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:

Quality Assurance and Safety: Medicines, EMP-HSS, 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/medicine

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

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No. 2, 2013

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.
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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.


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).


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 bradycardia-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:

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:

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:

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.


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
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 health-care professionals.

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

Reference:

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:
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 drug, 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 cinacalcet 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.


Combined hormonal contraceptives

Start of review of combined hormonal contraceptives
Europe. The EMA started a review of several combined hormonal contraceptives authorised in the EU. Combined hormonal contraceptives contain two types of hormones, an oestrogen and a progestogen. The review includes all contraceptives containing the following progestogens: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norgestromin 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.


Cyproterone- and ethinylestradiol-containing medicines

Review of Diane 35 and other medicines
Europe (1). The EMA started a review of Diane 35 and other 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 containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms, and will issue an opinion on whether the marketing authorisations for these medicines should be maintained, varied, suspended or withdrawn across the EU.

The Agency invites all stakeholders (e.g. healthcare professionals, patients’ organisations, general public) to submit data relevant to this procedure.

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Canada (2). Health Canada is currently conducting a review of all available safety information on the drug Diane-35. Health Canada has been monitoring the safety of Diane-35 on an on-going basis, as it does for all drugs on the market.

Blood clots are a rare but well-known side-effect associated with oral birth control pills and other hormonal products such as Diane-35. The current Canadian Product Monograph, including the patient information section, contains clear warnings regarding this issue. Health professionals are reminded that Diane-35 should not be used in patients with a history that puts them at risk for blood clots. Known factors that increase the risk of blood clots include smoking, being overweight (obesity), and a family history of blood clots.

Patients who think they are experiencing symptoms of a blood clot should seek immediate medical attention and mention any medications they may be taking, including Diane-35. Symptoms of a blood clot may include persistent leg swelling, leg pain or tenderness, chest pain, or sudden shortness of breath or difficulty breathing.

In Canada, Diane-35 is approved for the temporary treatment of severe acne in women who are unresponsive to other available treatments.

(See WHO Pharmaceuticals Newsletter No. 3, 2010 for revisions to prescribing information of stagliptin to include acute pancreatitis in the USA).

References:

Incretin Mimetic Drugs for Type 2 Diabetes

Reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas

USA. The US FDA is evaluating unpublished new findings by a group of academic researchers that suggest an increased risk of pancreatitis and pre-cancerous cellular changes called pancreatic duct metaplasia in patients with type 2 diabetes treated with a class of drugs called 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. The US FDA asked the researchers to provide the methodology used to collect and study these specimens and to provide the tissue samples so the Agency can further investigate potential pancreatic toxicity associated with the incretin mimetics.

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 US FDA has not reached any new conclusions about safety risks with incretin mimetic drugs. This early communication is intended only to inform the public and health-care professionals that the Agency intends to obtain and evaluate this new information. The US FDA will participate in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Cancer Institute’s (NCI) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer in June 2013 to gather and share additional information. The US FDA will communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report.

The US FDA advised that patients should continue to take their medicine as directed until they talk to their health-care professional at this time, and that health-care professionals should continue to follow the prescribing recommendations in the drug labels.

(See WHO Pharmaceuticals Newsletter No. 1, 2010 for revisions to prescribing information of stagliptin to include acute pancreatitis in the USA).

References:

Tetrazepam-containing medicines

Review started Europe. The EMA started a review of tetrazepam-containing medicines because of concerns over serious skin reactions with these medicines.

It is used to treat painful muscle spasms (cramps) mainly in patients with rheumatological diseases.

Following several reports of serious skin reactions in France, the French medicines agency performed a review of data on all side effects, especially skin reactions,
recorded in the French national pharmacovigilance database. The review showed that side effects affecting the skin occurred at a high rate in comparison with other benzodiazepines. In addition, concern was raised about the seriousness of some reported cases which include SJS, TEN, erythema multiforme and DRESS syndrome.

The EMA will review all available data on the safety of tetrazepam-containing medicines, in particular skin reactions, in order to assess any impact on the benefit-risk balance of these medicines. The Agency invites all stakeholders (e.g. health-care professionals, patients’ organisations and the general public) to submit data relevant to this procedure.

Reference:
A signal is defined by WHO 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. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase™. The database contains over 7 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC’s current routine signal detection process.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL (page 15). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC’s vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information, visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: info@who-umc.org.

