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WHO Pharmaceuticals NEWSLETTER

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

The aim of the Newsletter is to disseminate information on the safety and efficacy 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:

Safety and Vigilance: Medicines,

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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 newsletter includes two feature articles: a summary of discussions at the Fourteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) and the story so far on Integrating Pharmacovigilance in Seasonal Malaria Chemoprevention.

Contents

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Regulatory Matters

Safety of Medicines

Bosutinib

Risks of toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiform

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for bosutinib (Bosulif®) has been updated to include the risk of toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiform as clinically significant adverse reactions.

Bosutinib is used for the treatment of chronic myelogenous leukaemia in patients who are resistant or intolerant to prior drug therapies.

Cases of oculomucocutaneous syndrome (four cases), toxic epidermal necrolysis (one case) and erythema multiforme (four cases) have been reported in patients who were treated with bosutinib in Japan. The company core data sheet (CCDS) was also updated to include oculomucocutaneous syndrome as an adverse drug reaction.

Reference:
Revision of Precautions, MHLW/PMDA, 30 May 2017 *(www.pmda.go.jp/english/)*

Codeine, dihydrocodeine and tramadol

Cautions against use in children and teenagers under 18 years of age

Japan. The MHLW and the PMDA have announced that the package inserts for products containing codeine, dihydrocodeine and tramadol have been updated to include a precaution against use in children younger than 12 years and in teenagers between 12 and 18 years of age who are obese, have obstructive sleep apnoea syndrome, or have serious lung disease.

The above update is due to the fact that a serious case of respiratory depression with codeine use was reported in a patient under the age of 12 years who was an ultra-rapid metaboliser (UM) of CYP2D6 in Japan.

A precaution that codeine should not be used in patients younger than 18 years of age for pain relief after tonsillectomy or adenoidectomy was also considered appropriate to add.

Although the frequency of the genetic polymorphism causing UM is thought to be lower amongst the Japanese population compared to the US or European populations, the above precautions were added in view of the adverse drug reactions reported in Japan.

The risk of respiratory depression with codeine also exists with tramadol use. However, it should be noted that in Japan, no tramadol containing products have been approved for paediatric use.

Reference:
Revision of Precautions, MHLW/PMDA, 4 July 2017 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletters No.3, No.2 and No.1, 2017, No.5 and No.1 in 2016, No.6, No.5, No.4 and No.3 in 2015, No.5 and No.4 in 2013, and No.5 in 2012 for related information)

Daclizumab

Provisional restrictions for use

EU. The European Medicines Agency (EMA) has provisionally restricted the use of the multiple sclerosis medicine daclizumab (Zinbryta®) to patients with highly active relapsing and/or rapidly evolving relapsing disease that has failed to respond to treatment or cannot be treated with other medicines. In addition, it is contraindicated in patients with liver injury.

A review of daclizumab was commenced after a patient died from liver injury (fulminant liver failure) in an ongoing observational study. In addition there were four cases of serious liver injury reported. The risk of liver damage with daclizumab was known at the time it received market authorisation in the EU. Several risk management measures were put in place including the requirement to monitor liver function and educate health-care professionals and patients on the risk of liver damage.

Starting treatment with daclizumab is not recommended for patients with autoimmune diseases other than multiple sclerosis and caution should be used when giving daclizumab together with medicines that can damage the liver. Doctors should continue to monitor the liver function of patients receiving the medicine and closely watch patients for signs and symptoms of liver injury.

Once the review is concluded, the EMA will communicate further and provide updated guidance to patients and health-care professionals.

Reference:
News and press release, EMA, 7 July 2017 *(www.ema.europa.eu)*

Denosumab

Risk of osteonecrosis of the external auditory canal

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has revised the product information for all denosumab containing

products to include a warning on the risk of osteonecrosis of the external auditory canal.

Denosumab 60 mg solution for injection (Prolia®) is indicated for the treatment of osteoporosis in postmenopausal women and in men with an increased risk of fractures. It is also used to treat bone loss associated with hormone ablation in men with prostate cancer. Denosumab 120 mg solution for injection (Xgeva®) is indicated for the prevention of skeletal-related events in adults with bone metastases from solid tumours, and for the treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The MHRA is closely monitoring the use of bisphosphonates for the potential risk of osteonecrosis of the external auditory canal following published reports in the literature.

Worldwide, five reports of osteonecrosis of the external auditory canal have been received for patients treated with 60mg denosumab for osteoporosis.

The MHRA advised health-care professionals to consider the possibility of osteonecrosis of the external auditory canal in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 11:1, 21 June 2017 *(www.gov.uk/mhra)*

Direct-acting antivirals (DAAs)

Risk of hepatitis B virus reactivation

Singapore. The Health Sciences Authority (HSA) has updated package inserts for direct-acting antivirals (DAA)-containing products to include safety information regarding the risk of hepatitis B virus (HBV) reactivation.

DAAs are a class of drugs used for the treatment of hepatitis C virus (HCV) infection.

To date, the HSA has not received any local reports of HBV reactivation in patients receiving treatment with DAAs for HCV infection.

Several cases of HBV reactivation have been reported internationally in patients who were treated with DAAs for HCV infection. In some cases, the HBV reactivation had led to serious outcomes such as hepatic failure and death. Several national regulatory authorities have taken regulatory actions after conducting safety reviews to assess the risk of HBV reactivation associated with the use of DAAs for treatment of HCV infection.

The HSA encourages health-care professionals to be vigilant for HBV reactivation in patients who have a past or current HBV infection, and who have been prescribed DAA-containing products for the treatment of HCV infection.

Reference:
Product Safety Alerts, HSA, 26 May 2017 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.1, 2017, No.6 and No.3, 2016 for related information)

Domperidone

Risk minimisation of cardiovascular effects

Singapore. The HSA has re-assessed whether additional measures to further mitigate the cardiovascular (CV) risk associated with the use of domperidone are necessary. The HSA has updated package inserts for products containing domperidone to strengthen cardiovascular warnings and include recommendations on new dosing regimens and treatment durations.

Domperidone is a pro-kinetic and anti-emetic drug used for the treatment of dyspepsia, nausea and vomiting.

Risk factors that increase the risk of cardiotoxicity include: advanced age (>60 years old), underlying CV conditions, high domperidone dose (>30 mg/day) and concomitant use with QT prolongation drugs and CYP3A4 inhibitors. The HSA has received two cases of QT prolongation associated with domperidone (from 2006 to 2016). Considering that domperidone has been used in local clinical settings for a long period of time, and that there is a relatively low incidence of locally reported cardiac-related adverse events, the HSA concluded that the benefit-risk profile of domperidone remains favourable when used appropriately. Additional measures were recommended to mitigate the risk of cardiotoxicity, which included restricting its use in high risk patients.

Reference:
Product Safety Alerts, HSA, 26 May 2017 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.2, 2015, No.3 and No.1, 2014 for related information)

Dulaglutide

Risk of anaphylaxis and angioedema

Japan. The MHLW and the PMDA have announced that the package insert for dulaglutide (Trulicity®) has been updated to include the risks of anaphylaxis and angioedema as clinically significant adverse reactions.

Dulaglutide is indicated in type-2 diabetes mellitus to improve glycaemic control.

A total of two cases of anaphylaxis have been reported in patients treated

with dulaglutide in Japan. Cases of anaphylaxis and angioedema have also been reported overseas. In addition, the company core data sheet (CCDS) has been revised to include anaphylaxis as an adverse drug reaction.

Reference:
Revision of Precautions, MHLW/PMDA, 30 May 2017 *(www.pmda.go.jp/english/)*

Finasteride

Potential risk of serious muscle-related adverse effects

Canada. Health Canada has recommended that manufacturers update the product information for finasteride containing products (Propecia®, Proscar® and generics) to include information about the potential risk of serious muscle-related adverse effects.

Finasteride at a dose of 5mg is used to treat and control non-cancerous enlargement of the prostate gland (benign prostatic hyperplasia) and for treatment of androgenic alopecia at a dose of 1mg.

Health Canada reviewed the potential risk of serious muscle-related adverse events such as rhabdomyolysis, myopathy and muscle disorders such as pain, weakness, atrophy or stiffness.

At the time of this review, Health Canada had received 11 Canadian reports of serious muscle-related adverse effects. Four cases were thought to be possibly linked to finasteride use. In three of the four cases individuals recovered after stopping the use of finasteride (the outcome is unknown in the fourth case). There were not enough information to establish a link between finasteride and muscle-related adverse effects in the remaining seven reports.

Three additional cases of serious muscle-related adverse effects with the use of finasteride were reported in the literature. Two cases reported either myalgia with an increase in muscle enzymes, or rhabdomyolysis following the use of finasteride to treat hair loss in men. These patients recovered after they stopped using finasteride.

The WHO global database of Individual Case Safety Reports (ICSRs) contained 508 reports of serious muscle-related adverse effects suspected of being linked to the use of finasteride, mostly atrophy, weakness, myalgia and sudden, strong muscle tightening (spasms). There were not enough information in these reports to suggest a causal effect.

Health Canada's review of the available information concluded that the risk of serious muscle-related adverse effects with the use of finasteride cannot be ruled out.

Reference:
Summary Safety Review, Health Canada, 22 June 2017 (*www.hc-sc.gc.ca*)

Fluconazole and fosfluconazole

Risk of drug-induced hypersensitivity syndrome

Japan. The MHLW and the PMDA have announced that the package inserts for fluconazole (Diflucan®) and fosfluconazole (Prodif®) have been updated to include the risk of drug-induced hypersensitivity syndrome (DIHS) as a clinically significant adverse reaction.

Fluconazole and fosfluconazole (pro-drug of fluconazole) are antifungal medications used for fungal infections with *Candida* or *Cryptococcus.*

A total of two cases associated with DIHS with fluconazole use have been reported in Japan. Of these, a causal relationship could not be excluded in one of the cases. For fosfluconazole, one case associated with DHIS has been reported. The company core datasheet (CCDS) for fluconazole has also been updated.

Reference:
Revision of Precautions, MHLW/PMDA, 4 July 2017 *(www.pmda.go.jp/english/)*

Fulvestrant

Risk of falsely elevated oestradiol levels measured in the blood using immunoassays

Singapore. The HSA has stated that it is working with manufacturers to update the package insert for fulvestrant (Faslodex®) to include information on cross-reactivity with oestradiol (E2) immunoassays.

Fulvestrant is indicated for the treatment of oestrogen receptor (ER)-positive post-menopausal women and locally advanced or metastatic breast cancer, with disease relapse on or after adjuvant anti-oestrogen therapy, or with disease progression on therapy with an anti-oestrogen.

Medical and scientific literature together with international post-marketing reports suggest that fulvestrant can cross-react with E2 immunoassays which can result in falsely elevated E2 levels. This can and potentially lead to misinterpretations and unnecessary surgery or endocrine therapy modification.

To date, the HSA has not received any local ADR reports of falsely elevated E2 levels associated with the use of fulvestrant. However internationally, the EMA, Health Canada, the Therapeutic Good Administration (TGA) and the United States Food and Drug Administration (US FDA) have updated the product labelling with warnings of potential cross-reactivity.

The HSA has advised that health-care professionals should consider alternative methods to E2 immunoassays such as liquid chromatography-mass spectrometry, if their patient is taking fulvestrant.

Reference:
Product Safety Alerts, HSA, 26 May 2017 (*http://www.hsa.gov.sg/*)

Gadolinium agents in body scans

Restrictions on use

EU. The EMA has issued restrictions for the use of intravenous linear gadolinium agents to prevent the risk of brain deposition.

Gadolinium contrast agents are used to improve image quality with magnetic resonance scans.

As a result of the review, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended that gadoxetic acid and gadobenic acid should only be used for liver scans in situations where there is an important diagnostic need. In addition, gadopentetic acid should only be used for joint scans.

All other intravenous linear agents (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended.

The restrictions on linear agents can potentially be lifted if the companies concerned provide evidence that benefits outweigh the risk of brain deposition in an identified patient group, or if the products are modified so that gadolinium is not significantly retained in tissues.

Reference:
News and press release, EMA, 21 July 2017
(www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletter No.5, 2015: Possible risk of brain deposits with repeated use in the US)

Gold (I) sodium thiosulfate containing patch test products

Sensitization to gold (I) sodium thiosulfate

Japan. The MHLW and the PMDA have announced that the package inserts for patch test products containing gold (I) sodium thiosulfate have been updated to include a caution about sensitization to gold (I) sodium thiosulfate.

Patch test products containing gold (I) sodium thiosulfate are indicated for identification of allergens in allergic skin disease.

A total of seven cases associated with sensitization to gold (I) sodium thiosulfate have been reported in Japan. Of these, a causal relationship could not be excluded in four cases. In addition, data related to this safety issue are published in the literature.

Reference:
Revision of Precautions, MHLW/PMDA, 4 July 2017
(www.pmda.go.jp/english/)

Hydroxocobalamin

Risk of acute kidney injury

Japan. The MHLW and the PMDA have announced that the package insert for hydroxocobalamin (Cyanokit®) has been updated to include the risk of acute kidney injury as a clinically significant adverse reaction.

