World Health Organization

WHO Pharmaceuticals NEWSLETTER

2015 No.2

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:

Safety and Vigilance,

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

This Newsletter is also available on our Internet website:
http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring
Box 1051
751 40 Uppsala
Tel: +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: info@who-umc.org
Internet: http://www.who-umc.org

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 issue includes recommendations from the working groups of the thirty-seventh annual meeting of national pharmacovigilance centres that was held in Tianjin, China last year.

Contents

Printed by the WHO Document Production Services, Geneva, Switzerland

Table of Contents

Regulatory Matters

Safety of medicines

Signal

Feature

Abiraterone acetate

Risk of hypokalaemia, thrombocytopenia and rhabdomyolysis

Japan. The Ministry of Health Labour and Welfare (MHLW) and the Pharmaceutical and Medical Devices Agency (PMDA) have announced revisions to the package insert for abiraterone acetate (Zytiga®).

Abiraterone acetate is indicated for castration-resistant prostate cancer.

The MHLW/PMDA stated that cases of hypokalaemia and thrombocytopenia have been reported in patients treated with abiraterone acetate in Japan. The MHLW/PMDA also stated that cases of rhabdomyolysis have been reported in patients treated with abiraterone acetate in other countries and the company core datasheet (CCDS) has been updated to include information on rhabdomyolysis.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the following changes to the package insert:

- Patients with hypokalaemia or risks of hypokalaemia due to factors of complications or concomitant drugs should be added to the "Careful administration" section.
- An alert on hypokalaemia should be added in the "Important precautions".
- The following should be added to the "Clinically significant adverse reactions" section:
  - hypokalaemia
  - thrombocytopenia
  - rhabdomyolysis

Reference:
Revision of Precautions, 2 February 2015, MHLW/PMDA (*www.pmda.go.jp/english/*)

Aceclofenac

Updated cardiovascular advice in line with diclofenac and COX-2 inhibitors

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has announced that aceclofenac is now contraindicated in patients with certain established cardiovascular diseases.

Aceclofenac (Preservex®) is a non-steroidal anti-inflammatory drug (NSAID) licensed for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Aceclofenac has little pharmacological activity by itself; its main mode of action is through its metabolites which include diclofenac and 4'-hydroxy diclofenac.

In June 2013 the MHRA told health-care professionals about the new contraindications and warnings for diclofenac. This was after a review by European regulators concluded that the risk of arterial thrombotic events (myocardial infarction; stroke) with diclofenac is greater than with other non-selective NSAIDs and similar to the COX-2 inhibitors.

There are limited data available regarding the arterial thrombotic effects of aceclofenac. The treatment advice for aceclofenac has been updated in line with diclofenac and COX-2 inhibitors. This was based on aceclofenac's structural similarity to diclofenac and its metabolism to diclofenac.

The MHRA reminds prescribers to base the decision to

- prescribe an NSAID on an assessment of each patient's individual risk factors including any history of cardiovascular and gastrointestinal illness.
- Use the lowest effective dose for the shortest duration necessary to control symptoms. Periodically re-evaluate the patient's need for symptomatic relief and response to treatment.

When using aceclofenac to relieve pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, prescribers should:

- consider that aceclofenac is now contraindicated in patients with established:
  - ischaemic heart disease
  - peripheral arterial disease
  - cerebrovascular disease
  - congestive heart failure (New York Heart Association, NYHA, classification II-IV)
- switch patients with these conditions to an alternative treatment at their next routine appointment
- only start aceclofenac treatment after careful consideration of any significant risk factors for cardiovascular events, e.g.
  - hypertension
  - hyperlipidaemia
  - diabetes mellitus
  - smoking

Reference:
Drug Safety Update, MHRA, volume 8, issue 6: 5, January 2015 (*www.gov.uk/mhra*)

Ambroxol and bromhexine expectorants

Risk of allergy and skin reactions

EU. The European Medicines Agency (EMA) announced that the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed recommendations to update the product information for

ambroxol- and bromhexine-containing medicines with information about the small risk of severe allergic reactions and severe cutaneous adverse reactions (SCARs). The medicines are widely available in the EU for use as expectorants (to help clear mucus from the airways).

Ambroxol and bromhexine are mainly used by mouth as expectorants to help make the mucus thinner and therefore easier to be cleared away in patients with short- or long-term diseases of the lungs or airways.

