WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of this 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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This Newsletter is also available on our Internet website:
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News & Issues

Previous issues had warned readers of specific safety concerns with products such as gatifloxacin and infliximab. In this issue we bring you information on new or reinforced regulatory recommendations for these and other products along with safety information on others - or do we mean 'toxicity' information? In the feature article Professor Marcus Reidenberg writes 'We should not say drug safety when we mean drug toxicity'. What are your views on this? Do we need to be a bit more candid and avoid 'newspeak'? E-mail us your comments for a full discussion and we will publish them in the next issue of the newsletter.

The WHO International Working Group for Drug Statistics Methodology got together 22-23 March 2006 in Oslo, Norway for its 19th meeting. The Working Group meets twice a year and advises the WHO Collaborating Centre for Drug Statistics Methodology on the development and maintenance of the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) for drugs. There is some concern that the work of the Centre and the usefulness of the ATC/DDD system as a tool for drug utilization research are not well known in some parts of the world. We wish to address this gap and plan to include articles and other appropriate information on the ATC/DDD in future issues of the newsletter. In the meantime, if you wish for any specific information on the subject, write to us and we will do our best to help.

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Safety of Medicines

Feature

Adalimumab, Etanercept, Infliximab

Linked to HBV reactivation

Canada. Manufacturers of the anti-TNFα (anti tumour necrosis factor alpha) products etanercept (Enbrel), adalimumab (Humira) and infliximab (Remicade) have issued a `Dear Health-care Professional' letter and a public communication, both endorsed by Health Canada, advising of a possible association between use of these drugs and reactivation of hepatitis B virus (HBV) infection (1,2). In the letter, Amgen Canada (for Enbrel), Abbott Laboratories (for Humira) and Schering Canada Inc. (for Remicade) advise that HBV reactivation has been reported very rarely in patients with chronic HBV infection receiving these drugs; less than one adverse event per 10 000 treated patients has been reported cumulatively, with one report originating from Canada (1). According to the companies, clinically active HBV infection occurred after a latency period of three weeks to 20 months after starting treatment. They point out that as the majority of patients were receiving other immuno-suppressives, a direct causal relationship between anti-TNFα therapy and HBV relapse may be difficult to establish. Where patient outcome information was provided, most patients improved after receiving antivirals or stopping anti-TNFα therapy, but fatal outcomes have also occurred. The companies advise that patients at risk for HBV infection should be evaluated for previous evidence of HBV infection before starting anti-TNFα therapy. Furthermore, patients identified as chronic HBV carriers should be monitored for signs and symptoms of active HBV infection during treatment and for several months after stopping treatment. The Canadian Product Monographs for these products (Enbrel, Humira and Remicade) are being revised accordingly. In the communication, the companies say that patients who experience any symptoms of HBV infection should contact their doctor immediately, and warn that symptoms may occur several months after initiating anti-TNFα therapy (2).

References:

1. 'Dear Health-care Professional' letter from Amgen Canada, Abbott Laboratories Limited and Schering Canada Inc., 13 January 2006 (http://www.hc-sc.gc.ca).
2. Public Communication from Amgen Canada Inc., Abbott Laboratories Ltd and Schering Canada Inc., 18 January 2006 (http://www.hc-sc.gc.ca).

Atomoxetine

New warnings recommended

UK. Conclusions from an Europe-wide review on the health risks and benefits of atomoxetine (Strattera) highlighted that, overall, the balance of benefits and risks of (Strattera) remains positive in the treatment of attention-deficit hyperactivity disorder, but it was also concluded that warnings regarding seizures and abnormal heart rhythm risks should be added to the product information for the drug, according to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) (1). It was further concluded that prescribers should be reminded that (Strattera) should only be started by, and under the supervision of, a specialist, and that the current warning in the product information regarding the risk of suicidal thoughts and behaviour, and liver disorders, reflects the available data accurately, says the MHRA (1). The Patient Information Leaflet is to be updated and new advice is being issued to doctors, states the agency.

In a `Dear Colleague letter' (2), Professor Gordon Duff, from the Commission on Human Medicines, highlights the following new prescriber advice:

- (Strattera) has been associated with QT-interval prolongation and should be used cautiously in patients with congenital, acquired or a family history of QT prolongation; this risk could be increased if (Strattera) is given concomitantly with drugs that inhibit cytochrome P450 2D6, or cause QT-prolongation or electrolyte disturbances.
- (Strattera) is associated with a risk of seizures and should be used cautiously in patients with a seizure history, and discontinuation should be considered in patients with developing seizures or increased seizure frequency.
  Due to the risks of suicidal thoughts and behaviour, and severe hepatic liver injury, prescribers are reminded that patients should be monitored for signs of suicidal thoughts or behaviour, or depression, and referred for treatment if needed, and that (Strattera) should be discontinued in patients with laboratory evidence of liver injury or jaundice, says Professor Duff.

