WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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.

Contents

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TABLE OF CONTENTS

Regulatory Matters

Safety of medicines

Signal

Azithromycin

Risk of potentially fatal heart rhythms

USA. The U.S. Food and Drug Administration (FDA) warned the public that azithromycin (Zithromax® or Zmax®) can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias. The US FDA issued a Drug Safety Communication as a result of their review of a study by medical researchers as well as another study by a manufacturer of the drug that assessed the potential for azithromycin to cause abnormal changes in the electrical activity of the heart.

The US FDA recommended that health-care professionals should consider the risk of torsades de pointes and fatal heart rhythms with azithromycin when considering treatment options for patients who are already at risk for cardiovascular events. The US FDA noted that the potential risk of QT prolongation with azithromycin should be placed in appropriate context when choosing an antibacterial drug. Alternative drugs in the macrolide class, or non-macrolides such as the fluoroquinolones, also have the potential for QT prolongation or other significant side effects that should be considered when choosing an antibacterial drug.

Indications approved by the US FDA for azithromycin include: acute bacterial exacerbations of chronic obstructive pulmonary disease, acute bacterial sinusitis, community-acquired pneumonia, pharyngitis/tonsillitis, uncomplicated skin and skin structure infections, urethritis and cervicitis, genital ulcer disease.

References:
FDA Drug Safety Communication, US FDA 12 March 2013 (*www.fda.gov*).

Denosumab

Rare cases of atypical femoral fracture with long-term use

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that atypical femoral fractures have been reported rarely in patients with postmenopausal osteoporosis receiving long-term (≥2.5 years) treatment with denosumab 60 mg (Prolia©) in the on-going open-label extension study of the pivotal phase 3 fracture trial in postmenopausal osteoporosis (FREEDOM). During denosumab treatment, patients presenting with new or unusual thigh, hip or groin pain should be evaluated for an incomplete femoral fracture. Discontinuation of denosumab therapy should be considered if an atypical femur fracture is suspected, while the patient is evaluated.

Two cases of atypical femoral fracture have been confirmed. These events occurred rarely (in ≥ 1/10 000 to < 10/10 000 patients), based on 8,928 subjects being exposed to denosumab 60 mg in bone loss studies. The risk of atypical femoral fractures also exists for denosumab 120 mg (Xgeva©). The nature of the fractures seen with denosumab 60 mg is similar to the atypical femoral fractures seen with long-term bisphosphonate therapy.

Health-care professionals are advised that atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur and that the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture, as atypical femoral fractures are often bilateral (as noted from the bisphosphonates assessment).

Denosumab 60 mg is given once every 6 months for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Denosumab 120 mg is given once every 4 weeks for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

(See WHO Pharmaceuticals Newsletter No. 6, 2012 for fatal cases of severe symptomatic hypocalcaemia in the UK).

Reference:
Drug Safety Update, February 2013, Volume 6, issue 7, A1 MHRA, (*www.mhra.gov.uk*).

Fingolimod

Advice on enhanced cardiovascular monitoring

UK. The MHRA updated guidance on when enhanced cardiac monitoring is required following fingolimod (Gilenya®) treatment interruption on the basis of new clinical pharmacology analyses and dose titration data.

New advice is as follows;

Treatment interruption:

The same first-dose monitoring as for treatment initiation should be repeated if treatment is interrupted as follows:

• 1 day or more during the first 2 weeks of treatment.
• more than 7 days during weeks 3 and 4 of treatment.
• more than 2 weeks after one month of treatment.

If the treatment interruption is of shorter duration than the above, the next dose of fingolimod should be given as planned without repeating the first-dose cardiovascular monitoring.

Following pharmacological intervention to treat bradyarrhythmia-related symptoms after first dose:

As per current recommendations, patients requiring pharmacological intervention during the first dose monitoring should be monitored overnight in a medical facility. In these patients, it is now recommended to repeat the first-dose monitoring after the second dose of fingolimod.

Fingolimod is authorised to treat relapsing-remitting multiple sclerosis in patients whose disease has failed to respond to beta-interferon or is severe and getting worse rapidly.

