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

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

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

Safety and Vigilance: Medicines,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pvsupport@who.int

This Newsletter is also available at:
http://www.who.int/medicines

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from the WHO global database of individual case safety reports, VigiBase.

This newsletter includes a summary of discussions and key recommendations from the 15th meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

Contents

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Adrenaline interaction with antipsychotics

Hypotension: Contraindication revised

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have requested that precautions for adrenaline and antipsychotics (e.g. aripiprazole, Abilify®) preparations should be revised to specify that co-administration is not contraindicated if adrenaline is used for emergency treatment of anaphylaxis.

Adrenaline is the first-line drug used for treatment of anaphylaxis in Japan. Antipsychotic agents and adrenaline co-administration was previously contraindicated due to an interaction causing adrenaline reversal and hypotension.

The Japanese Society of Allergology requested to remove this contraindication. The PMDA investigated the safety of co-administration of adrenaline preparations used for the emergency treatment of anaphylaxis in patients who are on antipsychotic agents with α-blocking actions. The PMDA concluded that anaphylaxis is a fatal condition that requires prompt emergency treatment. Therefore use of adrenaline preparations for anaphylaxis is considered to be acceptable even though there is a risk of decreased blood pressure induced by adrenaline reversal.

Reference:
Revision of Precautions, MHLW/PMDA, 27 March 2018 *(www.pmda.go.jp/english/)*

Amlodipine

1. Risk of Alopecia

India. The National Coordination Centre - Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopeia Commission (IPC) has made a recommendation to the Central Drugs Standard Control Organisation (CDSCO) requesting that the drug safety label for amlodipine is revised to include alopecia as an adverse drug reaction.

Amlodipine is used for the treatment of angina, hypertension and coronary artery disease. Between July 2011 and August 2017, NCC-PvPI received seven individual case safety reports (ICSRs) of alopecia with amlodipine use. The cases were reviewed by Signal Review Panel (SRP)-PvPI, IPC and they showed a strong causal relationship between amlodipine and alopecia.

Reference:
Based on the communication from IPC, NCC-PvPI, India (*http://ipc.nic.in*)

2. Risk of Gingival Hypertrophy

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for amlodipine is revised to include gingival hypertrophy as an adverse drug reaction.

Between July 2011 and March 2018, NCC-PvPI received 44 ICSRs reporting gingival hypertrophy with amlodipine use. The cases were reviewed by the Signal Review Panel (SRP)-PvPI, IPC and they suggested a strong causal relationship between amlodipine and gingival hypertrophy.

Reference:
Based on the communication from IPC, NCC-PvPI, India (*http://ipc.nic.in*)

Antimalarial drugs

Risk of Stevens Johnson syndrome (SJS)

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for the artesunate combination antimalarial drug (artemether and lumefantrine) is revised to include the risk of Stevens Johnson syndrome.

Artemether-lumefantrine are used in combination for the treatment of uncomplicated malaria. Between July 2011 and March 2018, NCC-PvPI received four ICSRs of SJS with artemether and lumefantrine use. The cases were reviewed by SRP-PvPI, IPC, and a strong causal relationship between artemether, lumefantrine and SJS was suggested.

Reference:
Based on the communication from IPC, NCC-PvPI, India (*http://ipc.nic.in*)

Antimicrobials

Precautions against inappropriate use to prevent resistance

Japan. MHLW and PMDA have announced that the product information for antimicrobials will be revised to include instructions for prescribers to consult the Guidance for Appropriate Use of Antimicrobials to decide if administration of an antimicrobial is appropriate for the case they are treating.

The Guidance for Appropriate Use of Antimicrobials was developed in accordance with the National Action Plan on Antimicrobial Resistance 2016-2020 in Japan. The content of the guidance focuses on patients with acute respiratory tract infections and patients with acute diarrhoea.

PMDA examined current package inserts of antimicrobials, and concluded

that it is necessary to update the precautions concerning indications to urge prescribers to refer to the guidance to promote appropriate use.

Reference:
Revision of Precautions, MHLW/PMDA, 27 March 2018 *(www.pmda.go.jp/english/)*

Atypical antipsychotic

Potential risk of DRESS

Canada. Health Canada has announced that the product safety information for atypical antipsychotics will be updated to include the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Atypical antipsychotics are indicated to treat mental disorders including schizophrenia, bipolar disorder, and depression.

