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Prepared in collaboration with the WHO Collaborating Centre for International Drug Monitoring, Uppsala Sweden

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 "drug information officers" 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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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®.

As the Feature article, we have included a brief report from a recent WHO-led pharmacovigilance training event.

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Regulatory Matters

Safety of Medicines

Carbamazepine

Risk of Stevens Johnson's Syndrome.

India: The Central Drugs Standard Control Organisation (CDSCO) and the Signal Review Panel of the Pharmacovigilance Programme of India-Indian Pharmacopoeia (SRP-PvPI-IPC) have requested that all manufacturers of carbamazepine should include Stevens Johnson's Syndrome as an adverse reaction in the package inserts and on the official websites.

Carbamazepine is used as an anticonvulsant used in patients with epilepsy and in patients with trigeminal neuralgia.

In India, there are 122 reports of life threatening or fatal skin reactions (Stevens Johnson's Syndrome, Toxic Epidermal Necrolysis) that may have been caused by the use of carbamazepine formulations. Although Stevens Johnson's Syndrome is a known adverse effect of carbamazepine and is already included in some package inserts, the Subject Expert Committee (SEC) have recommended that all manufacturers should include the same information on this adverse effect. The CDSCO/PvPI have decided that it was necessary to revise the package insert to include screening of HLA-B* 1502 prior to initiating the carbamazepine treatment, as HLA-B* 1502 is a known factor for carbamazepine-induced Stevens Johnson's Syndrome.

(See WHO Pharmaceuticals Newsletters No.1, 2013: Potential risk of serious skin reactions associated with the HLA-A 3101 allele in United Kingdom)*

Reference:
Central Drugs Standard Control Organisation, February 2016 (*www.cdsco.nic.in*)

Cisplatin

Risk of blood clots in the veins (venous thromboembolism)

Canada. Health Canada has recommended that the prescribing information for cisplatin products should be updated to include warnings about the increased risk of venous thromboembolism.

Cisplatin, in combination with other treatments, is used to treat advanced bladder, testicular and ovarian cancers.

Health Canada conducted a review investigating a possible risk of venous thromboembolism with cisplatin treatment, following an update of prescribing information published in Japan.

The review concluded that cisplatin is linked to a higher risk of venous thromboembolism when used to treat patients with advanced bladder, testicular and ovarian cancers. Health Canada has therefore asked manufacturers of cisplatin products to update their prescribing information to include warnings about this risk.

At the time of the review, Health Canada had received 18 reports of venous thromboembolism with the use of cisplatin. All cases were determined to be possibly related to cisplatin. Among the reported cases, five had a fatal outcome, but the cause of death was inconclusive.

The WHO Global Individual Case Safety Report (ICSR) Database, Vigibase® had 520 reports of venous thromboembolism cases linked with cisplatin at the time of this review.

A published study in the literature also reported a greater risk of venous thromboembolism with patients treated with cisplatin, compared to non-cisplatin treated patients when used to treat solid tumours.

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

Entecavir hydrate

Risk of hepatic function disorder

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for entecavir hydrate (Baraclude®) should be revised to include risk of hepatic function disorder as a clinically significant adverse reaction.

Entecavir hydrate is used to suppress the replication of hepatitis B virus in chronic hepatitis B patients with confirmed hepatic function associated with active viral replication.

Cases of elevated liver enzymes AST and ALT have been reported during treatment with entecavir hydrate in Japan. Although it is difficult to distinguish whether the cause is due to entecavir or the primary disease (can also elevate levels of AST and ALT), the causality due to the drug could not be ruled out.

The package insert will be updated to include:
Hepatic function disorder:
AST and ALT may become elevated during treatment with this drug. If elevation of AST and ALT are observed, patients should be carefully monitored by conducting more frequent liver function tests, etc. If there are no signs of improvement in hepatic function based on test values, etc., appropriate measures such as discontinuation of

administration should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 16 February 2016 (*www.pmda.go.jp/english/*)

Eribulin mesylate

Risks of oculomucocutaneous syndrome (Stevens-Johnson Syndrome) and erythema multiforme

Japan. The MHLW and PMDA have announced that the package insert for eribulin mesylate (Halaven®) will be revised to include risks of oculomucocutaneous syndrome (Stevens-Johnson Syndrome) and erythema multiforme.

