WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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

No. 3, 2011

The WHO Pharmaceuticals Newsletter provides you with the latest safety reports, advice, warnings and other updates from regulatory authorities across the world.

In this edition of the WHO Pharmaceuticals Newsletter, you will also find a summary of discussions and recommendations from the Eighth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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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This Newsletter is also available on our Internet website:
http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring

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Printed by the WHO Document Production Services, Geneva, Switzerland

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Risk of methaemoglobinaemia

USA. The U.S. Food and Drug Administration (US FDA) notified health-care professionals and patients that the US FDA continues to receive reports of methaemoglobinaemia, a serious and potentially fatal adverse effect, associated with benzocaine products both as a spray, used during medical procedures to numb the mucous membranes of the mouth and throat, and benzocaine gels and liquids sold over-the-counter and used to relieve pain from a variety of conditions, such as teething, canker sores, and irritation of the mouth and gums. Methaemoglobinaemia is a rare, but serious condition in which the amount of oxygen carried through the blood stream is greatly reduced. In the most severe cases, methaemoglobinaemia can result in death.

The US FDA explained that methaemoglobinaemia has been reported with all strengths of benzocaine gels and liquids, and cases occurred mainly in children aged two years or younger who were treated with benzocaine gel for teething. The signs and symptoms usually appear within minutes to hours of applying benzocaine and may occur with the first application of benzocaine or after additional use. The development of methaemoglobinaemia after treatment with benzocaine sprays may not be related to the amount applied. In many cases, methaemoglobinaemia was reported following the administration of a single benzocaine spray.

The US FDA recommended that benzocaine products should not be used on children less than two years of age, except under the advice and supervision of a health-care professional. Adult consumers who use benzocaine gels or liquids to relieve pain in the mouth should follow the recommendations in the product label. Consumers should store benzocaine products out of reach of children.

(See WHO Pharmaceuticals Newsletter No.2, 2006 for report on mouth and throat use linked with methaemoglobinaemia in the USA and No.6, 2006 in Canada).

Reports in WHO Global ICSR database, Vigibase:

Benzocaine Topical products: Cutaneous, topical and transdermal

Number of reports: 74 (PT Methaemoglobinaemia)

Reference:
FDA Drug Safety Communication, US FDA, 7 April 2011 (www.fda.gov)

Bisphosphonates

Rare atypical fractures of the femur: a class effect of bisphosphonates

Europe. The European Medicines Agency (EMA) announced that the agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that rare atypical fractures of the femur are a class effect of bisphosphonates. Bisphosphonates include alendronic acid, clodronic acid, etidronic acid, ibandronic acid, neridronic acid, pamidronic acid, risedronic acid, tiludronic acid and zoledronic acid.

The CHMP confirmed that the benefits of bisphosphonates in the treatment and prevention of bone disorders continue to outweigh their risks, but that a warning of the risk of atypical femoral fractures should be added to the prescribing information for all bisphosphonate-containing medicines in the European Union. Such a warning had already been included in the product information for alendronate-containing medicines across Europe, following a review by the CHMP's Pharmacovigilance Working Party in 2008. It will now be extended to the whole bisphosphonate class.

The EMA advised prescribers of bisphosphonate-containing medicines to be aware that atypical fractures of the femur may occur rarely. If an atypical fracture is suspected in one leg, then the other leg should also be examined. Doctors who are prescribing these medicines for osteoporosis should regularly review the need for continued treatment, especially after five or more years of use. The marketing authorisation holders of bisphosphonate-containing medicines have been asked to closely monitor this issue.

(See WHO Pharmaceuticals Newsletters No.1, 2011 for safety measures against osteonecrosis and osteomyelitis of jaw in Japan and UK, and No.1, 2010, No.1, 2008, No.5, 2006 and No.6, 2004 for a review on the risk of osteonecrosis of the jaw in Europe, for alert on musculoskeletal pain in the USA, reports of osteonecrosis of the jaw in Australia, and reports of osteonecrosis of the jaw in the USA, respectively).

Reference:
Press release, EMA, 15 April 2011 (www.ema.europa.eu).