Anaphylactic reactions and SCARs, including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in patients receiving ambroxol. As ambroxol is a metabolite of bromhexine, the risk of anaphylactic and severe cutaneous reactions is considered to apply also to bromhexine.

The risk of anaphylactic reactions and SCARs with ambroxol or bromhexine is low. Frequencies of these side effects are unknown.

Health-care professionals should advise patients that they should stop treatment immediately if symptoms of progressive skin rash occur.

Reference:
Press release, EMA, 27 February 2015 (*www.ema.europa.eu*)

Apixaban

Risk of interstitial lung disease

Japan. The MHLW and the PMDA announced the revision of the package insert for apixaban (Eliquis®).

Apixaban is indicated for reduction of the risk of ischaemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

The MHLW/PMDA informed that cases of interstitial lung disease and haemorrhage including bloody sputum have been reported in patients treated with apixaban in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the following texts be added to the "Clinically significant adverse reactions" subsection of "Adverse reactions".

Interstitial lung disease: Interstitial lung disease may occur. Patients should be carefully monitored. If any abnormalities such as cough, bloody sputum, shortness of breath, dyspnoea, pyrexia, and abnormal chest sound are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If interstitial lung disease is suspected, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroid should be taken.

Reference:
Revision of Precautions, 17 February 2015, MHLW/PMDA (*www.pmda.go.jp/english/*)

Combined oral contraceptives and hormone replacement therapy

Risk of developing inflammatory bowel disease

Australia. The Therapeutic Goods Administration (TGA) has informed health-care professionals that the TGA is working with sponsors of combined oral contraceptives and hormone replacement therapy to ensure information regarding inflammatory bowel disease is included in the Product Information documents.

The TGA has evaluated recently published research that links an increased risk of inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease with the use of combined oral contraceptives (COCs). During assessment of this information, the TGA identified corresponding data that suggested hormone replacement therapy (HRT) was also a potential risk factor for development of IBD. The literature suggests that these risks may be increased in women who were smokers.

Progestogen-only contraceptive, HRT products and products containing tibolone as the active ingredient were not evaluated specifically, therefore the TGA could not determine the risk of IBD with these products.

One paper concluded that there was no difference in the IBD risk between oestrogen-only HRT products and oestrogen/progestogen combination HRT.

The TGA found that the literature had limitations. While the research did not confirm a causal relationship and the pathogenesis of IBD remained incompletely defined, the TGA concluded that health-care professionals should be made aware of this information.

While the Product Information (PI) documents for most COC products include a reference to the association between these drugs and IBD, this information is not consistent across all products.

Meanwhile, no PI documents for oestrogen/progestogen combination HRT products

contain information about a potential association with IBD.

The TGA is negotiating with the sponsors of COCs and oestrogen/progestogen combination HRT products to ensure adequate information is provided in their PI.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 1, February 2015 (*www.tga.gov.au*)

Dabigatran and dronedarone or amiodarone

Drug-drug interaction

Canada. Health Canada has reviewed the prescribing information for dabigatran (Pradaxa®), an anti-blood clotting drug, dronedarone (Multaq®) and amiodarone (Cordarone®), both used to control abnormal heart rates.

This revision is based on a review of information on the potential interaction between dabigatran and dronedarone or amiodarone that can raise the blood level of dabigatran and potentially increase the bleeding risk associated with it.

Dabigatran is used for the treatment and prevention of blood clots in the veins of legs and lungs, including patients with knee or hip replacement surgery. It is also approved for the prevention of stroke or blood vessel blockage due to blood clotting in patients with an abnormal heart rhythm called atrial fibrillation.

Amiodarone is approved for the treatment of certain abnormal heart rhythms called ventricular arrhythmias. Dronedarone is approved for the treatment of certain abnormal heart rhythms called atrial fibrillation.

Bleeding is a known risk of dabigatran. Bleeding of any type or severity may occur with the use of dabigatran, from minor bruising to major or severe bleeding in any part of the body. It is possible that amiodarone or dronedarone can block one of the mechanisms by which dabigatran is transported out of the body (P-glycoprotein) and eliminated. This may raise the blood level of dabigatran leading to an increased risk of bleeding.