Eribulin mesylate is used for unresectable or recurrent breast cancer.

The MHLW/PMDA stated that cases of oculomucocutaneous syndrome have been reported in Japan and cases of both oculomucocutaneous syndrome and erythema have been reported in other countries.

The package insert will be updated to include:

Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme: Oculomucocutaneous syndrome or erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 16 February 2016 (*www.pmda.go.jp/english/*)

Esomeprazole magnesium hydrate

Risk of rhabdomyolysis

Japan. The MHLW and PMDA have announced that the package insert for esomeprazole magnesium hydrate (Nexium®) will be revised to include risk of rhabdomyolysis as a clinically significant adverse reaction.

Esomeprazole magnesium hydrate is used to treat: ulcers (gastric, duodenal , anastomotic); reflux esophagitis, and Zollinger-Ellison syndrome. It is also used to suppress the relapse of gastric or duodenal ulcers when prescribing non-steroid anti-inflammatory drugs (NSAIDs) or low-dose aspirin. In addition, it is indicated for the eradication of *Helicobacter pylori*, in combination with antibiotics.

The MHLW/PMDA stated that cases of rhabdomyolysis have been reported in patients treated with esomeprazole

The package insert will be updated to include:

Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored. If symptoms including myalgia, feeling of weakness, increased creatinine kinase (creatine phosphokinase), or increased blood and urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 16 February 2016 (*www.pmda.go.jp/english/*)

Flunitrazepam

Precautionary measures for respiratory depression; and risk of apnoea, respiratory depression, and glossoptosis

Japan. The MHLW and the PMDA have requested that the package insert for flunitrazepam (Rohypnol®) should be revised to include advice on using precautionary measures to prepare and monitor for respiratory depression. In addition the package insert should be updated to include reports of apnoea, respiratory depression and glossoptosis.

Flunitrazepam is used for induction of general anaesthesia and sedation during topical anaesthesia.

Cases of respiratory depression with serious outcomes in patients, and cases of insufficient monitoring and delayed therapeutic measures have been reported with the use of flunitrazepam in Japan.

During the last three fiscal years in Japan, a total of 11 cases associated with respiratory depression have been reported (including eight cases for which a causal relationship to the product could not be ruled out; however, six of these cases used the drug for a condition not included as an approved indication).

A summary of the MHLW/PMDA's recommendations are as follows:

- Need for preparation of emergency analeptic drugs and flumazenil prior to administration as well as need for continuous monitoring of cardiorespiratory dynamics should be added as an important precaution to the package insert.

- Reports of serious outcomes and need for appropriate measures with apnoea, respiratory depression and glossoptosis should be added as clinically significant adverse reactions to the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 22 March 2016 (*www.pmda.go.jp/english/*)

Furosemide

Risk of interstitial pneumonia

Japan. The MHLW and the PMDA have requested that the risk of interstitial pneumonia is added as a clinically significant adverse reaction to the package insert for furosemide (Lasix® and Eutensin®) as a clinically significant adverse reaction.

Furosemide is used for treatment of several diseases and symptoms such as hypertension, oedema, pre-menstrual tension, stimulating excretion of urinary calculus, and oliguria due to acute or chronic renal failure.

Cases of interstitial pneumonia have been reported in patients treated with furosemide in Japan. In the last three fiscal years in Japan, a total of six cases associated with interstitial pneumonia have been reported (including two cases for which a causal relationship to the product could not be ruled out).

Reference:
Revision of Precautions, MHLW/PMDA, 22 March 2016 (*www.pmda.go.jp/english/*)

Fusafungine nose and mouth sprays

Risk of serious allergic reactions

EU. The European Medicines Agencys (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the marketing authorizations for fusafungine-containing medicines are revoked, so that the medicines can no longer be marketed in the EU. This recommendation follows a review by the PRAC which concluded that the benefits of fusafungine did not outweigh its risks, particularly the risk of serious allergic reactions.

Fusafungine is an antibiotic and anti-inflammatory nose and mouth spray used to treat upper airway infections such as rhinopharyngitis (common cold).

