WHO PHARMACEUTICALS NEWSLETTER

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 from the Uppsala Monitoring Centre's SIGNAL document.

The feature article in this issue gives you information about the Global Fund to fight AIDS, TB and Malaria, its core structures and opportunity to use Global Fund resources for pharmacovigilance strengthening.

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Ambrisentan

Contraindication regarding the use in patients with Idiopathic Pulmonary Fibrosis (IPF)

Canada. GlaxoSmithKline Inc., in consultation with Health Canada, informed health-care professionals that ambrisentan (VOLIBRIS®) is not indicated for idiopathic pulmonary fibrosis (IPF);

Ambrisentan, a selective endothelin A receptor antagonist, is indicated for the treatment of idiopathic ('primary') pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) in patients with WHO functional class II or III symptoms who have not responded to conventional therapy.

A clinical study in patients with IPF was prematurely discontinued due to lack of efficacy. Evaluation of the composite primary endpoint revealed higher rates of disease progression (including decreases in respiratory function, respiratory hospitalizations) or deaths in the ambrisentan group versus the placebo group.

Health-care professionals are reminded that the indication for the use of ambrisentan in the treatment of IPAH and PAH-CTD in patients with WHO functional class II or III symptoms who have not responded to conventional therapy remains unchanged. Treatment in patients with IPF should be discontinued and the individual patient's treatment should be reassessed promptly.

Reference:
Advisories, Warnings and Recalls, Health Canada, 9 July 2012 (www.hc-sc.gc.ca).

Doripenem

Updated dosing recommendations

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) recommended that the recommended dose of doripenem (Doribax®) to treat nosocomial pneumonia in patients with augmented renal function and/or infections with pathogens with possible decreased susceptibility has been increased to 1g every 8 hours given as a 4-hour infusion. Treatment duration of 10-14 days is usually required for patients with such infections and is often closer to 14 days for patients infected with pathogens such as *Pseudomonas* spp. and *Acinetobacter* spp. Previous dosing regimens for doripenem in such patients were found to be insufficient.

A recent review of study data on nosocomial pneumonia (including ventilator–associated pneumonia) indicates that the currently approved dose of doripenem is insufficient in patients with augmented renal function (particularly those with creatinine clearance (CrCl ≥ 150 mL/min) and/or infections with pathogens with possible decreased susceptibility and should be increased.

No changes to the recommended doripenem doses for treating nosocomial pneumonia (including ventilator-associated pneumonia) due to susceptible pathogens in patients with non-augmented renal clearance, or for treating complicated intra-abdominal infections and complicated urinary tract infections, are required.

(See WHO Pharmaceuticals Newsletters No. 2, 2012 for higher mortality rate and a lower clinical cure rate observed during a comparative clinical trial in Canada and No.4, 2012 for higher dosing needed in nosocomial pneumonia in Europe.)

Reference:
Drug Safety Update, August 2012, Volume 6, issue 1, A3 MHRA, (www.mhra.gov.uk).

Levofloxacin

Safety profile was unfavourable as first-line treatment

UK. The MHRA announced that levofloxacin may only be considered in the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis, community acquired pneumonia or complicated skin and soft tissue infections when other medicines cannot be prescribed, or have been ineffective. This restriction resulted from a review of overall efficacy and safety data, which suggested that the safety profile of levofloxacin was unfavourable as first-line treatment for these indications. The risks contributing to this assessment included serious hepatotoxicity, cardiac arrhythmia, severe skin reactions and tendon rupture.

Other licensed indications for oral and intravenous levofloxacin remain unchanged.

(See WHO Pharmaceuticals Newsletters No. 1 and 4, 2002 for reports of adverse reactions including tendinitis in Belgium and No.2, 2007 for reports of blood glucose, liver and biliary disorders in Canada.)

Reference:
Drug Safety Update, September 2012, Volume 6, issue 2, S2 MHRA, (www.mhra.gov.uk).

Ondansetron

Risk of QTc prolongation – important new

intravenous dose restriction

UK. The MHRA recommended that the new maximum single intravenous dose of ondansetron (Zofran®) for the management of chemotherapy-induced nausea and vomiting (CINV) in adults is now 16 mg (infused over at least 15 minutes).

This restriction follows a review of new study data, which showed that there is a greater risk of prolongation of the electrocardiographic-corrected QT interval (QTc), a known side effect of ondansetron, when it is used at the higher doses previously authorised for CINV. Prolongation of the QTc can lead to Torsade de Pointes (TdP), a potentially life-threatening cardiac arrhythmia. Although no cases of TdP were observed in the study, TdP has been reported in association with the use of ondansetron in clinical practice.

Health-care professionals are advised that

- A single dose of intravenous ondansetron given for the management of chemotherapy-induced nausea and vomiting in adults must not exceed 16 mg (infused over at least 15 minutes)
- Ondansetron should be avoided in patients with congenital long QT syndrome.
- Caution must be used if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. These include: electrolyte abnormalities; use of other medicines that prolong the QT interval (including cytotoxic drugs) or may lead to electrolyte abnormalities; congestive heart failure; bradyarrhythmias; and use of medicines which lower the heart rate
- Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration

The maximum recommended intravenous dose of ondansetron for the prevention and treatment of post-operative nausea and vomiting in adult patients is a single dose of 4 mg and this has not changed. In addition there are no changes in the recommended intravenous dosing for any indication in paediatric patients. There are no changes to the recommended dosing for oral or rectal ondansetron formulations in adult or paediatric patients in any indication.

