Safety and Efficacy Issues

Azithromycin: potential risk of QT prolongation

Singapore — Two recent research studies have strengthened the evidence regarding the potential risk of QT prolongation associated with the use of azithromycin. In the light of this latest data, healthcare professionals are advised to be aware of the risk of torsades de pointes and fatal arrhythmia when considering azithromycin as a treatment option for patients who are at risk for cardiovascular events. These patient groups include (1):

- Patients with known prolongation of the QT interval, a history of torsades de pointes and fatal arrhythmia when considering azithromycin as a treatment option for patients who are at risk for cardiovascular events.
- Patients on drugs known to prolong the QT interval.
- Patients with ongoing pro-arrhythmic conditions such as uncorrected hypokalaemia or hypomagnesaemia, clinically significant bradycardia, and patients receiving Class IA (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic agents.
- Elderly patients and patients with cardiac disease who may be more susceptible to the effects of arrhythmogenic drugs on the QT interval.

Azithromycin is an azalide, a subclass of macrolide antibiotics derived from erythromycin that is widely used both orally and intravenously for the treatment of upper and lower respiratory tract infections and other infections involving susceptible organisms. There are currently 17 registered azithromycin-containing products in Singapore, including the Zithromax® range of products, Zmax® and 11 other generic products.

Although closely related, macrolide drugs such as erythromycin and clarithromycin are known to increase the risk of serious ventricular arrhythmias and are associated with an increased risk of sudden cardiac death. Azithromycin has previously been reported to be better tolerated than other macrolides, and has minimal side effects (2). However, within the last year, two research studies have provided evidence on the risk of QT prolongation associated with azithromycin.

One of the studies published in the New England Journal of Medicine (3) in May 2012 suggested a higher risk of cardiovascular deaths and deaths from any cause in persons treated with a five-day course of azithromycin compared to persons treated with amoxicillin, ciprofloxacin, or no drug. There were some limitations to this study, such as potential bias due to lack of randomization to the antibacterial drugs, outpatient setting investigation where it is likely that few patients were treated for severe or life-threatening infections, and the method of determination of cardiovascular deaths through death certificates instead of full medical records. Despite these, the study was noted to be methodologically sound and supportive of the validity of the overall findings.

The estimated excess risk of cardiovascular death compared with amoxicillin varied considerably with patient baseline cardiovascular risk, from roughly one in
111,000 among healthier patients to one in 4100 among high-risk patients. The duration of the elevated risk of all-cause mortality and of cardiovascular death corresponded to the duration of azithromycin therapy. The increase in total deaths was determined to be attributed to cardiovascular deaths and not from other causes. The excess risk of cardiovascular death, especially of sudden death, was consistent with arrhythmias from drug-related QT prolongation.

The manufacturer of azithromycin also conducted a randomized, placebo-controlled parallel trial to assess the effects of azithromycin on the QT interval in 116 healthy adults (1). These subjects received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc* interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF** were 5ms (10), 7ms (12) and 9ms (14) with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

The US FDA has updated the azithromycin package inserts to strengthen the warnings and precautions section with information related to the risk of QT interval prolongation and Torsades de Pointes (4). Information regarding the results of the clinical QT study which showed that azithromycin can prolong the QTc interval has also been added.

Since 1996, the Health Sciences Authority (HSA) has received 181 adverse drug reaction reports associated with the use of azithromycin.

Apart from azithromycin, other macrolides such as erythromycin and clarithromycin or non-macrolides such as the fluoroquinolones, are known to have the potential for QT prolongation or other significant side effects. Healthcare professionals are advised to take into consideration these factors when prescribing antibacterial treatment for their patients.

References
4. FDA Drug Safety Communication. Azithromycin (Zithromax® or Zmax®) and the risk of potentially fatal heart rhythms at http://www.fda.gov/drugs/drugsafety/ucm341822.htm

Osteoporosis treatments: atypical femur fracture

New Zealand — In November 2009, Medsafe highlighted an association between alendronate and low-energy femoral shaft fracture (1).

Since then, similar cases have been published involving other bisphosphonates as well as denosumab (Prolia®).
Denosumab is a new treatment for osteoporosis that is approved but not currently available in New Zealand. Information on this risk is included in the data sheets for alendronate (Fosamax®), zolendronate (Zometa®) and pamidronate (Pamisol®).

To date there has been no confirmed association between strontium, teriparatide, raloxifene or hormone replacement therapy and atypical fractures of the femur.

Features associated with subtrochanteric and diaphyseal fractures include (2):

- Minimal to no trauma.
- Transverse fracture line on radiography.
- Prodromal pain.
- Unilateral cortical beaking and bilateral thickened diaphyseal cortices on radiography.
- Poor fracture healing.

