The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

This newsletter includes a feature articles describing recent WHO participated pharmacovigilance activity: APEC Harmonization Center (AHC) Pharmacovigilance Workshop in Seoul, Republic of Korea.

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## Regulatory Matters

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Feature

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Afatinib

Risk of toxic epidermal necrolysis (TEN) and erythema multiforme

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for afatinib (Giotrif®) has been updated to include the risk of toxic epidermal necrolysis (TEN) and erythema multiforme as clinically significant adverse reactions.

Afatinib is indicated for epidermal growth factor receptor (EGFR) mutation-positive unresectable or relapsed non–small-cell lung cancer.

A total of three cases of TEN and one case of erythema multiforme with afatinib use have been reported in Japan. Of these, a causal relationship could not be excluded in two cases and one case, respectively. The company core datasheet has also been updated to include the risk of TEN.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 13 September 2016 (www.pmda.go.jp/english)

Antidepressants

Risk of serious eye disorder (Angle-closure glaucoma)

Canada. Health Canada is working with manufacturers of 23 different antidepressant products to update the Canadian product information to include a warning of the potential risk of angle-closure glaucoma with the use of antidepressants.

Antidepressants are used for the treatment of depression, anxiety, obsessive compulsive disorder, insomnia, and post-traumatic stress disorder, among many other conditions.

Health Canada conducted a review and found a link between antidepressant use and the occurrence of angle-closure glaucoma.

At the time of the review, Health Canada received two reports of angle-closure glaucoma linked with the use of antidepressants via the Canada Vigilance Program. In total, there were 163 reports from different sources. There were 226 reports of pupil dilation (a well-known risk factor of angle-closure glaucoma) linked with the use of antidepressants from different sources. Of these Health Canada received 130 reports through the Canada Vigilance Program.

Reference:
Summary Safety Review, Health Canada, 12 August 2016 (www.hc-sc.gc.ca)

Antirabies vaccine

Risk of erythema multiforme

India. The National Coordination Centre - Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission (IPC, NCC-PvPI) has requested the revision of the drug safety label for antirabies vaccine to include erythema multiforme as a potential risk.

Antirabies vaccine is indicated for active immunization against rabies, both as prophylaxis and post bite cases.

NCC-PvPI has received two reports of erythema multiforme with exposure to antirabies vaccine between 2011 and 2015. The reports were reviewed by the PvPI signal review panel (PvPI-SRP), IPC.

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

Atypical antipsychotics

Risk of sleep apnoea

Canada. Health Canada recommends that the current product labels for atypical antipsychotics (aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) are updated to include the risk of sleep apnoea.

Atypical antipsychotics are used to treat mental health disorders including schizophrenia, bipolar disorder and, in some cases, depression.

Health Canada carried out a safety review to investigate risk of sleep apnoea with the use of atypical antipsychotics. This review was triggered by the submission of new safety information from the manufacturer of quetiapine (Seroquel®) which included cases of sleep apnoea in patients using quetiapine.

At the time of the review, Health Canada had received a total of 80 Canadian cases of sleep apnoea that were linked to the use of atypical antipsychotics. It could not be determined if these drugs caused sleep apnoea given the presence of other risk factors reported, for example obesity and/or the use of other medications. However, the link between the use of atypical antipsychotics and the risk of experiencing sleep apnoea could not be ruled out. There
were 490 international cases of sleep apnoea linked to atypical antipsychotics. Information from these cases suggests that there is a relationship between quetiapine, olanzapine, ziprasidone, clozapine, aripiprazole, and risperidone and sleep apnoea.

A review of the scientific literature identified three studies that supported the link between the use of atypical antipsychotics and the risk of experiencing sleep apnoea, despite reports of other medical conditions (obesity) and concomitant medications which may have played a role in the development of sleep apnoea.

Health Canada has concluded that there is a link between the use of atypical antipsychotics and sleep apnoea.

**Reference:**
Summary Safety Review, Health Canada, 16 August 2016 (www.hc-sc.gc.ca)

### Azithromycin

**Risk of acute generalized exanthematous pustulosis**

**India.** The IPC, NCC-PvPI has requested the revision of the drug safety label for azithromycin to include exanthematous pustulosis as a potential risk.

Azithromycin is used in the treatment of mild to moderate susceptible infection including respiratory tract infections, uncomplicated skin/skin structure, non-gonococcal urethritis cervicitis.

NCC-PvPI has received five reports of exanthematous pustulosis with exposure to azithromycin between 2011 and March 2016. The reports were reviewed by the PvPI-SRP, IPC and the WHO Collaborating Centre for International Drug Monitoring (UMC).

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

### Azosemide

**Risk of agranulocytosis and leukopenia**

**Japan.** The MHLW and the PMDA have announced that the package inserts for azosemide preparations (Diart® and others) have been updated to include the risk of agranulocytosis and leukopenia as clinically significant adverse reactions.

Azosemide is indicated for cardiac-induced oedema (congestive cardiac failure), renal-induced oedema, and hepatic-induced oedema.

A total of four cases associated with agranulocytosis and leukopenia have been reported in Japan. Of these, a causal relationship could not be excluded in two cases.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

**Reference:**
Revision of Precautions, MHLW/PMDA, 4 August 2016 (www.pmda.go.jp/english)

### Bcr-Abl tyrosine kinase inhibitors

**Risk of hepatitis B virus reactivation**

**1. Australia.** The Therapeutic Goods Administration (TGA) has worked with manufacturers to update the product information documents for Bcr-Abl tyrosine kinase inhibitors (TKIs; imatinib, nilotinib, dasatinib and ponatinib) by including a precautionary statement about the risk of HBV reactivation.

Bcr-Abl TKIs are indicated for the treatment of specific blood cancers including Philadelphia chromosome positive chronic myeloid leukaemia (CML).

Based on a review conducted by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), TGA considers that HBV reactivation is a class-effect of Bcr-Abl TKIs. The case reports received by the EMA indicated that HBV reactivation could occur at any time during Bcr-Abl TKI treatment.

The TGA informed health-care professionals that cases of HBV reactivation have occurred in patients who are chronic carriers of the virus after they received Bcr-Abl TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

**Reference:**

**2. Japan.** The MHLW and the PMDA have announced that the package inserts for Bcr-Abl TKIs (imatinib (Glivec®), nilotinib (Tasigna®), dasatinib (Sprycel®) and bosutinib (Bosulif®)) have been updated to include the risk of reactivation of HBV as an important precaution.

A total of four cases associated with reactivation of HBV have been reported in Japan. Of these, a causal relationship could not be excluded in one case. In addition, the company core datasheet has also been updated.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.
3. Singapore. The Health Sciences Authority (HSA) has stated that the local package inserts for Bcr-Abl TKIs (dasatinib (Sprycel®), imatinib (Glivec®) and nilotinib (Tasigna®)) have been updated to include the risk of HBV reactivation.

The HSA has received reports of hepatitis B infection that occurred in patients treated with imatinib, in 2005, 2011 and 2012 respectively.

The HSA has stated that the manufacturer has issued two ‘Dear Health-care Professional Letters’ to communicate the risk of HBV reactivation associated with the use of imatinib and nilotinib, respectively. The letters highlighted the need to screen patients for HBV infection before treatment.


Betamethasone

Risk of photosensitivity reaction

India. The IPC, NCC-PvPI has requested the revision of the drug safety label for betamethasone to include photosensitivity as a potential risk.

