Safety and Efficacy Issues

Rituximab: hepatitis B reactivation

Canada — Health Canada has informed healthcare professionals of updates to the recommendations for screening and management of hepatitis B virus reactivation in patients treated with rituximab (Rituxan®).

Rituximab is an anti-CD20 monoclonal antibody indicated in the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (also known as Wegener granulomatosis) and microscopic polyangiitis.

Use of rituximab has been shown to be associated with reactivation of hepatitis B virus in seropositive patients. It is advised that all patients be screened for hepatitis B virus (HBV) before initiation of treatment. Rituximab is not to be used in patients with active hepatitis B viral disease.

Prior to starting treatment in HBV seropositive patients, consultation with a liver disease expert is recommended to determine ongoing monitoring of HBV reactivation and its management.

The use of rituximab has been associated with HBV reactivation in patients with positive HBV surface antigen (HBsAg+ve) and in those with negative HBV surface antigen plus positive anti-HB core antibody (HBsAg-ve/HBcAb+ve), particularly when administered in combination with corticosteroids or chemotherapy.


Oral fluoroquinolones and retinal detachment

Canada — Oral fluoroquinolones are broad-spectrum antibacterial drugs indicated for the treatment of infections caused by susceptible strains of microorganisms (1–5). In Canada, there are five marketed oral fluoroquinolones: ciprofloxacin (first marketed in 1996), levofloxacin (1997), moxifloxacin (2000), norfloxacin (1986), and ofloxacin (1990). The risk of retinal detachment is not described in any of the oral fluoroquinolone Canadian product monographs.

Retinal detachment is characterized by a separation of the retina from the underlying tissue in the eye (6). Among the different types of retinal detachment, rhegmatogenous retinal detachment (RRD) is the most common. RRD results from retinal breaks caused by vitreoretinal traction. Risk factors commonly associated with retinal detachment include advancing age, previous cataract surgery, myopia and trauma. Patients generally present with symptoms such as light flashes, floaters, peripheral visual field loss and blurred vision.

Retinal detachment is a serious medical emergency that generally requires prompt surgical intervention (6, 7). According to a pharmacoepidemiological study, current use of oral fluoroquinolones was associated with an increased risk of developing retinal detachment (7). Ophthalmic fluoroquinolones were excluded from the study to avoid reverse causality bias. The study identified 445 cases of retinal detachment involving oral fluoroquinolone use in a cohort of 989 591 patients from British Columbia.
who visited an ophthalmologist between January 2000 and December 2007. Further research is needed to confirm whether there is a potential association between retinal detachment and fluoroquinolones as well as to clarify the mechanism of action.

As of 31 December 2012, Health Canada received one report of retinal detachment suspected of being associated with the use of an oral fluoroquinolone. The report described a 52-year-old woman who experienced retinal detachment after a course of ciprofloxacin prescribed to treat a bladder infection. Limited evidence linking retinal detachment to oral fluoroquinolones may explain the low level of reporting to Health Canada.

Extracted from the Canadian Adverse Drug Reactions Newsletter, Volume 23, number 3, 2013.

References

Hydroxyethyl starch solutions: kidney failure

Canada — Health Canada has informed healthcare professionals of updated information concerning blood volume expanders containing hydroxyethyl starch (HES) solutions recommending that these products no longer be used in critically ill patients with certain health conditions.

HES solutions are used to replace lost blood in patients who are critically ill and experience a sudden drop in blood pressure.

Specifically, HES solutions should not be used:

• In patients with sepsis.
• In patients with severe liver disease.
• In certain types of patients with impaired kidney function.

Some recent studies have compared HES with other blood volume expanders in critically ill patients with sepsis. These studies suggest that patients treated with HES are at a higher risk of kidney failure or death.


Ketoconazole: fatal liver injury

United States of America — The Food and Drug Administration (FDA) is taking several actions related to ketoconazole (Nizoral®) oral tablets. These include limiting use, warning of severe liver injuries and adrenal gland problems and advising that it can lead to harmful drug interactions with other medications.

The FDA has approved label changes and added a new medication guide to address these safety issues. As a result, ketoconazole oral tablets should not be considered as first-line treatment for any
fungal infection. Ketoconazole should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated.

Topical formulations of ketoconazole have not been associated with liver damage, adrenal problems, or drug interactions.