Hydroxocobalamin is indicated in the treatment of cyanogen and cyanide poisoning.

A total of two cases associated with acute kidney injury have been reported in Japan and the company core datasheet (CCDS) with this information has been updated.

Reference:
Revision of Precautions, MHLW/PMDA, 4 July 2017
(www.pmda.go.jp/english/)

Loperamide (high dose)

Risk of serious cardiac adverse events

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has updated the package inserts for all products containing loperamide with warnings and safety information related to the risk of serious cardiac adverse events with high doses.

Loperamide is an antidiarrhoeal medicine.

Between 2000 to December 2016, the NPRA has received 14 reports containing a total of 29 adverse events suspected to be related to loperamide use in Malaysia. More than half the adverse events (15 events, 52%) were related to skin disorders such as rash and pruritus. Other adverse events reported were anaphylaxis, shortness of breath, dizziness, dysaesthesia, face and mouth oedema, nausea, oculogyric crisriskis, stomatitis, and throat tightness. To date, the NPRA has not received any reports of cardiac adverse events related to loperamide use.

A search of the WHO global database of Individual Case Safety Reports (ICSRs), VigiBase, identified 7 431 individual case safety reports involving loperamide since year 1977. A total of 328 reports involved cardiac disorders such as ventricular tachycardia (60 reports), cardiac arrest (50), and torsades de pointes (46).

The NPRA has issued advice to health-care professionals, alerting them to potential risks of cardiac events, susceptible individuals, drug interactions, and management of suspected cardiotoxicity with loperamide use.

Reference:
Reaksi Drug Safety News, NPRA, No. 35, July 2017

(See WHO Pharmaceuticals Newsletter No.4, 2016: Serious heart problems with high doses in the US)

Loxoprofen

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for loxoprofen has been updated to include the risk of shock and anaphylaxis as clinically significant adverse reactions.

Loxoprofen is used for inflammation and pain relief.

A total of six cases associated with shock or anaphylaxis have been reported in Japan. Of these, a causal relationship could not be excluded in two cases.

Reference:
Revision of Precautions, MHLW/PMDA, 4 July 2017 *(www.pmda.go.jp/english/)*

Mefloquine

Risk of long-lasting and permanent neurological and psychiatric adverse events

Canada. Health Canada has recommended that the product information for mefloquine should be updated to explain the risk of vestibular damage more clearly. A checklist to assist health-care professionals in deciding whether to prescribe mefloquine to individual patients will be developed to prevent mefloquine from being prescribed to patients who are contraindicated (for example past or ongoing neurological or psychiatric conditions).

Mefloquine is a prescription drug to prevent and treat malaria.

Health Canada reviewed the potential risk of rare long-lasting (lasting for 90 days or more) and permanent neurological and psychiatric adverse events with the use of mefloquine.

From 1993 to 30 September 2016, Health Canada has received 27 Canadian reports of adverse events that were potentially long-lasting. In addition, 37 international reports (from databases and published literature) of adverse events included five reports of permanent damage to the vestibular system.

The vast majority of the reports (61 out of 64) were deemed to have a possible link between the use of mefloquine and the long-lasting or permanent adverse events. However, insufficient information was available to conclude that mefloquine use was responsible for the adverse event(s) reported.

The review also found that some patients were prescribed mefloquine even though the use was contraindicated because they had past or ongoing neurological or psychiatric conditions.

The current product information for mefloquine describes the potential for long-lasting neurological and psychiatric adverse events that aligns with the review findings. However, the risk of rare permanent vestibular damage could be more clearly explained.

Reference:
Summary Safety Review, Health Canada, 1 June 2017 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.6, 2013: Strengthened warnings on neuropsychiatric side effects in the United Kingdom and No.5, 2013: Risk of serious psychiatric and nerve side effects in the US)

Natalizumab

Use in pregnancy and haematological abnormalities in new-borns

Canada. Health Canada has updated the product information for natalizumab (Tysabri®) to include the risk of haematological abnormalities in new-borns whose mothers were treated with natalizumab during pregnancy.

Natalizumab is used to treat patients with the relapsing-remitting form of multiple sclerosis (MS).

Health Canada conducted a review of the potential risk of blood abnormalities in new-borns whose mothers were treated with natalizumab during pregnancy. The review included reports provided by the manufacturer and from publications in theliterature.

At the time of the review, Health Canada had received 15 reports of haematological abnormalities in new-borns whose mothers were treated with natalizumab during pregnancy from the manufacturer. None of the reports were from mothers treated in Canada.

It was determined that in 14 of the 15 reports the abnormalities in the new-borns' blood were potentially related to natalizumab treatment One of the cases could not be assessed due to missing information. The haematological abnormalities included anaemia, thrombocytopenia and leukocytosis.

Health Canada concluded that there is a potential for blood abnormalities to occur in new-borns whose mothers were treated with natalizumab during pregnancy.

Reference:
Summary Safety Review, Health Canada, 22 June 2017 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletter No.4, 2016: Potential risk of haemolytic anaemia in Canada)

Nivolumab

Risk of sclerosing cholangitis

Japan. The MHLW and the PMDA have announced that the package insert for nivolumab (Opdivo®) has been updated to include the risk of sclerosing

cholangitis as a clinically significant adverse reaction.

Nivolumab is used for treatment of: unresectable malignant melanoma; unresectable, advanced, or recurrent non-small cell lung cancer; unresectable or metastatic renal cell carcinoma; relapsed or refractory classical Hodgkin lymphoma; and relapsed or metastatic head and neck cancer.

A total of 10 cases associated with sclerosing cholangitis have been reported in Japan. Of these, a causal relationship could not be excluded in six cases.

Reference:
Revision of Precautions, MHLW/PMDA, 4 July 2017 *(www.pmda.go.jp/english/)*

Pneumococcal vaccine

Risks of injection site necrosis and ulcer

Japan. The MHLW and the PMDA have announced that the package insert for pneumococcal vaccine (Pneumovax NP®) has been updated to include the risk of injection site necrosis and injection site ulcer as clinically significant adverse reactions.

Pneumococcal vaccine is indicated for individuals and patients aged 2 years or older who are at risk for serious pneumococcal disease.
A total of seven cases associated with injection site necrosis or injection site ulcer have been reported in Japan. A causal relationship could not be excluded in all these cases.

Reference:
Revision of Precautions, MHLW/PMDA, 30 May 2017 *(www.pmda.go.jp/english/)*

Sulfasalazine

Risk of Stevens Johnson Syndrome and toxic epidermal necrolysis

India. The Pharmacovigilance Program of India, Indian Pharmacopeia Commission (PvPI, IPC) has made recommendations to the Central Drugs Standard Control Organisation (CDSCO) about revising the drug safety label for sulfasalazine to include Stevens-Johnson syndrome and toxic epidermal necrolysis as potential adverse drug reactions.

Sulfasalazine is indicated for the treatment of severe rheumatoid arthritis, ulcerative colitis and Crohn's disease.

Between 2011 and 2017, PvPI received 15 reports of Stevens Johnson syndrome and seven reports of toxic epidermal necrolysis with sulfasalazine use. The cases were reviewed by Signal Review Panel (SRP)-PvPI, IPC who concluded that there was a strong causal relationship between sulfasalazine and Stevens-Johnson syndrome and toxic epidermal necrolysis.

Reference:
Based on the communication from IPC, NCC-PvPI, India, July 2017 (*www.ipc.gov.in*)

Thalidomide, lenalidomide and pomalidomide

Risk of hepatitis B reactivation, herpes zoster and pulmonary hypertension

Malaysia. The NPRA has updated the package inserts for thalidomide, lenalidomide and pomalidomide to include information on the risk of hepatitis B reactivation, herpes zoster and pulmonary hypertension. Dear Health-care Professional Communication (DHPC) letters have also been issued.

Thalidomide is indicated for both multiple myeloma and erythema nodosum leprosum (ENL), whereas lenalidomide and pomalidomide are only indicated for multiple myeloma.

Cases of hepatitis B reactivation have been reported following treatment with thalidomide, lenalidomide and pomalidomide in patients who had a previous history of hepatitis B virus (HBV) infection. Some cases of HBV reactivation progressed to acute hepatic failure and resulted in death.

In addition, reactivation of varicella-zoster virus and disseminated herpes zoster have been reported for both thalidomide, lenalidomide and pomalidomide use.

In addition, thalidomide treatment has been linked to reports of fatal pulmonary hypertension cases.

The NPRA has received 105 reports with the use of these products (thalidomide: 20 reports with 47 adverse events; lenalidomide: 84 reports with 136 adverse events; pomalidomide: one report with one adverse event) between 2006 and December 2016. At the time of the communication, there were no reports related to hepatitis B virus reactivation, herpes zoster and pulmonary hypertension received by the NPRA.

Reference:
Reaksi Drug Safety News, NPRA, No. 35, July 2017

(See WHO Pharmaceuticals Newsletters No.1, 2017, No.5 and No.3, 2016 for related information)

Treprostinil

Risk of hyperthyroidism

Japan. The MHLW and the PMDA have announced that the package insert for treprostinil

(Treprost®) has been updated to include the risk of hyperthyroidism as a clinically significant adverse reaction.

Treprostinil is used to treat pulmonary arterial hypertension.

A total of two cases associated of hyperthyroidism have been reported with treprostinil use in Japan. A causal relationship could not be excluded in both cases.

Reference:

Revision of Precautions, MHLW/PMDA, 30 May 2017 *(www.pmda.go.jp/english/)*

Bendamustine off-label use

Increased mortality and reactivation of hepatitis B virus

The United Kingdom. The MHRA has warned that recent clinical trials have shown increased mortality when bendamustine (Levact®) was used in combination with other treatments outside its approved indications. The MHRA warned that the risk of opportunistic infections for all patients receiving bendamustine including those receiving off-label treatments may be greater than previously recognised.

Bendamustine is indicated for some forms of leukaemia, non-Hodgkin's lymphomas and multiple myeloma.

In clinical trials of non-approved combination therapies, bendamustine was associated with increased mortality and an unfavourable safety profile when used in combination with rituximab or obinutuzumab. Deaths were mainly due to infections including bacterial (sepsis, pneumonia) and opportunistic infections such as pneumocystis jirovecii pneumonia, varicella zoster virus, and cytomegalovirus infection. Some fatal cardiac, neurological, and respiratory toxicity were also reported.

Reactivation of hepatitis B virus in chronic carriers of the virus has been reported with bendamustine use. Some cases resulted in acute hepatic failure or a fatal outcome. Prescribers have been advised to closely monitor carriers of hepatitis B virus for signs and symptoms of active infection.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 12:2, 20 July 2017 *(www.gov.uk/mhra)*

Brimonidine gel

Risk of systemic cardiovascular effects

The United Kingdom. The MHRA has issued advice warning patients not to apply brimonidine gel (Mirvaso®) to irritated or damaged skin, including after laser therapy to minimise the risk of systemic absorption of brimonidine.

Brimonidine is indicated for the symptomatic treatment of facial erythema of rosacea in adults.

A routine European review identified a small number of post marketing reports with systemic adrenergic effects such as bradycardia, hypotension (including orthostatic hypotension), and dizziness. The cardiovascular events occurred following application of brimonidine gel after laser therapy to the skin in approximately 30% of the cases. Some patients required hospitalization.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 11:2, 21 June 2017 *(www.gov.uk/mhra)*

Dimethyl fumarate

Potential risk of kidney injury: insufficient evidence

Canada. Health Canada reviewed the risk of kidney injury with dimethyl fumarate (Tecfidera®) and concluded that at this time, there is little evidence of this association.

Dimethyl fumarate is used to treat symptoms of relapsing remitting multiple sclerosis.

At the time of the review, Health Canada had received a total of five Canadian reports of potential serious kidney injury from any cause (such as dehydration or damage to the kidney itself) with dimethyl fumarate use. Three reports did not have enough information to confirm kidney injury. While a possible link between dimethyl fumarate and kidney injury was found in the remaining two reports, other risk factors such as concomitant medications and dehydration were reported.

In a safety review of 41 international reports of serious kidney injury with dimethyl fumarate, one case described damage to the kidney confirmed by biopsy. While it was possible that dimethyl fumarate was linked to kidney damage, other causes such as the use of other medication could not be excluded.

A search of the scientific literature found no cases describing kidney injury in patients treated with dimethyl fumarate.

The findings of this review are already reflected in the product information.

Reference:
Summary Safety Review, Health Canada, 15 June 2017 (*www.hc-sc.gc.ca*)

Dipeptidylpeptidase-4 (DPP-4) inhibitors

Potential risk of heart failure

Canada. Health Canada reviewed the potential risk of heart failure with the use of dipeptidylpeptidase-4 (DPP-4) inhibitors (alogliptin, saxagliptin, sitagliptin and linagliptin) following a risk communication released by the US FDA. The review included all DPP-4 inhibitors available in Canada.

DPP-4 inhibitors, also known as gliptins, are used to treat type-2 diabetes in adults.

At the time of the review, Health Canada received nine Canadian reports of heart failure with use of DPP-4 inhibitors. There was a possible link between the use of a DPP-4 inhibitor and heart failure in eight of these reports however,

these eight reports also reported other risk factors.

