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

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

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 a brief report on the 40th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

Contents

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Feature

Amoxicillin containing products

Risk of thrombocytopenia

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for amoxicillin preparations have been updated to include the risk of thrombocytopenia as a clinically significant adverse reaction.

Amoxicillin is an antibiotic used for the treatment of a number of bacterial infections.

A total of nine cases of thrombocytopenia associated with use of amoxicillin have been reported in Japan. Of these, a causal relationship could not be excluded in five cases.

Reference:
Revision of Precautions, MHLW/PMDA, 17 October 2017 *(www.pmda.go.jp/english/)*

Chlorhexidine containing products

Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for chlorhexidine containing products, including over the counter preparations (Hibitane®, Acesclean®, Despakowa® and others) have been updated to include the risk of anaphylaxis as a clinically significant adverse reaction.

Chlorhexidine is generally used for disinfection.

A total of 12 cases associated with shock or anaphylaxis have been reported in Japan. Of these, a causal relationship could not be excluded in four cases.

Reference:
Revision of Precautions, MHLW/PMDA, 17 October 2017 *(www.pmda.go.jp/english/)*

(See page 10 and WHO Pharmaceuticals Newsletters No.2, 2017: Rare but serious allergic reactions in the USA and No.3, 2016: Serious allergic reactions in Canada)

Clozapine

Amendments to the patient monitoring programme

Spain La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) has reduced restrictions made in the patient monitoring programme on clozapine. It is no longer a requirement to send results of blood and laboratory tests to the AEMPS when prescribing clozapine.

Clozapine is an antipsychotic used to treat symptoms of schizophrenia and psychotic disorders associated with Parkinson's disease, when standard treatments are not effective.

Regular blood and laboratory tests (weekly and monthly leukocyte counts) have shown to be effective in preventing the occurrence of agranulocytosis and possible complications. However, in order to reduce the burden associated with sending blood results, the monitoring programme has been simplified:

It is not mandatory for prescribing doctors to send results of blood tests to the AEMPS, however this does not exempt them from carrying out the tests and keeping records of results in accordance to the license authorization conditions.

- Doctors no longer need to deliver the patient's chart at the time of prescription and pharmacies do not need to request it from the patient in order to dispense.
- Medicines that contain clozapine continue to be classified as medically controlled and, therefore, subject to dispensing requirements.

It should be remembered that blood and laboratory tests should be continued in patients undergoing treatment and prescription and dispensing conditions have not been modified.

Reference:
Información dirigida a profesionales sanitarios, AEMPS, 4 October 2017, Spain (*www.aemps.gob.es*)

(See WHO Pharmaceuticals Newsletter No.5, 2015: Modifications for monitoring neutropenia in USA)

Codeine-containing products

Contraindication in children and ultra-rapid metabolisers

Australia. The Therapeutic Goods Administration (TGA) has updated the product information documents for all prescription codeine preparations to include the restriction of use in children and ultra-rapid metabolisers. More specifically, codeine products should no longer be used in children under 12 years of age, or in children aged 12-18 years who have recently undergone surgery to remove their tonsils or adenoids. Codeine should also not be used by breastfeeding mothers or in patients known to be ultra-rapid metabolisers.

Most product information for over-the-counter codeine preparations now have warnings to not use them in children aged under 12 years.

From 1 February 2018, all "Pharmacy Medicine" and "Pharmacist Only Medicine" codeine-containing products will be rescheduled to "Prescription Only Medicine".

Reference:
Medicines Safety Update, TGA, Vol. 8, No. 5, November 2017 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.4, 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 for related information)

Daclizumab

Risk of serious liver damage

Europe. The European Medicines Agency's (EMA) has concluded that further restrictions on the use of the daclizumab (Zinbryta®) are necessary following a review of the medicine's effects on the liver.

Daclizumab is a medicine used to treat certain patients with relapsing forms of multiple sclerosis.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) review found that unpredictable and potentially fatal immune-mediated liver injury can occur during treatment with daclizumab and for up to six months after stopping treatment.

In order to reduce the risks, doctors should now only prescribe daclizumab for relapsing forms of multiple sclerosis in patients who have had an inadequate response to at least two disease modifying therapies (DMTs) and cannot be treated with other DMTs.

In addition, doctors should monitor patients' liver function (ALT, AST and bilirubin) at least once a month as closely as possible before each treatment and continue monitoring them for up to six months after treatments have stopped.

If the patient does not comply with monitoring requirements or the response to treatment is inadequate, doctors should consider stopping treatment.

It is recommended that the doctor should stop treatment if a patient has liver enzyme levels over three times the normal limit and refer patients with signs and symptoms of liver damage to a liver specialist.

Patients who test positive for hepatitis B or C infection should also be referred to a specialist.

Daclizumab must not be used in patients with pre-existing liver disease and should not be started in new patients with over two times the normal range of liver enzymes. It is recommended that doctors do not use daclizumab in patients with other autoimmune conditions.

The PRAC is also recommending that, in addition to the current educational materials, patients and health-care professionals in the EU should be given an acknowledgment form. The form will be used to confirm that doctors have discussed the risks with their patients and that the patients understand the importance of monitoring and checking for signs of liver damage.

Reference:
News and press releases, EMA, 27 October and 10 November 2017 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletter No.4, 2017: Provisional restrictions for use in EU)

DPP-4 inhibitors

Risk of arthralgia

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 labels for DPP-4 inhibitors to include arthralgia as a potential adverse drug reaction.

DPP-4 inhibitors are used for the treatment of type 2 diabetes mellitus.

Between July 2011 and August 2017, PvPI received 96 reports of arthralgia with DPP-4 inhibitors use. The cases were reviewed by Signal Review Panel (SRP)-PvPI, IPC who concluded that there was a strong causal relationship between DPP-4 inhibitors and arthralgia.

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

(See WHO Pharmaceuticals Newsletters No.3, 2017, No.6, 2015 and No.5, 2015 for related information)

Fingolimod

Contraindicated in patients with underlying cardiac pathology and risks of skin neoplasms

Spain After a periodic evaluation of safety data for fingolimod (Gilenya®), the AEMPS has recommended that health-care professionals should not use fingolimod in patients with underlying cardiac conditions.