(See WHO Pharmaceuticals Newsletters No. 5, 2011 for risk of abnormal heart rhythms in the USA.)

Reference:
Drug Safety Update, August 2012, Volume 6, issue 1, A2 MHRA, (*www.mhra.gov.uk*).

Paracetamol

New guidance on treating paracetamol overdose with intravenous acetylcysteine

UK. The MHRA announced that new simplified guidance on treating paracetamol overdose with intravenous acetylcysteine is in place. This includes an updated treatment nomogram. The new guidance is as follows:

- All patients with a timed plasma paracetamol level on or above a single treatment line joining points of 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion should receive acetylcysteine (Parvolex® or generics) based on a new treatment nomogram, regardless of risk factors for hepatotoxicity
- Where there is doubt over the timing of paracetamol ingestion including when ingestion has occurred over a period of one hour or more – 'staggered overdose' – acetylcysteine should always be given without delay (the nomogram should not be used)
- Administer the initial dose of acetylcysteine as an infusion over 60 minutes to minimise the risk of common dose-related adverse reactions
- Hypersensitivity is no longer a contraindication to treatment with acetylcysteine

Paracetamol overdose can result in liver damage which may be fatal. Intravenous acetylcysteine is the antidote to treat paracetamol overdose and is virtually 100% effective in preventing liver damage when given within 8 hours of the overdose. After this time efficacy falls substantially, affording only a very limited window of time in which to successfully prevent serious hepatotoxicity.

Previously, health-care professionals treating paracetamol overdose were advised to assess for risk factors of hepatotoxicity such as chronic alcohol consumption, co-medications and poor nutritional intake.

This resulted in two lines on the treatment nomogram – one for patients with risk factors and one for those without. The Commission on Human Medicines (CHM) review found that the evidence base to support the use of risk factors was poor and inconsistent, and that many of the risk factors for hepatotoxicity were imprecise and difficult to determine with sufficient certainty in clinical practice. By removing the need to assess risk factors for hepatotoxicity, the approved indication for acetylcysteine is greatly simplified to a single line on the paracetamol overdose treatment nomogram.

In the past there were also a substantial number of reports of administration errors with intravenous acetylcysteine, some of which had the potential to result in significant harm. A major contributory factor for these errors was the complex dosing regimen for intravenous acetylcysteine. The CHM recommended a number of measures to reduce the incidence of administration errors, most notably the introduction of weight-based dosage tables for adults and children to remove the need to calculate the dose.

The majority of common dose-related adverse reactions occur within the first hour of the initial infusion of acetylcysteine. Sufficient evidence of efficacy is available to support extending the time of the initial infusion from 15 minutes to 60 minutes in order to reduce the incidence of adverse reactions.

There are now no specific contraindications to acetylcysteine in the treatment of paracetamol overdose, including known hypersensitivity to any of the ingredients in the product. Even if a patient has a history of a previous reaction to intravenous acetylcysteine, the benefits of acetylcysteine outweigh the risks in such cases, and patients should receive treatment. Any 'hypersensitivity-like' reactions ascribed to acetylcysteine are likely to be anaphylactoid in nature; ie, they are not immunologically mediated and therefore may not occur on repeated exposure.

(See WHO Pharmaceuticals Newsletters No. 4, 2010 for risk of accidental overdose in UK, No. 1, 2011 for limitation of dosing and the potential risk of severe liver failure in the USA and No. 4, 2011 for the risk of unintentional overdosing in children in New Zealand and UK.)

Reference:
Drug Safety Update, September 2012, Volume 6, issue 2, A1 MHRA, (*www.mhra.gov.uk*).

Sildenafil

Recommendation against use in children for pulmonary arterial hypertension (PAH)

USA. The U.S. Food and Drug Administration (US FDA) notified health-care professionals and their medical care organizations that sildenafil (Revatio®) should not be prescribed to children (ages 1 through 17) for pulmonary arterial hypertension (PAH).

This recommendation against use is based on a recent long-term clinical pediatric trial showing that: (1) children taking a high dose of sildenafil had a higher risk of death than children taking a low dose and (2) the low doses of sildenafil are not effective in improving exercise ability. Treatment of PAH in children with this drug is not approved by the US FDA and a new warning, stating that the use of sildenafil is not recommended in pediatric patients has been added to the labeling.

The US FDA also advised patients and caregivers not to change the sildenafil dose or stop taking sildenafil without talking to a health-care professional. Health-care professionals were reminded that use of this product, particularly chronic use, in children is an off-label indication, not approved by the US FDA, and is not recommended.

Reference:
FDA Drug Safety Communication, US FDA 30 August 2012 (*www.fda.gov*).