In 2008, the US FDA made a request for further safety studies to assess the cardiovascular risks with the use of DDP-4 inhibitors.

Health Canada reviewed seven publications investigating the risk of heart failure in patients treated with DPP-4 inhibitors. Some authors found a link, while others did not. Most of the clinical trials did not, or could not, separate the risk associated with each DPP-4 inhibitor.

Health Canada's review of the available information concluded that the recently updated product safety information for DPP-4 inhibitors accurately describes the potential risk of heart failure when using these products.

Reference:
Summary Safety Review, Health Canada, 15 June 2017 (*www.hc-sc.gc.ca*)

Finasteride

Rare reports of depression and suicidal thoughts

The United Kingdom. The MHRA has stated that depression and, in rare cases, suicidal thoughts in men taking finasteride (Propecia® and Proscar®) have been reported.

Finasteride at a dose of 5mg is used to treat and control benign prostatic hyperplasia, whilst at a dose of 1mg it is used for treatment of androgenic alopecia. Some men have reported episodes of depressive illness and suicidal thoughts in association with the use of finasteride for male pattern hair loss.

Depression and suicidal thoughts have been reported in men with and without a previous history of depression. Depressed mood has been previously recognised with finasteride. A recent review of the evidence has suggested more significant depression can occur.

The MHRA advises health-care professionals to tell patients to stop taking finasteride immediately if they develop depression and to inform a health-care professional.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 10:1, 24 May 2017 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.1, 2016: Risk of suicidal thoughts and behaviour in Canada)

Gadolinium-based contrast agents for magnetic resonance imaging (MRI)

No harmful effects identified with brain retention

USA. The US FDA has stated that recommendations for the use of gadolinium-based contrast agents (GBCA) for magnetic resonance imaging (MRI), remain unchanged following investigations into the potential risk of adverse effects due to retention of gadolinium in the brain.

GBCAs are intravenous drugs used in diagnostic imaging procedures to enhance the quality of magnetic resonance imaging (MRI) or magnetic resonance angiography.

To date, a FDA review has not identified adverse effects due to gadolinium being retained in the brain after the use of GBCAs for MRI. All GBCAs may be associated with some gadolinium retention in the brain and other body tissues. However, because the FDA identified no evidence of gadolinium retention in the brain from any of the GBCAs, restricting GBCA use is not warranted at this time.

The FDA will continue to assess the safety of GBCAs.

Reference:
Drug Safety Communication, US FDA, 22 May 2017 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletter No.5, 2015: Possible risk of brain deposits with repeated use in the US)

Hydroxyethyl starch

Acute kidney injury in non-critically ill patients: not enough evidence

Canada. Health Canada investigated the potential risk of acute kidney injury (AKI) and death associated with hydroxyethyl starch products (Voluben® and Volulyte®).

Hydroxyethyl starch is used to treat low blood volume.

At the time of the review, Health Canada had not received any Canadian reports of AKI associated with the use of hydroxyethyl starch products in non-critically ill patients.

This safety review examined seven international reports of AKI with use of hydroxyethyl starch products in non-critically ill patients. Not enough information was available to establish a link between hydroxyethyl starch products and AKI, although a link could not be ruled out. Other risk factors, such as low blood volume, could have caused the condition.

Health Canada reviewed 13 published articles related to AKI with the use of hydroxyethyl starch products in non-critically ill patients. The studies did not suggest hydroxyethyl starches were associated with an increased risk of AKI in non-critically ill patients.

Reference:
Summary Safety Review, Health Canada, 30 June 2017 (*www.hc-sc.gc.ca*)

Nivolumab and pembrolizumab

Reports of organ transplant rejection

The United Kingdom. The MHRA has advised health-care professionals to consider the benefit of treatment with nivolumab or pembrolizumab versus the risk of possible organ transplant rejection for individual patients.

Nivolumab (Opdivo®) and pembrolizumab (Keytruda®) are indicated for the treatment of various cancers including: malignant melanoma, non-small-cell lung cancer, and relapsed or refractory classical Hodgkin's lymphoma.

A European review of global data concluded that nivolumab and pembrolizumab may increase the risk of rejection in organ transplant recipients. The review assessed all cases received up to November 2016 and identified nine patients who had a transplant rejection after receiving nivolumab and pembrolizumab.

Of the five patients receiving nivolumab, three had kidney transplant rejection, one had corneal transplant rejection, and one had skin graft rejection.

Four patients receiving pembrolizumab had kidney transplant rejection.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 12:3, 20 July 2017 *(www.gov.uk/mhra)*

Ticagrelor

Potential risk of severe skin adverse effects: not enough evidence

Canada. Health Canada reviewed the potential risk of severe skin adverse effects with ticagrelor (Brilinta®) after an increase in the number of severe cutaneous adverse drug (SCAR) reports were listed in the safety information provided by the manufacturer.

Ticagrelor is used with low-dose aspirin (acetylsalicylic acid) to reduce the risk of having a stroke, and cardiovascular related effects and mortality.

At the time of the review, Health Canada had received two Canadian reports of SCAR associated with the use of ticagrelor. Of these two reports, one showed a possible link between SCAR and the use of ticagrelor.

The safety review also looked at 40 international reports of SCAR associated with the use of ticagrelor. In four of the 40 reports, there was a possible link between SCAR and the use of ticagrelor.

In the literature, there were no evidence of an increased risk of SCAR with the use of ticagrelor.

Health Canada's review concluded that there was not enough information available to confirm that there is a link between the risk of SCAR and the use of ticagrelor.

Reference:
Summary Safety Review, Health Canada, 26 June 2017 (*www.hc-sc.gc.ca*)

Tramadol

Breastfeeding whilst taking tramadol is not recommended

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) has stated that breastfeeding while taking tramadol is not recommended. Small amounts of tramadol are found in breast milk and the effect of this on infants and new-borns is not fully known.

Tramadol is used for moderate to severe pain in adults and children from the age of two years.

In New Zealand, the Medicines Adverse Reactions Committee (MARC) reviewed the use of tramadol in children in June 2016.

Although very small amounts of tramadol and its active metabolite are found in breast milk, its safety in new-borns and infants has not been studied. There is a theoretical risk of breathing problems in the baby due to the opioid effects of tramadol. The Centre for Adverse Reactions Monitoring (CARM) has received one case report in a one-month-old where exposure to tramadol via breast milk was suspected to have caused a red rash. The baby was reported to have recovered and the rash was not considered severe or serious.

Reference:
Safety Information, Medsafe, 7 July 2017 (*www.medsafe.govt.nz/*)

(See WHO Pharmaceuticals Newsletters No.3, No.2 and No.1, 2017, No.6 and No.1 in 2016, No.6, No.5, No.4 and No.3 in 2015, No.5 and No.4 in 2013, and No.5 in 2012 for related information)

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 15 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. Signals are first communicated to National Pharmacovigilance Centres through SIGNAL (a restricted document from UMC), before being published in this Newsletter.
More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 25). 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, 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.

Desloratadine, loratadine and weight increase in children

Ms Ermelinda Viola and Dr Anita Conforti, Italy

Summary

In a signal detection screening focusing on paediatric patients, the association between desloratadine and weight increase was highlighted for children aged between 2 and 11 years. As desloratadine is a metabolite of loratadine, it was considered relevant to also include loratadine in the assessment. Loratadine and desloratadine are orally active, non-sedating, peripheral histamine 1 (H_1)-receptor antagonists used for the relief of the symptoms of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria. Up to 6 November 2016, 44 reports of weight increase due to desloratadine and 115 to loratadine were submitted to the WHO global database of individual case safety reports, VigiBase. Among the reports of weight increase, 11 for desloratadine and 11 for loratadine were related to paediatric patients (<12 years old). The association of desloratadine and weight increase in children (2-11 years) reached a significant statistical value, unlike that of loratadine. Weight increase is not listed as an adverse reaction for either loratadine or desloratadine, but the reaction of 'increased appetite' is documented in the product information for both drugs. A plausible mechanism of loratadine and desloratadine-induced weight increase can be presumed, due to the action of these drugs on H_1- and H_3-receptors, which are mediators of energy intake. This analysis supports the possible association between loratadine, desloratadine and weight increase that, when affecting children, could have significant health consequences, including cardiovascular diseases (mainly heart disease and stroke), diabetes and musculoskeletal disorders.

Introduction

Loratadine and desloratadine are orally active, non-sedating, peripheral histamine 1 (H_1)-receptor antagonists used for the relief of the symptoms of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.[1,2] They belong to the newer second-generation H_1-antihistamines that bind to, but do not activate histamine receptors, thereby blocking the actions of histamine or histamine agonists. Compared with early (first-generation) ones, second-generation antihistamines have greater receptor specificity, are safer, cause less sedation, due to a lower penetration of the blood-brain barrier, and are more efficacious and less likely to cause drowsiness or psychomotor impairment.[3]

Loratadine was approved by the United States Food and Drug Administration in 1993, while desloratadine was authorized throughout the European Union (EU) and the United States (US) in 2001. Desloratadine is the primary active metabolite of loratadine (as of 2015 loratadine was available in many countries over the counter), and it is still subject to medical prescription.[4,5]

In the EU loratadine is approved for use in adults and children over the age of 2 years while desloratadine is approved for use in adults and children over the age of 1 year.[1,6] In the US desloratadine is approved for patients of 6 months and older.[7] The recommended daily dose of desloratadine for adults and adolescents (12 years and over) is 5 mg, for children from 6 to 11 years 2.5 mg, from 1 to 5 years 1.25 mg and from 6 to 11 months 1 mg, while the recommended daily dose for loratadine is 10 mg for adults and

children above 12 years and children from 2 to 12 years are dosed by weight: 10 mg above 30 kg and 5 mg for body weight less than 30 kg.[1,6,7,8]

Loratadine and desloratadine achieve maximum plasma concentrations (Tmax) between 1-1.5 hours and 1.5-3.7 hours after administration, respectively. Increase in plasma concentrations of loratadine have been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in controlled trials, but without clinically significant changes (including electrocardiographic). The enzyme responsible for the metabolism of desloratadine is still unknown and no clinically relevant interactions were observed in clinical trials with desloratadine tablets in which erythromycin or ketoconazole were co-administered.[1,6]

Weight increase takes place when body mass increases, as a result of fat deposits, additional muscle tissue, or excess fluid. It can have many alternative causes and can either derive from the increase of appetite, a range of diseases or be due to use of drugs that potentially influence the physiologic hormone levels.[9]

In a signal detection screening focusing on paediatric patients, the association between desloratadine and weight increase was highlighted for children aged between 2 and 11 years. As desloratadine is a metabolite of loratadine, it was considered relevant to also include loratadine in this assessment.

Reports in VigiBase

Loratadine

One hundred and fifteen reports concerning weight increase, obesity and appetite increased (WHO-ART preferred terms) were retrieved from the WHO global database of individual case safety reports, VigiBase as per 6 November 2016. In 97 reports loratadine is the sole suspect drug. The reports originate from 22 countries and concern 70 women and 33 men (in 12 cases the gender was unknown), aged between 4 to 77 years with a median age of 35 years. Among these reports 11 are related to children from 2 to 11 years, which are further described below.

Loratadine paediatric cases

Paediatric cases related to the use of loratadine are summarized in Table 1. Loratadine is the sole suspect drug in nine out of these eleven cases. Time to onset, where specified, varies from hours up to seven months. Two cases (3 and 4) reported other suspected drugs of which only cetirizine is known to cause weight gain.[10] In five cases the patient recovered. Cases 1, 2, 5, 9 and 11 reported a positive dechallenge. Case 10 reported a negative dechallenge. In case 1, a positive rechallenge was described concerning a 10-year-old male patient who increased his weight of at least 4 kg in one to two months after starting loratadine treatment two seasons in a row, and recovered when the drug was withdrawn.

The association of loratadine and weight increase did not reach a significant statistical value in children [IC -0.31; IC_{025} -2.41 for age group 2-11 years].

Desloratadine

Forty-four reports concerning weight increase, obesity and appetite increased (WHO-ART preferred terms) were retrieved from VigiBase on 6 November 2016, excluding two duplicates. In 34 reports desloratadine is the only suspected drug. The reports originate from 18 countries and concern 32 women and 11 men (in one case the gender was unknown), aged between 20 months and 60 years with a median age of 34.5 years. Among these reports 11 are related to children from 2 to 11 years, which are further described below.

Desloratadine paediatric cases

Paediatric cases related to the use of desloratadine are summarized in Table 2. Desloratadine is the sole suspect drug in five out these eleven cases. Time to onset varies from hours up to 20 months. In two cases (3 and 9) a positive dechallenge and a positive rechallenge was reported. Case 9 described a 7-year-old male patient who experienced rapid increase in appetite from the first day of treatment with desloratadine. He gained 4.5 kg in two months. Desloratadine was withdrawn, after which his appetite went back to normal and his weight decreased. The drug was later reintroduced, this time also leading to increased appetite, but the patient's weight was controlled with a diet.