References:

1. Press Release. UK Medicines and Healthcare Products Regulatory Agency, 17 February 2006 (http://www.mhra.gov.uk).
2. Duff G. Strattera (atomoxetine) - conclusions of risk: benefit review. UK MHRA Commission on Human Medicines, 16 February 2006 (http://www.mhra.gov.uk).

Bevacizumab

Label to include information on PLS

USA. In response to two reports of bevacizumab (Avastin)-related reversible posterior leukoencephalopathy syndrome (PLS) published in the New England Journal of Medicine, Dr Hal Barron from Genentech, USA, has advised that the bevacizumab (Avastin) package insert will be updated. Genentech has agreed that the patients in the two reports meet the clinical criteria for reversible PLS. The company is investigating one additional case and is currently reviewing the global safety database for cases that have reversible PLS-associated clinical signs and symptoms. Genentech advises that it is important for physicians to be aware of the symptoms and signs of reversible PLS and of its association with hypertension; hypertension is a known bevacizumab (Avastin)-associated adverse reaction, and has been included in the package insert since the drug was approved in 2004. Genentech plans to update the package insert with a description of reversible PLS and with a recommendation to discontinue bevacizumab in the event of reversible PLS diagnosis. Appropriate actions will be implemented outside of the US by Roche, Genentech's corporate partner.

Reference:

Barron H. Reversible posterior leukoencephalopathy syndrome and bevacizumab. Reply. New England Journal of Medicine, 2 March 2006, 354:982.

Bosentan

Label to indicate liver adverse effects

USA. Cases of hepatotoxicity have been reported to Actelion Pharmaceuticals and, as a result, the US labelling for bosentan (Tracleer) has been changed, according to a `Dear Health-care Professional' letter issued by the company; health professionals are also being reminded of the importance of continued monthly liver function testing in bosentan recipients. According to Actelion, in one of the reported cases, a patient started to experience gradual increases in baseline ALT levels after about one year of starting bosentan and, after another nine months of treatment, she had markedly elevated levels of aminotransferase and bilirubin; furthermore, after bosentan was stopped, her bilirubin levels continued to increase and her AST and ALT levels remained elevated. The company believes that this case emphasizes the need to continue monthly monitoring for the duration of therapy, and to adhere to the recommended dosage adjustment and monitoring guidelines described in the labelling for the product.

Reference:

'Dear Health-care Professional' letter from Atelion Pharmaceuticals US, Inc., 1 March 2006 (http://www.fda.gov).

Gatifloxacin

Reinforced warnings in Canada, labelling changes in US

Canada, USA. Health Canada has advised patients with diabetes mellitus (DM) against the use of gatifloxacin (Tequin), due to concerns about blood glucose disorders (1) while the United States Food and Drug Administration (US FDA) has advised labelling changes for gatifloxacin (Tequin) in the US following continued serious reports of hyper- and hypoglycaemia (2).

Health Canada's advice against gatifloxacin use in patients with DM is based on recommendations from Bristol-Myers Squibb. Health Canada is currently reviewing the revised product information for gatifloxacin (Tequin) and, in the meantime, has recommended alternative therapies for patients with DM. Doctors who prescribe gatifloxacin (Tequin) to patients without DM have been recommended by the manufacturer to take enhanced precautions, and undertake medical monitoring, particularly in patients with risk factors, including patients who are aged ≥ 75 years, have kidney disorders or receive diabetes drugs, says Health Canada. (See WHO Pharmaceuticals Newsletter No. 1, 2006 for previous warnings from Health Canada).

The labelling changes for gatifloxacin (Tequin) in the US include a stronger warning on hyper- and hypoglycaemia, a contraindication for use in diabetic patients, and data to identify other risk factors for high and low blood sugar levels, including concomitant glucose-altering medications, older age and renal impairment (2). The US FDA says that it will continue to monitor gatifloxacin's (Tequin's) safety to ensure that the drug's benefits outweigh the risks.

References:

1. Public Advisory. Health Canada, 16 February 2006 (http://www.hc-sc.gc.ca).
2. 'Dear Health-care Provider' letter from Bristol-Myers Squibb Company, 15 February 2006 (http://www.fda.gov).

Hydroxycarb-amide

Label to include information on cutaneous vasculitis

USA, Canada. Bristol-Myers Squibb Company has advised that the labels for hydroxycarbamide preparations (Hydrea and Droxia in the US (1); Hydrea in Canada (2)) have been updated to include information on cutaneous

vasculitic toxicities occurring in patients with myeloproliferative disorders. The Warnings and Adverse Reactions sections of the labels have been updated to say that there have been reports of cutaneous vasculitic toxicities, including gangrene and vasculitic ulcerations, associated with hydroxycarbamide therapy in patients with myeloproliferative disorders, and that the toxicities occurred most often in patients who had received, or were receiving, interferon therapy. Bristol-Myers Squibb recommends that hydroxycarbamide be discontinued, should cutaneous vasculitic ulcerations develop. The Precautions and Dosing and Administration sections have been revised to warn that the drugs should be handled with care to decrease the risk of exposure, and that gloves should be worn when handling the bottles. In addition, the Precautions section of one of the products (Hydrea) now advises that, as elderly patients may be more sensitive to hydroxycarbamide, and are more likely to have reduced renal function, they may require a lower dose regimen.