Health Canada reviewed safety information for all atypical antipsychotics following voluntary updates by the manufacturers for olanzapine (Zyprexa®) and ziprasidone (Zeldox ®) to include the risk of DRESS in the product safety information.

Among 43 international reports of DRESS with the use of atypical antipsychotics, 11 reports met the definition of DRESS, and two reports showed a likely link between DRESS and the reported atypical antipsychotic.

Health Canada's review concluded that there may be a link between the risk of DRESS and the use of six other atypical antipsychotics including clozapine, quetiapine, risperidone, aripiprazole, paliperidone, and lurasidone.

Reference:
Summary Safety Review, Health Canada, 10 April 2018 (*www.hc-sc.gc.ca*)

Carbamazepine

Risk of DRESS

India. NCC-PvPI, IPC has made a recommendation to the CDSCO about the revision of the drug safety label for carbamazepine to include DRESS.

Carbamazepine is used for the treatment of partial seizures with or without secondary generalisation; trigeminal neuralgia; and bipolar disorder. Between July 2011 and March 2018, NCC-PvPI received 33 ICSRs of DRESS syndrome associated with carbamazepine use. The cases were reviewed by the Signal Review Panel (SRP)-PvPI, IPC who found a strong causal relationship between carbamazepine and DRESS syndrome.

Reference:
Based on the communication from IPC, NCC-PvPI, India (*http://ipc.nic.in*)

(See WHO Pharmaceuticals Newsletters No.1, 2017: HLA-B 1502 genotyping to minimize carbamazepine-induced severe cutaneous adverse reactions in Singapore; No.2, 2016: Risk of Stevens Johnson's Syndrome in India; No.1, 2013: Potential risk of serious skin reactions associated with the HLA-A 3101 allele in UK)

Carvedilol

Risk of hyperkalaemia

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for carvedilol is revised to include hyperkalaemia.

Carvedilol is used for the treatment of hypertension, mild to severe congestive heart failure (CHF), and left ventricular dysfunction (LVD). Between July 2011 and August 2017, NCC-PvPI received four ICSRs reporting hyperkalaemia with carvedilol use. The cases were reviewed by the Signal Review Panel (SRP)-PvPI, IPC which suggested a strong causal relationship between carvedilol and hyperkalaemia

Reference:
Based on the communication from IPC, NCC-PvPI, India (*http://ipc.nic.in*)

Cefixime

Risk of mouth ulceration

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the of drug safety label for cefixime is revised to include the risk of mouth ulceration.

Cefixime is used for the treatment of otitis media, respiratory tract infections, and uncomplicated UTIs. Between July 2011 and March 2018, NCC-PvPI received 17 ICSRs reporting mouth ulcerations with cefixime use. A review of the cases by Signal Review Panel (SRP)-PvPI, IPC suggested a strong causal relationship between cefixime and mouth ulceration.

Reference:
Based on the communication from IPC, NCC-PvPI, India (*http://ipc.nic.in*)

Dabigatran

Potential risk of liver injury

Canada. Health Canada will be working with the manufacturer of dabigatran (Pradaxa ®), to update the safety information to include the potential risk of severe liver injury.

Dabigatran is a blood thinner and is used to prevent certain blood clots from forming or reoccurring (e.g. in the veins of legs), and to treat blood clots in the veins and/or lungs.

Health Canada has reviewed the potential risk of liver injury with dabigatran. At the time of the review Health Canada received 27 Canadian reports and 105 international reports of severe liver injury using dabigatran. Of these reports, 4/ 27 Canadian and 16/105 international reports were assessed. A possible link

between liver injury and the use of dabigatran was shown in 3/4 and 13/16 of these reports respectively.

A review of the scientific literature did not find any published studies that showed increased risk of liver injury in patients treated with dabigatran.

Health Canada's review found that there may be a link between dabigatran and liver injury.

Reference:
Summary Safety Review, Health Canada, 7 May 2018 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.5, 2017: Risk of acute hepatic failure, hepatic function disorder, and jaundice in Japan)

Diclofenac

Risk of Nicolau syndrome

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for diclofenac is revised to include the risk of Nicolau syndrome.

Diclofenac is used for the treatment of acute musculoskeletal pain; arthritis; gout; spondylitis; migraine; and post-operative pain. Between July 2011 and March 2018, NCC-PvPI received six ICSRs of Nicolau syndrome with diclofenac use. A review of the cases by the Signal Review Panel (SRP)-PvPI, IPC suggested a strong causal relationship between diclofenac and Nicolau syndrome.