In case 2 the presence of oedema could represent a possible alternative cause of weight gain. The onset of reaction occurred six days after desloratadine treatment was stopped. Four of the 11 children (cases 4, 5, 6 and 7) were concomitantly taking montelukast but the summary of product characteristics (SmPC) of this drug does not describe weight gain or increased appetite as adverse reactions.[11]

Case 7 describes also facial oedema and overdose during treatment with desloratadine and montelukast, but the reaction occurred twelve days after stopping the treatment with desloratadine. The patient's mother noticed development of a left facial oedema and weight gain of about 1 kg in one month, especially on abdominal circumference. The treatment with montelukast was also stopped and restarted. No rechallenge of the reactions was reported. The reporter felt that left facial oedema and weight gain were in direct relation with therapy with montelukast.

The association of desloratadine and weight increase reached a significant statistical value in children [IC 2.28; IC_{025} 0.32 for age group 2-11 years].

Table 1. Case overview of paediatric reports in VigiBase of weight increase and appetite increased in association with loratadine

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reported reactions (WHO-ART)	Time to onset	Weight increase	Reporter qualification	Dechallenge/ Rechallenge	Outcome
1	10/M	-	Weight increase	Within 1 month	At least 4 kg in one to two months	Physician	Positive dechallenge/ Positive rechallenge	Recovered
2	7/M	Mometasone, clobetasone (both C)	Appetite increased, weight increase	Within 1 month	-	Physician	Positive dechallenge	Recovered
3	10/F	Beclometasone (S)	Puberty precocious, weight increase	-	-	Physician	Unknown	-
4	4/M	Cetirizine (S)	Hypersensitivity, weight increase	-	-	Other	Unknown	-
5	10/M	-	Agitation, appetite increased	Same day	-	Physician	Positive dechallenge	Recovered
6	8/M	-	Weight increase	1 month	4 kg in one month	Physician	Drug withdrawn	Unknown
7	10/F	Fluticasone (C)	Weight increase	7 months	5 kg above average	Physician, Pharmacist	-	-
8	8/F	Fluticasone (C)	Weight increase	7 months	5 kg above average	Physician, Pharmacist	-	-
9	8/M	-	Oedema pharynx, weight increase	-	-	Consumer	Positive dechallenge	Recovered
10	4/F	-	Appetite increased, weight increase	9 days	Had a weight of 30 kg after 2.5 years of treatment	Physician	Drug withdrawn	Not recovered
11	10/M	-	Thinking abnormal, weight increase	-	Excess weight more than 22%	Physician	Positive dechallenge	Recovered

Table 2. Case overview of paediatric reports in VigiBase of weight increase, obesity and appetite increased in association with desloratadine

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reported reactions (WHO-ART)	Time to onset	Weight increase	Reporter qualification	Dechallenge/ Rechallenge	Outcome
1	9/F	-	Weight increase	-	-	Physician	Unknown	-
2	10/F	Mometasone (S)	Oedema, weight increase	21 days	-	-	Drug withdrawn	-
3	10/F	-	Appetite increased, weight increase	14 days	-	Physician	Positive dechallenge/ Positive rechallenge	Recovered
4	6/M	Montelukast (S)	Abnormal weight gain*	12 months	-	Other Health Professional	Drug withdrawn	Unknown
5	6/F	Montelukast (S)	Abnormal weight gain*	9 months	-	Other Health Professional	Drug withdrawn	Unknown
6	7/M	Montelukast (S)	Abnormal weight gain*	20 months	-	Other Health Professional	Drug withdrawn	Unknown
7	4/M	Montelukast (S)	Face oedema, overdose, weight increase	12 days	1 kg in one month	Physician	Drug withdrawn	Not recovered
8	6/F	-	Weight increase	1 month	-	Consumer	Dose not changed	-
9	7/M	-	Appetite increased, weight increase	Same day	4.5 kg in two months	Pharmacist	Positive dechallenge/ Positive rechallenge	Recovered
10	8/F	Beclometasone/formoterol (S)	Weight increase	2 months	5 kg in six months	Consumer	Dose not changed	Recovering
11	11/F	-	Obesity	-	-	Other	-	Unknown

**Reported term*

Literature and Labelling

Weight gain is not mentioned in the United Kingdom (UK) SmPCs of loratadine and desloratadine.[1,6] Although increased appetite is described in the UK SmPC for loratadine[1] with an incidence of 0.5%, it is not listed in the UK SmPC for desloratadine. The US product label for desloratadine lists increased appetite as an adverse event occurring more frequently with the drug than with placebo only for the age group 12-23 months.[7] The adverse effects of desloratadine were studied by the manufacturer in three placebo-controlled clinical trials of 246 children between 6 months and 11 years of age. Paediatric subjects aged 6 to 11 years received 2.5 mg once a day, subjects aged 1 to 5 years received 1.25 mg once a day, and subjects 6 to 11 months of age received 1.0 mg once a day. In the 6 to 11 year age group, no individual adverse event was reported by two percent or more of the subjects. In the 12 to 23 month age group, adverse events reported for desloratadine and placebo in at least two percent of subjects receiving desloratadine syrup, and at a frequency greater than placebo, included appetite increased (3.1%, 1.6%).[7]

Moreover, in 2011 the Netherlands Pharmacovigilance Centre Lareb published a signal about desloratadine and increased appetite, describing three cases and concluding that an association was possible, due to similarity of desloratadine with loratadine.[12]

For other second-generation antihistamines, such as levocetirizine or cetirizine, weight gain is listed.[10,13]

In the literature, no information for desloratadine or loratadine and weight gain was found, but it is known that neuronal histamine and its receptors have been shown to regulate energy metabolism and are considered as anti-obesity targets. Several histamine receptor subtypes have been identified; of these, histamine H_1- and H_3-receptors have been specifically recognized as mediators of energy intake and expenditure.[14] This mechanism could probably represent a plausible explanation for weight gain due to antihistamines, even if second-generation H_1-antagonists, which include desloratadine, have high affinity and selectivity for the peripheral H_1-receptor. Specificity for the peripheral H_1-receptor site should avoid the potential for adverse effects on the central nervous system.[15]

Discussion and Conclusion

The review and analysis of all cases of weight increase, obesity and appetite increased for loratadine and desloratadine did not show that contributory factors such as concomitant drugs and or underlying disease were strong alternative explanations. These 115 cases for loratadine and 44 cases for desloratadine suggest that loratadine and desloratadine can increase weight, probably due to the increased appetite already documented in product information for loratadine and desloratadine, and children are affected as well as adults. Severe obesity in childhood is increasing in prevalence and is associated with considerable morbidity. Longitudinal cohort studies show that obesity during childhood is associated with medical comorbidity, and excess weight in childhood independently increases the risk of mortality related to the development of cardiovascular and metabolic disease in later life. It has also been linked with adverse effects on social, psychological, and academic development. Obese children are at a high risk of bullying, discrimination, lower health-related quality of life, and of impaired mental health. Drug therapies for children are limited, as is knowledge on their effect on weight and metabolism, so it is very important to detect any possible association between drugs and weight increase in paediatric patients. Weight gain reported among these cases, ranged between one and five kg, and rapid weight gain during infancy and early childhood may be a risk factor for general/ abdominal obesity later in life.[16]

The UK SmPC of loratadine lists increased appetite as an undesirable effect, but the desloratadine data for increased appetite, that emerged also in a paediatric study conducted by the manufacturer, do not appear in the UK SmPC for desloratadine, but only in the US product label. VigiBase paediatric reports on weight increase with loratadine and desloratadine represent 22 cases with a supportive temporal relationship and a positive dechallenge in seven cases. Eleven out of the 22 paediatric cases had no other medication reported, while one case reported concomitant use of another antihistamine (cetirizine) and six cases mentioned corticosteroids (in one case dermatological products) previously associated with weight increase. The assessment of these reports suggests that desloratadine and loratadine could induce weight increase and the high proportion of paediatric reports (25%) for desloratadine suggests the possibility that use of this drug may contribute to childhood obesity. This assessment highlights the need for further evaluation of weight increase reports with desloratadine and loratadine. The association of desloratadine and the WHO-ART preferred term weight increase reached a significant statistical value in paediatric patients but not for loratadine; however, the statistical associations derived do not independently establish or rule out causality.

In conclusion, we consider weight increase with loratadine and desloratadine a signal that should be taken into a greater consideration when prescribing this medication to children.

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Ruxolitinib and peripheral neuropathy

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Summary

Ruxolitinib is a selective Janus Associated Kinase (JAK) 1 and 2 inhibitor, which is at present indicated for myelofibrosis and polycythaemia vera. During a UMC signal detection screening in March 2016 the safety issue concerning axonal neuropathy in relation to ruxolitinib was noted. Literature shows that in patients treated with other JAK inhibitors peripheral neuropathy has been observed. In this review of 37 cases of ruxolitinib associated axonal and peripheral neuropathy reported to VigiBase, the WHO global database of individual case safety reports, we concluded that a causal association between ruxolitinib and peripheral neuropathy may exist, and represents a signal worth communicating so that stakeholders may act upon it.

Introduction

Ruxolitinib (INCB018424) is a selective inhibitor of the Janus Associated Kinases (JAKs) 1 and 2. These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.[1] Ruxolitinib has significant clinical

benefits in patients with myelofibrosis by reducing spleen size, ameliorating debilitating myelofibrosis-related symptoms, and improving overall survival.[2] Ruxolitinib has also been demonstrated to be superior to standard therapy in controlling the hematocrit, reducing the spleen volume, and improving symptoms associated with polycythemia vera.[3]

In the United States, ruxolitinib is at present approved for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post- polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis, as well as in patients with polycythemia vera who have had an inadequate response to, or are intolerant of, hydroxyurea.[4] In Europe also, ruxolitinib is authorized for myelofibrosis and polycythaemia vera, specifically for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis, as well as for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.[1]

The most commonly reported adverse reactions in clinical trials were haematological, and the most frequent non-haematological reactions were bruising, dizziness, headache, constipation and herpes zoster. Serious bacterial, mycobacterial, fungal and viral infections, including progressive multifocal leukoencephalopathy, have occurred during treatment with ruxolitinib, and physicians are advised to carefully observe patients receiving ruxolitinib for signs and symptoms of infections, and to initiate appropriate treatment promptly.[1,4]

Peripheral neuropathy may be caused by a number of drugs and is one of the main reasons for patients to prematurely terminate antineoplastic treatment. Drug- induced peripheral neuropathies are often characterized by the development of a subacute or chronic, symmetrical polyneuropathy with a predominant sensory involvement.[5] Molecular mechanisms of drug-induced peripheral neuropathies have been addressed in several studies and a number of mechanisms have been postulated, including cytotoxic inflammatory changes, mitochondrial toxicity and enhanced oxidative stress, microtubular function disruption, voltage-gated ion channel dysfunction, functional impairment of ion channels of the transient receptor potential family, induction of neuronal apoptosis in dorsal root ganglia, demyelination, and reduction of VEGF neuro-protective action.[5]

During a UMC signal detection screening in March 2016 which focused on recently approved drugs and adverse events reported with a serious outcome, the safety issue concerning axonal neuropathy in relation to ruxolitinib was observed. For this review the scope was widened to peripheral neuropathy.

Reports in VigiBase

As of 21 March 2016, VigiBase, the WHO global database of individual case safety reports, had five reports where ruxolitinib was reported as suspected of causing axonal neuropathy (MedDRA preferred term), and 32 reports of neuropathy peripheral (MedDRA preferred term). Most of these reports originated from the United States (28); others came from Austria (2), France (2), Ireland (1), Greece (1), Italy (1), Slovenia (1) and the United Kingdom (1).

In all 37 reports ruxolitinib was reported as the sole suspect drug. In 29 of them ruxolitinib was used for the indication myelofibrosis, in three cases the indication was polycythaemia, in one case the indication was lymphatic disorder and in four the indication was unknown. Twenty of the 37 cases were reported by a physician. Among the 36 reports where information on gender was provided, 19 patients were female and 17 patients male. The median age was 72 years (range 49 to 91 years).

Time to onset ranged from seven days up to three years. Information on outcome was provided in 15 reports and included five with no recovery where the action for ruxolitinib is unknown. In two cases there was no recovery after a dose reduction of ruxolitinib and in one the patient was recovering after dose reduction. The remaining cases included four negative dechallenges and three positive dechallenges. One positive dechallenge case had the restart of ruxolitinib in a lower dose, with an unknown outcome. In another positive dechallenge case, atorvastatin, which is a rare cause of peripheral neuropathy,[6] was withdrawn at the same time as ruxolitinib.

A review of concomitant drugs identified three cases where drugs known to be a common cause of peripheral neuropathy were reported (hydroxycarbamide in two reports and tacrolimus in one).[7,8] In four cases HMG-CoA-reductase inhibitors (simvastatin and atorvastatin), and in one bezafibrate, were reported as concomitant drugs. These are known to possibly cause peripheral neuropathy in rare cases.[9,10]

Reviewing the medical history identified two cases where the patient had previously used drugs known to cause peripheral neuropathy, namely hydroxycarbamide in one report and thalidomide in the other. In the second case, it its known that the patient experienced peripheral neuropathy while using thalidomide but information is lacking on action taken with thalidomide and outcome of neuropathy. Another case mentions that the patient was on chemotherapy (bortezomib) when the peripheral neuropathy occurred and that

ruxolitinib was used before and after the chemotherapy.