Betamethasone is a topical anti-inflammatory steroid.

NCC-PvPI has received six reports of photosensitivity with exposure to betamethasone between 2011 and March 2016. The reports were reviewed by the PvPI-SRP, IPC and the WHO Collaborating Centre for International Drug Monitoring (UMC).

Reference: Revision of Precautions, MHLW/PMDA, 4 August 2016 (www.pmda.go.jp/english/)

Cefixime

Risk of acute generalized exanthematous pustulosis

India. The IPC, NCC-PvPI has requested the revision of the drug safety label for cefixime to include acute generalized exanthematous pustulosis as a potential risk.

Cefixime is used in the treatment of urinary tract infections, respiratory tract infections and biliary tract infections.

NCC-PvPI has received three reports of acute generalized exanthematous pustulosis with exposure to cefixime between 2011 and March 2016. The reports were reviewed by the PvPI-SRP, IPC.

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

Ceftriaxone

Risk of Stevens Johnson Syndrome

India. The IPC, NCC-PvPI has requested the revision of the drug safety label for Ceftriaxone to include Stevens Johnson Syndrome (SJS) as a potential risk.

Ceftriaxone is indicated in the treatment of urinary tract infections, lower respiratory tract infections.

NCC-PvPI has received 27 reports of SJS with exposure to Ceftriaxone between 2011 and March 2016. The report was reviewed by the PvPI-SRP, IPC.

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

Cloxacillin

Risk of acute generalized exanthematous pustulosis

India. The IPC, NCC-PvPI has requested the revision of the drug safety label for cloxacillin to include acute generalized exanthematous pustulosis as a potential risk.

Cloxacillin is used for the treatment of infections of respiratory tract, skin and mucosa, and bone infection.

NCC-PvPI has received two reports of acute generalized exanthematous pustulosis with exposure to cloxacillin between 2011 and March 2016. The report was reviewed by the PvPI-SRP, IPC and the WHO Collaborating Centre for International Drug Monitoring (UMC).

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

Codeine-containing products

Risk of serious breathing problems in children and adolescents

Canada. Health Canada has worked with manufacturers to update the product safety information for prescription codeine to indicate that codeine should not be used in children and adolescents for the purpose of treating pain after surgery to remove tonsils or adenoids. Caution is also advised when using codeine in patients with breathing conditions, regardless of age.
Codeine-containing medicines are used to treat pain and reduce cough.

Recent safety reviews assessed the risk of serious breathing problems in children and adolescents treated with codeine.

At the time of the review, Health Canada had received a total of eight Canadian cases of breathing problems in patients under 18 years of age, possibly linked to codeine for the treatment of pain. Six of these cases occurred in children under 12 years of age, including three who died. Four of the eight cases occurred in children after surgery.

Amongst seven published international cases, codeine (used for pain) was suspected to be linked to serious breathing problems in patients under 18 years of age. Six of the seven cases occurred in children under 12 years of age, including four deaths. Five of the seven cases occurred in children after surgery. It was noted that children, in both published cases and cases received by Health Canada, had other medical conditions that could have contributed to the breathing problems.

For non-prescription codeine products, there were no cases of serious breathing problems that originated from Canada, and no new cases were reported in the scientific literature, overall no new evidence that would suggest a change in known risks of serious breathing problems was found.


(See WHO Pharmaceuticals Newsletter No.1, 2016: Risk of serious breathing problems in children and adolescents in Canada, and No.4, 2015, No.3, 2015, No.5, 2013, No.4, 2013 and No.5, 2012 for related information)

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**Corticorelin**

**Risk of shock and anaphylaxis**

**Japan.** The MHLW and the PMDA have announced that the package insert for corticorelin (hCRH "TANABE®") has been updated to include the risk of shock and anaphylaxis.

Corticorelin is used for secretory function test of hypothalamic, pituitary, and adrenocortical hormone.

A total of two cases associated with shock and anaphylaxis have been reported in Japan. A causal relationship could not be excluded in both cases.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference: Revision of Precautions, MHLW/PMDA, 13 September 2016 (www.pmda.go.jp/english/)

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**Denosumab**

**Risk of QT prolongation**

**Australia.** The TGA has updated product information documents for denosumab products to include the potential risk of QT interval prolongation associated with hypocalcaemia (a known adverse effect).

Denosumab is used for inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density.

This issue was identified during a TGA assessment of adverse event reports relating to this medicine.

The TGA stated that this updated information has harmonised the Australian product information with the European Union Summary of Product Characteristics for these products.


(See WHO Pharmaceuticals Newsletter No.4, 2015: No evidence of increased risk of cardiovascular events in Canada)

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**Eltrombopag olamine**

**Recommendations to change administration due to interaction with drugs and foods.**

**Japan.** The MHLW and the PMDA have announced that the package insert for eltrombopag olamine (Revolade®) has been updated to include advice on the administration interval between administration of eltrombopag and products such as antacids, milk products, and formulations containing multivalent cations (iron, calcium, aluminium, magnesium, selenium, zinc).

Eltrombopag olamine is indicated for chronic idiopathic thrombocytopenic purpura.

The company core datasheet has been updated based on the results of clinical pharmacokinetic studies in other countries.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference: Revision of Precautions, MHLW/PMDA, 13 September 2016 (www.pmda.go.jp/english/)
**Etanercept**

**Potential harm due to in utero exposure during pregnancy**

Canada. Health Canada is working with the manufacturer of etanercept (Enbrel®) on updating the product safety information to include information on the risks of birth defects due to in utero exposure during pregnancy.

Etanercept is used to treat inflammation of joints and skin which occurs when the body’s own defence system attacks the joints and/or the skin, including certain forms of arthritis and psoriasis.

Health Canada carried out a safety review after receiving information from a study of a long-term pregnancy registry.

At the time of the review, Health Canada had received seven Canadian reports of birth defects in the newborn babies of mothers treated with etanercept. The babies had one of many kinds of abnormalities in different parts of the body including the heart, skull and jawbone. Some reports noted that etanercept crossed the placenta from the mother to the baby. There was no pattern or unique kind of birth defect.

It was not possible to determine whether etanercept itself caused birth defects because many of the women that were represented in the pregnancy registry took other medications while taking etanercept.

Health Canada’s review noted that taking etanercept during pregnancy was associated with a lesser risk of experiencing a miscarriage but carried a potential risk of birth defects. The review could not conclude that etanercept alone was the cause of birth defects.

**Reference:**

Summary Safety Review, Health Canada, 4 August 2016 (www.hc-sc.gc.ca)

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**Fluoroquinolone antibacterial drugs for systemic use**

**Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system**

USA. The Food and Drug Administration has announced that the boxed warnings for fluoroquinolone antibacterial labels have been revised to include warning and precautions of disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient.

Fluoroquinolones are antibiotic medicines used to prevent or treat certain serious bacterial infections.

The FDA recommends that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and uncomplicated urinary tract infections. For some serious bacterial infections the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.

**Reference:**


(See WHO Pharmaceuticals Newsletter No.3, 2016: Restricting use in the USA)

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**Gabapentin**

**Risk of serious breathing problems (respiratory depression)**

Canada. Health Canada has recommended that the product information for gabapentin is updated to include a warning about the risk of serious breathing problems.

Gabapentin is used for treating epilepsy (seizures).

