, Switzerland, 27 – 29 November 2019

Many National Pharmacovigilance Centres (NPCs) in LMICs are now progressing from the basic pharmacovigilance of setting up a PV system and building a reporting culture to receiving Individual Case Safety Reports (ICSRs), performing an analysis on data collected and identifying signals. This progression requires specialised skills, and a workshop was organized by WHO to build capacity for analysis, signal detection and benefit harm assessments. The workshop was held in Geneva from 27 to 29 November and four countries were invited to attend: Ethiopia, Kyrgyzstan, Moldova and Ukraine. Facilitators included WHO staff from Headquarters, experts from the Medicines and Healthcare Products Regulatory Agency, MHRA, UK and staff from the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, UMC.

The focus was on priority medicines used to treat high burden diseases in the countries, such as MDR-TB and malaria. An integrated method was used, to include representatives from the National Pharmacovigilance Centres and representatives from TB and malaria programmes.

The workshop was designed to be hands-on, and the participants brought ICSRs from their countries to the workshop. During the course, participants completed causality assessments of their ICSRs, and also carried out a case by case signal or statistical signal detection on these reports. Once potential signals were identified, they were validated and assessed. At the end of the workshop participants formed a ‘mock’ safety committee, to provide their recommendations on the signals that were identified.

The integration of National PV Centres with National Disease Programmes from two different geographic regions and four different countries created an atmosphere of mutual collaboration and demonstrated the importance of sharing expertise, information and knowledge.

Med Safety App: an international mobile tool for drug safety

Kendal Harrison, Nitharna Sivarajah and Alicia Ptaszynska-Neophytou, Medicines and Healthcare products Regulatory Agency, Monica Plöen, Uppsala Monitoring Centre, Noha Iessa and Ayako Fukushima, World Health Organization

The Med Safety App, previously known as the WEB-RADR App, was developed through the Innovative Medicines Initiative (IMI) WEB-Recognising Adverse Drug Reactions (WEB-RADR) project. The WEB-RADR project was launched in September 2014, in response to the Call 9: 'WEBAE - leveraging emerging technology for pharmacovigilance'. Work Packages within the WEB-RADR project initially developed country-specific mobile applications (apps) in the United Kingdom (MHRA), Netherlands (Lareb) and Croatia (Halmed), which allow the reporting of Adverse Drug Reactions (ADRs) by healthcare professionals and members of the public and provide drug safety information to app users. Through collaboration between the WEB-RADR project, the World Health Organisation (WHO), the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC), and the MHRA, a generic version of the app, the Med Safety App, was developed for use in multiple countries. This made it possible for low- and middle-income countries (LMICs), and other non-EU countries within the WHO Programme for International Drug Monitoring, to adopt an individualised version of the Med Safety App (hereafter, the App) in their country ¹.

Before a country introduces the App, the National Pharmacovigilance Centre (NPC) works with WHO and technical partners (MHRA and WHO Collaborating Centre for International Drug Monitoring, UMC) to tailor information such as the logo, colour scheme, drug lists, news and language. Once the App is launched in a country it is free to download from the Google Play Store (Android) and App Store (iOS). Once downloaded, the initial user page provides a list of countries in which the App has been made available. Users should select their country of choice and language, and are then taken to the NPC tailored version of the App.