(See WHO Pharmaceuticals Newsletter No. 1, 2012 for safety review of a reported death after the first dose in the USA and for review of fingolimod and advise to intensify cardiovascular monitoring after first dose in EU, No. 2, 2012 in Canada, No.3 2012 for new advice to better manage risk of adverse effects on the heart in Europe and the US and No.1 2013 in Australia).

Reference:
Drug Safety Update, January 2013, Volume 6, issue 6, A1 MHRA, (www.mhra.gov.uk).

Idebenone

Voluntary withdrawal from the Canadian market

Canada. Santhera Pharmaceuticals, in consultation with Health Canada, informed of its decision to voluntarily withdraw idebenone (CATENA®) from the Canadian market, as of April 30, 2013. The withdrawal is based on the negative outcome of additional confirmatory efficacy studies required by Health Canada and is not the result of a specific safety concern. Prescribers are advised to discuss alternative treatment options with their patients before April 30, 2013.

Idebenone was authorized with conditions in Canada in July 2008 on the basis that it demonstrated promising evidence of clinical safety and efficacy in the symptomatic management of patients with Friedreich's Ataxia. One of the conditions of authorization was to provide confirmatory evidence of efficacy in further clinical studies. However, the additional studies completed to date failed to meet their primary efficacy endpoint.

No specific safety issues were identified that have prompted this action, and the withdrawal does not preclude the submission of a new application for market authorization in the future.

Since no prescriptions will be filled after close of business on April 30, 2013, prescribers are advised to discuss alternative treatment options with their patients as soon as possible. Santhera will not make CATENA® available through Health Canada's Special Access Programme. Also, Santhera will not recall CATENA® currently prescribed to patients. Therefore, prescribers have the option of allowing these patients to complete their current course of treatment.

Reference:
Advisories, Warnings and Recalls, Health Canada, 27 February 2013 (www.hc-sc.gc.ca).

Laropiprant and niacin

No longer for prescribing as preliminary trial failed to show benefit outweighs risks

UK (1). The MHRA advised not to start any new patients on Tredaptive™. Tredaptive™ is a fixed-dose combination product containing extended-release nicotinic acid (1000 mg) and laropiprant (20 mg), which has been indicated for the treatment of dyslipidemia, particularly in patients with combined mixed dyslipidemia and in patients with primary hypercholesterolemia. It has been used in combination with a statin when the cholesterol-lowering effect of statin treatment alone is not sufficient, or alone in patients unable to take statins.

The preliminary results of the study indicated that adding the drug to simvastatin did not provide significant additional benefit in reducing the risk of major vascular events such as heart attack and stroke, compared with statin therapy alone. In addition, a higher frequency of non-fatal but serious adverse events was seen in patients taking the drug with simvastatin, compared with patients taking simvastatin alone. These events included bleeding (intracranial and gastro-intestinal), myopathy, infections and new-onset diabetes. In the light of the latest evidence, the benefit-risk balance for the drug is considered negative, and the medicine has been recalled.

Europe (2). The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) confirmed the recommendation to suspend the marketing authorisations of Tredaptive™, Pelzont® and Trevaclyn® (nicotinic acid / laropiprant) used to treat adults with dyslipidaemia (abnormally high blood levels of fats such as triglycerides and cholesterol). The CHMP decision follows the recent recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC) to suspend these medicines.

In the meantime, the European Commission has taken temporary measures to suspend the marketing authorisation and supply of the medicines across the European Union (EU) and the marketing authorisation holder, Merck Sharp & Dohme Ltd, has announced that it is taking steps to suspend availability of the medicines across the EU.

The CHMP encourages patients currently taking these medicines to make a non-urgent appointment with their doctor to discuss their treatment. Doctors should no longer prescribe Tredaptive, Pelzont or Trevaclyn and should review patients' treatment options.

The review of Tredaptive, Pelzont and Trevaclyn was initiated in December 2012 after new data from a large, long-term study called HPS2-THRIVE became available.

Having reviewed the results of the study, the CHMP concluded that the benefits of Tredaptive, Pelzont and Trevaclyn no longer outweigh the risks and that their marketing authorisations should be suspended.

Reference:
(1) Drug Safety Update, January 2013, Volume 6, issue 6, S1 MHRA, (*www.mhra.gov.uk*).
(2)Press release, EMA, 18 January 2013 (*www.ema.europa.eu*).