Health Canada carried out a safety review to assess the possibility of respiratory depression in patients using gabapentin alone (when not taken with opioids). Health Canada concluded that there is evidence to support the risk of serious breathing problems with the use of gabapentin.

At the time of the review, Health Canada received one Canadian report, in which the use of gabapentin was considered to be related to respiratory depression.

The review gathered an additional 20 international reports related to serious breathing problems associated with gabapentin use from the scientific and medical literature as well as information received from drug manufacturers. In these reports, the drug was used in some patients for treating epilepsy and in other patients for other uses including pain management. In some reports, breathing problems appendied with discontinuation of gabapentin, and reappeared when the gabapentin was restarted. This finding supports the hypothesis that gabapentin use may have contributed to this adverse effects.

**Reference:**

Summary Safety Review, Health Canada, 16 September 2016 (www.hc-sc.gc.ca)
Granulocyte colony-stimulating factor (G-CSF) analogues

Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the package inserts for granulocyte colony-stimulating factor (G-CSF) analogues (filgrastim (Gran® and follow-on biosimilars), lenograstim (Neutoxin®), nartograstim (Neu-up®) and pegfilgrastim (G-Lasta®)) have been updated to include anaphylaxis as a clinically significant adverse reaction.

G-CSF analogues are used for mobilization of hematopoietic stem cells into peripheral blood, acceleration of an increase of neutrophil count in hematopoietic stem-cell transplantation and neutropenia.

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

In addition, the requirement to carry out a skin test has also been deleted.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 13 September 2016 (www.pmda.go.jp/english/)

Hydrocodone-containing products

Risk of serious breathing problems in children and adolescents

Canada. Health Canada is working with manufacturers to update the product information for hydrocodone containing products with the recommendation that they should not be used in children under 6 years of age.

Hydrocodone is an opioid prescription drug used to treat dry cough.

Health Canada’s safety review on hydrocodone investigated the risk of serious breathing problems in children. This safety review identified cases mainly when hydrocodone was used in children under 6 years of age.

At the time of the review Health Canada assessed a total of seven reports in children and adolescents who were exposed to hydrocodone and reported serious breathing problems. Two reports involved children that were seven and 15 years old; one case was assessed to be related to hydrocodone use, however the second report was un-assessable due to lack of sufficient information.

Internationally there were five reports in children under six years of age and upon further analysis three were considered related to hydrocodone use. Death was reported in two of these cases; one was considered related to the hydrocodone use.

A review of the published literature identified one international case of a 3-year old child that experienced serious breathing difficulties after use of hydrocodone and later died. Upon further review, the event was considered to be due to hydrocodone use.

Reference:

Ibuprofen

Risk of Stevens Johnson Syndrome/ toxic epidermal necrolysis

India. The IPC, NCC-PvPI has requested the revision of the drug safety label for ibuprofen to include Stevens Johnson Syndrome / Toxic Epidermal Necrolysis (SJS/TEN) as a potential risk.

Ibuprofen is anti-rheumatic drug.

NCC-PvPI has received 27 reports of SJS/TEN with exposure to ibuprofen between 2011 and March 2016. The reports were reviewed by the PvPI-SRP, IPC.

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

(See WHO Pharmaceuticals Newsletter No.4, 2012: Risk of Severe Cutaneous Adverse Reaction (SCAR) with NSAIDs in New Zealand)

Idelalisib

Risk of infection

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated the product information for idelalisib to include the risk of infection.

Idelalisib (Zydelig®) is indicated for chronic lymphocytic leukaemia (CLL) and Follicular lymphoma.

In March 2016, an in-depth EU safety review of idelalisib, including serious infections associated with idelalisib, was initiated following a signal from clinical trials. Precautionary and temporary safety measures were implemented and communicated in May 2016. The safety review concluded in July 2016, and updates to treatment
recommendations have been made. The benefits of idelalisib outweigh the potential risks in all current indications.

Three phase III clinical trials showed a signal of increased serious infections and infection-related mortality associated with idelalisib. The trials investigated the addition of idelalisib to standard therapy in first-line CLL, and to the treatment of relapsed indolent non-Hodgkin lymphoma (small lymphocytic lymphoma).

**Reference:**

(See WHO Pharmaceuticals Newsletter No.4, 2016: Risk minimization to prevent serious infections in the EU, and No.3, 2016 and No.2, 2016 for related information)

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**Lamotrigine**

**Risk of Stevens Johnsons Syndrome / toxic epidermal necrolysis**

**India.** The IPC, NCC-PvPI has requested the revision of the drug safety label for lamotrigine to include Stevens Johnson Syndrome / toxic epidermal necrosis (SJS/TEN) as a potential risk.

Lamotrigine is used for add-on therapy for partial and secondary generalized tonic-clonic seizures in adults not below 16 years of age.

NCC-PvPI has received 36 reports of SJS/TEN with exposure to lamotrigine between 2011 and March 2016. The reports were reviewed by the PvPI-SRP, IPC.

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

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**Itraconazole**

**Risk of photosensitivity reaction**

**India.** The IPC, NCC-PvPI has requested the revision of the drug safety label for itraconazole to include photosensitivity reaction as a potential risk.

Itraconazole is indicated for systemic aspergillosis and candidosis, cryptococcosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, blastomycosis and other rarely occurring systemic or tropical mycosis.

NCC-PvPI has received three reports of photosensitivity with exposure to itraconazole between 2011 and March 2016. The reports were reviewed by the PvPI-SRP, IPC.

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

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**Levonorgestrel-containing emergency hormonal contraception**

**Drug-drug interaction**

**The United Kingdom.** The MHRA has updated the product information for levonorgestrel emergency contraception to include information on the potential interactions with the use of medicines or herbal remedies that induce CYP3A4 enzymes.

Levonorgestrel-containing emergency contraception is used to prevent unintended pregnancy when taken within 72 hours (3 days) of unprotected intercourse or failure of a contraceptive method.

**Mannitol**

**Risk of hypokalaemia**

**India.** The IPC, NCC-PvPI has requested the revision of the drug safety label for mannitol to include hypokalaemia as a potential risk.

Mannitol is used for cerebral oedema, impeding acute renal failure, acute poisonings, and raised intraocular pressure.

NCC-PvPI has received 18 reports of cardiac arrest with exposure to mannitol between 2011 and 2015. The reports were reviewed by the PvPI-SRP, IPC.

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

Restrictions on usage due to neurological and cardiovascular adverse effects

Singapore. The HSA has recommended that the package inserts for metoclopramide containing products are updated to include restrictions on dose and duration of use.

Metoclopramide is indicated for the prevention and treatment of nausea and vomiting due to various conditions.

A review in the EU confirmed a relationship between the use of high doses or long-term use of metoclopramide and an increase in the risk of neurological adverse reactions, such as acute extrapyramidal symptoms and irreversible tardive dyskinesia. In addition, there were also very rare reports of serious cardiovascular reactions, particularly if metoclopramide was administered intravenously. Patients at risk of cardiovascular reactions include the elderly population, patients with cardiac conduction disturbances (including QT prolongation), uncorrected electrolyte balance, bradycardia, and those taking other medicinal products known to prolong the QT interval.

In Singapore, nearly one in five neurological adverse reports associated with metoclopramide received by the HSA from 1993 to August 2014 were reported in children. Overall, the local incidence rate of neurological adverse effects in adults and children did not exceed those reported overseas.