The Centre for Adverse Reactions Monitoring (CARM) has received two reports of fractures describing some of the features outlined above. In both cases, the patient was taking alendronate.

Atypical subtrochanteric fractures are rare, less than 0.1% of total fractures in a New Zealand study (3). For a population of 10,000 patients at high risk of fracture, bisphosphonate treatment might be expected to prevent 108 hip fractures (and around 750 other fractures) per year and result in three subtrochanteric fractures (2). Therefore, the benefit risk ratio for bisphosphonate treatment remains favourable.

In patients with atypical femoral fractures, bisphosphonate treatment should be considered as a possible cause. Interruption of bisphosphonate therapy may be necessary for fracture healing. Re-treatment should be considered if bone density again begins to fall and after a discussion of the benefits and risks with the patient.

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Ezogabine: retinal abnormalities and blue skin discoloration

**United States of America** — The Food and Drug Administration (FDA) has reported that ezogabine (Potiga®) can cause blue skin discoloration and eye abnormalities characterized by pigment changes in the retina. The FDA does not currently know if these changes are reversible. All patients taking ezogabine should have a baseline eye exam, followed by periodic eye exams.

Pigment changes in the retina have the potential to cause serious eye disease with loss of vision. It is not yet known whether the retinal pigment changes caused by ezogabine lead to visual impairment, although several patients have been reported to have impaired visual acuity.

The skin discoloration in the reported cases appeared as blue pigmentation, predominantly on or around the lips or in the nail beds of the fingers or toes, but more widespread involvement of the face and legs has also been reported. Scleral and conjunctival discoloration,
on the white of the eye and inside eyelids, has been observed as well. Skin discoloration generally occurred after four years of treatment with ezogabine, but has appeared sooner in some patients. Retinal abnormalities have also been observed in the absence of skin discoloration.

In light of this new safety information, all patients taking ezogabine or about to start, should have an eye exam followed by periodic eye exams thereafter. Ezogabine should be discontinued if ophthalmic changes are observed unless no other treatment options are available. If a patient develops skin discoloration, serious consideration should be given to changing to an alternate medication.


Incretin mimetics: risk of pancreatitis and pancreatic duct metaplasia

United States of America — The Food and Drug Administration (FDA) is evaluating unpublished new findings that suggest an increased risk of pancreatitis and pancreatic duct metaplasia in patients with type 2 diabetes treated with incretin mimetics. These findings were based on examination of a small number of pancreatic tissue specimens taken from patients after they died from unspecified causes.

Drugs in the incretin mimetic class include exenatide (Byetta®, Bydureon®), liraglutide (Victoza®), sitagliptin (Januvia®, Janumet®, Janumet XR®, Juvisync®), saxagliptin (Onglyza®, Kombiglyze XR®), alogliptin (Nesina®, Kazano®, Oseni®), and linagliptin (Tradjenta®, Jentadueto®). These drugs work by mimicking the incretin hormones that the body usually produces naturally to stimulate the release of insulin in response to a meal. They are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

The FDA has not reached any new conclusions about safety risks with incretin mimetic drugs but intends to obtain and evaluate this new information following participation in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Cancer Institute’s (NCI) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer held in June 2013 to gather and share additional information.


Incretin mimetics and GLP-1-based therapies: pancreatic risks

European Union — The European Medicines Agency (EMA) is investigating findings by a group of independent academic researchers that suggest an increased risk of pancreatitis and pancreatic duct metaplasia in patients with type 2 diabetes treated with glucagon-like peptide 1 (GLP-1) based therapies (GLP–1 agonists and dipeptidylpeptidase-4 (DPP–4) inhibitors).

The findings are based on examination of a small number of pancreatic tissue samples obtained from organ donors with and without diabetes mellitus, who died due to causes other than diabetes. The Agency’s Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) are currently investigating the information provided by the researchers to determine the need for possible further regulatory action.

The Agency has not reached any conclusions on this investigation. There is currently no change to the recommendations on the use of these medicines and no need for patients to stop taking their medicines.
There are also efforts underway to collect safety data on diabetes medicines from independent pharmacovigilance centres across the European Union. The SAFEGUARD study, a study that is funded by the European Commission and carried out within the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), is investigating, among others, evidence for drug-induced pancreatitis for GLP–1-based agents that were authorized before 2011, when the study started.