Buflomedil-containing medicines

Recommendation for suspension of oral buflomedil-containing medicines; review of injectable buflomedil continues

Europe. The European Medicines Agency (EMA) recommended that the supply of oral buflomedil-containing medicines be suspended in all European Union (EU) Member States where it is currently authorised. This is an interim recommendation pending the finalisation of the continuing review of the benefits and risks of buflomedil solution for injection. The Agency's Committee for Medicinal Products for Human Use (CHMP) will adopt an opinion at the end of the full review. Buflomedil, a vasoactive agent, is used to treat the symptoms of peripheral arterial occlusive disease (PAOD).

The EMA explained that the review of buflomedil was initiated following the decision of the French regulatory authority in February 2011 to suspend the marketing authorisation.

The CHMP considered all available data on the benefits and risks of oral buflomedil, including the benefit-risk assessment carried out by France, data from clinical studies, post-marketing surveillance and published literature, as well as from poison control centres in the EU. The Committee concluded that measures put in place by regulatory authorities had not been able to prevent serious side effects, especially related to overdose, from occurring. The CHMP also noted that the medicine had only been shown to have a limited benefit for patients, measured in terms of walking distance, and the studies assessed had a number of weaknesses. The Committee was therefore of the opinion that the benefits of buflomedil-containing medicines in the form of tablets or an oral solution do not outweigh their risks, and recommended that the supply of these medicines should be suspended throughout the EU.

The EMA advised that doctors should stop prescribing oral buflomedil and consider alternative treatment options, including managing underlying health problems which can increase the risk of PAOD, such as diabetes and high blood pressure.

(See WHO Pharmaceuticals Newsletter No.2, 2011 for the decision by Afssaps to suspend marketing authorizations of buflomedil containing products).

Reports in WHO Global ICSR database, Vigibase:

Buflomedil

Number of reports: 396 (SOC Cardiovascular Disorders, General, SOC Central & Peripheral Nervous System Disorders, SOC Heart Rate and Rhythm Disorders)

Most reported reactions (number of events):

Hypotension:	*35*
Dizziness:	*42*
Headache:	*35*
Tremor:	*39*
Vertigo:	*36*
Convulsions:	*56*
Tachycardia:	*31*

Reference:
Press release EMA, 20 May 2011 (www.ema.europa.eu).

Celecoxib

Marketing authorisation of celecoxib (Onsenal®) in familial adenomatous polyposis withdrawn

Europe. The EMA has finalised its review of the use of the COX-2 inhibitor celecoxib in the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP) and concluded that existing evidence of safety and efficacy does not support the use of celecoxib in FAP patients. This review follows Pfizer's voluntary withdrawal of the marketing authorisation of cerecoxib (Onsenal®) for FAP. Celecoxib-containing products are currently authorised in the European Union for the treatment of the symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. This review was initiated because of concerns that celecoxib may be used off-label in FAP indication following the withdrawal of Onsenal®.

The CHMP looked at the available data on the use of celecoxib in FAP patients and concluded that the benefit of celecoxib in FAP patients had not been sufficiently demonstrated and did not outweigh the increased risk of cardiovascular and gastrointestinal side effects, which would result from high dose and long-term treatment used in FAP patients.

Reports in WHO Global ICSR database, Vigibase:

Celecoxib

Number of reports: 4 (Indication: familial adenomatous polyposis)

Reported reactions (number of events):

Dyspepsia:	*1*
Gastric carcinoma:	*1*
Gastritis:	*1*
Rash:	*1*
Rash erythematous:	*1*

Reference:
Press release, EMA, 20 May 2011 (www.hc-sc.gc.ca).

Dolasetron mesylate

Withdrawal of 20 mg/mL intravenous injection due to potential risk of arrhythmias

Canada. Health Canada and Sanofi-Aventis Canada Inc. informed the withdrawal of dolasetron mesylate (ANZEMET®) intravenous injection as it is no longer indicated to prevent nausea and vomiting in adults undergoing chemotherapy.