The HSA has encouraged health-care professionals to take consider restrictions, dose and duration when prescribing metoclopramide.

Reference:
Product Safety Alerts, HSA, 21 September 2016 (http://www.hsa.gov.sg/)
(See WHO Pharmaceuticals Newsletter No.2, 2015: Risk of neurological adverse events in Australia, and No.1, 2015 and No.5, 2013 for related information)

Natalizumab

Risk of Progressive multifocal leukoencephalopathy (PML), granule cell neuronopathy and acute retinal necrosis

Japan. The MHLW and the PMDA have announced that the package insert for natalizumab (Tysabri®) has been updated to include the risk of progressive multifocal leukoencephalopathy (PML), granule cell neuronopathy and acute retinal necrosis in patients as clinically significant adverse reactions.

Natalizumab is indicated for the prevention of relapse and delaying the accumulation of physical disability in multiple sclerosis.

Cases of granule cell neuronopathy and acute retinal necrosis have been reported in other countries and the company core datasheet has also been updated. In addition, the EMA has taken new cautionary action to be alert for the risk of PML and acute retinal necrosis.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 4 August 2016 (www.pmda.go.jp/english/)

Olanzapine

Risk of drug-induced hypersensitivity syndrome (DIHS)

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

Olanzapine is indicated for schizophrenia and also used for improvement of manic and depressive symptoms in bipolar disorder.

A total of two cases associated with DIHS have been reported in Japan. Of these, a causal relationship could not be excluded in one case. The company core datasheet has also been updated. In addition, the EMA and the US FDA have taken action to alert for the syndrome.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 13 September 2016 (www.pmda.go.jp/english/)

Opioid pain or cough medicines combined with benzodiazepines

Serious risk of slowed or breathing difficulties and deaths

USA. The FDA has announced that the product labels for opioid and benzodiazepine preparations have been revised to include a warning of the risk of slowed or difficulties with breathing and deaths when opioids and benzodiazepines are combined.

Reference:
Revision of Precautions, MHLW/PMDA, 13 September 2016 (www.pmda.go.jp/english/)
(See WHO Pharmaceuticals Newsletter No.2, 2016: Risk of the rare brain infection Progressive multifocal leukoencephalopathy (PML) in the EU)
Opioids are used to manage moderate to severe pain. Benzodiazepines are widely used to treat conditions including anxiety, insomnia, and seizures.

The FDA reviewed several studies that showed serious risks are associated with the combined use of opioids and benzodiazepines, other drugs that depress the CNS, or alcohol. Based on these data, the FDA has required several changes to minimize risks reflected in the opioid and benzodiazepine product labels, and patient medication guides.

The FDA has recommended that health-care professionals should limit prescribing opioid pain medicines with benzodiazepines or other CNS depressants only to patients for whom alternative treatment options are inadequate.

Reference:

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**Pomalidomide**

**Risk of hepatitis B virus reactivation**

**Singapore.** The HSA is working with the marketing authorisation holder of pomalidomide (Pomalyst®) to strengthen the warnings on the risk of HBV reactivation in the package insert.

Pomalidomide is used in combination with dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least two prior treatment regimens (including lenalidomide and bortezomib) and have demonstrated disease progression in the latest treatment.

Cases of HBV reactivation have been reported following treatment with pomalidomide in combination with dexamethasone in other countries. In some of these cases, HBV reactivation was reported to have progressed to hepatic failure.

To date, the HSA has not received any local reports of HBV reactivation with pomalidomide use.

The HSA has encouraged health-care professionals to exercise caution when prescribing pomalidomide in patients previously infected with HBV and to establish the HBV status of their patients before initiating treatment with pomalidomide.

Reference:
Product Safety Alerts, HSA, 21 September 2016 (http://www.hsa.gov.sg/)
(See WHO Pharmaceuticals Newsletter No.3, 2016: Risk of hepatitis B reactivation in the United Kingdom)

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**Posaconazole**

**Potential over-dose or lack of efficacy due to switching between oral tablets and suspension**

**The United Kingdom.** The MHRA has announced that the product information for posaconazole has been updated to include warnings on the interchangeability of oral tablets and suspension.

Posaconazole (Noxafil®) is a broad-spectrum triazole antifungal used for the treatment and prevention of fungal infections.

Switching from posaconazole oral solution to tablets has resulted in cases of dose-related toxicity, whereas switching from tablets to oral solution has resulted in reports of under-dosing and lack of efficacy.

In the United Kingdom, the MHRA has received two reports of medication errors related to the substitution of posaconazole tablets with the oral suspension, at the same dose. One patient developed an infection which may have been due to under-dosing. A third case reported a patient with a prescription for posaconazole oral suspension which was substituted for the tablets. Headache and renal impairment were reported adverse effects in this patient.

Posaconazole tablets and the oral suspension are not directly interchangeable and require different dosing frequency, and administration instructions (with food) to achieve the same plasma drug levels.

The MHRA has updated the product information for posaconazole to clarify that the oral solution cannot be directly substituted for the oral tablet, or vice versa, at the same dose.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 2:2, September 2016 (www.gov.uk/mhra)

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**Ranitidine**

**Risk of cardiac arrest**

**India.** The IPC, NCC-PvPI has requested the revision of the drug safety label for ranitidine to include cardiac arrest as a potential risk.

Ranitidine is used for prophylaxis for peptic ulceration during NSAIDs treatment in patients with high risk.

NCC-PvPI has received one report of cardiac arrest with exposure to ranitidine between 2011 and 2015. The reports were reviewed by the PvPI-SRP, IPC.

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

**Riociguat**

**Contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias**

The United Kingdom. The MHRA has updated the product information for riociguat (Adempas®) to include the use of riociguat in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) as a contraindication.

Riociguat is authorized for use in patients with WHO Functional Class II–III inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or persistent or recurrent CTEPH after surgery, and in patients with WHO Functional Class II–III pulmonary arterial hypertension (PAH).

Interim results of the RISE-IIP randomised, double-blind, placebo-controlled, multicentre phase II trial showed increased mortality and an increased risk of serious adverse events in individuals treated with riociguat compared to placebo. Moreover, preliminary data indicated that riociguat did not provide a clinically significant benefit for these patients. As a result the trial was terminated early.

At the time of the interim assessment, 21 deaths had been observed: 17 patients assigned riociguat and four assigned placebo. The number of serious adverse events, which were mainly respiratory disease or lung infections, were also higher in the riociguat group than in the placebo group.

The benefits of riociguat in its approved indications continue to outweigh the risks.

**Reference:**
Drug Safety Update, MHRA, Volume 10, issue 1:1, August 2016 (www.gov.uk/mhra)

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**Rotavirus vaccine**

**Risk of intussusception**

**India.** The IPC, NCC-PvPI has requested the revision of the drug safety label for rotavirus vaccine to include intussusception as a potential risk.

Rotavirus vaccine is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3 and G4 when administered as a 3 dose series to infants between 6 to 32 weeks.

NCC-PvPI has received 10 reports of intussusception with exposure to rotavirus vaccine between 2011 and 2015. The reports were reviewed by the PvPI-SRP, IPC.