GLP–1-based therapies are also known as incretin mimetics. In the EU they include exenatide (Byetta®, Bydureon®), liraglutide (Victoza®), lixisenatide (Lyxumia®), sitagliptin (Effig®), Januvia®, Janumet®, Ristaben®, Ristfor®, Tesavel®, Velmetia®, Xelevia®), saxagliptin (Komboglyze®, Onglyza®), linagliptin (Jentadueto®, Trajenta®) and vildagliptin (Eucreas®, Galvus®, Icand®), Jalra®, Xiliarx®, Zomarist®).


**Belatacept: acute graft rejection**

**United Kingdom** — In agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA), the manufacturer of belatacept (Nulojix®) has informed healthcare professionals that an increased rate of acute graft rejection has been reported postmarket when corticosteroids have been rapidly tapered in patients at high immunologic risk for acute rejection.

Nulojix® in combination with corticosteroids and a mycophenolic acid is indicated for prophylaxis of graft rejection in adults receiving a renal transplant. It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to this belatacept-based regimen.

Corticosteroid tapering should be implemented cautiously, particularly in patients with 4–6 human leukocyte antigen (HLA) mismatches. The product information will be updated to include a warning on rapid tapering of corticosteroids in patients with high immunologic risk and provide information on the corticosteroid doses used and the populations included in the clinical studies supporting the approval of Nulojix®.

Nulojix® in conjunction with basiliximab induction, mycophenolate mofetil and corticosteroid taper to 5 mg/day by week 6 post-transplant, has been associated with an increased rate of acute rejection, particularly Grade III rejection in the postmarketing setting. These Grade III rejections occurred in patients with 4 to 6 HLA mismatches. This corticosteroid taper was more rapid than that used in the clinical studies supporting the approval of Nulojix®.


**Cinacalcet: fatal paediatric hypocalcaemia**

**United Kingdom** — A fatal case with severe hypocalcaemia has occurred in a paediatric investigational study of cinacalcet (Mimpara®). The manufacturer has suspended dosing, screening and enrolment in all paediatric cinacalcet investigational studies and is investigating this case to determine if any additional action is necessary.

Cinacalcet is approved only in adults. The product information warns of the risk of hypocalcaemia associated with cinacalcet. Therefore, patients should be carefully monitored for the occurrence of hypocalcaemia.

Cinacalcet is indicated for the treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease.
(ESRD) on maintenance dialysis therapy. Cinacalcet may be used as part of a therapeutic regimen including phosphate binders and/or vitamin D sterols, as appropriate.

Cinacalcet is also indicated for the reduction of hypercalcaemia in patients with parathyroid carcinoma, or primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines) but in whom parathyroidectomy is not clinically appropriate or is contraindicated.


Cilostazol-containing medicines: restricted use

European Union — The Committee on Medicinal Products for Human Use (CHMP) has recommended that the use of cilostazol-containing medicines in the treatment of intermittent claudication should be restricted. Cilostazol-containing medicines are available in the EU under the names Pletal® and Ekistol®.

The recommendations follow a review of current evidence which indicates that the modest benefits of these medicines are only greater than their risks in a limited subgroup of patients.

The Committee recommended that cilostazol should only be used in patients whose symptoms have not improved despite prior lifestyle changes. In addition, cilostazol-containing medicines should not be used in patients who have suffered severe tachyarrhythmia or recent unstable angina, heart attack or bypass surgery, or who take two or more antiplatelet or anticoagulant medicines such as aspirin and clopidogrel.

The Spanish Agency for Medicines and Health Products (AEMPS) asked the CHMP to carry out a review of these medicines following a number of reports of serious suspected side effects, in particular affecting the heart, as well as cases of serious bleeding.

References


Aqueous cream: skin irritation

United Kingdom — Aqueous cream is a widely used product topically applied as an emollient for the symptomatic relief of dry skin conditions such as atopic eczema, and as a soap-substitute for skin washing.

Although aqueous cream is useful as a leave-on emollient in a substantial proportion of patients with eczema, it is known that in some patients, especially in children, it can cause skin reactions, such as stinging, burning, itching and redness.

In light of new information from the published literature all data on the benefits and risks of aqueous cream, particularly when used in children with eczema, have been recently reviewed in the UK (1). An audit of 100 children attending a paediatric dermatology clinic reported that aqueous cream emollient was associated with an immediate skin reaction (stinging, burning, itching, and redness) within 20 minutes in 56% of exposures, compared with 18% with other emollients used (2). Furthermore, several studies reported alterations in skin physiology (thinning of the outermost layer of the skin and increased skin water loss) following application of aqueous cream as an emollient in adults, both with
and without eczema (3, 4). A summary of all the evidence reviewed is available in the public assessment report (5).

The causative agent may be sodium lauryl sulfate (SLS), contained in emulsifying wax which is one of the ingredients of aqueous cream. SLS functions as a stabilizer and cleansing agent and is a known skin irritant. However, aqueous cream products often contain other ingredients such as chlorocrescol, cetostearyl alcohol and parabens, which may also cause or contribute to adverse skin reactions.