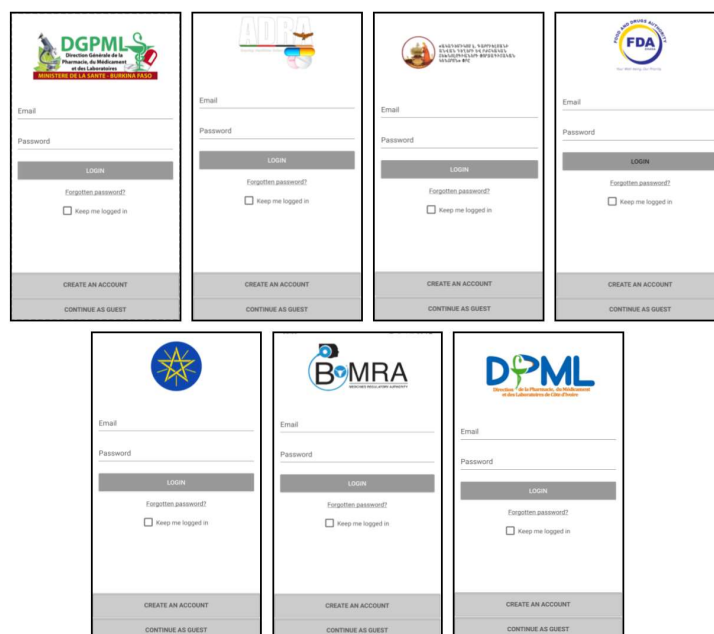


Figure 1. Landing page for the Med Safety App for different countries – Burkina Faso, Zambia, Armenia, Ghana, Ethiopia, Botswana, Cote d'Ivoire

The App is embracing technology to address an unmet need; Pierce et al.² and Oosterhuis et al.³ concluded that an app is an important tool for reporting adverse effects alongside other reporting methods and that it facilitates the report to be of a quality that is high enough to contribute to pharmacovigilance and signal

¹ World Health Organization. Pilot Mobile "app" for reporting suspected drug reactions launched in Burkina Faso and Zambia. *WHO Pharmaceuticals Newsletter* 2017; 3: 27. Available from: <http://apps.who.int/medicinedocs/documents/s23251en/s23251en.pdf>.

² Pierce, C.E. et al. Recommendations on the Use of Mobile Applications for the Collection and Communication of Pharmaceutical Product Safety Information: Lessons from IMI WEB-RADR. *Drug Saf.* 2019; 42(4): 477–489. DOI: 10.1007/s40264-019-00813-6.

³ Oosterhuis, I. et al. Characteristics, Quality and Contribution to Signal Detection of Spontaneous Reports of Adverse Drug Reactions Via the WEB-RADR Mobile Application: A Descriptive Cross-Sectional Study. *Drug Saf.* 2018; 41: 969. DOI:10.1007/s40264-018-0679-6.

detection. These benefits are particularly relevant in LMICs, where the prevalence of smartphones exceeds access to computers with wired internet connections.

Whilst the aim of pharmacovigilance is to improve patient outcomes and quality of life, there is also a financial benefit. The disease burden of ADRs, from the cost of treatments to hospital admissions, is hugely expensive⁴. Effective pharmacovigilance is shown to help identify ADRs to patients which enables prevention, or effective management of symptoms, which in turn saves money that can be diverted to other pressing health needs.

The App allows healthcare professionals and, if desired, patients to report suspected ADRs directly to the NPC and receive immediate acknowledgement of the submitted report. As the App uses the ICH E2B(R2) messaging standard, the Individual Case Safety Reports (ICSRs) can be transmitted directly to a national database that processes such standard messages, e.g. VigiFlow, which is an ICSR management system developed and maintained by the WHO Collaborating Centre for International Drug Monitoring, UMC. VigiFlow, is tailored for NPCs in the WHO Programme for International Drug Monitoring and has built-in support to share data to the WHO global ICSR database, VigiBase.

App users can read the latest drug safety information published by the NPC in the App, establishing a two-way exchange of information⁵. Additionally, App users can view global statistics on all reported ADRs in VigiBase, and, following creation of an account within the App, build a 'Watch List' of drugs of interest and keep a record of submitted reports. Further features include the ability to create and save reports without internet connection and use of the App in multiple languages, where made available by the NPC. Users can share news articles with their social networks, providing a key opportunity to engage non-app users through the spread of important drug safety information.

To date, the App has been launched in seven countries; Burkina Faso, Zambia, Armenia, Ghana, Ethiopia, Botswana and Cote d'Ivoire. The app was originally piloted in Burkina Faso and Zambia in June 2017 as a proof of concept to understand the potential benefit and sustainability. The success of the pilot was demonstrated in Burkina Faso as more ADR reports were received in the first nine months of the App pilot than all reports submitted prior the App launch⁶. Building on the success of the current App launches, the App will be rolled out in Uganda, Kyrgyzstan and Democratic Republic of the Congo by early 2020.