Health Canada reviewed information from Canadian adverse reaction reports, scientific literature, international safety data as well as what is known about the use of these products in Canada and internationally. The review evaluated the risk and suggested ways to minimize it.

At the time of the review, Health Canada had received 6 reports of bleeding in patients who were using dabigatran and dronedarone together, and 19 reports of bleeding in patients who were using dabigatran and amiodarone together.

Health Canada assessed that bleeding was possibly associated with the interaction between dabigatran and dronedarone in 4 cases, and between dabigatran and amiodarone in 7 cases.

At the time of this review, the WHO Vigibase® database contained 254 cases of events related to bleeding reported in patients using both dabigatran and amiodarone; and 199 cases of events related to bleeding in patients using both dabigatran and dronedarone. Most of these cases were from the United States (175 suspecting the dabigatran-amiodarone interaction and 185 suspecting the dabigatran-dronedarone interaction). While a drug-drug interaction may be suspected in these bleeding events, other causes cannot be ruled out as detailed case reports were not available.

At the time the safety review was completed, the available evidence supported that events related to bleeding may be associated with the drug-drug interaction between dabigatran and dronedarone or amiodarone.

Reference:
Safety Reviews, Health Canada, 12 February 2015 (*www.hc-sc.gc.ca*)

Domperidone

Serious abnormal heart rhythms and sudden death (cardiac arrest)

Canada. Health Canada has completed a safety review that evaluated the risk of serious abnormal heart rhythms and sudden death (cardiac arrest) with domperidone.

Domperidone is used to treat symptoms of slowed stomach emptying seen in people with some gastrointestinal (GI) disorders (e.g. gastritis or inflammation of the GI tract). Domperidone is also used to reduce symptoms such as nausea and vomiting caused by some drugs used to treat Parkinson's disease.

Changes in the electrical activity of the heart, such as QT prolongation, can lead to an abnormal heart rhythm. An abnormal heart rhythm refers to the heart beating too fast, too slow or irregularly. In some rare cases, fast, irregular heartbeats can cause death.

Domperidone is widely used in Canada. There were about 2,000,000 prescriptions for domperidone in Canada in 2013. At the time of this review, Health Canada had received 18 reports (no deaths) of serious adverse heart events with domperidone. Of these 18 reports, 12 reports were further evaluated to and domperidone was found to be

a possible cause for the development of cardiovascular events in most cases. However, it is difficult to determine to what extent domperidone contributed to the events because other conditions known to cause electrical heart problems were also present in many cases.

Risks are increased (i) in patients taking domperidone at doses greater than 30 mg a day, (ii) in patients over 60 years of age, and (iii) in patients taking domperidone together with drugs that can lead to increased domperidone blood levels or with drugs that are known to affect the electrical activity of the heart. This safety information applies to patients taking domperidone for any conditions.

At this time, to further reduce the risk of serious heart effects with domperidone, Health Canada has requested the following additional measures:

- Manufacturers should update the prescribing information of domperidone products to: indicate the risk of serious abnormal heart rhythms and sudden death (cardiac arrest); recommend a maximum daily dose of 30 mg; and to recommend restricting use in patients with certain medical conditions or taking other drugs.
- Drug Safety and Effectiveness Network should continue to conduct a study on heart effects in association with the use of domperidone in patients who have Parkinson's disease. This study is ongoing, and once its results become available, Health Canada will assess whether any further actions are required.

Reference:
Safety Reviews, Health Canada, 27 January 2015 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.1, 2014 and No.3, 2014 for related information on domperidone)

Donepezil

Risk of rhabdomyolysis and neuroleptic malignant syndrome

Canada. Health Canada has issued an Information Update to inform health-care professionals and Canadians of the risks of rhabdomyolysis and/or NMS for donepezil after conducting a safety review. The review evaluated the available information on the potential risk of rhabdomyolysis (muscle breakdown) and/or Neuroleptic Malignant Syndrome (NMS), a life-threatening neurological disorder associated with donepezil.

Donepezil is used to treat the symptoms of Alzheimer's disease. Donepezil has been marketed in Canada under the brand names Aricept® since 1997 and Aricept® Rapidly Disintegrating Tablet since 2006. As of November 2014, 16 companies have also received authorizations to sell generic donepezil in Canada.