Despite the potential irritant effects reported in the literature, in clinical practice aqueous cream used both as an emollient and a wash-off soap substitute has been useful in a substantial proportion of patients with atopic eczema.

On the basis of the review, aqueous cream labelling and the information leaflet will be updated with a warning on the potential of local skin reactions, and SLS will be listed as an ingredient (6–7).

References

Zolpidem products: lower doses recommended

United States of America — The Food and Drug Administration (FDA) has approved label changes specifying new dosing recommendations for zolpidem products (Ambien®, Ambien CR®, and Edluar®) because of the known risk of next-morning impairment.

FDA has also warned that patients who take the sleep medication zolpidem extended-release (Ambien CR®) — either 6.25 mg or 12.5 mg — should not drive or engage in other activities that require mental alertness the day after taking the drug because zolpidem levels can remain high the next day.

Also included in the updated label are the dosing recommendations previously published on 10 January 2013 in FDA Drug Safety Communication. The recommended initial dose of certain immediate-release zolpidem products (Ambien and Edluar®) is 5 mg for women and either 5 mg or 10 mg for men. The recommended initial dose of zolpidem extended-release (Ambien CR®) is 6.25 mg for women and either 6.25 or 12.5 mg for men. If the lower doses (5 mg for immediate-release, 6.25 mg for extended-release) are not effective, the dose can be increased to 10 mg for immediate-release products and 12.5 mg for zolpidem extended-release. However, use of the higher dose can increase the risk of next-day impairment of driving and other activities that require full alertness.

Valproate-related products: risks during pregnancy

United States of America — The Food and Drug Administration (FDA) has alerted healthcare providers and patients that medications including and related to valproate sodium can cause decreased IQ scores in children whose mothers took the medication during pregnancy. Therefore, these drugs are being contraindicated for migraine headaches. Valproate products include valproate sodium (Depacon®), divalproex sodium (Depakote®, Depakote CP®, and Depakote ER®), valproic acid (Depakene® and Stavzor®), and their generics.

Valproate products have several FDA-approved uses including: prevention of migraine, treatment of epilepsy and treatment of manic episodes associated with bipolar disorder. Women who can become pregnant should not use valproate unless it is essential to managing their medical condition.

Medicines that contain valproate already have a boxed warning for foetal risk, including birth defects. The recently published Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study found further evidence of the IQ risk.


Thalidomide: risk of second primary malignancies

Canada — Health Canada has informed healthcare professionals of important new safety information which has been added to the Product Monograph for thalidomide capsules (Thalomid®).

Thalidomide is an immunomodulatory agent indicated for the treatment of patients who are 65 years of age or older with previously untreated multiple myeloma, in combination with melphalan and prednisone.

Second primary malignancies, in particular, acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), have been observed in an ongoing clinical trial in patients with previously untreated multiple myeloma receiving the combination melphalan, prednisone and Thalomid® (MPT). AML and MDS have been rarely reported in the post-market setting.

Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies.


Botulinum toxin type B: serious risks

United Kingdom — Botulinum toxin type B (Neurobloc®) is indicated only for the treatment of cervical dystonia in adults. The Medicines and Healthcare Products Regulatory Agency (MHRA) recommends that prescribers adhere to the licensed indication as its safety outside these circumstances has not been established.

Cases of the known rare risk of toxin spread have been reported with all botulinum toxin products. Importantly, the cases with botulinum toxin type B were mostly reported with its off-label use.

All patients receiving any product containing botulinum toxin should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties, and be advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects may be life-threatening.
Magnesium sulphate during pregnancy: teratogenic effects

United States of America — The Food and Drug Administration (FDA) has advised healthcare professionals against using magnesium sulfate injection for more than 5–7 days to stop pre-term labor in pregnant women. This use of the drug is off-label. Administration of magnesium sulfate injection to pregnant women longer than 5–7 days may lead to low calcium levels and bone problems in the foetus, including osteopenia and fractures.

Magnesium sulfate is approved to prevent seizures in pre-eclampsia and for control of seizures in eclampsia.


Varenicline and bupropion: revision to consumer information

Canada — Health Canada has informed healthcare professionals that new information for varenicline tartrate (Champix®) and bupropion hydrochloride (Zyban®) has been added to the product information to indicate that nicotine replacement therapy (patches, gum, lozenges, etc.) should be considered before taking non-nicotine medicines.

This revision was based on available information about the treatments used to help people stop smoking. Nicotine replacement therapy should be considered before non-nicotine replacement.


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.