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

(See WHO Pharmaceuticals Newsletter No.5, 2015: Risk of Intussusception in Singapore and No.6, 2013: Risk of intussusception in Australia)

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**Sitafloxacin**

**Risk of thrombocytopenia and risk of psychiatric symptoms including confusion, delirium, and hallucination**

**Japan.** The MHLW and the PMDA have announced that the package insert for sitafloxacin (Gracevit®) has been updated to include the risk of thrombocytopenia and psychiatric symptoms (confusion, delirium, and hallucination) as clinically significant adverse reactions.

Sitafloxacin is an antibiotic medicine.

A total of two cases of thrombocytopenia and one case with psychiatric symptoms, suspected to be associated with the use of sitafloxacin have been reported in Japan. A causal relationship could not be excluded in the case with psychiatric symptoms.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

**Reference:**
Revision of Precautions, MHLW/PMDA, 4 August 2016 (www.pmda.go.jp/english)

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**Trabectedin**

**Risk of fluid leakage from small blood vessels (capillary leak syndrome)**

**Canada.** Health Canada has announced that the Canadian product information for trabectedin (Yondelis®) has been updated to include the potential risk of capillary leak syndrome.

Trabectedin is used alone to treat some advanced soft tissue cancers, or together with another drug to treat ovarian cancer, when other treatments do not work.

Health Canada carried out a safety review investigating the potential risk of capillary leak syndrome with the use of trabectedin.

At the time of the review, there were no Canadian cases of capillary leak syndrome reported with the use of trabectedin. However, there were 26 international cases reported. It was difficult to determine how much of a role trabectedin played in the reported cases of capillary leak syndrome because other health conditions could have explained some of the reported medical problems.

The literature review showed that capillary leak syndrome has been reported with other...
Regulatory Matters

Drugs, some of them being used to treat various cancers. Published scientific and medical literature did not find strong evidence of a link between capillary leak syndrome and the use of trabectedin.

Health Canada’s safety review concluded that there is a potential risk of capillary leak syndrome with the use of trabectedin.


Viscous lidocaine

Risk of severe side effects in infants and young children

Canada. Health Canada has updated the product information for viscous lidocaine 2% products to include a warning about the risk of severe adverse effects in infants and young children.

Viscous lidocaine 2% is used to reduce pain and discomfort in the mouth or to numb an area in the mouth before a medical exam or procedure.

A safety review was carried out by Health Canada after the US FDA issued a safety announcement indicating that this product should not be used in infants and children for teething pain, and that the labels must describe the risk of severe adverse effects such as seizures, severe brain injury, heart problems and death which have been reported in patients aged five months to four years in the US.

At the time of the review, there were no Canadian cases of serious adverse effects reported with the use of viscous lidocaine 2% products. The review of the international medical literature showed 13 reported cases of serious adverse effects with the use of viscous lidocaine 2% products in infants and young children.

Health Canada’s safety review concluded that there is a link between the use of viscous lidocaine 2% and severe adverse effects in infants and young children. Health Canada is working with the manufacturers of viscous lidocaine 2% products to update the Canadian product information to include these severe adverse effects.


(See WHO Pharmaceuticals Newsletter No.4, 2014: Should not be used to treat teething pain in the USA)
**Allopurinol**

**Serious cutaneous adverse reactions and the role of genotyping**

**Singapore.** The HSA has issued advice to health-care professionals about cautions required with the use of allopurinol to minimize risk of allopurinol-induced serious cutaneous adverse reactions (SCAR).

Allopurinol is recommended as first-line therapy for gout.

An HSA-initiated local multi-centre, case-control study found evidence of a strong association between HLA-B*5801 allele and allopurinol-induced SCAR, i.e. patients carrying the HLA-B*5801 allele have higher risk of developing allopurinol-induced SCAR (100 times) compared to one who does not have the allele. This is consistent with international data.

The frequency of HLA-B*5801 prevalence is estimated at 18.5% in Singapore (approximately one in five Singaporeans or one in five Chinese, one in 15 Malaysians and one in 25 Indians).

A cost-effectiveness analysis by Duke-NUS Graduate Medical School, in collaboration with the HSA and National University Health System, concluded that genotyping all patients with gout prior to initiation of allopurinol is currently not cost-effective.

The HSA has received nine allopurinol-induced SCAR reports between March and August 2016. In the majority of these cases, allopurinol was used for gout in Chinese patients.

The HSA has advised that while genotyping is not required as standard of care for new patients starting allopurinol, doctors may consider genotyping patients who have other pre-existing risk factors for allopurinol-induced SCAR such as renal impairment and to identify the patients who are at a greater risk of allopurinol-induced SCAR. Genetic testing, when ordered for at-risk patients, should not substitute for appropriate clinical vigilance and patient management.

**Reference:**
Product Safety Alerts, HSA, 21 September 2016 (http://www.hsa.gov.sg/)

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**Amodiaquine and sulfadoxine-pyrimethamine (Seasonal Malaria Chemoprevention)**

**Strengthening of supervised administration in children during mass drug distribution**

**Burkina Faso.** The Burkina Faso National Medicines Regulatory Authority (DGPMML) has issued a recommendation to strengthen the supervision of amodiaquine and sulfadoxine-pyrimethamine administration during mass drug distribution campaigns for seasonal malaria chemoprevention.

The recommendation follows an administration error that occurred in a 3-month-old child which led to hospitalization. In the absence of the child’s career, two amodiaquine tablets were administered instead of one amodiaquine and one sulfadoxine-pyrimethamine on day-1.

Seasonal malaria chemoprevention strategy was first implemented in 2014 in Burkina Faso. Doses of amodiaquine and sulfadoxine-pyrimethamine are administered to prevent malaria in children during periods of high transmission of malaria. The implementation strategy involves door to door distribution. The first dose on day-1 is supervised by a community health worker and consists of one amodiaquine tablet and one sulfadoxine-pyrimethamine. The remaining amodiaquine doses on day-2 and day-3 are administered by the child’s carer.

DGPMML recommend that there is tighter control on supervised intake of SMC regimens and calls for the development of innovative strategies to ensure safe administration.

**Reference:**
Based on the communication from Autorité Nationale de Réglementation Pharmaceutique, DGPMML, Burkina Faso, 2016

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**Eculizumab and multicomponent meningococcal B vaccine**

**Risk of haemolysis and low haemoglobin in patients vaccinated with multicomponent meningococcal B vaccine**

**Canada.** Health Canada has announced that the manufacturer of eculizumab (Soliris®) has updated the Canadian product information for eculizumab to include the risk of haemolysis with vaccines against *Neisseria meningitides* serogroup B.

Eculizumab is used to treat patients with Paroxysmal Nocturnal Hemoglobinuria, or atypical Haemolytic Uremic Syndrome. Patients receiving eculizumab are at increased risk of meningitis and should be vaccinated for meningitis before, or when they start treatment with eculizumab.

Multicomponent meningococcal B vaccine (Bexsero®) is used to protect against *Neisseria meningitidis* serogroup B.
Health Canada carried out a safety review of multicomponent meningococcal B vaccine after one year on the market. More reports of serious adverse effects were found in patients that were also treated with eculizumab compared to other patients. Health Canada conducted a follow up review of eculizumab to investigate further.

Health Canada's safety review of multicomponent meningococcal B vaccine found that low haemoglobin was a common adverse effect in patients treated with eculizumab, but not in other patients vaccinated with multicomponent meningococcal B vaccine.

To minimize the risk of haemolysis, the manufacturer recommends that patients who are already being treated with eculizumab should only be vaccinated when their disease is controlled and the eculizumab concentration in the blood is high.