Gilenya® is the only medication with fingolimod currently authorized in Spain. It is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (MS)).

During a periodic safety evaluation of fingolimod, an outstanding number of cases of polymorphic ventricular arrhythmias were detected after the administration of fingolimod.

Ventricular fibrillation and sudden death were among the cases described. In the deceased patients it was observed that there was a personal history of cardiac pathology.

Based on the evaluation, a number of risk minimization measures have been issued and this includes contraindication of use in patients with underlying cardiac conditions.

The AEMPS has also recommended that patients using fingolimod should be monitored for the appearance of skin lesions. Skin evaluations should be carried out at the beginning of the treatment and every 6-12 months afterwards.

The AEMPS has stated that cases of basal cell carcinoma as well as other skin neoplasms have been reported, including malignant melanoma, squamous cell carcinoma, Merckel cell carcinoma and Kaposi's sarcoma.

Reference:
Información dirigida a profesionales sanitarios, AEMPS, 6 November 2017, Spain (*www.aemps.gob.es*)

(See WHO Pharmaceuticals Newsletters No.1, 2016: Recommendations to minimise progressive multifocal leukoencephalopathy (PML) and skin cancer and No.5, 2015: Risk of progressive multifocal leukoencephalopathy in USA and Japan.)

Fluconazole

Risk of hyperpigmentation

India. The PvPI, IPC has made recommendations to the CDSCO about revising the drug safety label for fluconazole, to include hyperpigmentation as a potential adverse drug reaction.

Fluconazole is used for treatment of systemic mycosis and for prophylaxis of cryptococcal meningitis, oesophageal and oropharyngeal candidiasis, vaginal candidiasis and systemic candidiasis.

Between July 2011 and August 2017, PvPI received 12 reports of hyperpigmentation with fluconazole use. The cases were reviewed by SRP-PvPI, IPC who concluded that there was a strong causal relationship between fluconazole and hyperpigmentation in these cases.

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

Fluconazole (non-prescription)

Potential risks to pregnancy outcomes

Canada. Health Canada has recommended that the product safety information for all non-prescription fluconazole products should be updated to include the potential risk of pregnancy loss and birth defects and state that these products are not recommended for use by women who are trying to become pregnant.

Non-prescription (oral, 150 mg) fluconazole products are authorized to treat vaginal yeast infections.

Health Canada reviewed the potential risk of unwanted effects in pregnancy, including pregnancy loss (i.e., miscarriage or stillbirth) or birth defects (i.e., major congenital malformations) with non-prescription fluconazole use, in part because a recently published study suggested that such a risk may exist.

At the time of the review, Health Canada had received one Canadian report and three international reports of miscarriages that were possibly related to non-prescription fluconazole use. Five international cases were identified in the information received from the manufacturers describing birth defects that were possibly associated with non-prescription fluconazole use; however there was not enough information in any of these reports to conclude a causal relationship.

A search in the WHO global database of Individual Case Safety Reports (ICSRs), VigiBase, found 360 cases of pregnancy loss or birth defects reported in patients treated with fluconazole. There was not enough information in these reports to conclude that fluconazole caused these outcomes or to determine whether the women were taking low dose fluconazole (150 mg or less) or higher doses. Higher dose fluconazole products, available by prescription only, are known to have pregnancy-related risks and these are communicated in the product safety information.

In the pregnancy registry study that suggested a link between fluconazole use and unwanted effects in pregnancy, there was not enough information to conclude whether or not the fluconazole product itself was the cause.

Health Canada's review found that a link between the use of non-prescription fluconazole and the risk of unwanted effects in pregnancy cannot be made at this time based on the currently available information.

The manufacturers have voluntarily updated the product safety information in prescription only products. Health Canada has recommended that the product information for all other non-prescription fluconazole products should be updated in the same way.

Women continue to be advised to avoid use of non-prescription fluconazole products while pregnant.

Reference:
Summary Safety Review, Health Canada, 9 November 2017 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.3, 2017: Reminder not to use during pregnancy in Ireland and Caution in use during pregnancy in Malaysia and No.3, 2016: Risk of miscarriage in pregnancy: under investigation in the USA)

Green tea extract-containing natural health products

Potential risk of liver injury

Canada. Health Canada has decided to strengthen the cautionary risk statement in the monograph for green tea extracts to include the advice

on the potential risk of liver injury.
Green tea extract-containing natural health products are used to help manage weight loss (along with diet and exercise) and as a source of antioxidants for the maintenance of good health.

Health Canada reviewed the potential risk of liver injury associated with green tea extract because of ongoing reports of serious liver injuries worldwide, including a recent report in Canada.

Health Canada's review concluded that there may be a link between the use of green tea extract and the risk of rare and unpredictable liver injury. While this risk is already identified in Health Canada's green tea extract's monograph, warnings will be strengthened.

The safety review also recommended that green tea extract products should be used by adults only.

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

Ibrutinib

Risk of ventricular tachyarrhythmia, hepatitis B reactivation and infection

Australia. The TGA has updated the product information for ibrutinib (Imbruvica®) to include safety information relating to the risks of ventricular tachyarrhythmia, hepatitis B reactivation and opportunistic infections.

Ibrutinib is used for the treatment of certain types of blood cancers, including mantle cell lymphoma and Waldenstrom's macroglobulinaemia chronic lymphocytic leukaemia (including small lymphocytic lymphoma).

In a 2017 study of relevant case reports from post-marketing sources and clinical trial data, 11 cases of ventricular tachycardia/ventricular fibrillation and six additional cases of sudden cardiac death in patients exposed to ibrutinib were identified. In 12 of these 17 cases, the events occurred without any evidence of prior cardiac history.

There were 52 cases of ventricular tachyarrhythmias reported in post-marketing settings.

A cumulative review of data from clinical trials and post-marketing cases identified eight reports of hepatitis B reactivation in ibrutinib-treated patients and causality of ibrutinib was considered to be probable or possible.

Infections (including sepsis, neutropenic sepsis, bacterial, viral or fungal infections) have been observed in patients treated with ibrutinib. Some of these infections resulted in hospitalisation and, in some cases, death.

