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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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).

Antipsychotics

EMEA gives opinion on use in elderly people with dementia

Europe. The European Medicines Agency (EMEA) has concluded that antipsychotics are likely to be associated with increased mortality when used in elderly people with dementia. This Agency's Committee for Medicinal Products for Human Use gave its opinion following a request from UK health authorities.

The Committee reviewed available studies and said that although the studies suggest that the excess mortality observed with conventional antipsychotics may be greater than that observed for the newer atypical antipsychotics, this could not be confirmed due to the methodological limitations of these studies.

No conclusion could be drawn as to whether the risk differs between individual antipsychotics within the class of conventional antipsychotics. Therefore, until and unless better evidence becomes available, it cannot be excluded that the increased risk applies to all products of the class. At present, there is no clear mechanistic basis for the observed increased risk of mortality, and further data would be needed to explore this.

Reference:
Opinion of the Committee for Medicinal Products for Human Use, EMEA, 20 November 2008 (www.emea.europa.eu).

Codeine products

Babies at risk of morphine-related symptoms

Canada. Health Canada has advised the public, especially breastfeeding mothers, about the very rare but serious health risk to breastfed babies posed by codeine use in mothers. This follows a 'Dear Health-care Professional' letter issued by the pharmaceutical company Janssen Ortho highlighting the possibility of morphine-related adverse events in breastfed babies of nursing mothers, especially ultra-rapid codeine metabolisers, who receive paracetamol /codeine (Tylenol with Codeine NO 2, 3, 4 and Elixir). Once ingested, codeine is converted by the body into morphine. Signs and symptoms of morphine toxicity include constipation and over-sedation in mothers and drowsiness, sedation, breathing difficulties, difficulty breast feeding and decreased tone in babies. The company has advised health-care professionals to prescribe codeine-containing products for the shortest period of time and at the lowest effective dose.

To minimize morphine exposure in breastfed babies, Health Canada has advised nursing mothers to consult a doctor before starting any codeine-containing product, to use the lowest effective dose for the shortest period of time if treatment is necessary, to contact a doctor if the breastfed baby is sleepier than usual or has difficulty breast feeding, and to seek immediate medical attention if the baby has difficulty breathing or is limp.

Reference:
'Dear Health-care Professional' letter from Janssen-Ortho Incorporated, 6 October 2008 (www.hc-sc.gc.ca).

(Also see WHO Pharmaceuticals Newsletter No. 2, 2007 for related information from the Medical Products Agency in Sweden.)

Colchicine

Adverse events prompt advice on drug choice

Australia. The Therapeutic Goods Administration (TGA) has advised that, in most cases, colchicine should be used for short-term periods and only where non-steroidal anti-inflammatory drug (NSAID) therapy is contraindicated or has failed. So far the Agency has received 243 reports for colchicine, including 53 describing blood dyscrasias such as neutropenia (15), thrombocytopenia (10), pancytopenia (10), leukopenia (8) and agranulocytosis (4), and an additional report describing sepsis and extensive severe maculopapular rash.

Of these cases, 21 had not recovered at the time of reporting and nine described a fatal outcome associated with renal failure, multi-organ failure or overwhelming sepsis. Colchicine was the sole suspected drug in 16 of the reports of blood dyscrasias but other drugs were also suspected in all of the reports that described a fatal outcome.

Colchicine is used to treat acute gout, but it has a narrow therapeutic index with significant potential for toxicity and severe drug interactions.

In mid-2007, the Agency required updates to (the Colgout and Lengout) product information to limit colchicine use to only where NSAID treatment is contraindicated, has failed or has caused unacceptable side effects; and to limit the maximum cumulative dose to 6 mg over four days in otherwise healthy adults (with washout intervals of at least three days if additional treatment is needed).
New Zealand's Medicines and Medical Devices Safety Authority (Medsafe) also advises that colchicine be limited to second-line treatment for acute gout, when NSAIDs are contraindicated. (See *WHO Pharmaceuticals Newsletter* No. 1, 2006.)

Reports in WHO Global ICSR database, VigiBase:

Colchicine

1589 reports in total.
Most reported relevant reactions:
Anaemia 23 (1 fatal case)
Anaemia aplastic 10 (3)
Marrow depression 12 (6)
Pancytopenia 42 (6)
Sepsis 23 (7)
Renal failure acute 68 (4)
Renal failure chronic 12 (2)
(more than one reaction may be mentioned in each report).