Februaryostat and Hepatic failure
Dr. Richard Hill, Australia

Febuxostat is a xanthine oxidase inhibitor (the same mechanism of action as allopurinol) indicated for the chronic management of hyperuricaemia in patients with gout. It was approved in Europe in 2008 and in the US in 2009.

A signal for hepatic failure associated with febuxostat use was found in the WHO Global Individual Case Safety Report (ICSR) database, VigiBase™ in October 2012 with six reports (two fatal) and IC 2.50 (IC025 1.13). Five of the reports are from the US and one from Germany. The reports are outlined in the table below:

Hepatic failure was added to the Warnings and Precautions section of the US Product Information (PI) for febuxostat in November 2012, but has not yet been added to the UK Summary of Product Characteristics (SPC).2,3 The US PI states that liver function should be tested at baseline and on development of symptoms that may indicate liver injury, and that febuxostat should be ceased if ALT is ≥ three times ULN. However, the reports in VigiBase indicate that hepatic failure, sometimes fatal, may occur with rapid onset after starting febuxostat. The lack of reversibility of hepatic enzyme increases seen in clinical trials is also of concern.
As of 2 December 2012, VigiBase contained 449 reports for febuxostat, including also ten reports of hepatic function abnormal, eight reports of hepatic enzymes increased, and six reports of jaundice.

In clinical trials of febuxostat, the incidence of alanine transaminase (ALT) ≥ three times the upper limit of normal (ULN) was 2-5% in the febuxostat groups (but not dose-related), 2% in the allopurinol group, and <1% in the placebo group.1 Reversibility of ALT and aspartate transaminase (AST) values to normal or below baseline was seen in 19/57 patients in the febuxostat groups, 10/17 for allopurinol, and 2/2 for placebo.

Response from Teijin Pharma Limited

Through routine signal detection activities and periodic analysis, the Marketing Authorization Holders (Teijin Pharma Ltd in Japan, Takeda Pharmaceuticals U.S.A., Inc. in North America, and Menarini International Operations Luxembourg S.A in Europe) have identified hepatic failure (HF) as a potential signal for febuxostat. Evaluation of this signal is challenging as patients with gout often have several co-morbidities and are on several concomitant medications.

Most of collected HF reports present confounding factors, with co-morbid conditions, and other co-suspect medications. Additionally, some of these reports have insufficient information for causality assessment. Therefore current data do not allow to establish a causal relationship with febuxostat.

Evaluation of hepatic events was presented in Europe with the variation#23, where hepatitis and jaundice, but not HF, were inserted in the EU-PI. HF events were reviewed again along the PSUR#8 (up to 20-Apr-2012). The analysis indicated that a causal relationship with febuxostat was confounded by alternative etiologies, co-suspect medications and co-morbidities. While two new cases (last in the below table) have been reported following the last review, these cases do not change the risk assessment or conclusion of the above mentioned review.

There have been 11 cases describing HF events. An independent expert review board (Liver safety evaluation committee, LSEC) has also analyzed the reports, key factors for all eleven ICSRs are briefly displayed in the below table.

Conclusions

Based on the careful review of hepatic events, it is not possible to establish a causal relationship and the benefit risk profile of febuxostat remains unchanged at this time. The MAHs are committed to continue close monitoring of all reported serious hepatic events. The MAHs will implement

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**Table 1: VigiBase™ reports of febuxostat and hepatic failure**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Suspected drug(s)</th>
<th>Duration of use</th>
<th>Reaction(s)*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>M</td>
<td>febuxostat</td>
<td>15 days</td>
<td>hepatic failure, haematemesis</td>
<td>died</td>
</tr>
<tr>
<td>83</td>
<td>F</td>
<td>febuxostat, levofloxacin</td>
<td>19 days, 6 days</td>
<td>hepatic failure, vasculitis allergic</td>
<td>recovered</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>febuxostat</td>
<td>7 months</td>
<td>hepatic failure, rash</td>
<td>unknown</td>
</tr>
<tr>
<td>75</td>
<td>F</td>
<td>febuxostat, levofloxacin</td>
<td>3 months</td>
<td>hepatic failure, thrombocytopenia, renal failure, GI haemorrhage, rash</td>
<td>recovered</td>
</tr>
<tr>
<td>35</td>
<td>F</td>
<td>febuxostat</td>
<td>unknown</td>
<td>hepatic failure, renal failure, acute</td>
<td>unknown</td>
</tr>
</tbody>
</table>

*Reactions stated in WHO-ART terms (WHO Adverse Reaction)

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**References**


appropriate actions to communicate and manage the risk.