References:

1. Communication from Bristol-Myers Squibb, 20 January 2006 (http://www.fda.gov).
2. 'Dear Health Professional' letter from Bristol-Myers Squibb Canada, 1 March 2006 (http://www.hc-sc-gc.ca).

Ximelagatran

Withdrawn due to adverse liver effects

UK. AstraZeneca has decided to withdraw the anticoagulant melagatran / ximelagatran (Exanta™) from the market. This is based on new patient safety data of serious liver injury in a trial (EXTEND trial) examining the use of the product in extended venous thromboembolism (VTE) prophylaxis in orthopaedic surgery (OS) up to 35 days post-operatively. The ongoing clinical trials will be discontinued and patients switched to other treatments. AstraZeneca estimates that approximately 400 patients are currently being prescribed the drug for short-term prevention of VTE following OS. The company advises that it is important that patients do not stop melagatran / ximelagatran (Exanta™) treatment without consulting their doctor. Regulatory files in OS and other indications in the US, Europe and elsewhere will now be withdrawn. The new patient report indicates a potential risk of severe liver injury, with an observation of rapid onset of signs and symptoms in the weeks following the end of the 35 days treatment. AstraZeneca is advising that no new patients should be commenced on melagatran / ximelagatran (Exanta), and that doctors should consider switching current recipients to an alternative anticoagulation while taking the patient's circumstances into account and ensuring uninterrupted anticoagulation.

Reference:

AstraZeneca Press Release, 14 February 2006 (http://www.astrazeneca.com).

Aprotinin

Reports of serious cardiovascular, cerebrovascular and kidney effects

USA, Canada. The US FDA has issued a Public Health Advisory, warning doctors and patients that the results of two studies have linked aprotinin (Trasylol) injection with an increased risk of serious adverse effects such as kidney disorders, myocardial infarction (MI) and stroke in patients undergoing artery bypass graft surgery. According to the advisory, the agency is evaluating the results of these studies more closely, along with other scientific literature and reports to the US FDA Medwatch programme to determine whether labelling changes or any further actions are required. Meanwhile, the Agency advises healthcare providers to monitor patients carefully for toxicity, especially to their kidneys, heart or central nervous system (CNS), and report any adverse events promptly to Bayer, the drug manufacturer, or via Medwatch. Furthermore, the Agency advises that physicians should consider limiting use of aprotinin to situations where the clinical benefit of reduced blood loss is essential to the medical management of the patient and outweighs the potential risks. In Canada, Bayer HealthCare has written to

2. 'Dear Health-care Professional' letter from Bayer HealthCare, February 2006 (http://www.bayerhealth.ca).

Benzocaine

Mouth and throat use linked with methaemoglobinaemia

USA. The US FDA has issued a Public Health Advisory to highlight that the use of benzocaine sprays (including Cetacaine, Hurricaine and Topex) in the mouth and throat has occasionally been linked with methaemoglobinaemia, a potentially life-threatening condition. The agency also advises that the Veterans Health Administration has announced the decision to cease benzocaine spray use for the local numbing of mouth and throat mucous membranes for minor surgical procedures or tube insertion.
The US FDA warns that methaemoglobinaemia has occurred when benzocaine sprays were used for a longer duration or more frequently than recommended. The agency suggests the following points for consideration when using benzocaine sprays in the mouth or throat:

- Patients with breathing problems, or who smoke, are at greater risk for methaemoglobinaemia-related complications.
- The use of products with

be carefully monitored for methaemoglobinaemia.
- Blood analysis for methaemoglobinaemia should be done using a co-oximeter.
- A change to chocolate-brown blood colour may be a danger sign.
- Patients with suspected methaemoglobinaemia should be promptly treated.

The US FDA advises that it has received adverse event reports of symptoms probably indicating methaemoglobinaemia associated with the use of benzocaine sprays, but that these reports had been received over a period of many years and that this event is uncommon. The US FDA reports that it is reviewing available safety information for these products, but is not planning to remove them from the market at this time.

Reference:
Public Health Advisory. United States Food and Drug Administration, 10 February 2006 (http://www.fda.gov).

Ergot derivatives

Reports of fibrotic complications

Australia. Fibrotic complications, including pericarditis, and pleural or retroperitoneal fibrosis, are