Ibrutinib continues to have a favourable risk-benefit profile for treating patients with indications specified in the Australian product information.

Reference:
Medicines Safety Update, TGA, Vol. 8, No. 5, November 2017 (*www.tga.gov.au*)

Levetiracetam

Risk of neuroleptic malignant syndrome

Japan. The MHLW and the PMDA have announced that the package insert for levetiracetam (E Keppra®) has been updated to include the risk of neuroleptic malignant syndrome as a clinically significant adverse reaction.

Levetiracetam is used for the treatment of seizures in epilepsy patients.

A total of three cases associated with neuroleptic malignant syndrome have been reported in Japan. Of these, a causal relationship could not be excluded in two cases.

Reference:
Revision of Precautions, MHLW/PMDA, 17 October 2017 *(www.pmda.go.jp/english/)*

Linagliptin

Risk of interstitial pneumonia

Japan. The MHLW and the PMDA have announced that the package insert for linagliptin (Trazenta®) has been updated to include the risk of interstitial pneumonia as a clinically significant adverse reaction.

Linagliptin is a medicine used for type-2 diabetes mellitus.

A total of 20 cases associated with interstitial pneumonia have been reported in Japan. Of these, a causal relationship could not be excluded in four cases.

Reference:
Revision of Precautions, MHLW/PMDA, 17 October 2017 *(www.pmda.go.jp/english/)*

Moxifloxacin (oral dosage form)

Risk of rhabdomyolysis

Japan. The MHLW and the PMDA have announced that the package insert for moxifloxacin (Avelox®) has been updated to include the risk of rhabdomyolysis as a clinically significant adverse reaction.

Moxifloxacin is an antibiotic used for the treatment of a number of bacterial infections.

Two cases associated with rhabdomyolysis have been reported in Japan, of which causal relationship could not be excluded.

Reference:
Revision of Precautions, MHLW/PMDA, 17 October 2017 *(www.pmda.go.jp/english/)*

Terbinafine

Risk of acute generalized exanthematous pustulosis

India. The PvPI, IPC has made recommendations to the CDSCO about revising the drug safety label for terbinafine to include acute generalized exanthematous pustulosis as a potential adverse drug reaction.

Terbinafine is indicated for the treatment of fungal infections.

Between July 2011 and August 2017, PvPI received four reports of acute generalized exanthematous pustulosis with terbinafine use. The cases were reviewed by SRP-PvPI, IPC who concluded that there was a strong causal relationship between terbinafine and acute generalized exanthematous pustulosis in these cases.

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

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)

Avoid during pregnancy

France. L'Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) has reminded health-care professionals that the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are contraindicated during the second and third trimesters of pregnancy and not recommended for use during the first trimester.

ACE inhibitors and ARBs are indicated for the treatment of hypertension in adults.

The ANSM stated that, despite the recommendation not to use ACE inhibitors and ARBs during the first trimester and the contraindications in the second and third trimesters, pregnant women continue to be exposed during pregnancy, which may have serious or even fatal consequences for the fetus or new born.

Reference:
Point d'information, ANSM, 18 October 2017, France (*www.ansm.sante.fr*)

(See WHO Pharmaceuticals Newsletter No.4, 2012: Fetal malformations and candesartan use in pregnancy in Australia)

Chlorhexidine

Risk of serious allergic reactions

Singapore. The Health Sciences Authority (HSA) has informed health-care professionals about the outcome of its review on the known risk of allergic reactions, including anaphylactic reactions, with chlorhexidine-containing products.

Chlorhexidine is a broad-spectrum antiseptic which is effective against gram-positive and gram-negative bacteria on the skin and is widely used to reduce the risk of bacterial infection.

This review was conducted following recent international safety alerts regarding serious allergic reactions reported with antiseptic products containing chlorhexidine.

The review concluded that there was no significant increase in the total number of adverse event reports associated with chlorhexidine hypersensitivity received by the HSA over the past years. Fifteen reports of anaphylactic reactions related to chlorhexidine were identified over a span of 36 years (1981 to 2017).

Health-care professionals are advised to inform patients to stop using the product and seek immediate medical attention if they experience symptoms of a serious allergic reaction, such as wheezing, swelling of the face, or severe rashes.

Reference:
Product Safety Alerts, HSA, 29 September 2017 (*http://www.hsa.gov.sg/*)

(See Page 5 and WHO Pharmaceuticals Newsletters No.2, 2017: Rare but serious allergic reactions in the USA and No.3, 2016: Serious allergic reactions in Canada)

Clozapine

Potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has reminded health-care professionals that clozapine (Clozaril®, Denzapine®, Zaponex®) is contraindicated in patients with paralytic ileus and when prescribing clozapine, particular care should be taken in patients at risk of constipation.

Clozapine is an atypical antipsychotic drug.

In the United Kingdom, there have been 370 reports of gastrointestinal obstruction associated with clozapine between 3 August 1993 and 11 September 2017. In this time period, there have also been 135 reports of faecaloma and 86 of paralytic ileus.

The risk of gastrointestinal adverse effects is long established with clozapine. Warnings are provided in the Summary of Product Characteristics and Patient Information Leaflet and in the British National Formulary. However, in August 2017, a Coroner investigating a death raised concerns to the MHRA that health-care professionals might have a lack of awareness about the risk of pseudo-obstruction or paralytic ileus and the fast onset.

Patients are advised that if they develop constipation, they should tell their doctor immediately before taking the next dose of clozapine.

The MHRA stated that it is vital that constipation is recognised early and actively treated.

Reference:
Drug Safety Update, MHRA, Volume 11, issue 3: 4, October 2017 *(www.gov.uk/mhra)*

Febuxostat

Potential risk of heart-related death

USA. The US Food and Drug Administration (FDA) has alerted the public that preliminary results from a safety clinical trial showed an increased risk of heart-related death with febuxostat (Uloric®).

Febuxostat is approved to treat gout in adults.

The product information for febuxostat already carries a warning about cardiovascular events, based on information from clinical trials that showed a higher rate of heart-related problems in patients treated with febuxostat compared to an alternative treatment, allopurinol. These problems included heart attacks, strokes and heart-related deaths. As a result, the FDA required an additional post market safety clinical trial to increase understanding of these differences.