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Co-Suspect drugs</th>
<th>Latency</th>
<th>Reactions</th>
<th>Outcome</th>
<th>Medical history</th>
<th>Causality (Reporter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 Male</td>
<td></td>
<td>49 days</td>
<td>Hepatorenal syndrome</td>
<td>Fatal</td>
<td>Obesity, chronic alcoholism, choledolithiasis</td>
<td>Unlikely related, alcohol induced hepatitis</td>
</tr>
<tr>
<td>70 Male</td>
<td></td>
<td>15 days</td>
<td>Acute HF, oesophageal haemorrhage, nausea</td>
<td>Fatal</td>
<td>Chronic alcohol use, choledolithiasis</td>
<td>Not related, chronic alcohol use</td>
</tr>
<tr>
<td>69 Male</td>
<td>Tramadol</td>
<td>240 days</td>
<td>Acute HF</td>
<td>Recovered with sequelae</td>
<td>Cryptogenic cirrhosis, end stage CKD, dialysis, type II diabetes</td>
<td>Unlikely related</td>
</tr>
<tr>
<td>46 Male</td>
<td></td>
<td>390 days</td>
<td>Acute HF</td>
<td>Recovering</td>
<td>Alcohol abuse</td>
<td>Possibly related to febuxostat but acute liver decompensation while consuming an excessive amount of alcohol</td>
</tr>
<tr>
<td>83 Female</td>
<td>Levofloxacin</td>
<td>18 days</td>
<td>HF, leukocytoclastic vasculitis</td>
<td>Recovering</td>
<td>CRF, CHF</td>
<td>Related to febuxostat and levofloxacin</td>
</tr>
<tr>
<td>64 Male</td>
<td></td>
<td>7 months</td>
<td>HF, rash pruritic</td>
<td>Fatal</td>
<td>Hepatic function abnormality, CRF, alcohol consumption</td>
<td>Probably or possibly related</td>
</tr>
<tr>
<td>45 Male</td>
<td></td>
<td>~7 months</td>
<td>HF, renal failure acute</td>
<td>Unknown</td>
<td>Unknown</td>
<td>N/A</td>
</tr>
<tr>
<td>35 Female</td>
<td>Allopurinol</td>
<td>3 Weeks</td>
<td>HF, renal failure, rash</td>
<td>Recovered with sequelae</td>
<td>Gout &amp; HTN</td>
<td>Not related, Alt. etiology is dehydration</td>
</tr>
<tr>
<td>83 Male</td>
<td>digoxin, phenprocoumon</td>
<td>~7 months</td>
<td>Acute HF, toxicity to various agents</td>
<td>Fatal</td>
<td>CRF stage IV</td>
<td>Possibly related</td>
</tr>
<tr>
<td>45 Male</td>
<td></td>
<td>Unknown</td>
<td>HF</td>
<td>Unknown</td>
<td>Intolerant to colchicine and indocin</td>
<td>Not assessable</td>
</tr>
</tbody>
</table>

Propylthiouracil and Stevens-Johnson syndrome, Erythema multiforme and Epidermal necrolysis

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Summary
In October 2012 the WHO Global Individual Case Safety Report (ICSR) database, Vigibase™, had a total of 30 ICSRs concerning Stevens-Johnson syndrome, erythema multiforme or epidermal necrolysis in relation to propylthiouracil as the suspected drug. Propylthiouracil is an antithyroid drug indicated for treatment of hyperthyroidism, including Graves’ disease, in patients intolerant of methimazole. According to labelling information, propylthiouracil has an established association with dermatological events such as erythema nodosum, exfoliative dermatitis and rash. A previously documented literature case regarding Stevens-Johnson syndrome together with the findings of this assessment indicates that there is cause for further investigation.