Reference:
Australian Adverse Drug Reactions Bulletin 27:18, 2008 (www.tga.gov.au)

Drug-induced hyponatraemia

Antidepressants and diuretics top list for adverse event

Australia. Australia's Adverse Drug Reactions Advisory Committee (ADRAC) has released figures of drug-induced hyponatraemia reports it has received since May 2005. Of the 307 reports, 227 implicated a single drug as the suspected cause, mainly antidepressants (78) and diuretics (126).
In 33 reports involving an antidepressant, either a serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) was implicated. Severe hyponatraemia was documented in 101 reports. Hydrochlorothiazide, indapamide, carbamazepine, paroxetine, venlafaxine and sertraline were most commonly associated with severe hyponatraemia. In 80 of the 307 reports, more than one agent was implicated and most of these reports involved the combined use of a diuretic with an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an SSRI or an SNRI.

A total of 162 patients had recovered, 56 patients had not recovered and the outcome was unknown for 61 patients. Two hyponatraemia-related deaths were also reported.

Reference:
Australian Adverse Drug Reactions Bulletin, 27:19-20, 2008 (www.tga.gov.au).

Drugs affecting renin-angiotensin-aldosterone system

Reports of renal adverse events

Sweden. The Swedish Medical Products Agency (MPA) has received 465 reports of renal adverse reactions associated with drugs affecting the renin-angiotension-aldosterone system. Specifically, the Swedish Adverse Drug Reactions Database contains 314 reports of renal adverse reactions and hyperkalaemia associated with ACE inhibitors, 57 reports associated with angiotensin II receptor antagonists and 94 associated with spironolactone.

Reference*:*
Internet document, Swedish Medical Products Agency, 17 October 2008 (www.lakemedelsverket.se).

Efalizumab

Boxed Warning to highlight risk of serious infections

USA. Following the US FDA's postmarketing surveillance, the labelling for efalizumab (Raptiva) will be changed to include a Boxed Warning highlighting the risk of life-threatening infections, including progressive multifocal leukoencephalopathy (PML). The Agency also requires the submission of a Risk Evaluation and Mitigation Strategy (REMS), which will include a patient medication guide and a timetable for assessment of the REMS.

The Boxed Warning for the psoriasis therapy will highlight the risk of bacterial sepsis, invasive fungal disease, viral infection, PML and other opportunistic infections. The labelling will also be updated to include data from juvenile animal studies (equivalent to humans aged 1–14 years). The results indicated a potential risk for permanent immuno-suppression with

repeat administration of efalizumab in this age group. Currently, the drug is not approved for children aged less than 18 years.
The Agency advises that patients receiving efalizumab should be educated to recognize the signs and symptoms of infection, PML, anaemia, thrombocytopenia, worsening psoriasis or arthritis, or a nervous system disorder. If such signs appear, they should seek immediate medical attention.

The US FDA had, in the past, recommended a change to the labelling of the drug to include monitoring for thrombocytopenia (see *WHO Pharmaceuticals Newsletter No. 1, 2004*).

Reports in WHO Global ICSR database, VigiBase:

Efalizumab

(Not specifying whether life-threatening or not)
Clostridial infection 2
Infection 31
Infection bacterial 10
Infection bacterial 10
Infection fungal 4
Infection secondary 1
Infection staphylococcal 13
Infection susceptibility increased 1
Infection viral 4
Sepsis 14
Herpes simplex 13
Herpes zoster 28
Moniliasis 7
Pneumonia 24.

***Reference*:**
Media Release, US FDA, 16 October 2008 (www. fda.gov).

Epoetin-α

Trial data lead to safety review

USA. The US FDA is reviewing the safety of epoetin-α (Eprex) after receiving preliminary safety findings from a clinical trial in Germany that showed increased mortality in patients receiving epoetin-α for acute ischaemic stroke.

According to the US FDA, epoetin-α doses used in this trial were "considerably higher" than the doses recommended for the treatment of anaemia. The Agency says that it is aware of other trials using epoetin-α for potential neuroprotective effects, however, the findings in the German trial suggest the need to closely monitor epoetin-α recipients in other trials for adverse outcomes and to evaluate whether potential benefits for enrolled patients outweigh the risks.