The safety trial was conducted in over 6,000 patients with gout, treated with either febuxostat or allopurinol. The preliminary results show that overall, febuxostat did not increase the risk of combined cardiac events compared to allopurinol. However, when cardiac outcomes were evaluated separately, febuxostat showed an increased risk of heart-related deaths and death from all causes.

Reference:
Drug Safety Communication, US FDA, 11 November 2017 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletter No.3, 2016: Risk of heart failure in Canada)

Finasteride

Risk of depression and suicidal thoughts

France. L'ANSM has informed patients and health-care professionals of the risk of depression and suicidal thoughts with the use of finasteride.

L'ANSM recommends treatment interruption and additional monitoring should be considered if patients experience a change in mood during treatment with finasteride. Cases of depression and, more rarely, suicidal ideation have been observed in men treated for hair loss with finasteride 1 mg. The risk of depression is also associated with finasteride 5 mg treatment for benign prostatic hypertrophy.

Finasteride at a dose of 1mg (Propecia® and generics) is indicated for the treatment of androgenic alopecia and, at a dose of 5mg (Chibro-Proscar® and generics), is indicated to treat and control benign prostatic hyperplasia.

Since the commercialization of Propecia®, psychiatric adverse effects have been reported, suggesting a possible link between finasteride and depression or suicidal thoughts. The risk of depression is also mentioned in the Summary of Product Characteristics (SmPC) and package leaflet of Chibro-Proccar®.

Following the latest European safety report on these medicines, the EMA has requested an amendment to the information documents for all 1 mg and 5 mg medicinal products to warn health professionals and patients about the risk of mood changes, suicidal ideation and depression. Finasteride treatment should be discontinued in the presence of any psychiatric symptoms.

The ANSM also reminds health care professionals that adverse drug reactions related to decrease in libido, erectile dysfunction and ejaculation disorders can persist after stopping the drug.

Reference:
Point d'information, ANSM, 26 October 2017, France (*www.ansm.sante.fr*)

Flupirtine-containing medicines

Review of benefit risk balance

Europe. The EMA has initiated a safety review of the benefits and risks related to the use of flupirtine-containing medicines for pain relief.

Flupirtine is an analgesic used to treat acute pain in patients who cannot use other pain medicines such as opioids or nonsteroidal anti-inflammatory medicines (NSAIDs).

The review was requested by the German medicines authority and follows a previous EMA review in 2013 which introduced measures to restrict the use of these medicines due to concerns of serious liver problems.

Risk minimization measures included limiting the use of flupirtine to no more than two weeks and introducing liver function tests before and during treatment. The EMA also requested that studies were conducted to show if these restrictions were effective in reducing the risks. Results suggest that despite a reduction in the overall use of flupirtine, it is still being used outside the restrictions introduced in 2013. Furthermore, cases of serious liver damage associated with this medicine have continued to be reported.

EMA's PRAC has therefore begun a further review to re-evaluate the benefits and risks for these medicines and decide whether additional regulatory actions should be taken.

Reference:
News and press releases, EMA, 27 October 2017 *(www.ema.europa.eu)*

Gabapentin

Risk of severe respiratory depression

The United Kingdom. The MHRA has stated that gabapentin (Neurontin®) has been associated with a rare risk of severe respiratory depression even without use of concomitant opioid medicines.

Gabapentin is an anti-epileptic drug indicated for:

- partial seizures with and without secondary generalisation
- peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

In the United Kingdom, there have been 50 reports of respiratory depression or dyspnoea associated with gabapentin between 19 February 1996 and 1 September 2017. Of these cases, 17 report opioids as co-suspect or concomitant medications.

The MHRA has advised health-care professionals to be aware of the risk of central nervous system (CNS) depression, including severe respiratory depression, with gabapentin and to consider whether dose adjustments might be necessary in patients at higher risk of respiratory depression, including elderly people, patients with compromised respiratory function, respiratory or neurological disease, or renal impairment, and patients taking other CNS depressants.

Reference:
Drug Safety Update, MHRA, Volume 11, issue 3: 2, October 2017 *(www.gov.uk/mhra)*

Hydroxyethyl-starch containing medicines

New review of benefit-risk balance

Europe. The EMA has initiated a safety review of benefits and risks of medicines containing hydroxyethyl-starch (HES).

HES containing products are used for the management of hypovolaemia (low blood volume) caused by acute (sudden) blood loss, where treatment with alternative infusion solutions known as 'crystalloids' alone is not considered to be sufficient. HES medicines are given by infusion into a vein and are used as blood volume expanders to prevent shock following acute bleeding.

The review was after utilization studies indicated that HES-containing medicines were being used outside their authorised uses, including in critically ill patients and those with sepsis and kidney injury, despite restrictions introduced in 2013 to reduce the risks of kidney problems and deaths.

The drug utilization studies had been requested by EMA's PRAC in 2013 in order to verify adherence to restrictions.

The PRAC will review the results of these studies and all other available data, and assess the impact on the benefit-risk balance of HES-containing medicines for infusion, and issue a recommendation on whether marketing authorizations should be maintained, varied, suspended or withdrawn across the EU.

Reference:
News and press releases, EMA, 27 October 2017
(www.ema.europa.eu)

Intraocular injections of a compounded triamcinolone, moxifloxacin and vancomycin (TMV) formulation

Not recommended for use during cataract surgery

USA. The US FDA has stated that the prophylactic use of intraocular vancomycin, alone or in a compounded drug combining multiple active ingredients such as triamcinolone, moxifloxacin, and vancomycin (TMV) formulation, is generally not recommended for use during cataract surgery because of the risk of haemorrhagic occlusive retinal vasculitis (HORV).

Intraocular vancomycin is used by many ophthalmologists during cataract surgery with the intent of preventing postoperative endophthalmitis. There is no FDA-approved vancomycin formulation for intraocular injection. The formulation is usually prepared at the surgical site or obtained in advance of surgery from a compounding pharmacy.

The FDA received a report in August 2017 of bilateral HORV in a patient following injections of a compounded TMV formulation in each eye after cataract surgery procedures that were done two weeks apart.

