WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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

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

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This Newsletter is also available on our Internet website:
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No 5 & 6, 2008

NEWS & ISSUES:

This is a consolidated volume that combines issues 5 & 6 of the newsletter. It covers new safety information and regulatory decisions in countries taken these last two months: UK medicines authority conclude that the paracetamol-asthma study needs further validation; rimonabant is suspended due to serious psychiatric events associated with its use; and Australia records new reports of tendon disorders with fluoroquinolones.

In the Feature article, the Signal Reviewer cautions that thrombotic events reported with drotrecogin may in fact represent a manifestation of the underlying disease process, rather than an adverse reaction.

With this last issue for the year, we wish you a healthy holiday season and thank you for your interest in our work.

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Safety of Medicines

Feature

Aspirin with either phytosterols or calcium

Will require formal drug approval process

USA. The United States Food & Drug Administration (US FDA) has sent Warning Letters to Bayer HealthCare concerning two unapproved, over-the-counter (OTC) aspirin products: Bayer Women's Low Dose Aspirin + Calcium (Bayer Women's) and Bayer Aspirin with Heart Advantage (Bayer Heart Advantage).

According to the Agency, "these products are new drugs and thus they must undergo the US FDA's drug approval process. The US FDA will take enforcement action against manufacturers found to be violating the law or attempting to circumvent the drug approval process".

The medicines, which contain aspirin with either phytosterols or calcium, are unapproved new drugs that require an approved new drug application in order to be legally marketed. In addition to being labelled for use as a pain reliever, both products are labelled for use in reducing the risks of heart disease. Bayer Women's is also labelled for use in "fighting" osteoporosis. Neither product has been approved by the US FDA for such uses. These drug uses require a health-care professional's diagnosis and supervision, and therefore these products cannot be labelled for use by consumers and sold OTC. Under its OTC drug monograph system, the US FDA allows some drugs to be marketed without first obtaining Agency approval. These drugs must comply with regulations that set requirements for the drugs' labelling and formulation, as well as the indications for which the drugs can be marketed.

Reference:
Media Release, US FDA, 28 October 2008 (www. fda.gov).

Fentanyl transdermal delivery system

Defect in device leads to suspension

Europe. The EMEA has recommended the suspension of the marketing authorization of a system (Ionsys) for the transdermal delivery of fentanyl, an opioid analgesic. This drug delivery system marketed by Janssen-Cilag International NV, has a defect that could lead to patients being overdosed. It has been authorized in the European Union (EU) since January 2006 and is indicated for the in-hospital management of acute, moderate to severe post-operative pain. The system is activated on demand by the patient in response to pain.

There have been no reports of serious adverse events associated with the malfunction of the device, in particular no reports related to self-activation of the system, or of overdose as a result. However, the Janssen-Cilag recalled all systems from the EU in September 2008 as a precautionary measure. As a consequence, Ionsys is unavailable and patients have been switched to alternative treatments.

Reference:
EMEA, 20 November 2008 (www.emea.europa.eu).

Herbal medicines

New packaging to combat misinformation

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has announced that any approved herbal product will now have a Product Licence number or Traditional Herbal Registration number on its packaging. Products labelled in this way meet assured standards of safety, quality, and patient information.

The Agency has been made aware of several cases where a product sold as "Goldenroot Complex" (promoted as a herbal alternative to Viagra for erectile dysfunction) has been incorrectly advertised on the internet as regulated and approved by the MHRA. There are no products that contain Golden Root (*Rhodiola rosea*) in the UK that are licensed or registered for erectile dysfunction.
In recent months the MHRA has been tackling what it calls poor and dangerous practices in the herbal medicines sector.

Reference:
Drug Safety Update, MHRA, 2(4):10, 2008 (www.mhra.gov.uk).

Natalizumab

Stronger PML warnings recommended

Europe. The EMEA has recommended updating the product information for natalizumab (Tysabri) to increase the awareness about risk of progressive multifocal leukoencephalopathy (PML) in patients with relapsing-remitting multiple sclerosis. The recommendation follows the reporting in July this year of two PML cases in patients receiving

natalizumab for multiple sclerosis.

The EMEA said that it still believes that the benefits of treatment with natalizumab in patients with relapsing-remitting multiple sclerosis outweighs its risks. However, it recommends strengthening the existing warning on PML risk. The Agency also requested an update to the 'Physician Information and Management Guidelines for Multiple Sclerosis Patients on Tysabri', to assist doctors in differentiating PML with multiple sclerosis relapse and managing suspected cases of PML.

In 2006, natalizumab was voluntarily withdrawn from the US market due to reports of PML and later reintroduced through a special restricted distribution and risk management program (see *WHO Pharmaceuticals Newsletter No.4, 2006*).

Reports in WHO Global ICSR database, VigiBase:

Natalizumab

Progressive multifocal leukoencephalopathy 9 reports (all reported from USA).

Reference:

EMEA, 25 September 2008 (www.emea.europa.eu).

OTC cough and cold medicines

New label warns against use in children under four

US. The US FDA welcomes new labelling for over-the-counter (OTC) cough and cold medicines that specifies that they should not be given to children under four years of age. This follows the voluntary decision by pharmaceutical companies to change the labelling because of the risk of dosing errors and accidental ingestions.
In addition, the Consumer Healthcare Products Association (CHPA), the trade association representing manufacturers in the USA, says that leading manufacturers of children's OTC cough and cold medicines are involved in the design and implementation of initiatives to encourage appropriate use of these medicines. The CHPA has also expanded its national education programme, which focuses on providing information for parents and caregivers.
The US FDA says that although this new labelling is not consistent with its current OTC monograph, it will not object to the provisions excluding the medicines from children under four years.