Introduction
The drug-ADR combination of propylthiouracil and Stevens-Johnson syndrome was highlighted during testing of a new quantitative method for detecting potential signals at the UMC in 2012.1 A search of the WHO Global ICSR database, VigiBase™, showed additional reports of erythema multiforme and epidermal necrolysis which were also included in this assessment.
Hyperthyroidism is a common disorder characterised by thyroid gland overactivity resulting in excessive synthesis and secretion of thyroid hormones. The commonest cause of hyperthyroidism is the autoimmune condition Graves' disease. Excess thyroid hormone over-stimulates metabolism and exacerbates the effect of the sympathetic nervous system causing anxiety, increased perspiration, palpitations, tachycardia, tremors, digestive system hypermotility etc. Women are 2-10 times more likely to develop hyperthyroidism than men.2

Propylthiouracil (PTU) is a thiouracil-derived drug used to treat hyperthyroidism, including Graves' disease. It is also used to alleviate symptoms of hyperthyroidism in preparation for thyroidectomy or radioactive iodine therapy in patients who are intolerant of methimazole (carbimazole) and in the treatment of thyroid storm. PTU acts by inhibiting the formation of thyroid hormones. It does not interfere with the existing triiodothyronine within the thyroid or circulating in the blood, nor does it affect thyroid hormone activity. PTU is usually given orally. Initial doses range from 200 to 400 mg daily, although in severe cases initial doses of 600 to 1200 mg daily have been used. Once the patient's thyroid gland function normalises the dose is gradually reduced to a maintenance dose of 50 to 150 mg daily.6

Stevens-Johnson syndrome (SJS) is an immune-complex-mediated hypersensitivity reaction that involves the skin and mucous membranes. It is characterized by mucous ulceration, conjunctivitis and epidermal necrosis. SJS is a rare, serious and potentially fatal disorder that is often, but not always, due to drugs. Drugs commonly implicated in SJS include antibiotics, non-steroidal anti-inflammatory drugs, allopurinol and anti-convulsants.3,4

Erythema multiforme (EM) is a similar reaction to SJS and has at times been described as synonymous. In the 1990’s however, Bastuji and Roujeau suggested that EM should be restricted to patients with typical target lesions or raised edematous papules, with or without mucosal involvement, and that SJS should be used for a syndrome characterised by mucous membrane erosions and widespread small blisters that arise on erythematous or purpuric maculae that are different from classic targets.7

Epidermal necrolysis (EN) like SJS, is a severe epidermolytic disorder usually caused by drugs, although other causes such as infection can occur. EN and SJS are considered by many to be the same disease, differing only by their extent of skin detachment, where in the case of EN a larger proportion of the body surface area is affected. SJS and EN can be life-threatening. The average reported mortality rate of SJS is 1-5%, and of EN is 25-35%. Elderly patients and those with a large surface area of epidermal detachment are at a higher risk.6,9

Reports in VigiBase

Stevens-Johnson Syndrome

Report factors

In October 2012 there were 12 ICSRs in VigiBase relating to PTU and SJS. The reports came from diverse geographical locations: four of the 12 reports were from North America, two from Europe, one from Australia and five from Asia. Thailand had the single largest number of reports (four). The first reported case was in 1975 and the latest was from 2010.

Data on causality assessment, co-morbidities and concomitant medications was limited. Further data were available, in the form of the original reports from National Pharmacovigilance Centres (NCs), on ten of the reports.

Patient factors

All but one of the patients were female. Patient ages ranged from 32 to 73 years, with a median age of 48 years. Only two reports provided information on patient co-morbidities. One patient died, five patients recovered, one patient had not recovered at the time the report was made, and the status of the remaining five patients was either unknown or not recorded.

Drug factors

PTU was the only drug suspected of causing SJS in nine of the patients. The remaining three patients received other drugs in addition to PTU that were thought to be responsible for the adverse event, namely tetracycline, carbimazole or cefuroxime. Doses of 100 mg to 400 mg daily of PTU were used; however, dosage was not recorded in 5 of the cases. Time to onset of SJS ranged from 6 to 35 days from initiation of therapy with PTU. Three cases did not provide sufficient information to determine time to onset of the outcome.

Erythema multiforme

Report factors

There were 14 ICSRs submitted where PTU was the suspected drug in relation to EM between 1985 and 2011. Four of the reports were from Europe, five from the US and five from Thailand. The majority of the reports had limited information, but further data was collected from seven original reports provided by NCs.

Patient factors

The majority of the reports related to female patients, with only two of the reports concerning men. Ages ranged from 21 to 73 years with a median age of 44.5 years. Only four reports had information on any medical history. One report
Propylthiouracil – Stevens-Johnson syndrome, Erythema multiforme and Epidermal necrolysis

regarding a 73-year-old woman from the US also had SJS reported. One patient died and the report states that the reaction might have been contributory. Three patients had recovered at the time of report writing (one with sequelae), seven had not, and for the remainder there was no information regarding outcome.