The App has been downloaded by more than 5,000 users. The benefits of the App are the greatest when it is used in conjunction with strong local messaging on the importance of ADR reporting and promotional activities. For example, Armenia launched the App (7 May 2019) with an official ceremony attended by the Minister of Health and Deputy Minister of Health. The Minister of Health provided a demonstration of how to use the App, its functionalities and encouraged app usage. A video of this presentation was circulated on social media channels such as Twitter and Facebook, and the Minister shared information from his Facebook account. An organised and thorough communications plan was implemented utilising a range of materials such as electronic posters, infographics, brochures and news articles, and the event had national television coverage. As a result, Armenia saw 900 downloads within the first week of the App launch. Other countries who have adopted the App have taken a similar approach; Ethiopia's Minister also attended the launch event and proactively shared information about the event on Twitter. Continued promotion and awareness raising of the App post-launch is essential to attract new users, while exploiting the App's news feature helps retain existing users. Learnings from the successes of existing Med Safety countries are shared with new adopters to help support their own launches and the local success of the App.

The impact of greater engagement will take longer to realise, however, fostering a culture of pharmacovigilance will be an important step forwards in the improvement of patient safety internationally. The App can be used as a general tool to support NPC's activities, but it can also be launched alongside disease programmes to support the introduction of novel medicines and vaccines which target diseases such as tuberculosis and malaria. The App can be a powerful tool to build post-marketing knowledge of the safety profile of medicines and vaccines in the real-world setting. When introducing a new medicine, the safety profile is typically limited; this limitation is because clinical trials expose the medicine to small patient groups which may not be as diverse, for example in ethnicity and disease burden, as the target population. In addition, since new medicine programmes often deliver medicines to a large number of patients in a short space of time, having the App at the point of care is invaluable for real-time safety surveillance and the rapid identification of new safety risks.

The App is continuously being improved and enhanced. Such enhancements include the ability to trigger pop-up notifications for targeted messaging to users, to send photos to the NPC as part of an ADR report, and the introduction of multiple tailored reporting forms.

⁴ Pirmohamed, M. et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004; 329. DOI: 10.1136/bmj.329.7456.15.

⁵ De Vries, S.T et al. Interest in a Mobile App for Two-Way Risk Communication: A Survey Study Among European Healthcare Professionals and Patients. *Drug Saf*. 2018. 41: 697. DOI: 10.1007/s40264-018-0648-0.

⁶ World Health Organization. Integrating Pharmacovigilance in Seasonal Malaria Chemoprevention: the story so far. *WHO Pharmaceuticals Newsletter* 2017; 4: 33. Available from: <https://apps.who.int/iris/bitstream/handle/10665/258800/WPN-2017-04-eng.pdf>.

If you are interested in learning more about Med Safety App or wish to adopt the App, further information can be found on the WEB-RADR project website at <https://web-radr.eu/med-safety/>.

Case study: Med Safety App in Ghana

The Med Safety App was launched in Ghana by a representative of the Honorable Minister of Health on 25th June 2019. The Chief Executive Officer of the Food and Drugs Authority (FDA), Mrs. Delese Darko, gave a warm welcome and was optimistic that the App will improve ADR reporting rates and improve patient safety in Ghana.

Prior to the launch of the App, the FDA utilised social media platforms, radio and television to inform the general public about the importance of the App and raise awareness. Since the launch date, distribution of flyers and engagement with professional associations and consumers has continued. For example, a presentation during the Annual General Meeting of the Pharmaceutical Society of Ghana resulted in over 400 downloads of the Med Safety App.

As of 31 October 2019, four months after the launch date, there have been 1,200 downloads and 57 ADR reports received through the App. Of these, 49 reports (86%) were submitted by healthcare professionals and the remaining 8 reports (14%) from patients.

Continuous engagement and awareness on the benefits of the App is seen as the key success factor and currently the FDA is developing strategies, including short videos, to educate patients and healthcare professionals to download and use the App.



The Chief Executive of the FDA, Mrs. Delese A. Darko delivering the welcome address at the Med Safety app launch in Ghana, 25 June 2019.