References:

1. Media Release, US FDA, 8 October 2008(www.fda.gov).
2. Statement from CHPA on the Voluntary Label Updates to Oral OTC Children's Cough and Cold Medicines, CHPA, 7 October 2008 (www.chpa-info.org).

Rimonabant

Suspended over psychiatric adverse events

Europe. The EMEA has recommended the suspension of the marketing authorization for obesity drug rimonabant (Acomplia), over serious psychiatric adverse events. The Agency said that new postmarketing data and ongoing clinical trials indicated that serious psychiatric disorders may be more common than observed in the clinical trials for the initial assessment of the medicine.

In addition, the Agency believes that the effectiveness of rimonabant in clinical practice is lesser than was expected on the basis of the clinical trials, because available data indicate that patients generally take rimonabant only for a short period. WHO published a Drug Alert to share the above information with other Member States.

Rimonabant has been authorized in the EU since June 2006 as an adjunct to diet and exercise for the treatment of obese patients or overweight patients with associated risk factors. Warnings about psychiatric side effects, in particular depression, have been included in the product information since rimonabant was first authorized. The product information has been continuously updated and strengthened to include further contraindications and upgraded warnings on these concerns to manage the risks associated with the use of rimonabant.
Reports of depression, psychiatric disorders, hypoglycaemic reactions, paranoia, rash, tremor and headache with five fatal cases were recently reported in the UK. (*See WHO Pharmaceuticals Newsletter No. 3, 2008.*)

Reports in WHO Global ICSR database, VigiBase:

Rimonabant

Psychiatric disorders: 168
Most reported reactions:
Aggressive reaction 15
Agitation 46
Amnesia 11
Apathy 22
Suicide attempt 51
Anxiety 39
Nervousness 15
Hallucination 15
Depression 105
Emotional lability 36
Insomnia 29
Paroniria 12
Sleep disorder 30

References:
1. Media Release, EMEA, 23 October 2008 (www.emea.europa.eu).
2. Alert No. 119, Information Exchange System, WHO, 25 October 2008 (www.who.int/medicines).

Topical papain-containing products

Not approved for marketing

USA. The US FDA said that no topical drug product containing papain has been approved and that companies marketing any topical drug products containing papain must stop by 24 November 2008; similarly, those involved in shipping these products must stop doing so by 21 January 2009.

The Agency acted after receiving reports of serious adverse events associated with use of papain-containing products, including hypersensitivity reactions leading to hypotension and tachycardia.

Reference:
Media Release, US FDA, 23 September 2008 (www.fda.gov).

Xanthoanthrafil-containing sexual dysfunction products

Little known chemical; may pose serious health risks

Canada. Health Canada has warned the public not to use Eros Fire, a product promoted to enhance sexual performance, as this product may pose serious health risks. The product was found to contain xanthoanthrafil (also known as benzamidenafil), which is not indicated on the label.
Xanthoanthrafil is a new chemical substance and is currently not authorized for use in Canada. Little information is available about this substance, including its safety when used in humans. It likely shares similar properties with known prescription drugs used to treat erectile dysfunction and may pose similar serious health risks, especially in patients with pre-existing medical conditions such as heart problems, those who may be taking heart medications, or those who may be at risk for strokes.

Reference:
Health Canada, 28 October 2008 (www.hc-sc.gc.ca).

Swissmedic campaigns against illegal imports

Switzerland's medicines regulator, Swissmedic, has launched an awareness campaign to combat a rise in illegal imports in the country. As part of the campaign, Swissmedic specialists trained pharmacists on how to recognize counterfeit medicines. In recent years, Switzerland has seen a rise in the number of seizures of about 40% a year and it is estimated that the number of seized drug shipments will be over 600 by the end of 2008. Swissmedic estimates that at least 50 000 drug shipments a year are imported illegally into the country.

Reference:
Swissmedic, 14 November 2008 (www.swissmedic.ch).

Medical information

Patients and consumers to take on larger roles

The EMEA has extended the scope of its procedure for consulting patients and consumer representatives on the quality of the information that the Agency publishes about authorized medicines.

Building on its positive experience of involving patients and consumer representatives in reviewing package leaflets at the time of renewal of the marketing authorization (five years after the initial authorization is granted) for a medicine, the scope of the procedure will now be extended to include a review of the package-leaflet information for new medicines too.

Patients and consumer representatives will continue to be involved in reviewing summaries of the European public assessment reports that the EMEA routinely publishes for authorized medicines.

Reference:
EMEA, 27 November 2008 (www.emea.europa.eu).

Advertising Regulations from MHRA

In a sign of the growing importance of the internet medicine sales, the Medicines and Healthcare products Regulatory Agency (MHRA) has published advice for consumer websites about the rules governing the advertising of medicines. The MHRA wants to help companies work within the parameters of the Medicines Advertising Regulations. The guidance covers all websites registered in the UK or aimed at UK consumers which provide services that may lead to the prescription and or the supply of a prescription only medicine. Examples include diagnosis and treatment services for erectile dysfunction or treatment for wrinkles.
The guidance is 'designed to give advice to advertisers who are looking to advertise their services and inform customers without promoting specific medicines and thereby coming within the scope of the Advertising Regulations."

Reference:
MHRA, 26 November 2008 (www.mhra.gov.uk).