Lenalidomide

Risk of serious hepatic adverse drug reactions

UK. The MHRA advised that hepatic function should be routinely monitored (with the same frequency as haematological monitoring), particularly in patients with a history of, or concurrent, viral liver infection, or when lenalidomide is given at the same time as other medications known to be associated with liver injury.

The MHRA also advised that prescribers should consider the possibility of lenalidomide-induced liver injury in patients presenting with otherwise unexplained deterioration of liver function. Impairment of liver function generally resolves when lenalidomide treatment is stopped. Once abnormal liver function parameters return to baseline, resumption of treatment with lenalidomide at a lower dose may be considered.

It is reminded that lenalidomide is excreted predominantly by the kidney. It is important to adjust the dose of lenalidomide in patients with renal impairment to avoid high plasma levels which may increase the risk of severe hepatotoxicity, as well as haematological side effects.

Elevations of liver enzymes occur in 1-10 patients out of every 100 treated with lenalidomide for multiple myeloma in clinical trials; the majority of these are non-serious. Serious (potentially fatal) liver injuries such as acute hepatic failure, toxic hepatitis, hepatocellular hepatitis, and cholestatic hepatitis have been reported overall in <1% of treated patients.

Lenalidomide is authorised in combination with dexamethasone for treatment of multiple myeloma in patients who have received at least one previous treatment.

Reference:
Drug Safety Update, January 2013, Volume 6, issue 6, A2 MHRA, (*www.mhra.gov.uk*).

Roflumilast

Risk of suicidal behaviour

UK. The MHRA advised that roflumilast (Daxas®) is not recommended for patients with a history of depression associated with suicidal ideation or behaviour. Patients and caregivers should be asked to notify the prescriber and their healthcare provider of any changes to behaviour or mood, and any suicidal ideation. Such symptoms include preoccupation with suicidal thoughts, and self-harm. Roflumilast should be discontinued if new or worsening psychiatric symptoms or suicidal behaviour are identified.

If patients have existing psychiatric symptoms, or if concomitant treatment is intended with other medicines likely to cause psychiatric symptoms, roflumilast treatment should only be started or continued after careful assessment of the benefits and risks.

Roflumilast is a phosphodiesterase-type-4 (PDE4) inhibitor used for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis. It is indicated for adult patients with a history of frequent exacerbations as 'add-on' to bronchodilator treatment.

Reference:
Drug Safety Update, January

2013, Volume 6, issue 6, S2 MHRA, (www.mhra.gov.uk).

Telaprevir

Serious skin reactions

Canada. Vertex Pharmaceuticals (Canada) Incorporated, in collaboration with Health Canada, informed of new important safety information regarding serious skin reactions with telaprevir (INCIVEK™) combination treatment. Telaprevir, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease.

Fatal and non-fatal serious skin reactions, including Toxic Epidermal Necrolysis (TEN), Stevens Johnson Syndrome (SJS), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported in patients receiving Telaprevir combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive the combination treatment after a serious skin reaction was identified.

For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, telaprevir, peginterferon alfa and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should also be considered. Patients should be promptly referred for urgent medical care.

A new Serious Warnings and Precautions box for Serious Skin Reactions has been added to the telaprevir Product monograph (PM) to reflect this new information. The Warnings and Precautions section has also been updated.

It is advised that patients should be informed about potential serious skin reactions which may require urgent treatment in a hospital and may result in death. The treating physician will decide if they need treatment or if they need to stop taking telaprevir, or any other medication. It is recommended to advise patients not to stop taking telaprevir combination treatment without talking with helath-care professionals.

(See WHO Pharmaceuticals Newsletter No. 1, 2013 for new boxed warning - serious skin reactions in the USA).

Reference:
Advisories, Warnings and Recalls, Health Canada, 22 February 2013 (www.hc-sc.gc.ca).