Ketoconazole tablets can cause liver injury, which may potentially result in liver transplantation or death. Serious liver damage has occurred in patients receiving high doses of ketoconazole for short periods of time as well as those receiving low doses for long periods. Some of these patients had no obvious risk factors for liver disease.

Ketoconazole tablets may cause adrenal insufficiency and healthcare professionals should monitor adrenal function in patients who have existing adrenal problems or in patients who are under prolonged periods of stress such as those who have had a recent major surgery or who are under intensive care in the hospital. Ketoconazole tablets may interact with other drugs and result in serious and potentially life-threatening outcomes.


Olmesartan medoxomil: enteropathy

United States of America — The Food and Drug Administration (FDA) is warning that the blood pressure drug olmesartan medoxomil (Benicar®, Benicar HCT®, Azor®, Tribenzor®, and generics) can cause sprue-like enteropathy.

Symptoms include severe, chronic diarrhoea with substantial weight loss. The enteropathy may develop months to years after starting olmesartan, and sometimes requires hospitalization. If patients taking olmesartan develop these symptoms and no other cause is found, the drug should be discontinued, and therapy with another antihypertensive started.

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) approved for the treatment of high blood pressure, alone or with other antihypertensive agents, and is one of eight marketed ARB drugs. Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan.


Ado-trastuzumab emtansine: name confusion

United States of America — The Food and Drug Administration (FDA) is alerting healthcare professionals that the use of the incorrect nonproprietary name for the breast cancer drug ado-trastuzumab emtansine (Kadcyla®) in some medication-related electronic systems poses a risk of mix-up with trastuzumab (Herceptin®) and may result in medication errors. The dosing and treatment schedules for ado-trastuzumab emtansine and trastuzumab, another breast cancer drug, are quite different, so confusion between these products could lead to dosing errors and potential harm to patients.

The FDA-approved nonproprietary name ado-trastuzumab emtansine should be used. However, some third-party publications, compendia references, health information systems (e.g., electronic health record systems and systems used for pharmacy prescription processing, wholesaler ordering, pharmacy ordering, etc.) and sites on the Internet are incorrectly using the United States Adopted Name (USAN), which is “trastuzumab emtansine,” and omitting the “ado” prefix and hyphen. Use of this truncated version may cause confusion.
It is important for drug information content publishers to identify drug products by the FDA-approved proprietary (brand) and nonproprietary names that are used in FDA-approved drug labels.


**Anticholinergics and cognitive impairment**

**Australia** — Anticholinergics are a class of drug that blocks muscarinic actions of acetylcholine with a wide range of effects. Drugs with definite anticholinergic properties include antiemetics (promethazine®), anti-Parkinson agents (benztropine), gastrointestinal spasmolytics (propantheline), bladder spasmytics (oxybutinin, tolterodine) and antidepressants (imipramine) (1).

Precautions for anticholinergics include using with caution in elderly patients who are more sensitive to adverse events associated with these drugs. In particular, confusion can be precipitated or worsened. When used in elderly patients, anticholinergics should be initiated at a low dose and increased slowly to the lowest effective dose.

Two recent long-term studies examined cognitive impairment in older patients.

One of those studies followed 13 004 patients aged 65 and older for two years (2). The other study followed 1652 African American subjects over 70 years of age, for six years (3). These patients experienced a 1.43 times increased risk of developing cognitive impairment compared to patients not taking a drug with definite anticholinergic properties. Also, the risk increased with the number of anticholinergics being used.

Consideration should be given to routine measurement of cognitive function in older patients taking drugs with anticholinergic properties for any indication, including non-nervous system indications. It may be possible to lower the anticholinergic burden by replacing such drugs with alternatives that do not have anticholinergic properties.


**References**


**Diclofenac : new safety advice**

**European Union** — The Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh) has endorsed new safety advice for diclofenac-containing medicines in the form of capsules, tablets, suppositories or injections. The new advice aims to minimize cardiovascular risk.

This follows a recent review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC), which found that the effects of systemic diclofenac are similar to those of selective COX-2 inhibitors particularly when diclofenac is used at a high dose and for long-term treatment. The PRAC therefore recommended that the same precautions already in place should be applied to diclofenac.
Clinical-trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events associated with the use of diclofenac, particularly at high dose (150 mg daily) and in long-term treatment.

Use of diclofenac is contraindicated in patients with established congestive heart failure, ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.

Patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.

References


New recommendations for intravenous iron-containing medicines

**European Union** — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has completed its review of intravenous iron-containing medicines used to treat iron deficiency and anaemia associated with low iron levels. The CHMP concluded that the benefits of these medicines are greater than their risks, provided that adequate measures are taken to minimize the risk of allergic reactions.

All intravenous iron medicines have a small risk of causing allergic reactions which can be life-threatening if not treated promptly. The Committee therefore concluded that iron preparations should only be given in an environment where resuscitation facilities are available. In addition, a test dose is no longer recommended but instead caution is warranted with every dose of intravenous iron that is given, even if previous administrations have been well tolerated.

The CHMP also considered that intravenous iron medicines should not be used during pregnancy unless clearly necessary. Treatment should be confined to the second or third trimester, provided the benefits of treatment clearly outweigh the risks to the unborn baby.

The review of intravenous iron medicines was triggered by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM)


**Vemurafenib: DRESS syndrome**

**Singapore** — Healthcare professionals have been informed of the risk of RAS-mutant malignancy progression and DRESS syndrome associated with vemurafenib (Zelboraf®). The risk of RAS-mutant malignancy progression is based on a single report from a literature article about a 76 year-old male patient with stage IV melanoma in whom accelerated growth of a pre-existing NRAS-mutated chronic myelomonocytic leukemia (CMML) was observed shortly after initiation of treatment with
vemurafenib. Based on its mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. Vemurafenib should be used with caution in patients with prior or concurrent cancers associated with RAS mutations.

In addition, cases of DRESS syndrome have been reported with the use of vemurafenib with onset ranging from 7 to 25 days. Treatment should be permanently discontinued if a patient develops DRESS syndrome. The package insert for Zelboraf® will be updated to reflect the new safety information.


Mefloquine: risk of neurological and psychiatric effects

United States of America — The Food and Drug Administration (FDA) is advising the public about strengthened and updated warnings regarding neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride.

Neurological side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations.

Neurological side effects can occur at any time during drug use and can last for months to years after the drug is stopped, or can be permanent.


Calcitonin: changes to availability

Canada — Health Canada has advised of important changes to the availability and recommended conditions of use of drugs containing calcitonin. Calcitonin is used as a nasal spray to treat osteoporosis in postmenopausal women, and as an injection to treat Paget disease and hypercalcaemia.

A safety review conducted by Health Canada has concluded that there is a slightly increased risk of cancer associated with prolonged use. A review of the benefits and risks of the nasal spray products found that there was not enough evidence of benefit to continue using calcitonin nasal sprays in treating osteoporosis.

As a result of these reviews, calcitonin nasal spray products will no longer be authorized for sale in Canada as of 1 October 2013.
Calcitonin injectable products will continue to be authorized for sale in Canada. The benefits of these products are considered to outweigh the risks when the product is used as directed. However, the labels for calcitonin injectable products are being updated to include a new warning and to recommend that treatment with calcitonin solution for injection be limited to the shortest possible time, using the minimum effective dose. Treatment of symptomatic Paget disease with calcitonin medicine should be limited to patients who are unable to use other treatments.


Metoclopramide: changes to use

European Union — The European Medicines Agency’s Committee on Medicinal Products for Human Use (CHMP) has recommended changes to the use of metoclopramide-containing medicines, including restricting the dose and duration of use to minimize the known risks of potentially serious neurological side effects.

Metoclopramide-containing medicines have been authorized separately in individual Member States with differing licensed indications such as nausea and vomiting or gastrointestinal motility disorders.

The review of metoclopramide was carried out at the request of the French medicines regulatory agency (ANSM), following continued safety concerns over side effects and concerns over efficacy. The review confirmed the known risks of neurological effects such as short-term extrapyramidal disorders. The risk of acute neurological effects is higher in children, although tardive dyskinesia is reported more often in the elderly, and the risk is increased at high doses or with long-term treatment. The evidence indicated that these risks outweighed the benefits of metoclopramide in conditions requiring long-term treatment. There have also been very rare cases of serious effects on the heart or circulation, particularly after injection.

The Committee recommended that metoclopramide should only be prescribed for use up to five days, that it should not be used in children below one year of age and that in children over one year of age, it should only be used as a second-choice treatment for the prevention of delayed nausea and vomiting after chemotherapy and for the treatment of post-operative nausea and vomiting.