Literature and Labelling

Neuropathy is not described in current ruxolitinib drug labels[1,4] and no literature reports on peripheral neuropathy have been found for ruxolitinib.

Discussion and Conclusion

Peripheral neuropathy is a common adverse effect of several chemotherapeutic agents such as taxanes, platinum agents, vinca alkaloids, thalidomide, and bortezomib, a proteasome inhibitor. No single mechanism explaining the peripheral neuropathy has been identified and the precise pathophysiology remains complex.[11] A number of mechanisms for drug-induced peripheral neuropathy have been postulated, including immune-based demyelination.[5]

In clinical trials there was at least one case of peripheral neuropathy potentially related to ruxolitinib among the 39 patients in the essential thrombocythemia cohort in an ongoing phase 2 study.[12,13]

Of these 37 cases on ruxolitinib suspected to cause peripheral neuropathy in VigiBase, it is not possible to draw any conclusions regarding a possible mechanism, but it should be noted that other immunomodulatory drugs such as TNFα blocking molecules may cause peripheral neuropathy via demyelination.[5]

For some other JAK inhibitors, peripheral neuropathy has been commonly observed. At one institution, treatment-emergent peripheral neuropathy was documented in 44 of 100 myelofibrosis patients treated with the JAK1/2 inhibitor momelotinib,[14] and with XL019, a selective JAK2 inhibitor, peripheral neuropathy was observed in seven out of nine patients in a phase 1 trial.[15] This substance was also used in a study of 30 patients with myelofibrosis where central and/or peripheral neurotoxicity (including later onset of classical "glove and stocking" sensory peripheral neuropathy) developed in all patients, leading to termination of the study.[16]

In the present case series, there were two cases with obvious indications of significant confounding, namely the case where the patient experienced peripheral neuropathy while using thalidomide and the case where the patient was on chemotherapy when the peripheral neuropathy occurred. Among the other 35 reports there were medicines with known potential to cause peripheral neuropathy listed in eight reports. In none of them, however, were these drugs reported as suspected, and five of these drugs were lipid lowering agents, commonly used in this elderly population.

In light of a possible class effect and a possible mechanism, these cases constitute a signal of peripheral neuropathy induced by ruxolitinib, and this merits further investigation to assess the need for updating relevant product information.

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Response from Novartis

Background

This document provides Novartis' comment on the draft of "Ruxolitinib and peripheral neuropathy" which concluded that a causal association between ruxolitinib and peripheral neuropathy may exist and which will be published in Signal from UMC – WHO Collaborating Centre for International Drug Monitoring. Peripheral neuropathy was fully evaluated as a potential signal in the Jakavi® (ruxolitinib) PSUR 5 (23 Aug 2014 – 22 Feb 2015) based on a literature report[1] describing treatment-emergent peripheral neuropathy (TE-PN) with momelotinib (a JAK-1/2 inhibitor that also targets TYK2[2]). As a result of evaluating peripheral neuropathy and discussing it with health authorities, it was ultimately concluded that at this time, peripheral neuropathy does not constitute an important potential risk and should be continued to be monitored as part of routine pharmacovigilance activities for ruxolitinib.

The evaluation of ruxolitinib does not support the hypothesis that peripheral neuropathy is class-related, as the kinase selectivity and pharmacological profile of other JAK inhibitors differs from that of ruxolitinib, e.g. due to inhibition of non-JAK family kinases. For instance, momelotinib, originally described as a selective JAK1/2 inhibitor, is also a potent TBK1/IKKε inhibitor (IC_{50}=58 nM and 42 nM, respectively).[3] In contrast, ruxolitinib fails to inhibit TBK1 or IKKε in this assay (IC50 >1 μM for both).

Two other JAK inhibitors were associated with neurotoxicity which resulted in termination of further clinical development. The first one, XL019, a highly selective JAK2 inhibitor was associated with central and/or peripheral neurotoxicity in all patients. Since neurotoxicity, particularly CNS neurotoxicity has been rare or absent in studies of other JAK2 inhibitors and its almost universal occurrence with XL019, suggests likely an undefined, off target effect.[4] Another potent selective JAK 1/2 inhibitor, AZD 1480, was associated with low grade neurotoxicity that was considered unacceptable in long term therapy.[5]

In addition, there was a single literature report of a distal symmetric polyneuropathy in a patient treated with tofacitinib (Xeljanz®), a JAK1/3 inhibitor for rheumatoid arthritis.[6]

Epidemiology

Neurological manifestations including peripheral neuropathy have been reported with myeloproliferative neoplasms. Peripheral neuropathy in patients with polycythemia vera was explained with the underlying mechanism of hypoxia due to increased blood viscosity and abnormal platelet aggregation associated with the disease.[7,8,9] In a report from Kawasaki Y et al.[10] neurological disturbance of the lower extremities was seen in a patient due to extramedullary hematopoietic mass complicated with primary myelofibrosis. In a study that reviewed 28 patients with a PV diagnosis, 11 experienced paresthesia. In 13 (46%) patients, clinical examination revealed features suggesting polyneuropathy. Nerve conduction indexes were abnormal in 20 (71%) patients, suggesting the presence of a predominantly sensory axonal polyneuropathy.

No literature reports of peripheral neuropathy linked to ruxolitinib were retrieved.

Data from interventional trials

There were no clear differences in the incidence rates of peripheral neuropathy (narrow SMQ) observed in the randomized periods in the two phase III studies in myelofibrosis (Study CINCB18424-351 and Study CINC424A2352) and polycythemia vera (CINC424B2301 and CINC424B2401). In MF, the incidence was 3% in ruxolitinib arm vs 2.2% in control arms. In PV, in the incidence was 2.7% in ruxolitinib arm vs. 3.2% in control arm.

In longer term follow-up in both MF and PV, exposure-adjusted analysis showed no disproportionate increase in frequency with prolonged exposure.

Data from the safety database

Novartis global safety database was searched cumulatively through 22 Feb 2017, with the following PTs: Neuropathy peripheral/Polyneuropathy/Peripheral motor neuropathy/Peripheral sensorimotor neuropathy/Peripheral sensory neuropathy/Axonal neuropathy and retrieved 103 cases (with 107 events). Of these, in 42 cases, the event was confounded by medical conditions (such as pre-existing neuropathy, diabetes mellitus, thyroid disorder) and concomitant medications (such as statins, thalidomide and its anologues) which are either associated with or can lead to neuropathy. In five cases, due to implausible temporal relationship or negative rechallenge, the role of ruxolitinib in relation to the events was unlikely. In 55 cases, limited information precluded complete medical assessment. In the remaining case, due to positive dechallenge and absence of strong explanation, the role of ruxolitinib in poly-neuropathy was considered possible.

Disproportionality analysis

Traditional safety signal detection activities for all marketed products (both, multinational and mono-national) are supported by a data mining tool, the Empirica Signal System™ (ESS) applied to the Novartis safety database. The disproportionality analyses use the MGPS (Multi-Item Gamma Poisson Shrinker) statistical algorithm and statistical hits are considered when the lower limit of the confidence interval (EB05) is greater than 2. Quantitative analysis using Novartis safety database in the Empirica signal system was performed for peripheral neuropathy and did not reveal a technical signal (defined as EB05>2), with a maximal EB05 of 1.487 through March 2017.

Conclusions

At this time, it is not possible for the sponsor to conclude that peripheral neuropathy is caused by JAK inhibition based on the currently available clinical trial and postmarketing safety data coupled with the known mechanistic data of ruxolitinib. However, the MAH agrees with UMC and will continue monitoring peripheral neuropathy by applying routine pharmacovigilance as well as data mining technologies. The safety topic will be presented again, should future data indicate causality.

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Correction: We regret the typographic error in WHO Pharmaceuticals Newsletter No.3, 2017, pg 19, Introduction, Line 3-6. The sentence should read "It is indicated for the treatment of neuropathic pain, **postherpetic** neuralgia, diabetic peripheral neuropathy, fibromyalgia, epilepsy and for generalised anxiety disorder."

CAVEAT DOCUMENT

Accompanying statement to data released from VigiBase®, the WHO international database of suspected adverse drug reactions

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 pharmacovigilance network, the WHO Programme for International Drug Monitoring (PIDM). The information is stored in VigiBase®, the WHO international database of suspected adverse drug reactions (ADRs). It is important to understand the limitations and qualifications that apply to this information and its use.

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 (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

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 reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase® make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

If in doubt or in need of help for interpretation of country specific data, UMC recommends to contact the concerned NC before using the data.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Confidential data

According to WHO policy and UMC Guidelines, ADR reports sent from the WHO PIDM member countries to VigiBase® are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted 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 UMC must include a statement:

(i) regarding the source of the information
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of 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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Fourteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)

25-26 April 2017
WHO, Geneva

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on Pharmacovigilance policy and issues related to the safety and effectiveness of medicinal products. A summary of discussions and key recommendations from the 14th meeting of ACSoMP is provided below.

WHO Medicines Safety & Vigilance (SAV/Rx): updates

2020 Strategy Focus: The goals and core strategy of SAV/Rx for 2017-2018 are very much aligned with its overall 2020 strategy with the prevailing theme of "no country left behind: worldwide pharmacovigilance for safer medicines, safer patients". The 2020 strategy is focused on building comprehensive, sustainable, results-driven pharmacovigilance (PV) systems. This strategy focuses on developing the right infrastructure, ensuring that good quality data are collected, analysed, used for decision-making and appropriately shared with public health programmes.

Collaboration: Much emphasis has been placed on encouraging global collaboration through platforms such as the WHO Annual Meeting of National PV Centres and knowledge-sharing in PV through the WHO Pharmaceuticals Newsletter and other publications. The bulk of this effort is focused on expanding regional and local networks and partnerships. WHO SAV/Rx continues to take a lead role in convening expert committees, for example, ACSoMP or the International Working Group on Drug Statistics Methodology. Country-level support is focused on the development of tools, approaches and norms for low and middle income countries (LMIC), supporting national assessments, providing technical support, training through interactive workshops, and in providing surveillance and risk management support.

Implementation Approach: The current process, which is being reviewed, is as follows:
1. At the WHO National PV Centres' Annual Meeting, feedback and recommendations on the plans and strategies for the WHO Programme for International Drug Monitoring (PIDM) are sought from Member States.
2. The WHO HQ SAV/Rx team and WHO Collaborating Centres (CCs) then integrate feedback and recommendations into work-plans.
3. Approval and advice are sought from expert committees on annual plans.
4. Grants are sought from donors to ensure sustainable resourcing for PV work.
5. Deliverables and results are shared with Member States at the WHO Annual Meeting of National PV Centres and through publications and presentations at other conferences and key meetings.

2017 Goals: Key SAV/Rx objectives for the year include further initiating new members into the WHO PIDM, aligning PV indicators into a Global Benchmarking Tool (GBT) for National Regulatory Agencies (NRA), assess country 'PV readiness' to support the risk evaluation of emerging products in new markets, drawing institutional development plans to address gaps in PV, supporting the implementation of new technologies, e.g. Mobile adverse events (AE) and adverse drug reaction (ADR) Reporting App in collaboration with the IMI WEB-RADR project[1] in a few Member States, providing continued support to public health programmes (PHP), delivering training on regulatory aspects, e.g. PV inspection workshops and MedDRA, as well as continuing work to encourage collaboration and knowledge-sharing among Member States.

PV Patient & HCP Engagement: More work needs to be conducted by the PV community to increase engagement with the broader health-care community. Further discussion on the right type and the amount of information to provide to patients is needed to ensure the prevention and management of ADRs. It is very important that messages are tailored to the appropriate stakeholder; the current approach adopted for communication in the labelling of medicines needs some improvement, e.g. with 'boxed' warnings in the US, where prescription habits vary greatly; in some cases, this results in a complete lack of a medicine's use rather than signifying controlled use.

[1] The Innovative Medicines Initiative (IMI) WEB-RADR project, focuses on the evaluation of the use of mobile technologies in pharmacovigilance to Recognise Adverse Drug Reactions (RADR). One of the project products is a mobile app for patients and health-care professionals to report suspected adverse drug reactions to national EU regulators. The mobile app is an enabler of two-way data flow and an information portal. The mobile app will have been introduced into 2-3 pilot countries with the ability to scale-up its use by year end, including in Zambia, Burkina Faso. The affordability and accessibility of the app are still being tracked through the pilot schemes; at year end, the WHO SAV/Rx team will report on how the pilot countries have fared. A maintenance working group is being set-up, and the Terms of Reference (ToR) for this group are being outlined.