Reference:
Summary Safety Review, Health Canada, 16 September 2016 (www.hc-sc.gc.ca)

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**Fingolimod**

**Risk of Progressive Multifocal Leukoencephalopathy (PML)**

**Canada.** Health Canada has requested that the manufacturer of fingolimod (Gilenya®) continue to provide information on the risk of progressive multifocal leukoencephalopathy (PML).

Fingolimod is used to treat multiple sclerosis in adult patients with relapsing-remitting multiple sclerosis, who do not respond well or are unable to tolerate other treatments (one or more) for multiple sclerosis.

Health Canada carried out a safety review and concluded that there was a possible link between PML and fingolimod use.

At the time of the review, there were four international case reports of suspected PML linked to fingolimod use. There were no Canadian case reports.

During the time the review was conducted, the product information for fingolimod was updated by the manufacturer to warn about this potential risk. Health Canada has requested that the manufacturer continue to monitor for this potential risk and provide Health Canada with any new information.

Reference:

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

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**Isotretinoin**

**Potential risk of psychiatric adverse events**

**Australia.** The TGA has reminded health-care professionals of the potential risk of psychiatric adverse effects with the use of isotretinoin, and the need for careful psychological assessment before and during treatment.

Isotretinoin (Roaccutane® and generics) is indicated for the treatment of severe cystic acne. However, because of significant adverse events associated with its use, isotretinoin should be reserved for patients with severe cystic acne who are unresponsive to conventional therapy, including systemic antibiotics.

The TGA stated that psychiatric adverse reactions, including depression and suicidality, are a known risk associated with the use of isotretinoin and are adequately communicated in the Australian Product Information and Consumer Medicine Information. However, the TGA’s assessment recommended that health-care professionals should be reminded that clinically significant depression can occur in patients taking this medicine and care should be taken in patients with a history of psychiatric disorders.

Reference:
Medicines Safety Update, TGA, Vol. 7, No. 4, August (www.tga.gov.au)

(See WHO Pharmaceuticals Newsletter No.1, 2015: Possible risk of psychiatric disorders in the United Kingdom)
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 individual case safety reports (ICSRs) available in VigiBase®, the WHO international database of suspected adverse drug reactions. The database contains over 14 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.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 24). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC’s vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. 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.

**Dimenhydrinate and erythema multiforme/Stevens Johnson Syndrome**

*Mr Daniele Sartori, Uppsala Monitoring Centre*

**Summary**

Dimenhydrinate is the 8-chlorotheophylline diphenhydramine derivative used as symptomatic treatment in allergies, motion sickness or nausea. As of October 2015, there were 73 cases for the MedDRA preferred terms Stevens Johnson Syndrome (SJS) and erythema multiforme (EM) in association with dimenhydrinate in VigiBase®, the WHO international database of suspected adverse drug reactions. The two drug-event combinations were disproportionately highlighted, with respective IC values of 2.52 and 1.90. There appears to be grounds for a signal specific to Asian patients, in the light of known sensitivity to severe skin reactions in this population, a reasonable time to onset, the similarity to case reports documented in the literature, and reoccurrence of reactions after re-exposure. Furthermore, the theophylline moiety of dimenhydrinate may play a role in the onset of SJS/EM. Despite limitations, such as potential reporting bias and reporting format constraints, there appears to be a signal for dimenhydrinate and severe skin reactions. As an adjunct to recent guidance from the Thai FDA, it is advisable to inform health-care professionals in other countries as well of this suspected safety issue.

**Introduction**

Dimenhydrinate is an antihistamine drug used to alleviate allergic symptoms. Its structure is composed of a diphenhydramine and an 8-chlorotheophylline moiety. The former is the true antihistamine, while the latter – a stimulant – acts as buffer against sedating effects.

Stevens Johnson Syndrome (SJS) is a potentially fatal, immune-mediated condition, characterized by epidermal necrosis without dermal inflammation. Acute symptoms are skin, mucosae and eye lesions, fever and sore throat. Typically, SJS is perceived as a drug-induced effect; the most common drugs associated with it are antibiotics (sulfonamides in particular), HIV antiretroviral treatment, carbamazepine or aromatic anticonvulsants, allopurinol and NSAIDs (oxicam type).1

Erythema multiforme (EM) is divided in two categories: minor and major. The latter is characterized by mucosal involvement in addition to target lesions, and is often drug-induced.2

Patients are at a higher risk of developing SJS during the first two months of treatment with the aforementioned drugs.2 The human leukocyte antigen (HLA-) B*1502 has been identified as a positive predictor of genetic susceptibility to carbamazepine-induced SJS in Han Chinese, Malays and Thais. Additionally, HLA-B*5801 positive Chinese7 and Thai2 are considered to be predisposed to drug-induced SJS. A strong association between HLA-B*1502 and severe skin reactions has not been identified in large-scale studies involving Europeans, as opposed to HLA-B*5801, where allopurinol and aromatic antidepressants were the most commonly involved drugs.2 There are a number of conditions
associated with SJS/EM, such as infections, namely herpes simplex infection and AIDS, as well as chronic pulmonary inflammatory conditions.

**Reports in VigiBase®**

**Stevens Johnson Syndrome**

As of October 2015 there were, after removal of suspected duplicates, 49 cases of dimenhydrinate in association with the MedDRA Preferred Term Stevens Johnson Syndrome in VigiBase®, the WHO international database of suspected adverse drug reactions. They come from Thailand (32), Germany (14), Malaysia, Suriname and Canada (one each). The combination was highlighted with an IC of 2.52 and an IC_{97.5} of 2.10. Reports have been subdivided into two groups, based on country of origin of the reports.

**South-East Asian reports**

These 33 patients were mostly female (female to male ratio of 26:7) and had an average age of 56.1 years (median 64.0), ranging from 5 to 86 years. The time to onset was reported in 31 cases, and averaged around 2.5 days (median 1 day), with a minimum of 0 to a maximum of 29 days. The seriousness was not reported for these cases. The indication was nausea or dizziness in eight cases and fever in one. Dimenhydrinate was the only suspected drug in 25 cases out of 33 and the only one reported in 13. Other co-suspects included anti-muscarnics to treat diarrhoea, antihelminthics such as albendazole, other antihistamines (chlorphenamine, cinnarizine, cyproheptadine, flunarizine), anti-nausea agents (metoclopramide), antibiotics (norfloxacin, cloxicillin) and in one case carbamazepine and paracetamol.

Sixteen patients were taking other concomitants, including paracetamol alone or in combination with orphenadrine in eight cases, other antihistamines (flunarizine, chlorphenamine, loratadine, cetirizine, cyproheptadine), vitamins of the B complex, dexamethasone, gastroprotectors (domperidone, omeprazole), cough remedies (bromhexine, dextromethorphan), antibiotics (levofloxacin) and antihypertensives (amlodipine, simvastatin). Patients were generally taking one to two drugs.

Only terms belonging to a clinical picture of Stevens Johnson Syndrome, such as Stevens Johnson Syndrome, rash, pruritus, and fever were reported and in one case exclusively EM was co-reported.

