WHO PHARMACEUTICALS NEWSLETTER

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

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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/medicines

Further information on adverse reactions may be obtained from the WHO Collaborationg Centre for International Drug Monitoring
Box 1051
751 40 Uppsala
Tel: +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: sten.olsson@who-umc.org
Internet: http://www.who-umc.org

Contents

No. 3, 2010

In this issue of the Newsletter we bring you a feature on a workshop on pharmacovigilance for countries in the West African region that was recently held in Accra, Ghana. The purpose of the workshop was to help countries in the region develop pharmacovigilance programmes where they do not exist and for strengthening existing programmes. Read more about the workshop in the 'Feature article'.

In addition to the regular information about Regulatory Matters and Safety of Medicines, the Newsletter gives you an article about collaborative participation of inspectors from national Medicines Regulatory Authorities (MRAs) in inspections coordinated by the WHO Prequalification of Medicines (PQM) Programme. The purpose of this strategy is better involvement of inspectors from MRAs of developing countries, and other interested Member States, in inspections organized by the WHO-PQM and training of inspectors from these countries.

Printed by the WHO Document Production Services, Geneva, Switzerland

TABLE OF CONTENTS

Regulatory Matters

Safety of Medicines

Feature

Bufexamac

Revocation of marketing authorizations recommended because of high risk of contact allergies

Europe. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended that marketing authorisations for bufexamac-containing medicines be revoked throughout the European Union (EU). Bufexamac is a non-steroidal anti-inflammatory drug (NSAID) that is used as topical formulations to treat dermatological diseases (eczema and dermatitis) and proctological conditions (haemorrhoids and anal fissure).

The Committee conducted a review of the safety and effectiveness of bufexamac. The risk of developing a contact allergic reaction to bufexamac is high, and the risk is even higher in patients with pre-disposing conditions, such as certain forms of eczema, for which bufexamac is frequently prescribed. The allergic reactions can be serious enough to require hospitalization. The CHMP also noted that bufexamac causes reactions to get worse with repeated exposure. Furthermore, because the allergic reactions caused by bufexamac are very similar to the disease being treated, it can lead to delays in the diagnosis or treatment of the patient's condition. It is also likely that the difficulty to differentiate between a treatment failure and an allergic reaction has led to the cases of contact allergic reaction being underreported. In addition to this, the data to support the effectiveness of bufexamac are very limited.

Based on the available information, the CHMP concluded that the benefits of the bufexamac-containing medicines did not outweigh its risks and therefore recommended that they be taken off the market across the EU. Doctors are advised to stop prescribing medicines containing bufexamac; alternative anti-inflammatory treatments are widely available.

Reports in WHO Global ICSR database, Vigibase:

Bufexamac

Total number of reports: 648

Most reported reactions (number of events):

Bullous eruption	*24*
Pruritus	*73*
Dermatitis	*24*
Eczema	*215*
Dermatitis contact (contact allergy)	*216*
Rash	*32*
Rash erythematous	*97*
Rash maculo-papular	*27*
Urticaria	*32*

Reference:
Press release, Questions and answers, EMA, 22 April 2010 (www.ema.europa.eu).

Drospirenone-containing combined oral contraceptive

Update on the risk of venous thromboembolism

UK. The MHRA has provided an update on the risk of venous thromboembolism (VTE) in association with the combined oral contraceptive containing drospirenone (Yasmin). According to the Drug Safety Update, recently published studies suggest that the risk of VTE associated with Yasmin may be slightly higher than previously estimated, and somewhere between the risk associated with combined pills containing levonorgestrel (known as 'second generation') and those containing desogestrel or gestodene (known as 'third generation'). The Agency adds that because of some limitations in the methodology of these recent studies, further analyses are needed before any firm conclusions can be drawn. In the meantime, prescribers are advised to be aware of the new evidence when discussing the most suitable type of contraceptive for any woman who wants to start or switch contraception.

In addition, the MHRA states that all hormonal contraceptives are highly effective and safe, and have important health benefits, including those from avoiding unplanned pregnancy. When used appropriately, the benefits of all combined oral contraceptives far outweigh the risk of VTE. The risk of a venous thrombosis in women who use Yasmin is, as with other combined oral contraceptives, smaller than the risk of VTE associated with pregnancy. As with all oral contraceptives, the Patient Information Leaflet for Yasmin already contains extensive warnings about the risk of VTE. These warnings include the information that in healthy women taking any contraceptive pill, including Yasmin, about 20 to 40 cases of VTE are expected to occur in every 100 000 women each year, depending on the type of progestogen. The corresponding figure for women not using a contraceptive pill is about 5 to 10 cases per 100 000 each year. By comparison, about 60 cases of VTE are expected to occur in every 100 000 pregnancies.