WHP Collaborating Centres for Pharmacovigilance

WHO SAV works with 4 Collaborating Centres to advance pharmacovigilance (PV) in countries. These are, in the order in which they were established, the WHO Collaborating Centre for: International Drug Monitoring, Sweden; Advocacy and Training in Pharmacovigilance, Ghana; Strengthening Pharmacovigilance Practices, Morocco, and Pharmacovigilance in Education and Patient Reporting, the Netherlands. The 4 WHOCCs were invited, as observers, to the 14th ACSoMP Meeting. The Committee had the following feedback to all 4 Centres:

On-line Training: Much of the training sessions outlined by the centres is conducted in a face-to-face setting. It was suggested this may limit outreach, and that supplementary online training programs that can be pre-recorded with standard Q&As should be leveraged for the more standard work streams. It was noted that the UMC has already invested in building an online platform for training and numerous training videos can be found on the UMC YouTube channel. In addition, the British Pharmacological Society (BPS) has created an online assessment platform which includes questions on PV and PV communication that the General Medical Council (GMC) has made mandatory for prescribers. However, one of the challenges of using online technologies is ensuring its maintenance.

Harmonizing Training: It was also recommended that the training carried out by centres should leverage alternate global resources and more importantly should be coordinated to reduce duplication, to ensure harmonized content and maintenance of the curricula. In addition other available course material and resources should be leveraged in training, e.g. the International Society of Pharmacovigilance (ISOP) course material, the WHO-ISoP PV core curriculum, the WHO CC Accra's PV Toolkit, and resources made available by the UMC on their website and through social media channels. A more challenging aspect of training is that universities will only add PV to their curricula if examiners are willing to test students on the subject; a majority of PV training at universities is run through practical workshops supporting more mature students to qualify for regulatory roles.

The Committee recommended that all PV training activities across all centres should be mapped and included in the WHO repository of training courses and materials.

PV Career Path: It was remarked that students who join relevant doctoral programmes have more success in developing a career path for themselves in PV, and this subsequently results in more sustainable engagement in PV. To encourage participation and ensure long-term engagement, the vocation prospects for trained individuals must be considered when creating training opportunities. The UMC is in the early stages of setting-up a collaboration between UMC and the Consortium for Advanced Research Training in Africa (CARTA) which will offer PhD stipends for PV in Africa.

Active surveillance: WHO/SAV has published a series of handbooks in active surveillance approaches. All 4 Collaborating Centres have supported WHO in advancing these approaches in countries. ACSoMP advised that an overview and a guide on active surveillance best practices and applications will be developed by WHO, building on experience to date, emphasising what currently works and what doesn't. The Committee noted that the new CIOMS Guide to Active Vaccine Safety Surveillance should be leveraged when developing such a best practice guidance, to help with the broader goal of harmonizing PV efforts in vaccines and medicines.

WHO-BMGF Smart Safety Surveillance/Project Triple-S: Optimizing post-marketing surveillance of priority medicines and vaccines in low and middle-income countries

Access to medicines and vaccines in low and middle-income countries (LMIC) has improved in the last few years. But there has not been a proportionate improvement in pharmacovigilance. This is of particular concern given the number of products in the development pipeline that will be launched exclusively in LMIC or simultaneously, in both LMIC and in High Income Countries (HIC), with little experience from advanced settings for LMICs to rely upon. LMIC must, therefore, be supported to introduce new products, to identify, assess, and adequately manage the risks associated with these products. In September 2016, the WHO Safety and Vigilance (SAV) team signed an agreement with the Bill and Melinda Gates Foundation (BMGF) to manage a project to optimise post-marketing surveillance of priority medicines and vaccines in LMIC. The overriding project goal is to ensure timely and adequate ADR reporting and review, and action on ADR data in LMIC where priority Global Health products will be introduced. This will be achieved by implementing smart safety surveillance systems for three pilot products (two medicines and one vaccine) in a few pilot countries of varying PV readiness by:

1. Strengthening the functionality of current PV systems
2. Building capacity to analyse safety data
3. Improving capacity to use PV data for regulatory decision-making
4. Supporting the collaboration between public health programmes and the PV community

Project Triple-S should ideally implement a "launch and leave" system, which enables local stakeholders to manage safety monitoring for all products in the long-term.

It is critical that the project's PV efforts are sustained beyond the pilot, and so much advocacy work has been conducted since 2015 to engage external partners who can support the project by providing technical expertise, financial investment or coordination capabilities. To date, three key external partner meetings have been held; multiple partners have already provided their commitment to support the pilot. In addition, joint media communications from the BMGF and WHO have been published to generate interest in PV and in the pilot.

Pilot products: Criteria to help choose the pilot products were created and tested with external stakeholders and WHO disease-control programmes. The criteria focused on emerging LMIC launches, product approval type, prioritising on those with accelerated/conditional approval, the nature of adverse events identified in the clinical development, public health impact, and exclusive target populations. The criteria used and a proposed shortlist of medicinal products were fully endorsed by the ACSoMP committee. It was further recommended that the criteria used to choose the three pilot products should be shared in a joint WHO and BMGF communique or publication.

Normative: WHO/SAV established a working group to develop an up-to-date global set of indicators to assess LMIC for PV readiness within the context of Project Triple-S. These indicators are drawn from the WHO PV Indicators published in 2015 and other recognized global PV and assessment tools. The indicators were chosen for their ability to capture the core PV development aspects embedded in in Project Triple-S encompassing policy, law and regulation, system structure and stakeholder coordination, signal generation and data management, capacity for risk assessment and risk management, communication and resourcing. These selected indictors will be used to measure the in-place PV infrastructure, competence, capacity and gaps in LMIC, to study their capacity to assess and act on the benefit-harm information of the Pilot products in Project Triple-S.

Country Assessments: Project Triple-S' success will depend on the target countries' ability to adopt and implement PV. An assessment of the potential target countries, and of relevant local stakeholders will be critical to ensure success. It was recommended that countries with PV systems of varying maturity be included in the pilot phase, to help understand the types of countries and systems that will benefit the most from external support. The pilot phase will include four to six countries. The pilot products will be used to build or enhance PV systems/capacity, while the processes and systems will be used to strengthen the data and information on these products.

End-to-end PV for policy decisions: ACSoMP members noted that Project Triple-S will be a "game-changer" in the PV space, in particular with its focus on building an end-to-end PV system which will very likely impact future product launches, but the entire safety data set that can instigate policy decision-making will likely not be available in Project Triple-S' three-year timeframe. Nonetheless, impact and success can be measured through an assessment of the number of reports, their quality, and the ability of LMIC to analyse and use the data for decisions.

Risk Management Plans (RMP): It was noted that industry often pays little attention to local risk management plan requirements in developing markets. Often this is because many NRA do not request this information from industry; regulatory requirements for PV are inconsistent and minimal in many LMIC, many NRAs simply request periodic safety update reports. RMP will be an integral part of the PV protocol in Project Triple-S; a spectrum of training activities has been embedded, including establishing a vigilance framework, ensuring that there is regulatory capacity for managing new submissions, close engagement with industry, outlining a risk management plan as part of a drug or vaccine's application process and ensuring the feasibility of RMP in local settings.

Collaboration between medicines and vaccines: The importance of close collaboration and aligned evaluation of both medicines and vaccines work is well recognized within Project Triple-S. The WHO teams are equally involved, and representatives from both ACSoMP and the Global Advisory Committee on Vaccine safety (GAVCS) will converge to form the Project Advisory Group (PAG), to ensure good alignment between medicinal and vaccines vigilance.

Advisory Input: WHO/SAV proposed inviting the co-chairs of ACSoMP as lead members of Project Triple-S Advisory Group, with other WHO Expert Committee members brought in as needed, for scientific guidance and oversight of specific project activities. This approach was endorsed by the members of ACSoMP. The ACSoMP fully endorsed Project Triple-S and the Committee co-chairs agreed to provide expert input as part of the Project Advisory Group (PAG).

Pharmacovigilance Success Stories: A key goal of Project Triple-S is to strengthen PV systems and practices. Although not all LMIC have resources to implement a comprehensive end-to-end PV system, this is the long-term goal. Understanding any individual successes in one or more key PV aspects in LMIC is critical to ensure optimal approaches to PV. WHO/SAV undertook a review of LMIC that have demonstrated success in at least one specific PV function, to understand the reasons for the success and use the lessons learnt to develop a 'best practice' guidance to support PV development and implementation in LMIC. Six countries were included in the study that used a structured interview to gain insight on a specific PV topic per country, e.g. strategies

that underpin the integration of PV in public health programmes (PHP); how to build a resilient PV infrastructure; introducing electronic reporting, etc. Insights were then analysed to identify interventions and "good working" practices that may lead to success. ACSoMP members agreed that this work is of particular importance because agencies that fund PV frequently request a measure of success in PV. It was recommended that the final summary and guideline capture the impact of PV in each country, the perceived challenges and successes, and finally, the potential consequences of not having a PV system in place. The Committee recommended that the final output be published and presented at the WHO Annual Meeting of National PV Centres in 2017.

CIOMS update

Key CIOMS developments that are of interest to ACSoMP, such as CIOMS Working Group on Drug Induced Liver Injury, were briefly highlighted. In addition to the CIOMS Guide to Active Vaccine Safety Surveillance, a draft on safety communication in vaccines, created in collaboration with WHO and, ISoP, is in the pipeline. The committee noted that WHO SAV will work closely with CIOMS to develop this protocol and will reach out to WHO CCs to pressure-test and refine the outcome.

Integration of PV with broader initiatives - 'Coalition of Interested Partners'

As an increasing number of individual organizations have become involved in Strengthening Regulatory Systems, the WHO is in the process of establishing a 'Coalition of Interested Partners' or CIP framework to achieve better coordination, efficiency, outcomes and sustainability of these efforts in the same target Member States (MS) or region, to achieve better public health outcomes. The core objective is to create a more coordinated approach by defining roles and responsibilities amongst all stakeholders, share planned activities, reduce redundancies and identify opportunities for complementary action, and create a single development plan for countries involving all stakeholders.

The WHO is well positioned to lead this coordination effort by virtue of its mandate and experience. In general there has been a positive move towards regional collaboration in regulatory systems strengthening (RSS) as showcased by the African Medicines Regulatory Harmonization (AMRH) initiative, RSS discussions in South East Asia on malaria elimination, the "Call for Action" at the first Intergovernmental Authority for Development (IGAD) regulatory conference and the PV stakeholders meeting that took place in Rabat this year. Although regional meetings show a positive reception to CIP, it's critical that individual Member States agree to the coalition approach.

No additional funding will be sought through this initiative; current donor relationships will be maintained. The Project Triple-S will also be used as a pathfinder pilot, establishing a more collaborative approach to PV knowledge-sharing, capacity building and implementation approaches, and reducing redundancies.

In December 2015, the concept was first presented at the second international consultation on the WHO global regulatory authority benchmarking tool. In 2016, the CIP framework approach was further developed with a meeting held at the Bill and Melinda Gates Foundation (BMGF) offices in Washington DC, and then again at a pre-International Conference of Drug Regulatory Authorities (ICDRA) meeting in Cape Town. The first pilot on the CIP approach was launched in Dhaka, Bangladesh, in May 2016; this is on-going. All relevant services and target countries are currently being mapped and a taskforce is being formed to lead development and implementation.

The committee congratulated the team on this important effort, fully endorsed the approach and agreed that Project Triple-S should take full advantage of the CIP approach. The committee requested that the proceedings of the CIP taskforce are published and recommended that a small PV working group be established to support this initiative.

The cardiotoxicity of antimalarials. A Report from the WHO Evidence Review Group

The cardiotoxicity of antimalarial medicines has received renewed interest in recent years following the 'Thorough QT' assessment of the dihydroartemisinin-piperaquine formulation approved by the European Medicines Agency, which showed evidence of QT interval prolongation. Piperaquine is a bisquinoline antimalarial that is structurally related to chloroquine. Many drugs among the quinoline and structurally-related medicines affect myocardial depolarization and repolarization. WHO currently recommends the artemisinin-based combination treatment dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria. This treatment is being considered alongside other antimalarial medicines for preventive therapy and mass drug administration.

To inform WHO recommendations, a group of experts met in October 2016 to review evidence on the cardiotoxicity risk of quinoline antimalarials and structurally-related medicines in people with and without

clinical malaria. The following recommendations were proposed by the WHO Evidence Review Group (ERG) for consideration by the WHO Malaria Policy Advisory Committee and the WHO Advisory Committee on Safety of Medicinal Products:

1. Apart from halofantrine, antimalarial medicines that prolong the QT/QTc interval, such as quinine, chloroquine, artesunate-amodiaquine and dihydroartemisinin-piperaquine, have been associated with a low risk of cardiotoxicity.
2. Drug-induced QT/QTc interval prolongation is a surrogate indicator for increased risk of drug-induced torsade de pointes (TdP), a potentially lethal polymorphic ventricular tachycardia. Risk factors for drug-induced QT/QTc prolongation include female gender, structural heart disease, genetic defects of cardiac ion channels, electrolyte disturbances, bradycardia, hepatic impairment, and concomitant use of medications that prolong the QT/QTc interval or increase drug levels. Antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution in individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmias, or who are already taking medicines that can prolong the QT/QTc interval.
3. Dihydroartemisinin-piperaquine and artemether-lumefantrine have been the most intensively studied antimalarial drugs. No sudden deaths have been attributed to cardiotoxicity following artemether-lumefantrine. However, among ~200 000 treated individuals with close follow-up, one possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported. This finding is consistent with the risk of fatal cardiotoxicity associated with other QT/QTc-prolonging medicines in current use.
4. Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, reveals no evidence of a significant difference in the risks of cardiotoxicity following exposure to piperaquine, chloroquine or amodiaquine at the current recommended doses. The risks of cardiotoxicity of piperaquine-containing medicines are probably similar for healthy volunteers and malaria patients.
5. Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk. Further studies are needed to identify genetic polymorphisms and other pre-existing conditions that may contribute to the risk of drug-induced cardiotoxicity. More evidence on the potential cardiotoxicity of chloroquine, amodiaquine and primaquine is needed.