No cases of HORV were reported in a retrospective analysis of medical records of 922 patients (1541 eyes) who underwent cataract surgeries with intravitreal injections of compounded TMV formulations from November 2013 to December 2015. The adverse event being reported here serves as a reminder that intraocular administration of vancomycin, including when the vancomycin is one of multiple active ingredients in a compounded drug, can result in HORV.

Reference:
Drug Safety Communication, US FDA, 3 October 2017
(www.fda.gov)

Isotretinoin

Rare reports of erectile dysfunction and decreased libido

The United Kingdom. The MHRA has stated that cases of sexual dysfunction, predominantly involving erectile dysfunction and decreased libido, have been reported rarely in patients taking oral isotretinoin (Roaccutane®) for severe acne.

In the United Kingdom, the MHRA have received 14 Yellow Card reports of sexual

dysfunction associated with isotretinoin between the 1985 and 7 September 2017. In the same time period, there have been 49 reports of erectile or ejaculation dysfunction, and 23 reports of decreased or loss of libido associated with isotretinoin.

The MHRA has advised health-care professionals to be aware of reports of sexual adverse effects, including erectile dysfunction and decreased libido, in patients taking oral isotretinoin, indicated for severe acne. The exact incidence of these adverse reactions is unknown but is considered to be rare.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 3: 3, October 2017 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.1, 2017: Potential risk of impotence (erectile dysfunction) in Canada)

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 16 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. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version.
More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 20). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. For more information, 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.

Natalizumab and rapidly evolving central nervous system lymphoma

Mr Daniele Sartori and Dr Birgitta Grundmark, Uppsala Monitoring Centre

Summary

Natalizumab is an α4b1-integrin inhibitor which limits lymphocyte passage through the blood–brain barrier. With its immunomodulation properties it is approved and mainly used for the treatment of multiple sclerosis (MS). In the United States it is approved also for Crohn's disease.

As of May 2015 there were 16 cases of central nervous system lymphoma (CNSL) in association with natalizumab reported to VigiBase, the WHO global database of individual case safety reports, originating from five countries. The combination was highlighted in VigiBase with an IC value of 3.12 in the third quarter of 2013. A literature review has brought forward five cases, four of which are included in the VigiBase case series here presented. After the elimination of duplicates and the gathering of literature cases, 12 cases have been considered for discussion. The age of the patients ranges from 28 to 59 years, with a median of 44 years. None of the patients was reported to be immunocompromised. Patients were diagnosed with CNSL after the third dose in six cases, after the seventh in two, while in three patients a biopsy was performed before the third. Only one case reflected a longer treatment of 21 cycles before the onset of CNSL.

Differential diagnosis between CNSL and MS may be difficult, which has to be taken into account when assessing the signal. A consistent pattern of very short duration of treatment before diagnosis, apparent abrupt and rapid development of disease, a median age of reported cases outside high-incidence age ranges and altered immunosurveillance in the CNS mediated by natalizumab in immunocompetent patients suggest that natalizumab potentially has a role in a rapid progression of CNSL.

Introduction

Natalizumab is a recombinant humanized antibody that prevents lymphocytes from entering the central nervous system (CNS) and the small intestine.[1] Natalizumab selectively binds to the α4 subunit of the α4b1 integrin complex (Very Late Antigen, VLA4) inhibiting its interaction with vascular cell adhesion molecule 1 (VCAM-1), thus interfering with the extravasation of lymphocytes. It thereby reduces inflammatory activity in the brain, for instance in multiple sclerosis (MS). Treatment is administered through intravenous infusions of 300 mg once per month.[2] Natalizumab's approved indications are relapsing remitting MS, and in the United States also Crohn's disease. It is mainly used for the treatment of MS which is mirrored in that in over 90% of the total number of case reports for natalizumab in VigiBase (121,115 reports as of Q3 2016) MS is stated as the indication for treatment.

MS is an autoimmune chronic inflammatory condition, the pathogenesis of which is still to be fully characterized, but it is accompanied by a dysregulation of the blood-brain barrier leading to an increased permeability and

trafficking of lymphocytes. Natalizumab has positive effects in MS, thanks to its VLA4-VCAM-1 complex inhibiting action. In healthy individuals, the vascular parenchyma of the blood–brain barrier restricts the access to the CNS, making it an immunoprivileged site. VCAM-1 is minimally expressed on endothelial blood brain barrier cells, but pro-inflammatory stimuli (such as tumour necrosis factors or interleukins) and chronic inflammatory conditions (such as MS) trigger its upregulation, facilitating lymphocyte entry into the CNS.[3]

Primary central nervous system lymphoma (CNSL) is mainly of the diffuse large B-cell type.[4] It is a rare disease with incidence rates higher in males than females (0.8 vs 0.5 per 100,000 person-years)[5] and the median age of diagnosis is 65 years. The incidence rate in the age range between 55 and 64 year-olds is 0.85 (0.83-0.93, 95% CI) per 100,000, in the age range 45 to 54 years it is 0.45 (0.42-0.48, 95% CI) per 100,000, the rate from ages 35 to 44 is 0.27 per 100,000 (0.25-0.30, 95% CI), and between 20 and 34 years the rate is 0.11 (0.10-0.12, 95% CI).[6]

The most prominent risk factor for primary CNSL is immunosuppression, e.g. AIDS-related.[7] Epstein-Barr virus (EBV) has been consistently found in immunosuppressed primary CNSL patients, although immunosuppression may also promote CNSL in EBV-negative patients.[8] EBV positive lymphomas in the central nervous system of immunocompetent individuals are rare and usually secondary to lymphomas originating elsewhere.[9,10] Diagnostic imaging of CNSL and MS can overlap and one may be misinterpreted for the other. Both conditions initially respond well to high doses of steroids. Brain biopsy can rule out MS if a present lymphoma has not been significantly affected by steroid treatment.[11] Development of malignancies in MS has been linked to immunosuppressive therapies, but not significantly associated with immunomodulators.[12] MS patients were in the past considered to be at a lower risk of malignancies[13], though recently an increase in breast cancer risk has been pointed out.[14]

Reports in VigiBase

As of May 2015, there were a total of 16 cases of natalizumab in association with the MedDRA preferred term "Central nervous system lymphoma" in VigiBase, the WHO global database of individual case safety reports; after removal of duplicates 12 cases remained. All cases were serious, save one, the seriousness of which was not reported. The countries of origin were: United States (n=5), United Kingdom (n=3), Germany (n=2), Australia and France (1 each).