Serious allergic reactions have occurred soon after the use of these sprays and involved bronchospasm (excessive and prolonged contractions of the airway muscles leading to difficulty breathing). Although serious allergic reactions are rare, they can be life-threatening, and no measures have been identified to sufficiently reduce this risk. Evidence for beneficial effects of fusafungine is weak, and upper airway diseases are generally mild and self-limiting.

In addition there are concerns for the potential for fusafungine to promote antibiotic resistance. The evidence of this is weak, however the risk cannot be ruled out.

Patients and health-care professionals should note that medicines will remain available while a final decision is pending. Further information will be issued in due course.

Reference:
Press release, EMA, 12 February 2016 (*www.ema.europa.eu*)

Idelalisib

Risk of a particular type of lung infection (*Pneumocystis jirovecii* pneumonia)

EU. The EMA's PRAC has issued provisional advice for doctors and patients using the cancer medicine idelalisib (Zydelig®) to ensure that it continues to be used as safely as possible.

In the EU, idelalisib is authorised for the treatment of:

- chronic lymphocytic leukaemia in patients who have received previous treatment as well as in previously untreated patients who have certain genetic mutations in their cancer cells. It is used in combination with rituximab.
- a type of non-Hodgkin lymphoma called follicular lymphoma where it is used on its own.

The PRAC recommends that all patients treated with idelalisib should receive antibiotics to prevent a particular type of lung infection (*Pneumocystis jirovecii* pneumonia). Patients should also be monitored for infection and have regular blood tests for white cell counts (low counts can increase their risk of infection). Idelalisib should not be started in patients with a generalised infection. It should also not be started in previously untreated patients with chronic lymphocytic leukaemia (CLL) whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation).

These are provisional recommendations which the PRAC has issued, as a precaution, to protect patients

while the medicine is being reviewed. The review was initiated after an increase in the rate of serious adverse events including deaths (mostly due to infection) was observed in three clinical trials.

Further information on the review of idelalisib will be provided as necessary and once the review is concluded.

Reference:
Press release, EMA, 11 and 18 March 2016 (*www.ema.europa.eu*)

Imatinib mesylate

Decline in kidney function during long-term treatment

Canada. Health Canada is working with manufacturers of imatinib mesylate (Gleevec®) to include additional safety information on the decline of kidney function into the Canadian Product Monograph.

Imatinib is a tyrosine kinase inhibitor. It is used as a chemotherapy agent to treat several solid tumours or blood cancers, such as chronic myeloid leukaemia (CML).

Following a publication in the medical literature, Health Canada conducted a safety review which concluded that there is sufficient evidence to consider a potential causal link between imatinib and decline in kidney function during long

Information from six clinical trials suggested that patients on long-term treatment with imatinib gradually lost some of their kidney function at a rate that may be faster than normal. The progressive loss of kidney function was greatest in the first year of therapy. Over time, gradual losses of kidney function linked with imatinib treatment may contribute to the development or worsening of some kidney diseases.

The following safety information will be included into the Canadian Product Monograph:

- Long term treatment with imatinib may result in decline in renal function. Patients treated with imatinib in clinical studies had a decrease over time in estimated glomerular filtration rate (eGFR). Monitoring for renal function should be undertaken before initiating therapy and periodically thereafter.

Reference:
Summary Safety Review, Health Canada, 7 March 2016 (*www.hc-sc.gc.ca*)

Inhaled corticosteroids for chronic obstructive pulmonary disease

Risk of pneumonia

leading to breathing difficulties.

Corticosteroids are anti-inflammatory medicines used for a wide range of conditions. Beclomethasone, budesonide, flunisolide, fluticasone propionate and fluticasone furoate are authorised and marketed as inhalation formulations for use in COPD.

The recommendation follows a review by PRAC which confirms that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the Committee's view is that the benefits of inhaled corticosteroids continue to outweigh their risks. The PRAC also looked whether there were any differences in the risk of pneumonia between different corticosteroid containing medicines, and did not find conclusive evidence of a difference. Pneumonia remains a common side effect for all of them.

PRAC recommend that there should be no changes to the way these medicines are used; however, doctors and patients should be vigilant for signs and symptoms of pneumonia in patients with COPD as the clinical features of pneumonia overlap with those of exacerbations of the underlying disease.

Reference:
Press release, EMA, 18 March 2016 (*www.ema.europa.eu*)