***Reference**:*
Drug Safety Update, MHRA Volume 3, Issue 9, April 2010 (www.mhra.gov.uk).

Irinotecan

Association between UGT1A1 variant alleles and neutropenia

Singapore. Health Sciences Authority (HSA) informed health-care professionals of association between the enzyme uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) variant alleles and irinotecan-induced severe neutropenia. Irinotecan is used for the treatment of patients with advanced colorectal cancer. Common adverse events associated with irinotecan are diarrhoea, vomiting, nausea and neutropenia. Patients with the variants of the UGT1A1 gene, UGT1A1*28 or UGT1A1*6 are at greater risk of adverse reactions in association with irinotecan.

After reviewing the distribution of UGT1A1 variants in the three major ethnic groups of Singapore (Chinese, Malay and Indian) and the potential impact on the population, the HSA says that the package inserts of all irinotecan-containing products would be updated to include the following cautionary statements: the active metabolite of irinotecan, SN-38, is metabolized predominantly by UGT. It has been reported that patients who are homozygous (UGT1A1*6/*6 or UGT1A1*28/*28) or heterozygous (UGT1A1*6/*28) in allele UGT1A1*6, UGT1A1*28 may be at increased risk for serious adverse reactions (especially neutropenia) caused by reduced glucuronidation of SN-38. Added caution should be exercised when administering in such patients.

Reference:
Adverse Drug Reaction News, April 2010, Vol.12, No.1, HSA (www.hsa.gov.sg).

Naltrexone for extended-release injectable suspension

Medication Guide required for patients

USA. Alkermes and the US FDA notified health-care professionals and patients of an update to the prescribing information of naltrexone for extended-release injectable suspension (Vivitrol) to strengthen language regarding the risk of injection site reactions based on post-marketing reports that had been received prior to June 2009. Naltrexone for extended-release injectable suspension (Vivitrol) is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting. The US FDA required that a Medication Guide be provided to all patients. Health-care professionals are advised to counsel patients about the risks and benefits of naltrexone for extended-release injectable suspension (Vivitrol) before an initial prescription.

***Reference**:*
Safety Information, US FDA 4 May 2010 (www.fda.gov).

Parenteral amphotericin B

Risk of fatal overdose

UK. The MHRA warned that there is a potential risk of fatal overdose due to confusion between lipid-based and non-lipid-based formulations of parenteral amphotericin B.

Parenteral amphotericin B is available as lipid-based and non-lipid based formulations for the treatment of fungal infections. The appropriate dose and method of administration differ between those formulations of amphotericin B. The Agency emphasizes that they are not interchangeable.

The MHRA says that cases of fatal overdose have resulted when a non-lipid-based formulation of amphotericin B (Fungizone) has been mistakenly administered instead of a lipid-based formulation. Amphotericin B overdoses may result in potentially fatal cardiac or cardiorespiratory arrest. The total daily dose of Fungizone should not exceed 1.5 mg/kg. Health-care professionals are advised to verify the product name and dose before administration, especially if the dose prescribed exceeds 1.5 mg/kg.

***Reference**:*
Drug Safety Update, MHRA Volume 3, Issue 9, April 2010 (www.mhra.gov.uk).

Promethazine hydrochloride injection

Boxed warning added

Canada. Health Canada informed health-care professionals and the public of changes to the prescribing information, including the addition of a boxed warning, for promethazine hydrochloride injection. Injectable promethazine is an antihistamine drug that is used to treat a wide range of conditions, including certain types of allergic reactions, motion sickness, nausea, vomiting and as a sedative. The warning includes the following safety information:

- Promethazine is not to be used in children under the age of two years due to the potentially fatal risk of respiratory depression.
- Caution should be used when administering promethazine in children aged two and up: health care professionals are recommended to use the lowest effective dose, and the use of other drugs that may also slow breathing should be avoided.
- Promethazine is not to be injected subcutaneously due to the risk of serious tissue injury.
- The preferred route of administration for promethazine is deep intramuscular injection. Other routes of injection, particularly into arteries or veins, have been associated with serious tissue injury.
- Regardless of where on the body the drug is injected, promethazine has the potential to occasionally cause chemical irritation and in rare cases severe tissue damage at the site of injection, including cases of gangrene. Patients should immediately report any persistent or worsening pain or burning sensation they feel at the site of injection.

(See WHO Pharmaceuticals Newsletters No. 6, 2009 & No. 1, 2010 and No. 5, 2009 for warnings on the risk of severe tissue injury in New Zealand and the USA, respectively).