The combination had been highlighted in Q3 2013 with an IC of 3.12. As a comparison, as of June 2016, there were 247 reports of CNSL in VigiBase, 141 reported in relation with immunosuppressants, 84 with anti-neoplastics (mainly reporting progressive lymphoma disease) and 26 with immunostimulants. As of Q3 2016, the combination natalizumab-central nervous system lymphoma has an IC of 3.18.

In the case series considered, eight patients were female and four were males. Their average and median age were 46 and 44 years respectively, age ranging from 28 to 59 years. Natalizumab was the only suspected drug in 11 reports and in the remaining one methylprednisolone, azathioprine, interferon beta-1a, methotrexate and cytarabine were co-suspects (although the last two were given as CNSL therapy). The duration of natalizumab treatment before diagnosis ranged from 1 to 21 cycles, with a median of 3. CNSL cases reported with natalizumab are summarized in Table 1.

Literature and Labelling

The EU SmPC for natalizumab states the following regarding malignancies: "No differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over two years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded". The summary safety profile further states: "in placebo-controlled trials in 1,617 MS patients treated with natalizumab for up to two years (placebo: 1,135)".[2] Known active malignancies are, as per the EU SmPC, listed as contraindications while the US FDA label lists lymphoma as a contraindication to treatment.[15]

A literature review revealed five case reports documenting CNSL in association with natalizumab. Four of them have been identified as cases already present in VigiBase (see "Literature Reference" column in Table 1), based on patient demographics, concomitant drugs, reported events and case narratives. An abstract reports two cases (not included in the case series) with sparse information, one of which concerned a 38-year-old woman diagnosed with primary CNSL 22 months after starting natalizumab, which concludes that CNSL should be carefully considered in patients suspected of having MS, and that biopsies should be considered in patients with unusual lesions. It also adds that natalizumab should be used with care if CNSL is suspected as it decreases immunosurveillance and allows lesions to expand rapidly.[16]

Table 1. Overview of case reports of central nervous system lymphoma in association with natalizumab in VigiBase

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Duration of treatment	Reported reactions (MedDRA preferred terms)	Comments	Literature reference
1	40/M	Antidepressants (C)	21 cycles	B-cell lymphoma, Non-Hodgkin's lymphoma, cerebral lymphoma, central nervous system lymphoma	EBV negative HIV negative Azathioprine one month washout before natalizumab treatment	Schweikert et al.[17]
2	40/M	-	7 cycles	Cerebral lymphoma	Treated with interferon beta 1b, later with beta 1a and steroids for flare ups. Discontinuation of previous treatments in favor of natalizumab Lymphoma confirmed by biopsy	-
3	28/M	-	7 cycles	Cerebral lymphoma	Three years before diagnosis 4 doses of mitoxantrone received. Six months before diagnosis, patient MRI did not show lymphoma. EBV IgG present EBV IgM absent HIV negative	Na et al.[25]
4	40/F or 44/F	Azathioprine, methylprednisolone (both S) Interferon beta 1a (C)	3 cycles	Death, diffuse large B-cell lymphoma	Diagnosis confirmed through biopsy JC negative EBV negative Cumulative dose of 12 g of azathioprine, stopped four years before natalizumab first dose	Matzke et al.[26]
5	55/F	-	3 cycles	Central nervous system lymphoma	Age at higher risk for CNSL	Sharaf et al.[27]
6	58/F	-	3 cycles	Central nervous system lymphoma, acute confusion state, brain lesion, bladder infection	Age at higher risk for CNSL Biopsy confirmed CNSL JC negative ruled out suspicion of PML	-
7	-/F	-	3 cycles	Central nervous system lymphoma, medication error	Initially diagnosed with MS, treated with natalizumab. Drug was stopped when MS was "later discovered" to be CNSL	-
8	45/M	Sertraline, pantoprazole, baclofen, paracetamol (all C)	3 cycles	Central nervous system lymphoma, diffuse large B-cell lymphoma, enterococcal bacteraemia, urinary tract infection pseudomonal	Initially diagnosed with MS, treated with natalizumab. Suspect of misdiagnosis Treatment interrupted after MRI and biopsy confirmed CNSL. Causality unrelated.	-
9	39/F	Tramadol, hydrocortisone, methylprednisolone, levetiracetam, amitriptyline, lorazepam, tocopherol, ethinylestradiol/ drospirenone, clonazepam, ondansetron, colecalciferol, amphetamine/ dextromethamphetamine, esomeprazole, oxycodone, prednisone, phenytoin, zolpidem (all C)	3 cycles	Central nervous system lymphoma, convulsion, bradyarrhythmia, multiple sclerosis	Diagnosis confirmed through biopsy Attention deficit disorder Familial history of epilepsy 16 year history of MS Status epilepticus triggered hospitalization and diagnosis of lymphoma Causality was reported as unrelated	-
10	41/F	-	2 cycles	Central nervous system lymphoma	Diagnosis confirmed through biopsy Lesion detected by MRI which grew "rapidly" after therapy with natalizumab Causality according to reporter: unrelated despite reporter noted deterioration of condition	-
11	56/F	Modafinil, prednisone, cyclophosphamide, fluoxetine (all C)	1 cycle	Central nervous system lymphoma, post lumbar puncture syndrome, multiple sclerosis relapse, pneumonia, infection	Age at higher risk for CNSL Sjögren's syndrome as added risk Time of diagnosis: approximately 2 weeks	-
12	59/F	Omeprazole, hydrochlorothiazide/ olmesartan, medoxomil/ amlodipine besilate, temazepam, pravastatin, risedronic acid (all C)	1 cycle	Central nervous system lymphoma, acute respiratory failure	Age at higher risk for CNSL Limited number of cycles strongly argue against a role of natalizumab	-