New data have shown that intravenous administration of the injectable form of dolasetron mesylate is associated with QTc prolongation, to an extent which may potentially result in serious arrhythmias at the doses recommended for the prevention of nausea and vomiting. Therefore Sanofi-aventis Canada Inc. will be removing the injectable form from the Canadian market as of May 10, 2011.

The injectable form of dolasetron mesylate should no longer be used to prevent nausea and vomiting associated with chemotherapy. However, dolasetron mesylate tablets for oral use may still be used as the risk of developing an abnormal heart rhythm with the oral form of this drug is considered less than that seen with the injectable form.

Caution should be exercised with respect to the administration of dolasetron mesylate tablets in patients with renal impairment, elderly patients and in patients with conditions which increase the risk of arrhythmias, such as underlying heart conditions, existing heart rate or rhythm problems, concomitant use of drugs known to affect ECG, bradycardia, and electrolyte imbalance.

(See WHO Pharmaceuticals Newsletter No.1, 2011 for reports of abnormal heart rhythms in the USA.)

Dolasetron

Number of reports: 153 (SOC Cardiovascular Disorders, General, SOC Heart Rate and Rhythm Disorders, SOC Myo-, Endo-, Pericardial & Valve Disorders), including 98 reports of Dolasetron intravenous injection

Most reported reactions (number of events of all products and that of i.v. injection form in the blacket):

Hypotension:	*39 (33)*
Bradycardia:	*29 (21)*
Cardiac arrest:	*26 (21)*
AV block:	*10 (7)*
Tachycardia:	*20 (11)*
Myocardial infarction:	*8 (4)*

Reference:
Advisories, Warnings and Recalls, Health Canada, 26 April 2011 (www.hc-sc.gc.ca).

Ipilimumab

Risk Evaluation and Mitigation Strategy (REMS) - Severe immune-mediated adverse reactions

USA. The US FDA announced that Bristol-Myers Squibb informed health-care professionals about the risk evaluation and mitigation strategy (REMS), developed in collaboration with the US FDA, that is required to ensure that the benefits of ipilimumab (Yervoy®) outweigh the risks of severe and fatal immune-mediated adverse reactions. The REMS consists of a Communication Plan to inform health-care professionals of the serious risks of ipilimumab, to facilitate early identification of these risks, and an overview of recommended management of patients with moderate or more severe immune-mediated adverse reactions.

Ipilimumab was approved March 2011 with the Prescribing Information including a Boxed Warning stating that use of the product can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to

months after discontinuation of ipilimumab.

The US FDA advised health-care professionals to read the boxed warning and the accompanying full Prescribing Information for a complete description of these risks and their management and to discuss the risks that may be associated with therapy with patients and their caregivers. Clinicians were advised to permanently discontinue ipilimumab and initiate systemic high dose corticosteroid therapy for identified severe immune-mediated reactions and to assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy and evaluate clinical chemistries including liver function tests and thyroid function tests at baseline and before each dose.

Reference:
FDA Drug Safety Communication, US FDA, 6 April 2011 (www.fda.gov).

Prasugrel

Rare but serious hypersensitivity reactions

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has advised that health-care professionals should be aware of the risk of rare but serious hypersensitivity reactions including, very rarely, angioedema; some of which occurred in patients with a history of hypersensitivity to clopidogrel when prescribing prasugrel (Efient®). Prasugrel is a thienopyridine, belonging to the same class of medicines as clopidogrel, and acts as an inhibitor of platelet activation and aggregation. Co-administered with aspirin, prasugrel is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction) undergoing percutaneous coronary intervention.

As at April 2011, nine cases of hypersensitivity reactions including, very rarely, angioedema have been reported worldwide in association with use of Prasugrel in approximately 727 000 patients. Some cases have occurred in patients with a known history of hypersensitivity to clopidogrel, but others have no history of clopidogrel exposure. At present, the mechanism for these allergic reactions is unclear. The time to onset of symptoms ranged from immediately after treatment to up to 5–10 days later.

Health-care professionals are also advised to monitor for signs in all patients, including those with a previous known history of hypersensitivity reactions to thienopyridines and to inform patients of the potential risk of hypersensitivity reactions, including angioedema when prescribing prasugrel.