Simvastatin

Updated advice on drug interactions - updated contraindications

UK. The MHRA announced that simvastatin is now contraindicated with ciclosporine, danazol and gemfibrozil and that the maximum recommended dose for simvastatin in conjunction with amlodipine or diltiazem is now 20 mg/day.

According to the MHRA, considering the risk of myopathy associated with simvastatin, recent analysis of clinical trial data, spontaneously reported cases and drug- drug interaction studies has resulted in further changes to the simvastatin prescribing information.

The changes include contraindications to concomitant use with certain medicines and maximum dose recommendations when simvastatin is taken with a number of other medicines, as these interactions may increase plasma concentrations of simvastatin which is associated with an increased risk of myopathy and/or rhabdomyolysis.

A full updated listing of all the interactions associated with increased risk of myopathy/rhabdomyolysis is;

- Contraindicated with simvastatin: itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (eg, nelfinavir), nefazodone, ciclosporin, danazol and gemfibrozil
- Do not exceed 10 mg simvastatin daily with: Other fibrates (except fenofibrate)
- Do not exceed 20 mg simvastatin daily with: amiodarone, amlodipine, verapamil and diltiazem
- Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.: Fusidic acid
- Avoid grapefruit juice when taking simvastatin

(See WHO Pharmaceuticals Newsletter No. 4, 2011 and No.1, 2012 for new restrictions, contraindications, and dose limitations in the USA.)

Reference:
Drug Safety Update, August 2012, Volume 6, issue 1, S1 MHRA, (*www.mhra.gov.uk*).

Statins

A risk of diabetes mellitus

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) advised health-care professionals to be aware of the association of new-onset type 2 diabetes mellitus (T2DM) with the use of statins and to monitor at risk patients according to best practice guidelines.

Recent publications have suggested that there may be an association of new-onset T2DM with the use of statins. The Medicines Adverse Reactions Committee (MARC) have reviewed the relevant studies and concluded that there is a small, but statistically significant association, particularly in patients already at risk of T2DM. Nevertheless, the MARC considered that the benefits of statin treatment clearly outweigh any risk of developing new-onset T2DM.

A total of six meta-analyses were reviewed by the MARC. The studies all had limitations and suggest that other individual risk factors may also contribute to the association. The risk factors included:

- raised fasting glucose level (5.6 to 6.9mmol/L)
- body mass index greater than 30kg/m2
- raised triglycerides
- history of hypertension.

There was insufficient data to exclude an effect with any individual statin or to support a dose-dependent relationship.

Reference:
Prescriber Update Vol. 33 No. 3, September 2012 (*www.medsafe.govt.nz/*).

Strontium ranelate

Venous thromboembolism and serious skin reactions

Australia. The Therapeutic Goods Administration (TGA) advised health-care professionals of additional contraindications and precautions for strontium ranelate (Protos®), to help manage the risk of venous thromboembolism (VTE) and serious skin hypersensitivity reactions. Strontium ranelate is indicated for the treatment of postmenopausal osteoporosis to reduce the risk of fracture, and for the treatment of osteoporosis in men at increased risk of fracture.

The risk of VTE was found to be higher in patients with a previous history of VTE, and in patients who are temporarily or permanently immobilised. A higher rate of VTE was also identified in elderly patients aged >80 years receiving strontium ranelate, compared to placebo.

Post-marketing surveillance has identified cases of severe skin reactions, such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in patients prescribed strontium ranelate. However, the overall occurrence of serious skin reactions was low. Since these conditions are best managed with early diagnosis and immediate discontinuation of any suspect medicines, it is important that health-care professionals are aware of the time-to-onset, signs and symptoms of these conditions.

The Australian Product Information was updated to include strengthened advice for managing the risk of VTE and serious skin hypersensitivity reactions as follows.

New contraindications:
- Current or previous venous thromboembolic events, including deep vein thrombosis and pulmonary embolism
- Temporary or permanent immobilisation (e.g. post-surgical recovery or prolonged bed rest)

New precautions for venous thromboembolism:
- In patients over 80 years at risk of VTE, ongoing treatment with strontium ranelate should be re-evaluated

- In the event of an illness or a condition leading to immobilisation, strontium ranelate should be discontinued as soon as possible and adequate preventive measures taken. Therapy should not be restarted until the event has resolved and the patient is mobile.
- strontium ranelate should be stopped if VTE occurs

New precautions for serious skin hypersensitivity reactions:

- Patients should be advised of the signs and symptoms and monitored closely for skin reactions
- The highest risk for occurrence of SJS or TEN is within the first weeks of treatment and usually around 3-6 weeks for DRESS
- If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease)) are present, strontium ranelate treatment should be discontinued immediately
- Early diagnosis and immediate discontinuation of the suspected drug is associated with a better prognosis of SJS, TEN or DRESS. Recovery from DRESS could be slow and recurrences have been reported in some cases after discontinuation of corticosteroid therapy.
- If the patient has

update of warnings regarding serious skin reactions in Europe.)

Reference:

Medicines Safety Update Vol 3, No. 4, August 2012 (www.tga.gov.au).