The ACSoMP committee fully endorsed this comprehensive review and recommended that the findings be published in an open access journal. ACSoMP members noted that a simple risk minimization algorithm (exclusion criteria), that can be used by physicians in case management, should be developed by the WHO Global Malaria Programme in consultation with ACSoMP. A further recommendation was made that language in patient and physician information packages is carefully reviewed so as not to over-amplify the risks of cardiotoxicity.

Safety Monitoring in Seasonal Malaria Chemoprevention (SMC) in the Sahel region

SMC is defined as "the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season, with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk, to prevent malaria. SMC is recommended in areas of high seasonal malaria transmission throughout the Sahel sub-region. Preventive treatment composed of sulfadoxine–pyrimethamine plus amodiaquine should be given to children aged 3–59 months at monthly intervals for 4 months, (provided both drugs retain sufficient antimalarial efficacy). Twelve African countries have included SMC since 2013. By 2016 the drugs had been administered to 16 million children.

Pharmacovigilance is being integrated into the SMC programme to detect and report all adverse events (AEs) related to SMC medicines with a focus on serious reactions, to define the safety profile of the drugs in SMC, and to strengthen PV systems in target countries. It started with a situational analysis that highlighted weaknesses in the Safety Monitoring Systems, and the training required for PV and malaria programme staff. Workshops were then conducted to strengthen PV country expertise, comprehensive support was provided to ensure effective implementation of safety monitoring, with a safety committee to review the outputs.

In general not all SMC ADR data seem to get reported to VigiBase, the WHO global Individual Case safety Reports (ICSR) database. The Reporting frequency seems to be a bit higher for phone (SMS)-based reporting than reporting through Cohort Event Monitoring (CEM), while both SMS and CEM reporting were higher than through spontaneous reporting systems. Due to the high frequency of vomiting, a risk management algorithm was created to help HCPs manage post-drug administration vomiting. There was some concern that the serious ADRs were reported only through emails, when requested, and not routinely to VigiBase. An assessment needs to be conducted on a larger scale to understand if this is a larger problem or specific to SMC. In addition, the current systems (VigiFlow) and practices of reporting to VigiBase must be assessed further to understand any additional reasons for the under-reporting.

Longer-term training and funds for the national PV department are essential to sustain and apply what was learned. The benefit of SMC can be quantified through the malaria surveillance systems. It showed 40-60% reduction in malaria cases in this vulnerable population. It was noted that the benefit-risk profile of SMC is positive and ACSoMP endorsed the activities undertaken so far to support the safe implementation of SMC.

Pharmacovigilance of TB Medicines

The goal of this session was to update ACSoMP committee on safety data on bedaquiline

USFDA: There were fewer than 100 cases of multi-drug resistant TB (MDR TB) in the US in 2015. Bedaquiline is designated an orphan drug and in 2012 received accelerated approval based on surrogate data (time to sputum culture conversion over 24 weeks) with a boxed warning for two safety issues: increased mortality and QT prolongation. Approval was conditional based on seven post-marketing requirements and two post-marketing commitments focused on registry formation and additional clinical data collection. Bedaquiline is not widely used in the US; to date, the USFDA has not identified any important new safety signals, and subsequently, only limited label changes and safety precautions have been added since approval.

EMA: In Europe, bedaquiline was authorised by the EMA in 2013. Orphan drug designation was also assigned to bedaquiline and conditional approval was granted requiring additional monitoring efforts. Safety evaluation based on spontaneous reports is challenging because it is difficult to isolate individual effects of the drug on a patient due to severe comorbidities, concomitant medications and previously failed TB treatments. The RMP was important to identify risks including QT prolongation and increased transaminases. A confirmatory Phase III trial (STREAM) was requested in addition to an MDR registry, but they have both been slow to recruit subjects.

India: Bedaquiline was made available in India for 'compassionate, named patient use' before it was approved in May 2015 under the conditional access program, to be made available through the Revised National Tuberculosis Programme (RNTCP). Guidelines for use were approved in November 2015. A detailed procedure for recording and reporting ADRs was established and the Programmatic Management of Drug Resistant Tuberculosis (PMDT) guidelines were modified to include bedaquiline-specific information. In addition, patient information booklets, consent forms, cohort event monitoring forms and suspected ADR forms were developed.

A software bridge allows the seamless transfer of PV data between the TB programme database and the National PV database. A data safety committee has been set-up to assess the benefit-harm profile, and recommend regulatory action, if required. Regular meetings and health worker training workshops have taken place since 2016. Guidelines have been developed to support bedaquiline use, data entry and to emphasise the importance of pharmacovigilance.

389 patients have been enrolled so far. 155 ADRs have been reported; commonly reported ADRs include nausea, vomiting, anaemia, alanine aminotransferase (ALT) increase, acne, T-wave inversion, QT prolongation, lipase increase, abdominal pain and hypotension. In view of the potential safety benefit and unmet need, the Data & Safety Monitoring Committee (DSMC) has recommended the scale-up of access to all TB-sites capable of implementing the conditional approval protocol.

The Committee recommended that, given the scale-up of treatment, safety data from US FDA and EMA be shared with India. A pilot assessment of the ease and efficiency of collecting safety information from global regulatory sources should be conducted. The response time and quality of information provided should also be assessed. The Committee also noted that the experience from India would be useful in implementing data linkages between public health programmes and National PV databases in other countries.

Global Programme to Eliminate Lymphatic Filariasis (GPELF) – Alternative Mass Drug Administration Strategies

Lymphatic Filariasis (LF) is endemic in 73 countries with 946 million at risk of infection. The GPELF was launched in 2000 to stop transmission through Mass Drug Administration (MDA) and to reduce suffering and improvement of quality of life, through morbidity management and disability prevention (MMDP). MDA involves a combined dose of 2 medicines given annually to an entire at-risk population in the following way: albendazole (400 mg) together with either ivermectin (150–200 mcg/kg) or with diethylcarbamazine citrate (DEC) (6 mg/kg). The MDA strategy takes time, mapping takes longer than 5 years typically and post-MDA surveillance can run for greater than 4 years.

Currently, 28 countries are not on track to achieving elimination. Alternative strategies are needed to reduce the time required to interrupt transmission. The new WHO guidelines (under development) will include a review of a new triple combination option of albendazole, ivermectin and diethylcarbamazine and an increased frequency of current MDA combinations compared to the current annual regimens. To date, efficacy, measured by a reduction in microfilaria levels (Mf) of the new triple combination therapy shows excellent results.

In the 'current' MDA strategy (that is, not triple combination therapy), observed adverse events (AEs) are more common in highly infected patients and areas of high endemicity, most frequent after the first MDA round, with a reduction after each round of treatment, and is more serious with filarial co-infections. This is thought to be due to the overall stress on the immune system in clearing MF. MF levels are lower in subsequent annual treatments during MDA. ACSoMP members have been providing feedback on safety monitoring and related -issues and can provide additional input before final submission of the new WHO GPELF guideline.

Pharmacovigilance Curriculum for Undergraduate Programmes in Universities

In collaboration with SAV/Rx, the WHO CC in Lareb is developing an undergraduate pharmacovigilance curriculum, to ensure that future health-care professionals are well equipped to manage ADRs and to improve patient safety in the long-term. The curriculum should enable the student to:

1. Understand the importance of pharmacovigilance in the context of pharmacotherapy
2. Prevent ADRs when possible
3. Recognize ADRs when they occur
4. Respond to ADRs (management, including treatment of ADRs)
5. Report an ADR

In order to develop these competencies, the student needs to have knowledge of clinical pharmacology, including pharmacokinetics and pharmacogenetics, pharmacotherapy, pathophysiology, the basics of drug development and registration, and the role of searching for and interpreting scientific literature. ACSoMP recommended that other than the core principles mentioned, communication of safety data and the ability to explain an ADR or AE should also be included. The Committee endorsed the framework outlined and recommended that the curriculum, when developed, should be published.

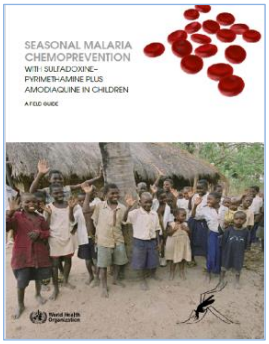
Measuring the Impact of Pharmacovigilance Activities

Throughout ACSoMP 2017, much discussion centred on measuring the impact of PV. The approach used by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) was outlined. As PV teams work through the risk management cycle, it's important to understand how well they are operating, how effective they are, and if they can do better. The PRAC strategy on measuring PV activities was adopted in January 2016, and includes an evaluation of processes, e.g. signal detection, risk minimisation, product-related risk minimisation activity, stakeholder engagement and the identification or development of methods. A pilot was carried out by PRAC in 2016 to test the integration and prioritisation of measuring PV impact in regulatory practice. A workshop on measuring the impact of PV was then carried out. Recommendations from the workshop are to make use of robust science, ensure transparency and clarity of concepts, make use of innovative technologies, ensure prioritisation into public health criteria, ensure there is systematic and routine data collection for all processes, leverage a multi-stakeholder collaboration, including patients and HCPs. Going forward, PRAC will team up with the European Network of Centres for Pharmacovigilance and Pharmacoepidemiology (ENCePP), patients, HCPs, and industry to develop this further. In addition, two studies initiated in April 2017 on diclofenac and hydroxyzine will be used to measure the success of PV implementation.

Integrating Pharmacovigilance in Seasonal Malaria Chemoprevention: the story so far

Since the WHO issued a recommendation in 2012 for pharmacovigilance (PV) to be strengthened where it exists, and instituted where it does not exist in countries implementing seasonal malaria chemoprevention (SMC), huge efforts have been made by various stakeholders to integrate PV in SMC programmes.(1) At the time the recommendation was issued, countries eligible for SMC varied in their PV capacity, some had an established PV system, and others had no formal National PV Centres and were not part of the WHO Programme for International Drug Monitoring (PIDM). And then there were those with a rudimentary PV system that were not fully functional.

This article describes WHO led initiatives that took place after the 2012 recommendation to improve PV in countries implementing SMC, and outlines the impact that activities have made on reporting.



SMC field guide, WHO, July 2013

What is SMC and who is implementing it?

Seasonal malaria chemoprevention (SMC) is defined as the intermittent administration of full treatment courses of antimalarial medicines during the malaria season to prevent malaria illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk. This consists of a combination of amodiaquine and sulfadoxine-pyrimethamine (AQ + SP) administered to children aged between 3 and 59 months at monthly intervals beginning at the start of the transmission season, for up to four months during the malaria transmission season, provided both drugs retain sufficient antimalarial activity. Countries adopted SMC as early as 2012 in Chad and Mali. Following 2012, more countries have implemented SMC and in 2016, 12 countries (Burkina Faso, Cameroon, Chad, Gambia, Ghana, Guinea, Guinea Bissau, Mali, Niger, Nigeria, Senegal, Togo) deployed a total of approximately 73 million doses in children aged between 3 months to 5 years, with the exception of Senegal where SMC was administered to children up to the age of 10 years.

Interventions and progress of integrating pharmacovigilance in 2015

April 2015: Recommendations made at the WHO Advisory Committee on Safety of Medicinal Products (ACSOMP)

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003 to provide advice to WHO and through WHO to the Member States of WHO, on safety issues relating to medicinal products. ACSoMP meets once a year to discuss ongoing PV topics, and in April 2015, SMC was on the agenda.(2) In this meeting, ACSoMP recommended that all adverse events (both serious and non-serious events) should be collected in countries where SMC will be launched; and WHO should work with partners to ensure this. ACSoMP also recommended that an independent regional committee should be established by WHO to review the safety data from the SMC initiative and to report to ACSoMP.

PV support for SMC should build on existing systems; in the absence of a PV system in a country, SMC should be leveraged to introduce PV within the country.

May 2015, Workshop for Seasonal Malaria Chemoprevention and Pharmacovigilance

In order to build and/or strengthen PV systems in SMC countries, a workshop providing basic pharmacovigilance training was organized by WHO in collaboration with the London School of Hygiene and Tropical Medicines (LSHTM) in May 2015.(3) The workshop was hosted by the WHO Collaborating Centre for Strengthening Pharmacovigilance practices in Rabat, Morocco. The aim of the workshop was to help Sub-Saharan African countries develop an appropriate PV plan in preparation for the implementation of SMC scheduled to commence between July and August 2015. Participants included representatives of national PV centres and those responsible for PV in National Malaria Control Programmes.