The index case, brought forward by Schweikert et al, concerns a 40-year-old male who developed CNSL after 21 doses of natalizumab. The patient was initially diagnosed with MS through MRI and CSF analysis at the age of 37 and responded well to methylprednisolone. He underwent treatment with interferon beta-1a after a year and was later diagnosed with remitting relapsing MS after an MRI showed new white matter lesions. A brain biopsy was performed, which was consistent with MS. Treatment with interferon was suspended and azathioprine was started. The worsening of his condition prompted new methylprednisolone pulses and after a one-month washout period from azathioprine the patient was started on natalizumab. Roughly two years later, a new brain biopsy showed a diagnosis of CNSL, and natalizumab was discontinued. PCR for EBV was negative, as well as HIV tests, suggesting immunocompetence and arguing against an immunosuppression-related lymphoma.[17]

An additional case was presented by Phan-Ba et al: a 40-year-old male, complaining of blurred vision, headaches and attention disorder and with a 20-year history of MS was treated with two courses of natalizumab after two high steroid pulses. An EBV negative CNSL was diagnosed and treated with polychemotherapy, leading to reduction of tumour mass. The authors suggested a natalizumab-dependent lymphomagenesis to be unlikely, instead discussing its potential to speed up lymphoma progression.[18]

Discussion and Conclusion

CNSL has so far not been noted as an issue in long-term study results on the safety of natalizumab.[19,20] This is not to be expected in smaller studies considering the rarity of the disease per se. The cases in VigiBase, which complement the ones found in the reviewed literature, may still support a potential association between the medicinal product and the events.

The occurrence of 12 cases of uncommon malignancy in temporal relation to treatment with natalizumab raises questions on the possibility of causality. Six of the cases (cases 1, 2, 3, 4, 8, 9) occurred in patients far below the median age of CNSL diagnosis, five of which showed a consistent time to diagnosis pattern with a median of three administrations and hence only three months prior to the diagnosis. These six patients were not reported to be immunocompromised. The reporters of three cases (cases 8, 9, 10) considered the CNSL to be unrelated to natalizumab.

Two cases (cases 11 and 12) were identified only after one dose of treatment making a role of natalizumab less plausible. In addition, a patient's age could increase the risk of independent development of CNSL, which should also be accounted for in cases 5 and 6 (albeit these two were diagnosed within median range of treatment duration).

A clinical finding reported to be indicative of an immunosuppression-related lymphoma is the presence of EBV: two cases (cases 1 and 4) were found to be EBV negative and another one (case 3) did not have an active EBV infection. Epstein-Barr virus can be identified in almost every (99%) patient affected by MS.[21] Given that profound immunosuppression can induce CNSL and that MS patients are treated with immunosuppressive agents, it should also be noted that previous treatments such as azathioprine may have oncogenic effects.[22] Nevertheless, natalizumab is not known to induce strong immunosuppression, moreover in the patient who had been treated with azathioprine the cumulative dosage was low (12 grams).

Cases 7 and 8 both report the events as patients being misdiagnosed with MS, later changed to CNSL. These findings highlight the necessity of thorough differential diagnostic investigations.

It is worth noting that in most cases the patients have been diagnosed with MS several years before the initiation of natalizumab or the occurrence of CNSL. This may either point in the direction of a causal role of the drug or in a confounding by indication; the reason for the initiation of a new drug being an as yet undetected or misdiagnosed CNSL. The reason for changing to, or initiation of natalizumab is not clearly stated in any of the reports, however, the approved indication for natalizumab is second-line treatment for patients in whom first-line treatments have failed and for patients with rapidly evolving severe relapsing remitting MS. However, in some of the cases (cases 1 and 3), there is documentation of a thorough investigation before the initiation of the drug (e.g. MRI, biopsy) without any indication of an existing CNSL before start of treatment with the drug.

In light of this, a hypothesis could be that natalizumab may play a role in the rapid progression of a pre-existing cerebral lymphoma. This could be supported by the mechanism through which natalizumab exerts therapeutic action, which might also make it a promoter of malignant cell growth by reducing CNS immunosurveillance. Within the case series, the original extract of case 10 reports a rapid growth of a previously identified lesion after two infusions of natalizumab, compatible with the history of the case presented by Phan Ba et al.

In conclusion, despite uncertainties regarding a causal role of natalizumab in the rapid progression of central nervous system lymphoma[23, 24], the addition of VigiBase data to existing literature case reports may add sufficient evidence to discuss the need for an update of the safety profile of natalizumab. The presented case series includes CNSL

patients well below the median age of diagnosis, not reported to have been immunocompromised at the time of investigations and with consistent time to diagnosis. Moreover, a natalizumab-induced reduction in CNS immunosurveillance is proposed as a plausible biological mechanism for the evolution or potentiation of CNSL. Confounding due to missed CNSL diagnosis and attribution of symptoms to MS progression as opposed to CNSL growth/progression should be accounted for. At the same time there appears to be a need for thorough diagnostic investigations before initiating natalizumab as a second or later line of treatment in MS, given the overlapping symptoms and imaging of the two conditions, the apparent improvement of CNSL lesions after steroid treatment and the possibility that natalizumab may have a role in rapid progression of CNSLs.

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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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The 40th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring

The WHO annual meeting of National Pharmacovigilance Centres (NPCs) is a platform for countries from around the world to meet and discuss pharmacovigilance issues. Each year an NPC participating in the WHO Programme for International Drug Monitoring hosts the meeting, and this year the National Drug Authority in Uganda welcomed delegates to the Speke Resort, Muyonyo in Kampala. More than 150 representatives from over 50 countries travelled to the resort to attend the four-day meeting from 7 to 10 November 2017.

The meeting was opened by Dr Morries Seru, the commissioner of Health Services, Ministry of Health, Uganda. An enchanting ambience was created by Public Health Ambassadors Uganda, who performed a skit. The skit touched upon numerous important issues related to reporting of adverse effects, and was successful in communicating the importance of pharmacovigilance (PV) in a creative manor.

Preconference workshop

On 6 of November a preconference workshop on Medical Dictionary for Regulatory Activities (MedDRA) in Pharmacovigilance was organized. MedDRA is a rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans. MedDRA was developed in the early 1990s, and was based on terminology belonging to the Medicines and Healthcare products Regulatory Agency (MHRA). It was developed using the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) process by ICH partners.