Reference:
Based on the communication from IPC, NCC-PvPI, India (*http://ipc.nic.in*)

Eperisone

Anaphylactic reaction

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has announced that the package insert for eperisone has been updated to include anaphylactic reaction as an adverse reaction.

Eperisone is a centrally acting skeletal muscle relaxant, used for treatment of muscle spasm accompanied by pain and spastic paralysis caused by nervous system disease.

This recommendation announced by the MFDS was based on expert advice following the evaluation of a signal for reports with serious adverse events by the Korea Institute of Drug Safety and Risk Management (KIDS). At the time of the review, KIDS identified three cases of anaphylactic reactions in patients treated with eperisone. A causal relationship could not be excluded in any of these cases.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, March 2018

Gadolinium based contrast agents (GBCAs)

Potential neurological adverse effects

Canada. Health Canada is working with manufacturers to make additional changes to the product information for gadolinium based contrast agents (GBCAs). The changes state that macrocyclic GBCAs are preferable to linear GBCAs in patients who may need repeated GBCA doses, as well as in children and pregnant women.

GBCAS are used to view certain body tissues on magnetic resonance imaging (MRI) scans. There are two structurally distinct categories of commercially available GCBAs in Canada: linear and macrocyclic. Both types are marketed in Canada.

Health Canada carried out a second review of the risk of gadolinium build-up in the brain and the unknown potential neurological adverse effects. Evidence from published and unpublished studies together with seven international case reports of build-up in the brain linked to the use of GBCAs suggests that risk of gadolinium build-up in the brain is higher with repeated use of GBCAs and with linear GBCAs. This risk was considered to be potentially greater in children, pregnant women, and in people receiving multiple doses of GBCAs. At the time of the review, no neurological adverse effects were linked to gadolinium build-up in the brain.

Reference:
Summary Safety Review, Health Canada, 1 May 2018 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.2, 2018: Omniscan® and intravenous iv Magnevist® no longer authorised; and restrictions of use for other linear agents in UK; No1. 2018: Gadolinium retention in body in Japan and USA; No. 5, 2017: Retention of gadolinium in the brain in New Zealand; No.4, 2017: Restrictions on use in EU, No harmful effects identified with brain retention in USA; No.5, 2015: Possible risk of brain deposits with repeated use in USA)

Isoniazid

Potential risk of pancreatitis

Canada. Health Canada is working with manufacturers to update the safety information for all isoniazid containing products to include the potential risk of pancreatitis.

Isoniazid is indicated to treat tuberculosis.

Health Canada reviewed the potential risk of pancreatitis with the use of isoniazid following an update to the product safety information in the United States.

Health Canada reviewed three Canadian reports, 14 international reports, and published reports and journals in the scientific literature. Health Canada concluded that there is a rare but potential

risk of pancreatitis with the use of isoniazid.

Reference:
Summary Safety Review, Health Canada, 10 May 2018 (*www.hc-sc.gc.ca*)

Lamivudine

Risk of hearing loss

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for lamivudine is revised to include hearing loss as an adverse reaction.

Lamivudine is used for the treatment of HIV infection in combination of at least two other antiretroviral drugs. Between July 2011 and March 2018, NCC-PvPI received eight ICSRs that reported hearing loss with lamivudine use. A review of cases by the Signal Review Panel (SRP)-PvPI, IPC suggested a strong causal relationship between lamivudine and hearing loss.

Reference:
Based on the communication from IPC, NCC-PvPI, India (*http://ipc.nic.in*)

Lamotrigine

1. DRESS syndrome

Republic of Korea. MFDS has announced that the package insert for lamotrigine has been updated to include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome as an adverse reaction.

Lamotrigine is an anticonvulsant drug, used for the treatment and prevention of partial and primary generalized tonic-clonic seizures.

During the evaluation process of reports with serious adverse events, KIDS reviewed one fatal case and subsequently suggested a link between the use of lamotrigine and DRESS syndrome.

This recommendation announced by the MFDS was based on results from the investigation of serious adverse events and expert advice.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, March 2018

2. Serious immune system reaction

USA. The US Food and Drug Administration (FDA) has requested that the drug labels and prescribing information for lamotrigine (Lamictal®) include a new warning about the risk of hemophagocytic lymphohistiocytosis (HLH).

Lamotrigine is indicated for seizures and bipolar disorder.

