World Health Organization

WHO Pharmaceuticals NEWSLETTER

2016
No.5

WHO Vision for Medicines Safety

No country left behind: worldwide pharmacovigilance for safer medicines, safer patients

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.

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

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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 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.

Contents

Printed by the WHO Document Production Services, Geneva, Switzerland

Table of Contents

Regulatory Matters

Safety of Medicines

Signal

Feature

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 2 226 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:
Medicines Safety Update, TGA, Vol. 7, No. 4, August *(www.tga.gov.au)*

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.

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

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.

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

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

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 billiary 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

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/)*

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).

Product Characteristics for these products.

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

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

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