**Drug factors**

PTU was the only suspected drug in 10 of the reports. In the remaining 4 reports the patients had been taking other drugs that may have contributed to the reaction, namely ibuprofen, paracetamol or cefuroxime. Information on doses of PTU was very limited, but when given they ranged from 50 mg to 1000 mg. Time to onset of reaction ranged from 1 day to 28 months (although one report indicated 11 years and one might assume a coding error) in the nine cases this information was given.

**Epidermal necrolysis**

**Report factors**

Four ICSRs from Thailand and one from the UK were assessed in relation to PTU and epidermal necrolysis. In three of these cases original reports provided additional information. The adverse events occurred between 1993 and 2007.

**Patient factors**

All five patients were female and their ages ranged from 30 and 69 years, with a median age of 43. In one report co-morbidities were reported (apart from Graves’ disease the patient also had Crohn’s disease, egg and milk allergy, penicillin allergy and short bowel syndrome). One patient died (PTU was the sole suspected drug), two recovered (one with sequelae) and the other two had not recovered at the time of report writing.

**Drug factors**

PTU was the sole suspected drug in four of the reports and in one report propranolol was also suspected. Three reports had at least one concomitant drug known to cause EN, but there was limited information on duration of use. In two cases the drug was withdrawn and the reaction abated. The dose was recorded in four reports and ranged from 150 to 300 mg daily. All five cases had information on time to onset, which ranged from 1 day to 35 days.

**Literature and Labelling**

A literature search found one case where SJS and acute interstitial nephritis developed in a 90-year-old woman after 5 weeks of PTU therapy for hyperthyroidism. The patient presented on admission with a generalized macular purpuric eruption accompanied by oral and genital mucosal erosions; acute renal failure was also present.

Despite PTU withdrawal and corticosteroid treatment, intense desquamation occurred and the patient died 15 days after hospital admission. Histopathological studies of a skin biopsy were compatible with SJS.

Apart from the above, no other cases were identified on searching the literature. The US Product Information (PI) lists erythema nodosum, exfoliative dermatitis, skin ulcers, skin pigmentation, urticaria and rash. Drugdex mentions the occurrence of maculopapular rashes in 5-6% of patients using PTU and methimazole with variable onset.

**Discussion**

SJS, EM and EN are all serious ADRs that may be caused by a wide range of drugs, but may also have infectious, malignancy-related or idiopathic causes. They can affect patients of all ages and races and, although SJS and EN are slightly more common in women, the large proportion of women affected in these cases can also be explained by hyperthyroidism being more prevalent in women. The indication for PTU, hyperthyroidism, is unlikely to explain the outcome of SJS, EM or EN however co-morbidities, such as infection, might.

The ICSRs identified have variable amounts of detail with limited information for assessment of causality. Where a causal link between drug and outcome was given, nine were thought to be ‘possible’ and nine ‘probable’. PTU was the sole suspected drug in 23 of the reports (77%). Most reports (22 of 30) provided information to establish that drug exposure preceded development of the ADR. This supports the hypothesis that these adverse reactions may be linked to PTU, however incomplete information regarding duration of therapy, timing of event, and concomitant drug use and co-morbidities makes this uncertain. Information on positive dechallenge was given in six cases; however, there were no recorded re-challenges.

**Conclusion**

There is a general lack of information in the case reports; however, there is sufficient information to suggest that this is a signal as it provides information on a possible causal relationship between propylthiouracil and Stevens-Johnson syndrome, erythema multiforme and epidermal necrolysis that was incompletely documented previously. Given the serious nature of the outcome, further evaluation is warranted.

**Addendum**

As of February 2013 there were 13 ICSRs for Stevens-Johnson syndrome, 14 ICSRs for erythema multiforme and 6 ICSRs for epidermal necrolysis.
References


Propylthiouracil – Stevens-Johnson syndrome, Erythema multiforme and Epidermal necrolysis

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CAVEAT DOCUMENT

Accompanying statement to data released from the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, VigiBase. It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not.

Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

Any publication, in whole or in part, of information obtained from UMC must include a statement:

(i) regarding the source of the information,
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.