Hemophagocytic lymphohistiocytosis (HLH) causes an uncontrolled response by immune system. HLH typically presents as a persistent fever.

Since lamotrigine's authorization approval in 1994, the FDA identified eight cases worldwide of confirmed or suspected HLH associated with the medicine in children and adults. The FDA has determined that there is reasonable evidence to show that lamotrigine caused the HLH in these eight cases based on the timing of events and order in which they occurred.

Reference:
Safety Alerts for Human Medical Products, US FDA, 25 April 2018 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletters No.2, 2015: Risk of serious skin disorders in Japan)

Meropenem

Risk of hypokalaemia

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for meropenem is revised to include the risk of hypokalaemia as an adverse drug reaction.

Meropenem is used for the treatment of nosocomial infections such as septicaemia, febrile neutropenia, intra-abdominal and pelvic infection, and for cystic fibrosis. Between July 2011 and March 2018, NCC-PvPI received 33 ICSRs of hypokalaemia reported with the use of meropenem. A review of cases by the Signal Review Panel (SRP)-PvPI, IPC, suggested a strong causal relationship between meropenem and hypokalaemia.

Reference:
Based on the communication from IPC, NCC-PvPI, India (*http://ipc.nic.in*)

Propofol

Contraindication in pregnant women removed

Japan. MHLW and PMDA have announced that precautions of propofol preparations (Diprivan®) should be revised to remove the contraindication of use during pregnancy. Propofol can be used by pregnant women or women who may be pregnant provided the potential benefits outweigh the risks.

Propofol is indicated for induction and maintenance of general anesthesia.

Propofol is used for therapy in pregnant women in Europe and the United States. For this reason the MHLW requested the PMDA to conduct an investigation into the use of propofol during pregnancy. As a result, PMDA concluded that the above-mentioned revision to safety precautions of propofol is acceptable.

Reference:
Revision of Precautions, MHLW/PMDA, 27 March 2018 *(www.pmda.go.jp/english/)*

Sevoflurane

Potential risk of bradycardia in children with Down syndrome

Canada. Health Canada has requested that manufacturers of sevoflurane containing products strengthen the existing product safety information to include information about the risk of bradycardia in children with Down syndrome (DS).

Sevoflurane is an anesthetic drug used during surgery or other medical procedures.

Health Canada re-assessed the potential risk of bradycardia with use of sevoflurane in children with DS following evidence that was published since the last safety review in 2014.

Of 17 internationally identified reports of bradycardia in children with DS, there was a link between bradycardia and the use of sevoflurane in three reports.

Health Canada concluded that there is a link between sevoflurane and the risk of bradycardia in children with DS.

Reference:
Summary Safety Review, Health Canada, 9 April 2018 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.3, 2015: Severe low heart rate in children with Down syndrome in Canada)

inflammatory bowel disease.

Following evaluation of serious adverse events, KIDS reviewed one death case and subsequently suggested a link between the use of sulfasalazine and DRESS syndrome.

This recommendation announced by the MFDS was based on investigation results and expert advice.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, March 2018

(See WHO Pharmaceuticals Newsletters No. 4, 2017: Risk of Stevens Johnson Syndrome and toxic epidermal necrolysis in India)

Valproate medicines

Contraindicated in women and girls of childbearing potential

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that valproate containing products (Epilim®, Depakote®) must not be used in women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place due to the teratogenic risk.

Valproate medicines are indicated for the treatment of epilepsy and bipolar disorder.

Valproate is highly teratogenic and evidence supports that use in pregnancy leads to physical

contraception had little impact on prescribing. Data from the Clinical Practice and Research Datalink show that pregnancies continue to be exposed to valproate medicines. Additionally, patients have reported that they still are not receiving the necessary information to make an informed decision in many cases.

The review recommended new measures to avoid valproate exposure in pregnancy.

Reference:
Drug Safety Update, MHRA, 24 April 2018
(www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletters No.3, 2017: Risk of developmental disorders in UK; No. 2, 2016: Risk of abnormal pregnancy outcomes in UK; No. 2, 2015: Risk of abnormal pregnancy outcomes in UK; No. 1, 2015: Further restriction of the valproate use in women and girls in Ireland; No. 5, 2014: Fetal exposure and cognitive impairment in Australia; No.6, 2013: Risk of neurodevelopmental delay in children following maternal use in UK; No. 3, 2013: Contraindicated for pregnant women for prevention of migraine headaches in USA)