The aim was to standardize international medical terminology for regulatory communication. In order to maintain the terminology and add terms, as medical knowledge grows, the ICH MedDRA Maintenance and Support Services Organization, MSSO has developed a maintenance process to ensure that MedDRA maintains a logical structure and consistency. VigiFlow, developed by the Uppsala Monitoring Centre and is a web-based individual case safety report management system, is available for use by National Pharmacovigilance Centres of the WHO PIDM. In the past it contained integrated international terminologies such as the WHO-Adverse Reaction Terminology (WHO-ART) dictionary as well as MedDRA. Many countries using VigiFlow enter data using WHO-ART, however the system will be using only MedDRA in the future, hence the need to support countries to switch from WHO-ART terminology to MedDRA was identified, and a training workshop was organized.

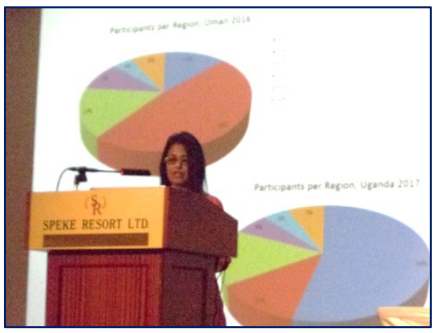
Over 100 participants from over 30 countries arrived early in Kampala, to attend the MedDRA pre-course. Presentations on making the transition from WHO-ART to MedDRA and an introduction to MedDRA were made. Participants were then split into working groups and completed exercises together.

Meeting Structure and content

This year, the meeting consisted of closed and open sessions. The closed session was by invitation only, and only nominees selected by PV focal points from NPCs were invited. In the open session, non-state actors such as the Bill and Melinda Gates Foundation (BMGF), International Society of Pharmacovigilance (ISOP), Council for International Organizations of Medical Sciences (CIOMS), and representatives from pharmaceutical industry (International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)) were invited.

Closed session

At the end of each annual meeting of NPCs, participants are invited to suggest topics for the forthcoming annual meeting. This sets the agenda of the next meeting so that it reflects the needs of Member States. The theme of the 2017 meeting was "Smart-Safety Surveillance: When resources are limited". The meeting sessions consisted of plenaries, updates, working groups, problems of current interest and tutorials.



In the first plenary, Dr Shanthi Pal from WHO reported back on progress and achievements that WHO and WHO Collaborating Centres have made on the recommendations of the previous Annual Meeting in Oman Muscat 2016. Following this, an overview of the concept and progress of the Smart Safety Surveillance initiative was presented. An example of implementing a regional mechanism to strengthen PV capacity in the Caribbean was described. The second plenary on day-2 of the meeting consisted of success stories from Croatia, Democratic Republic of Congo, Japan and Uganda.

Updates

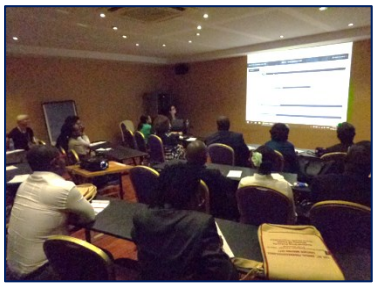
Updates were given on ongoing PV studies in India and research on patient reporting and risk sprints; reporting mobile phone technology for ADR reporting in Burkina Faso and Zambia; and development of the PV undergraduate curriculum.

Signals of Current interest

This session consisted of short presentations based on abstracts that were submitted prior to the meeting. Approximately 15 participants had the opportunity to present and discuss PV issues. A range of topics were presented which ranged from antibacterial resistance, signals identified with HIV, malaria and TB medicines, signals with reproductive health products and other particular ADRs of concern.

Tutorials

Six different tutorials ran parallel to each other on each day and participants had the opportunity to choose three tutorials in total. The tutorial sessions included topics such as VigiFlow, active surveillance and developing a PV bulletin.



Working Groups

Eight working groups were offered over a period of two days. Prior to the workshop, delegates were provided with a list of objectives and outcomes and had the opportunity to attend two workshops of preference. During each workshop, moderated discussions were held and attendees formulated and agreed on a list of recommendations that were specifically targeted at WHO, WHO CCs and/or the NPCs. A delegated rapporteur amongst the workshop participants presented to the whole delegation during the plenary session on the last day of the meeting. Working groups consisted of: 1) PV inspections: Needs, Capacity, Cooperation; 2) Risk Management Plans (RMPs) for teratogenic drugs; 3) Scope of Pharmacovigilance; 4) Risk Minimization Measures: Implementation & Responsibilities; 5) How do we measure impact of PV; 6) Role of Pharmacovigilance Centres in promoting quality use of medicines; 7) Communication of Pharmacovigilance actions; 8) Benefit-Risk Assessment: approaches.

The recommendations from the working groups will be available in the next issue of the WHO Pharmaceuticals Newsletter.

Introducing the WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services

We are pleased to announce that the Pharmacovigilance Programme of India (PvPI), Indian Pharmacopeia Commission (IPC), in Ghaziabad has been designated as the WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services. WHO works with a network of more than 700 Collaborating Centres in 80 countries to support the implementation of mandated work. PvPI will support the WHO Programme for International Drug Monitoring to deliver WHO strategies and operational plans in pharmacovigilance. A work plan and terms of reference have been jointly agreed to include the following:

- Support WHO to develop relevant tools and guidelines for enhancing Pharmacovigilance (PV) practice in low and middle income countries (LMIC) in Asia and beyond.
- Contribute to capacity building of WHO Member States to establish high quality pharmacovigilance systems for medical products.
- Scientific support to countries for pharmacovigilance in public health programmes (e.g. Tuberculosis, Neglected Tropical Diseases, Vector Borne Diseases, HIV-AIDS, Immunization Programmes) and regulatory issues.
- Work-sharing and joint activities in regulatory pharmacovigilance

More information about the WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services can be found on the WHO Medicines Safety website:

http://www.who.int/medicines/regulation/medicines-safety/about/collab-centres-india/en/