In adults, it may be used for the prevention and treatment of nausea and vomiting such as that associated with chemotherapy, radiotherapy, surgery and in the management of migraine. In addition, the maximum recommended doses in adults and children should be restricted, and higher strength formulations removed from the market.


Glucagon-like-peptide-1 therapies: no immediate concern

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has finalized a review of GLP-1-based diabetes therapies. The Committee concluded that presently available data do not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines.

The rise of type-2 diabetes is a major public-health challenge. GLP-1-based therapies are effective treatments for type-2 diabetes and add to the available medication options. The term
‘GLP-1-based therapies’ comprises two classes of medicines: glucagon-like-peptide-1 (GLP-1) agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors.

A review was initiated following publication of a study that suggested an increased risk of pancreatitis and pancreatic-duct metaplasia in patients with type-2 diabetes treated with GLP-1-based therapies. Following the review of the publication and consultation of a panel of experts, the CHMP considered that the study itself had a number of methodological limitations which preclude a meaningful interpretation of the results.

These medicines already carry warnings in their product information but the CHMP considered that there would be value in harmonizing the wording to provide consistent advice.

Two large independent studies funded by the European Commission have been under way since 2011 to study the risk profile of diabetes treatments in general. First results of these studies are expected in 2014.

References

Ergot derivatives: restricted use

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended restricting the use of medicines containing ergot derivatives. These medicines should no longer be used to treat several conditions involving blood circulation problems or problems with memory and sensation, or to prevent migraine headaches, since the risks are greater than the benefits in these indications. A review of data showed an increased risk of fibrosis and ergotism.

Ergot derivatives indicated for these conditions will have their marketing authorizations suspended. In some EU Member States, ergot derivatives are also authorized for other indications: dementia, including Alzheimer disease, and treatment of acute migraine headache. They will remain authorized for use in those indications.

The review was initiated due to concerns identified by the French National Agency for the Safety of Medicine and Health Products (ANSM) in a national pharmacovigilance review in 2011.

Fibrosis can be a serious, sometimes fatal disease. The CHMP noted that there is a plausible mechanism by which ergot derivatives could cause fibrosis and ergotism. Given that the evidence for benefit in these indications was very limited, the CHMP concluded that the benefits in the concerned indications did not outweigh the risk of fibrosis and ergotism.


Flupirtine-containing medicines: restricted use

European Union — The Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh) has endorsed new recommendations to restrict the use of oral flupirtine medicines and suppositories. These medicines should now only be used for treating acute pain in adults who cannot use other painkillers, such as non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids and
treatment should not last longer than two weeks.

Patient liver function should be checked after each full week of treatment and treatment should be stopped if the patient has any signs of liver problems. Flupirtine must also not be used in patients with pre-existing liver disease or alcohol abuse problems or in patients taking other medicines known to cause liver problems.

The recommendations follow a review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC). In addition to oral medicines and suppositories, the review also covered injectable flupirtine medicines which were being given as a single injection for pain following surgery. The PRAC concluded that the benefits of injectable flupirtine continue to outweigh their risks when used in this way.

Flupirtine is a non-opioid used to treat pain, such as that associated with muscle tension, cancer, menstrual and pain following orthopaedic surgery or injuries. It was first introduced as an alternative painkiller to opioids and NSAIDs. Subsequently, multiple other actions such as muscle relaxation were identified. Flupirtine works as a selective neuronal-potassium-channel opener.


Interim guidelines on bedaquiline for tuberculosis

The World Health Organization has issued interim guidance on the use of the anti-TB medicine, bedaquiline, which received accelerated approval by the US Food and Drug Administration on 31 December 2012. In view of the urgent need to combat multidrug-resistant TB (MDR-TB) with improved drugs, WHO has provided recommendations based on clinical trial data.

The MDR-TB epidemic registered 310 000 new cases in 2011. However, only 19% of people thought to be infected are receiving some kind of treatment. It is hoped that bedaquiline — which has been shown in trials to be potentially effective against Mycobacterium tuberculosis — could become a powerful tool in much-needed treatment regimens that will be significantly shorter, more effective and less toxic than the current regimen which involves a two-year course of up to 20 pills per day and eight months of daily injections.


Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious or unexpected adverse drug reactions. A signal is defined 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”. All signals must be validated before any regulatory decision can be made.