PV Progress

Prior to the PV workshop in May, Chad was not a member of the WHO Programme for International Drug Monitoring (PIDM). Following implementation of a PV development plan formed during the workshop in May, Chad became an associate member of the WHO PIDM in August 2015.

Interventions and progress of integrating pharmacovigilance in 2016

February 2016: meeting to share country experiences and lessons learnt

A successive meeting was convened by WHO in February 2016 to share country experiences and lessons learned.(4) The workshop was again hosted by the WHO Collaborating Centre for Strengthening Pharmacovigilance Practices, in Rabat and organized in collaboration with WHO and LSHTM.

Countries presented their key achievements and challenges associated with integrating PV. Participants expressed that not enough time was given to training PV in countries. Moving forward, it was agreed that that training should extend to doctors/nurses/pharmacists in district hospitals. Another challenge was that information flow was too slow/stagnant (i.e. reports of suspected adverse drug reactions were slow to reach the national PV centre national malaria control programme, and most did not reaching the WHO global database of Individual Case Safety Reports). Technology was identified as a key tool to assist with reporting, for example the use of e-reporting and mobile apps.

Tailored WHO-ISOP PV modules for SMC training

Following a request for training materials, WHO developed a PV training and implementation guide for integrating PV in SMC. The aim of the manual is to adapt the WHO-ISOP Pharmacovigilance curriculum to present a PV training programme tailored for healthcare professionals and community workers involved in the distribution, administration and safety monitoring of medicines used for SMC during mass drug administration campaigns. In addition to fundamental PV principles there is a focus on the pharmacology and ADRs associated with SMC and other antimalarial medications. Two versions of the curriculum have been designed to meet the learning needs of 1) healthcare professionals at district level and 2) community health workers.

June 2016: Recommendations made at the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)

In June 2016, ACSoMP reviewed the draft of the WHO–ISOP PV curriculum adapted for the purpose of SMC-specific PV training modules for the purpose of use in PV trainings that will be carried out in countries implementing SMC. The Committee endorsed the training material and emphasized the importance of: involving PV centres in the training, timing training session well before SMC-launch, and tailoring-training for SMC.(5) The Committee also reiterated its previous recommendation that all adverse events (both serious and non-serious events) should be collected in SMC. In addition, a safety review committee has been established, to review PV data from SMC in countries and to provide advice on any risk management plans.

September 2016: PV Workshop targeting health care professionals in district hospitals , Burkina Faso

Following the development of PV modules tailored to SMC, a workshop was designed for doctors, nurses and pharmacists working in district hospitals in Burkina Faso. The concept of a district investigation team was introduced and there was an emphasis on how to manage and communicate serious adverse events. PV focal persons at national level from other SMC countries were invited to participate with the aim that they organize their own training sessions in the future. The workshop aimed to introduce PV training using the WHO-ISOP curriculum with a focus on SMC medicines. Material is structured to support the train the trainer format.

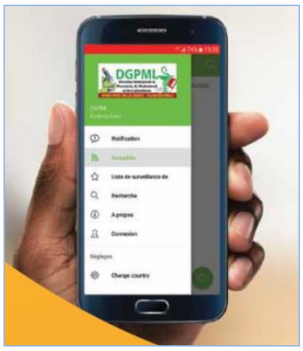
Interventions and progress of integrating pharmacovigilance in 2017

April 2017: Recommendations made at the WHO Advisory Committee on Safety of Medicinal Products (ACSOMP)

ACSoMP highlighted that funding for capacity building and maintenance is important to ensure successful implementation. It was noted that evidence collected so far, showed that the benefit-risk profile of SMC is positive and ACSoMP endorsed the activities undertaken to support the safe implementation of SMC. There was some concern that serious ADRs were not routinely reported and an assessment to understand if this is a problem specific to SMC or if it occurs on a larger scale was recommended.

May 2017: Pilot Mobile 'APP' for reporting suspected adverse drug reactions launched in Burkina Faso

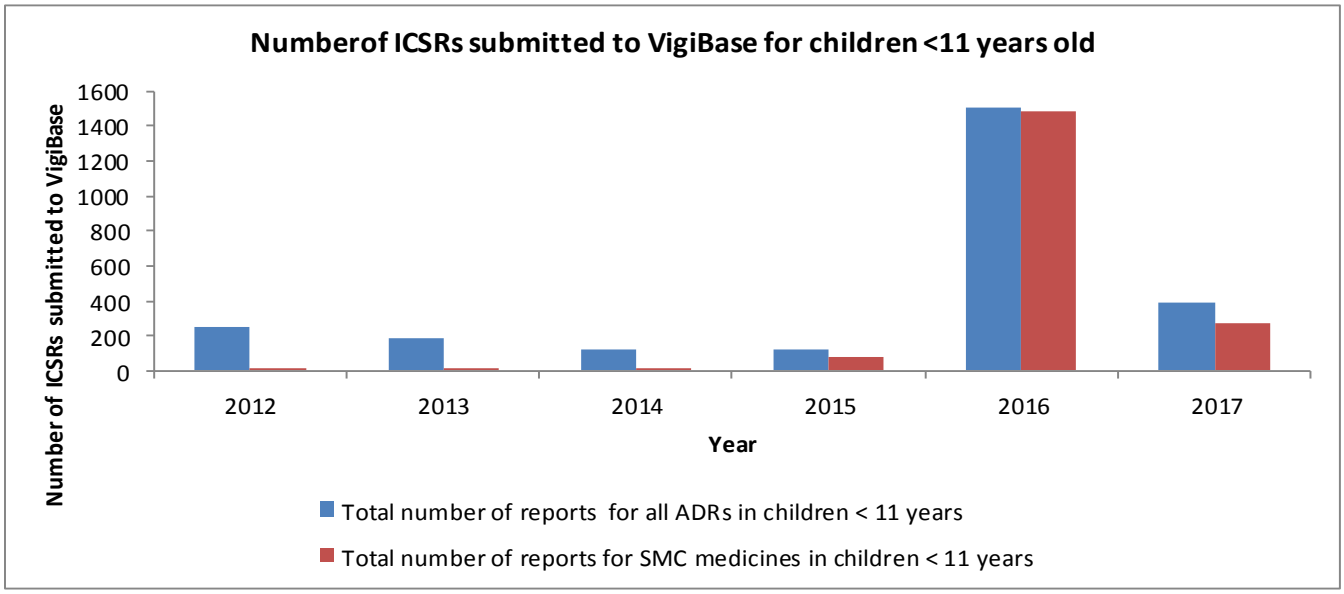
Recent technological advances have led to the development of mobile apps for reporting ADRs, many of which allow reports to be made offline with the possibility of sending the report later when the user is online and internet access is available.



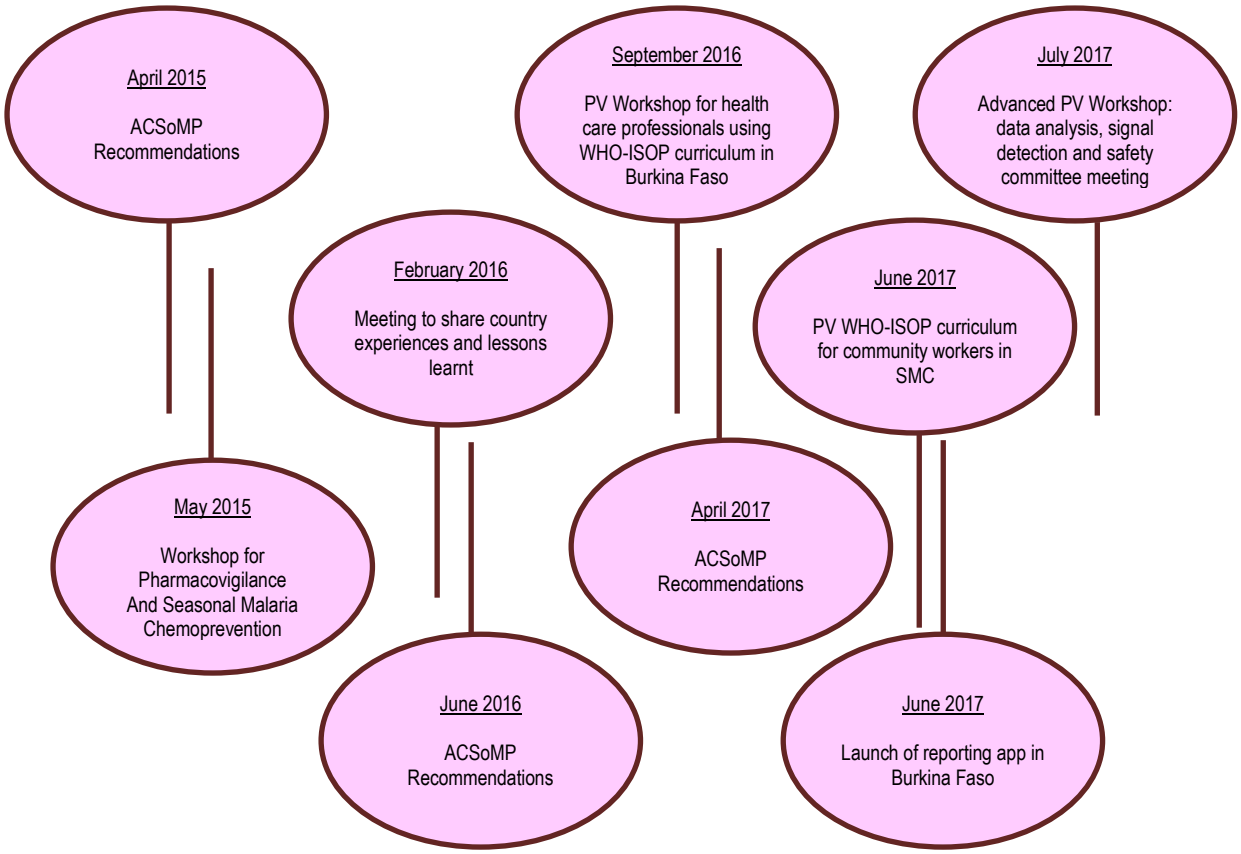
The "Web-Recognising Adverse Drug Reactions (WEB-RADR)" project is supported by the European Commission's Innovative Medicines Initiative, and explores the volume, breadth and quality of social media data, and consequently, where they may add value from a pharmacovigilance perspective. One of the work packages of this initiative is dedicated to developing a mobile app for reporting ADRs. The WEB-RADR team in collaboration with WHO worked with representatives from Burkina Faso to customize the app for use in Burkina Faso. After preliminary testing, the app went live on 8 May 2017.(6) A widespread awareness campaign, involving leaflets, interviews on the radio, television and an official launch ceremony was conducted. The app is expected to increase reporting of suspected adverse drug reactions that occur with SMC and shorten the time in which reports reach the WHO global database of ICSRs, VigiBase.

July 2017: Advanced workshop for integrating PV in SMC.

An advanced workshop for integrating PV in SMC was organized by WHO from 3 to 14 July 2017. The workshop built on previous training on integrating PV in SMC by focusing on managing, reviewing and analyzing data collected from SMC campaigns. The workshop was held in the WHO Collaborating Centre for Strengthening Pharmacovigilance Practices in Rabat. Representatives from National PV Centres and malaria programme managers from Cameroon, Chad, Guinea, Mali and Togo attended. Participants brought all case reports for SMC obtained in their countries to the workshop with them. They were assigned a facilitator who guided them through the processes of: reviewing the case safety reports for completeness seriousness and expectedness; performing causality assessments; and signal detection. At the end of the workshop, participants joined the Safety review committee meeting. During this meeting signals identified were discussed and follow-up recommendations were made.



The number of Individual Case Safety Reports (ICSRs) submitted to the global database of ICSRs, VigiBase for medications in children under the age of 11 years has increased following interventions made in 2015. Most of the reports contain medicines used in SMC.



Activities performed by WHO and WHO Collaborating Centres to strengthen pharmacovigilance practices in Seasonal Malaria Chemoprevention.

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Fourth Asia Pacific Pharmacovigilance Training Course In Mysuru, India

JSS University and Uppsala Monitoring Centre hosts the fourth Asia Pacific Pharmacovigilance Training course at JSS University in Mysuru, India - ***29 January 2018 to 9 February 2018***

JSS University's Asia Pacific Pharmacovigilance Training course offers a programme to a about 30 professionals each year, in collaboration with Uppsala Monitoring Centre at the College of Pharmacy in Mysuru, India. Previous courses have taken place in Mysuru in February 2015, January 2016 and January 2017.

Participants study topics essential to effective pharmacovigilance, including sessions to strengthen the performance of members of the WHO Programme, such as pharmacovigilance best practice and tools, signal detection, regulatory aspects and reporting culture.

There is also a management component to help participants improve their capacity to bring about sustainable change in their countries. Issues related to health economics, communications, fundraising and risk management are covered. Training, built around lectures, workshops and hands-on exercises, takes place in an open and engaging environment.

For more information you may visit JSS University website and UMC website.

To register for the course, please go to this online form: Registration form at the JSS University website.

Any queries about the course should be sent to: pvtraining@jssuni.edu.in