Rhabdomyolysis is a condition that results in the breakdown of muscle tissue. Typical clinical symptoms include muscle pain, fever, weakness, nausea, and dark urine. Rhabdomyolysis can lead to life-threatening abnormal heart rhythms and kidney failure. Rhabdomyolysis can be drug-induced, but can also happen due to chemicals causing muscular damage, physical overexertion or other causes.

NMS is a rare life-threatening condition with changes in the nervous, muscular and cardiovascular systems. Symptoms of NMS include fever, mental changes, agitation, delirium, and muscle rigidity that can potentially lead to rhabdomyolysis. NMS is most often associated with the use of antipsychotics and dopamine enhancing drugs.

The prescribing information for donepezil has been updated to include the possible risks of rhabdomyolysis and NMS. It is important for health-care professionals and patients to be aware of the possibility of these rare serious reactions, and for steps to be taken for early detection of rhabdomyolysis and/or NMS.

Reference:
Safety Reviews, Health Canada, 21 January 2015 (*www.hc-sc.gc.ca*)

Lamotrigine

Risk of serious skin disorders

Japan. The MHLW and the PMDA made an urgent request for the package insert of lamotrigine (Lamictal®), to be revised to include additional cautions against serious skin disorders.

Cases of serious skin disorders associated with lamotrigine in post market reports included many cases that failed to comply with the recommended dosage and frequency of administration. In January 2012, the PMDA posted advice on the proper use of lamotrigine on its website.

A total of 16 cases of serious skin disorders leading to death have been reported (Dec 2008 -Jan 2015) in patients treated with lamotrigine in Japan (the estimated number of users is approximately 376 000 patients).

Previously, (September 2014 to December 2014), there were reports of 4 cases of serious skin disorders leading to death, in which causality between the serious skin disorders and the drug could not be ruled out in patients treated with lamotrigine in

Japan. In all 4 cases, treatment with lamotrigine did not comply with the recommended dosage and frequency of administration as stated in the package insert. In addition, lamotrigine was not discontinued until the symptoms became serious.

Based on expert advice and available evidence, the MHLW/PMDA concluded that this issue should be addressed in an urgent manner and warned that health-care professionals should comply with the dosage and administration as stated in the package insert of this drug.

MHLW/PMDA recommend that:

- During the initial phase of treatment, lamotrigine should not be used at doses higher than the recommended dosage and frequency of administration.
- When used concomitantly with sodium valproate, lamotrigine should be administered on alternate days for the first 2 weeks (only for adult patients).
- Lamotrigine should not be used at higher than recommended dosages or and frequencies of administration even during dose titration before maintenance dose is established.
- A dose increase should not be attempted earlier than the specified timing.
- Effort towards early detection and treatment of skin disorders should be care professionals should consult a dermatologist at an early stage, and appropriate measures should be taken.
- Patients and their family should be advised to see a doctor immediately and inform a doctor or pharmacist that they are being treated with this drug if a rash and/or the above symptoms occur.

Reference:
Revision of Precautions,
16 February 2015,
MHLW/PMDA
(*www.pmda.go.jp/english/*)

Memantine hydrochloride

Risk of hepatic dysfunction and jaundice

Japan. The MHLW and the PMDA announced that revision of the package insert for memantine hydrochloride (Memary®) was necessary.

Memantine hydrochloride is used for preventing progression of dementia symptoms in patients with moderate to severe Alzheimer's type dementia.

The MHLW/PMDA stated that cases of hepatic dysfunction and jaundice have been reported in patients treated with memantine hydrochloride in Japan.

Based on expert advice and

pyruvate transaminase), alkaline phosphatase, bilirubin, etc. may occur. Patients should be carefully monitored. If any abnormality is observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:
Revision of Precautions,
17 February 2015,
MHLW/PMDA
(*www.pmda.go.jp/english/*)

Metoclopramide

Risk of neurological adverse events

Australia. The TGA has announced that the Product Information for metoclopramide has been updated to include a new contraindication and changes to dosing and duration of use, to reduce the risk of neurological adverse events.

Metoclopramide is a widely used antiemetic and gastro-prokinetic drug. It has a number of approved indications, the most common being to control nausea and vomiting which may be associated with the following conditions:

- intolerance to essential drugs with emetic properties
- uraemia
- radiation sickness
- malignant disease