References:
Drug Safety Update, May 2011, Volume 4, Issue 10, A1, MHRA (www.mhra.gov.uk).

Rosiglitazone

Risk Evaluation and Mitigation Strategy (REMS) - Risk of cardiovascular events

USA. The US FDA notified health-care professionals and the public of new restrictions to the prescribing and use of rosiglitazone-containing medicines. These medicines to treat type II diabetes are sold under the names Avandia®, Avandamet® (contains rosiglitazone and metformin), and Avandaryl® (contains rosiglitazone and glimepiride). Health-care providers and patients must enroll in a special program in order to prescribe and receive these drugs. The US FDA has modified the REMS for Avandamet and Avandaryl because previously, the REMS consisted of only a Medication Guide. The REMS, which now includes a restricted access and distribution program, applies to all three rosiglitazone products.

(See WHO Pharmaceuticals Newsletter No.2, 2011 for suspension of marketing authorizations in New Zealand, No.6, 2010 for new restrictions due to the risk of cardiovascular events in Canada and No.5, 2010 for suspension of marketing authorizations in Europe, new restrictions in the USA and reports in WHO global ICSR database.)

Reference:
FDA Drug Safety Communication, US FDA, 18 May 2011 (www.fda.gov).

Stavudine

Use only when there are no appropriate alternatives, and for the shortest possible time

UK. The MHRA has advised that stavudine (Zerit®) should only be used when there are no appropriate alternatives, and for the shortest possible time, because of an increased risk of potentially severe adverse effects in patients receiving stavudine compared with alternative HIV treatments. Stavudine is a nucleoside reverse transcriptase inhibitor (NRTI) indicated in combination with other antiretroviral products for the treatment of HIV-1 infection in adults and children.

The MHRA reviewed worldwide safety data (including case reports, clinical studies, and published literature) with stavudine and found that cases of potentially fatal lactic acidosis have been reported, both within the first few months of stavudine treatment and also substantially later. An increased risk of lipoatrophy compared with other NRTIs has also been identified. The incidence and severity of lipoatrophy seems to be cumulative over time, and is often not completely reversible on stopping stavudine. Peripheral neuropathy also occurs frequently, reported in up to 20% of patients treated with

to use only in individuals for whom there are no other appropriate treatment alternatives, and only for the shortest period possible in these individuals.

Health-care professionals are also advised to switch all other patients, including those starting and those continuing stavudine, to appropriate alternative therapy as soon as possible and to frequently assess patients taking stavudine for evidence of mitochondrial toxicity, and discontinue treatment if appropriate, if toxicity occurs.

Reference:
Drug Safety Update, April 2011, Volume 4, Issue 9, A2, MHRA (www.mhra.gov.uk).

Tigecycline

Increased mortality in clinical trials - use only when other antibiotics are unsuitable

UK. The MHRA has advised that tigecycline (Tygacil®) should only be used when other antibiotics are unsuitable, because an analysis of pooled results from clinical trials of tigecycline versus comparator drugs in a range of infections has shown numerically higher mortality rates in patients receiving tigecycline. Tigecycline is a glycylcycline antibiotic approved for the

(33 of 2 206) patients receiving comparator drugs.

A larger analysis adding results from trials of tigecycline use in unapproved indications (diabetic foot infections, nosocomial pneumonia, and treatment of resistant pathogens) also showed numerically higher overall mortality rates in patients treated with tigecycline versus those treated with active comparators.

The MHRA explained that the cause of these findings is unknown. The possibility that tigecycline has a poorer efficacy and/or safety profile than the comparator drugs cannot be excluded. Patients who develop superinfections, particularly nosocomial pneumonia, seem to be at particular risk of having a poor outcome, including death.

Health-care professionals are advised that numerically higher mortality rates have been reported in patients treated with tigecycline in clinical studies in approved and unapproved indications, compared with patients treated with other antibacterial agents. Patients who develop superinfections, particularly nosocomial pneumonia, seem to be at particular risk of having a poor outcome. Patients should be closely monitored for the development of superinfections. If medically indicated, they should be switched to alternative antibiotic treatment which has