Dimenhydrinate was withdrawn in 18 cases, the reaction abated in 13 cases but no effect was observed in five. When the reaction abated, the outcome was noted as ‘recovered’ or ‘recovered with sequelae’ in nine patients, not recovered in two and unknown in two. Where no effect was observed, the outcome was recovered and recovered with sequelae in two, not recovered in two and unknown in one. No information on dechallenge was provided for the remaining 15 cases. The outcome of these cases was recovered or recovered with sequelae in seven, not recovered in six and unknown in two. One positive rechallenge (with no information on dechallenge) was reported, the outcome of this case was not recovered at the time of reporting.

In the 13 cases where dimenhydrinate was the only reported drug, the average time to onset was 3.4 days with a median of 0 days. When the reaction abated, the outcome was noted as ‘recovered’ or ‘recovered with sequelae’ in nine patients, ‘not recovered’ in two and unknown in two. In the remaining nine cases, it is unknown whether the drug was discontinued, however, the outcome was reported in seven: three patients fully recovered, while four had not recovered at the time of reporting. The case with positive rechallenge described above was included in this set of reports.

**Other countries’ reports**

Among the 16 cases there were more females than males (female to male ratio of 10:6), with an average of 56.8-years (median 70). Time to onset was reported in 13 cases, it was of 6.4 days on average (median of 5.5), with a minimum of 0 and a maximum of 18 days. There were ten serious cases, one non-serious and five in which seriousness was not reported. Two cases co-reported toxic epidermal necrolysis (TEN). Dimenhydrinate was the only suspected drug in two cases, other co-suspects were anti-inflammatory/antipyretics or chronic pain treatments (opiates, -coxibs, NSAIDs) in 11 cases, antibiotics in 11 cases (penicillins, cephalosporins and “sulfa” antibiotics), anticoagulants in nine (such as acetylsalicylic acid or heparins), sedatives (benzodiazepines, Valeriana officinalis) in seven cases, anti-hypertensive and/or diuretics in seven, anti-epilepsy medication in three (carbamazepine, phenytoin, lamotrigine) and gout treatment in two (allopurinol, colchicine). On average, patients in this cohort were taking around 16 medications. Only one case was reported with no co-suspects and no concomitants.

There were other conditions, such as chronic heart failure, constipation, chronic obstructive pulmonary disease, angina pectoris, migraine, osteoporosis and cancer. Co-reported adverse reaction terms mostly belonged to a clinical picture of SJS and were: fever, skin discoloration, erythema and macules, as well as mucosal involvement (of the lip, nose and eyes) or blistering. Urinary tract infection and TEN were each also reported in one case.

In three cases the reaction abated after drug withdrawal (although dimenhydrinate was never
withdrawn alone), in one the reaction was fatal despite withdrawal, while another patient was rechallenged with unknown outcome. The outcome of the reaction was recovered/recoversing in eight cases, fatal in two and not recovered in three. In one of the two fatal cases, SJS was attributed to pantoprazole and to the patient’s cholangitis. The remaining fatal case concerns a young woman who was hospitalized due to SJS after about a month of dimenhydrinate use (the reported time to onset was of 0 days).

**Erythema multiforme**
The cases associated with the MedDRA PT Erythema multiforme were 24, the majority of which came once again from Thailand (22 cases) while one case each came from Iran and the Republic of Korea. The combination of dimenhydrinate and EM had an IC of 1.90 and an IC₅₀ of 1.28.

Twenty patients were females, while the rest were males. The average age was 59 years (median of 62), with a minimum of 25 and a maximum of 80 years. Time to onset was reported in 22 cases, being 1.8 days on average (median of 1), with a minimum of 0 and a maximum of 11 days. One case was reported as serious, while seriousness information was missing for the rest of the reports. In all cases but one dimenhydrinate was the only suspected drug, while in 12 it was the only one reported. Concomitant medications were reported in 12 cases; among the most frequent there were antihistamines, such as cinnarizine, flunarizine and chlorphenamine, in five cases, NSAIDs such as paracetamol and acetylsalicylic acid in three, benzodiazepines in another three cases and vitamins in two. Other co-reported drugs were acid neutralizers, antidiabetics, etilefrine, pentoxyfylline, prednisolone, but were reported only once. Patients were generally taking one or two drugs, with one patient taking four.

The drug was withdrawn in 15 cases, in 12 the reaction abated, while in three no effect was observed. There were two positive rechallenges. When the drug was withdrawn and the reaction abated the outcome was recovered, recovered with sequelae and not recovered in four cases each. When there was no effect after withdrawal, the outcome was always ‘not recovered’. The outcome of the two cases with positive rechallenge was recovery and recovery with sequelae.

Only three cases co-reported other adverse events: drug eruption, dermatitis bullous and pruritus. In one case the original reported term was “erythema multiforme severe”.

**Literature and Labelling**
Stevens Johnson Syndrome is not labelled for dimenhydrinate, either on the MHRA label⁸ or in Martindale⁹ or DailyMed¹⁰. However, a communication was issued this June by the Thai FDA that urges caution when using dimenhydrinate, due to severe skin reactions, including SJS, TEN and fixed drug eruption.¹¹

A review of the literature highlighted two case reports of interest. The first one involves a young Iranian man, aged 17, who repeatedly complained of symptoms of SJS after administration of dimenhydrinate for motion sickness. The boy took the drug at least three times, in two instances the symptoms were mild, self-limiting and not systemic. However, in the third and last instance there appeared genital and mouth ulcers along with systemic reactions (itching, redness). The diagnosis of SJS was confirmed by biopsy and after a recommendation to avoid dimenhydrinate and a one-year follow-up there was no re-occurrence of the reaction.¹²

The second case concerns a 22-year-old female from China. The woman suffered from periorbital oedema and generalized rash after dimenhydrinate administration, worsening to erythema multiforme after treatment with chlorphenamine and hydroxyzine. On two occasions, she had taken paracetamol and pamabrom (8-bromotheophylline) and suffered from similar episodes. Allergic tests for paracetamol yielded negative results. The authors concluded that the theophylline moiety (pamabrom and 8-chlorotheophylline) may have triggered the reaction, because the patient had taken diphenhydramine and paracetamol separately on other occasions without any consequences.¹³

**Discussion**
Two case series have been considered in this assessment. In the first one, SJS cases were grouped by country of origin to highlight features such as differences in demographics, time to onset, co-reported medications and adverse event terms. The second case series involved patients who were reported to have experienced EM.

Stevens Johnson Syndrome patients from Thailand or Malaysia were overall treated for mild conditions or were taking fewer drugs than those from the rest of the world. In the cases where paracetamol or paracetamol combinations, known to be associated with SJS, were reported as concomitant, dimenhydrinate was considered as suspected instead. Although the two drugs were taken during the same time interval, reporter suspicion indicates that a role of dimenhydrinate cannot be completely excluded. In one instance, only paracetamol was considered a suspected drug and along with carbamazepine it would appear to be a more likely explanation for SJS. Other co-reported drugs are known to cause SJS such as albendazole, norfloxacin, cloxacillin, bromhexine; additionally, antibiotics indicate active infection.
which can predispose to SJS. These confounded cases are a small minority of the total (4/33). Furthermore, nine patients recovered on dechallenge, six of whom were not taking any co-suspect or were being treated with concomitants known to induce SJS. Because the condition is known to occur within the first two months of treatment, a time to onset with an average of 2.5 days and a maximum of 29 appears to be within reasonable limits of a drug-induced effect. This is further strengthened by the positive rechallenge reported. On the other hand, although SJS occurrence after short latency has been registered, the time to onset in this case series seems atypical when compared to the average 2-3 weeks. Previous use of dimenhydrinate or NSAIDs may have fostered the occurrence of hypersensitivity reactions.