***Reference**:*
Advisories, Warnings and Recalls, Health Canada
26 April 2010
(www.hc-sc.gc.ca).

Reports in WHO Global ICSR database, Vigibase:

Promethazine

Injection site reactions (number of events):

	Subcutaneous injection	*Total*
Injection site mass	*1*	*18*
Injection site necrosis	*3*	*36*
Injection site pain	*1*	*123*
Injection site reaction	*5*	*301*
Injection site inflammation	*0*	*89*

Propylthiouracil

Boxed Warning on serious liver injury including liver failure

USA. The US FDA has added a Boxed Warning to the label for propylthiouracil, to include information about reports of severe liver injury and acute liver failure, some of which have been fatal, in adult and paediatric patients using propylthiouracil. Propylthiouracil is used for the treatment of hyperthyroidism. In addition, health-care professionals have been notified of the following information:

- When initiating hyperthyroid treatment, propylthiouracil should be reserved for patients who cannot tolerate methimazole or for patients for whom radioactive iodine therapy or surgery is not appropriate treatment.
- Propylthiouracil may be the treatment of choice when an anti-thyroid drug is needed during and just prior to the first trimester of pregnancy. Fetal abnormalities have been seen with methimazole use during the first trimester of pregnancy.
- Propylthiouracil is not recommended for use in paediatric patients, except in rare instances in which other alternative treatments are not appropriate.

As part of a Risk Evaluation and Mitigation Strategy, the US FDA is also requiring that a *Medication Guide* be given to every patient filling a prescription for propylthiouracil.

The US FDA conducted a search of post-marketing adverse event reports for propylthiouracil submitted to the Agency from 1969 to June 2009, and identified 34 cases of severe liver injury associated with this medicine. Of these, 23 cases were in adult patients and 11 were in paediatric patients. Of the 23 adult cases, 13 deaths and five liver transplants were reported. Among the 11 paediatric cases, two cases resulted in death and seven patients required a liver transplant; one patient died while on the transplant list. The Agency also evaluated post-marketing adverse event reports on methimazole from 1969 to June 2009, and identified five cases of severe liver injury reported with methimazole. All five cases were in adult patients and three resulted in death. Based on these findings and a review of the medical literature, the Agency concluded that use of propylthiouracil is associated with a higher risk for clinically serious or fatal liver injury compared to methimazole in both adult and paediatric patients.

The US FDA also reviewed post-marketing data on birth defects, and found that congenital malformations were reported approximately three times more often with prenatal exposure to methimazole compared to propylthiouracil (29 cases with methimazole and 9 cases with propylthiouracil). The Agency also says that there was a distinct and consistent pattern of congenital malformations associated with the use of methimazole, but not with propylthiouracil. Approximately

90% of the congenital malformations with methimazole were craniofacial malformations (e.g. scalp epidermal aplasia [aplasia cutis], facial dysmorphism and choanal atresia). In the majority of cases, there were multiple malformations which frequently included a combination of craniofacial defects and gastrointestinal atresias or aplasias. These specific birth defects were associated with the use of methimazole during the first trimester of pregnancy. They were not found when the medicine was given later in pregnancy. A consistent pattern of birth defects associated with the use of propylthiouracil was not found. The US FDA concluded that there is no convincing evidence of an association between propylthiouracil use and congenital malformations, even with use during the first trimester.

Reports in WHO Global ICSR database, Vigibase:

Propylthiouracil

Number of reports (SOC liver and biliary system disorders, and additional terms containing liver or hepatic): 269

Most reported reactions (number of events):

SGOT increased	*21*
SGPT increased	*28*
Hepatic failure	*31*
Hepatic function abnormal	*50*

Reference:
Safety Information, US FDA 21 April 2010 (www.fda.gov).

Rivastigmine transdermal patch

Serious adverse events related to medication errors / misuse

Canada. Novartis Pharmaceuticals Canada Inc. and Health Canada have informed health-care professionals and the public that serious adverse events including death have occurred following rivastigmine overdose due to medication errors and misuse of rivastigmine transdermal patch (Exelon patch). The Product Monograph is being revised to further emphasize the following safety information:

- Health-care providers should inform patients and caregivers on the proper use of rivastigmine patch prior to initiating therapy, and advise them to strictly follow instructions on patch usage;
- Only one transdermal patch should be applied per day to healthy skin on one of the recommended locations: the upper or lower back, or upper arm or chest;
- The previous day's patch must be removed before applying a new patch to a different skin location after 24 hours of use;

fatal outcomes, have been reported with rivastigmine transdermal patch (Exelon patch) worldwide. The most frequently reported causes of overdose are failure to remove the patch before applying a new patch and application of more than one patch at the same time. The typical symptoms reported in association with overdose include nausea, vomiting, diarrhoea, hypertension, hallucinations, salivation, sweating, respiratory depression and convulsions. Bradycardia and/or syncope may also occur.

Reference:
Advisories, Warnings and Recalls, Health Canada 5 May 2010 (www.hc-sc.gc.ca).

Saquinavir mesilate

Association with QT and PR interval prolongation

Canada. Health-care professionals were warned about prolongations of QT and PR intervals associated with saquinavir mesylate (Invirase), based on the findings of an electrocardiogram study with saquinavir mesylate and ritonavir in healthy volunteers. Saquinavir mesylate in combination with ritonavir and other antiretrovirals is indicated for the treatment of HIV-1 infected adult patients. The letter sent to health-care professionals states that dose-