Tolvaptan

New warning regarding a potential risk of liver damage

Canada. Otsuka Canada Pharmaceutical Inc. (Otsuka) in consultation with Health Canada informed of a risk of liver injury associated with the use of tolvaptan (Samsca®). Tolvaptan has the potential to cause irreversible and potentially fatal liver injury. During a large clinical trial in about 1400 patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD), three patients out of the 958 treated with tolvaptan (60-120 mg daily), developed serious liver injuries (ALT > 3x ULN with concomitant Total Bilirubin > 2X ULN). All three patients improved following discontinuation of treatment. Tolvaptan is not approved for the treatment of ADPKD.

It is advised that liver tests should be performed promptly, if a patient reports symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Tolvaptan should be immediately discontinued and appropriate treatment initiated. Investigations should be performed to determine the cause. Tolvaptan should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with the drug.

The ability to recover from liver injury may be impaired in patients with hyponatremia in the setting of underlying liver disease, including cirrhosis. Limiting the duration of SAMSCA® therapy may reduce the risk of developing liver injury.

In other clinical trials of tolvaptan, including the trials supporting the approved indication, liver damage has not been reported. However, these data are not adequate to exclude the possibility that these patients are at an increased risk for irreversible and potentially fatal liver injury. Limiting the duration of tolvaptan therapy may reduce the risk of developing liver injury.

The Canadian Product Monograph is currently being updated to reflect on this new safety information regarding the use of the drug.

Tolvaptan is approved to treat certain patients with clinically important, non-hypovolemic hyponatremia.

(See WHO Pharmaceuticals Newsletter No. 3, 2012 for over-rapid increase in serum sodium and risk of serious neurological events in UK and No. 1, 2013 for potential risk of liver injury in the USA).

Reference:
Advisories, Warnings and Recalls, Health Canada, 27 February 2013 (www.hc-sc.gc.ca).

Cinacalcet

Cautions against use in children

Canada. Following the death of a child enrolled in a clinical trial in the United States, Health Canada reminded health-care professionals and consumers that cinacalcet (Sensipar®) is not approved for use in patients under 18 years of age. Amgen, the manufacturer of the dug, recently halted all pediatric clinical trials of the drug after the death of a 14-year-old patient who developed very low blood calcium levels during a trial. It has not been determined whether cinaclcet had a role in the patient's death.

Health Canada is currently reviewing available safety information and will consider updating the labelling information, as appropriate.

Cinacalcet is used for treating disorders of the parathyroid gland that result in high blood calcium levels.

Reference:
Advisories, Warnings and Recalls, Health Canada, 7 March 2013 (*www.hc-sc.gc.ca*).

Combined hormonal contraceptives

Start of review of

etonogestrel, gestodene, nomegestrol, norelgestromin and norgestimate.

The review of these contraceptives was requested by the French medicines agency (ANSM) following concerns in France about the risk of venous thromboembolism (VTE or blood clots in veins). The risk of VTE with combined hormonal contraceptives is known to depend on both the level of oestrogen and the type of progestogen they contain. While the overall risk with these products is low, the risk is known to be higher for some progestogens than the risk associated with the progestogen levonorgestrel.

The EMA will now review all available data on the risk of VTE with these contraceptives and issue an opinion on whether any changes are needed to their prescribing advice across the EU. The review will also cover the risk of arterial thromboembolism (blood clots in arteries, which can potentially cause a stroke or heart attack). This risk is very low and is not currently known to be higher with any particular type of progestogen.

Previous EMA reviews of combined oral contraceptives concluded that their absolute risk of VTE is low and extensive information on the risk and its management is included in their product information.

medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms, following the decision by the French medicines regulatory agency (ANSM) to suspend Diane 35 and its generics in France within three months.

These medicines are widely used across Europe. They have been authorised at the level of individual Member States for many years. In France, they are only authorised for the treatment of acne, but in a number of other Member States they are also authorised for the treatment of acne in women who wish to receive oral contraception, as well as for the treatment of other skin conditions.

The French decision follows a review by ANSM of reports of venous and arterial thromboembolism (VTE and ATE, the formation of blood clots in the veins or arteries) in association with Diane 35 and its generics since their marketing authorisation. Although the risk of VTE with these medicines has been known for many years, ANSM considered this risk to outweigh its moderate benefits in treating acne, for which alternative treatments are available. In addition, it noted that in France these medicines are widely used off-label as a contraceptive.

The EMA will now review all available data on the risk of VTE and ATE with medicines