Patients from other, non-Asian countries, were generally being treated for chronic conditions or infections, with an average of 16 drugs per patient. Aside from the potential interactions arising from over-medication and the underlying conditions, such as infections, in nearly every case (11/16), the dimenhydrinate contribution remains hard to assess due to allopurinol (2 cases), anti-epileptics known to rarely cause SJS (carbamazepine, lamotrigine and phenytoin) and NSAIDs – though very rarely associated with this reaction. Only one case is indicative of a dimenhydrinate-induced SJS; it involves a 22-year-old female who was hospitalized, and later died, due to SJS/TEN after the prescription of dimenhydrinate a month earlier.

Erythema multiforme patients were treated for minor ailments, mostly allergies and sleep disturbances. Only three of them were taking paracetamol but it was reported as concomitant. Reporter suspicion should be weighed carefully before dismissing dimenhydrinate as a potential contributive agent in these cases. Except for one case, where mefenamic acid, labelled for erythema multiforme, was co-suspect, dimenhydrinate was always the only suspected drug and the only one reported in 12 cases. Among these 12 cases, there were six recoveries (with or without sequelae) on dechallenge, and one positive rechallenge with recovery on dechallenge. With an average time to onset of 1.8 days, in keeping with a drug-induced reaction. EM, there is a strong hint of a causal role of dimenhydrinate, although such a short time to onset is atypical for EM.

Stevens Johnson Syndrome and erythema multiforme are two skin conditions known to be drug-induced in many cases. Recent findings have shown Chinese, Thais and Malys to be more prone to developing these reactions, especially with allopurinol as the causative agent. Interestingly, the large majority of the patients in the two case series considered were Thai, which could indicate regional specificity or may be related to usage. It should be noted however, that these patients were not affected by chronic conditions, infections or taking multiple drugs, at least in the majority of the cases, unlike patients from other countries.

Tan and Sklar suggested the 8-bromotheophylline moiety to have been responsible for erythema multiforme, and similarly it could be postulated that the 8-chlorotheophylline component in dimenhydrinate might have played a role in the development of either SJS or EM. In fact, both molecules are identical in their xanthine group and differ only in the halogen in position 8 (bromine or chlorine).

Although there is no evidence that correlates xanthines with SJS or EM, there are two case reports of theophylline, another xanthine, and severe erythema multiforme and SJS.

There are some limitations to this assessment. As the predisposition to SJS/EM in some Asian populations is well-described, physicians could be more prone to diagnosing SJS/EM, or more inclined to report it. Thailand is, in VigiBase®, the main contributor to Continental Asia reports when it comes to these skin conditions (48% of Continental Asia reports) and Continental Asia adds 30% of the total reports with the MedDRA PT Stevens Johnson Syndrome alone, which may point to a reporting bias.

Based on the limited number of reports indicating seriousness, it might seem that a majority of the cases were not considered serious. Important to note is that most of the cases were reported to VigiBase® in a format in which seriousness cannot be reported in a structured way. However, out of the 13 reports where seriousness could be reported, 11 actually indicated a serious reaction. Unreported seriousness can lead to speculations around the nature of the diagnosis. Skin detachment is a medical concern that often results in hospitalization, which is one of the criteria for being considered a serious reaction. Limitations in the reporting format also account for interpretative issues in regards to the outcomes of drug discontinuation (for instance, cases reporting positive dechallenge but outcome not recovered).

Conclusions

The majority of the assessed cases from Asian countries appear to be supportive of severe skin reactions after use of dimenhydrinate. This is supported by a reasonable time to onset, known genetic predisposition to SJS/ TEN of Thais, Han Chinese and Malays, and structural similarity between dimenhydrinate xanthine moiety and pamabrom, associated with EM in a case report. Furthermore, these cases were less confounded by concomitant medications and underlying conditions compared to cases from other countries. Because the predisposition is known for
drugs other than dimenhydrinate, there could be a regional sensitivity to skin-related conditions that inflates the number of reports following the administration of a drug. Despite limitations, and as an adjunct to the guidance from the Thai FDA, it is advisable to inform health-care professionals in other countries as well of this suspected safety issue. Over-the-counter availability of dimenhydrinate can constitute a challenge in avoiding undesirable effects, as interaction between physicians or pharmacists and patients is reduced in favour of access to treatment, underlining the role of pharmacovigilance centres in communicating the responsible use of medicines and the availability of other antihistamines.

References


Signal

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.

UMC; other National Centres do not.

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Summary

‘Asia-Pacific Economic Cooperation (APEC) Harmonization Center (AHC) Pharmacovigilance Workshop’ was held on 5 September, 2016 in Novotel Ambassador Hotel in Seoul, Republic of Korea. The workshop was organized by the AHC and approximately 180 participants attended. Twelve speakers and panellists, including from U.S. Food and Drug Administration, the Ministry of Food and Drug Safety (MFDS) in Korea, National Pharmacovigilance centres in APEC region, WHO, UMC and Lareb contributed. Participants engaged in lively discussions on several pharmacovigilance issues.

Introduction

The Regulatory Harmonization Steering Committee (RHSC) was formed in 2008 in the APEC region, in order to promote a strategic and coordinated approach to regulatory convergence and capacity building. The AHC, in partnership with APEC RHSC, aims to provide a platform for regulatory priorities among APEC member economies.

This workshop was organized as a part of the APEC RHSC ‘Roadmap to Promote Regulatory Convergence on Pharmacovigilance and Medical Device Vigilance’. Similar workshops were also organised in 2012, 2013 and 2015.

The workshop brought together regulators, industry representatives, and experts from academia to facilitate the harmonization and convergence of pharmacovigilance in the APEC economies.
The workshop was officially opened by Dr Yeowon Sohn, Director of the AHC, followed by the remarks by Dr Kyeong-Ho Lee, Chairman of the Korea Pharmaceutical Manufacturers Association.

In Session I, various pharmacovigilance activities within and beyond the APEC region were shared. Presentations on national pharmacovigilance systems in Asia-Pacific region highlighted the importance of concerted efforts to improve the quality of Adverse Event (AE) reports. Pharmacovigilance activities in Europe were also presented.

Session II consisted of a presentation and panel discussion on reporting and collecting AE. UMC presented on the aspects to be considered for high quality and reliable reports, highlighting the importance of creating positive reporting culture and good communication. Active discussion with panellists on the various methods and efforts to improve the quality of reports were made, and the tools and methodologies for effective communication were shared.

Lastly, AE evaluation was covered in Session III. Structured approaches to Benefit-Risk (B-R) assessment and the challenges in decision-making were presented. The following panel discussion was about data sources and effective methods for B-R assessment on the basis of cases from APEC economies. In the discussion, panel noted that there has been a steady increase in patient involvement in the B-R considerations.

The participants expressed that the workshop provided an opportunity to broaden their knowledge and understanding in AE reporting and evaluation, and indicated the contents were “relevant” and “helpful” for their daily work.

Feedback and comments from the participants and speakers will be analysed and used for developing programs that address needs of the APEC economies. The AHC expressed its commitment to provide an educational platform for regulatory harmonization within the APEC region.

WHO will continue to support pharmacovigilance activities in the APEC region as well as other pharmacovigilance activities with regional cooperation.