The trial was a double-blind multicentre investigation involving 522 adult patients with ischaemic stroke who were randomized to receive IV epoetin-α 40 000 units/day for three days or placebo. Over 90 days after trial initiation, 16% of epoetin-α recipients died, compared with 9% of placebo recipients. More patients in the epoetin-α group died of intracranial haemorrhage than those in the placebo group (4% vs 1%).

Reports in WHO Global ICSR database, VigiBase:

Epoetin-alpha

Totally 3918 reports (death 188).

***Reference*:**
Media Release, US FDA, 26 September 2008 (www. fda.gov).

Erlotinib

Liver disorders reported

USA. Hepato-renal syndrome and liver failure have been reported in patients receiving erlotinib (Tarceva) in a pharmacokinetic study, according to OSI Pharmaceuticals, Inc. and Genentech, Inc.

In the study, patients had advanced solid tumours and moderate liver impairment (Child-Pugh criteria) that was a result of advanced cancer with liver involvement. Of the 15 patients, 10 died on treatment or within 30 days of the last erlotinib dose. One died of liver failure, one died of hepatorenal syndrome and eight died from progressive disease; six of the patients who died had baseline total bilirubin levels that suggested severe, rather than moderate, liver impairment.

The companies advise that Precaution sections on hepatotoxicity, renal failure and patients with hepatic impairment, have been updated to communicate this safety information, and moved to the Warnings section of the erlotinib prescribing information. The labelling now indicates that the drug should be "used with extra caution" in patients who have a total bilirubin level of >3×ULN (Upper Limit of Normal), and that patients with liver impairment should be monitored closely during erlotinib therapy. The labelling also advises that erlotinib dosing should be interrupted or discontinued if there are severe changes in liver function.

Reference:
'Dear Health-care Professional' letter from OSI Pharmaceutical Inc. and Genentech Inc. September 2008 (www.fda.gov).

Reports in WHO Global ICSR database, VigiBase:

Erlotinib

Totally 1961 reports:
Liver disorders 92
Urinary system disorders 171.

Fentanyl patches

MHRA issues overdose advice

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has advised health-care professionals to be cautious when prescribing and dispensing fentanyl patches as the Agency has received reports of adverse events and death following unintentional overdose.

Factors identified as possibly related to overdose include accidental exposure, dosing errors and exposure of the patch to a heat source. Some reports also involved inappropriate prescribing of fentanyl patches, like prescribing in unlicensed indications and in opioid-naive patients.

Fentanyl is a potent opioid analgesic and could lead to respiratory depression in opioid-naive patients and, hence, should only be prescribed to patients who have previously tolerated opioids.

(See *WHO Pharmaceuticals Newsletter No. 4, 2005* for reports of death involving misuse and abuse of Fentanyl transdermal patches (Duragesic) in Canada.)

Reference:
Drug Safety Update 2:2-3, MHRA, 2 September 2008.

Fluoroquinolone

New reports of tendon disorders

Australia. Australia's ADRAC has announced that it has received another 23 reports of tendon disorders associated with fluoroquinolone use since the last alert in 2006, bringing the total to 183.

These 23 reports described Achilles tendinitis (n = 13), tendon rupture (6), and tendon pain and swelling (4). Most reports involved patients (4 females; 15 males) aged over 56 years who received ciprofloxacin for 2−14 days. However, tendon disorders were also reported in younger patients and in those who received fluoroquinolones for more than one 1 month. In 19 cases, a fluoroquinolone (mainly ciprofloxacin) was the only drug suspected, but concomitant prednisone was also suspected in four cases.

According to ADRAC, patients should be advised to discontinue fluoroquinolone therapy at the first sign of tendon pain, swelling or inflammation. If tendinitis is suspected, they should avoid using the affected area and contact their doctor immediately with regard to switching to a non-fluoroquinolone drug. Recently, the US FDA had notified health-care professionals that a Boxed Warning and Medication Guide were to be added to the prescribing information to strengthen existing warnings about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones for systemic use.
(See *WHO Pharmaceuticals Newsletter No. 3, 2008*).

Reports in WHO Global ICSR database, VigiBase:

A total of 5196 reports of tendon disorders on 17 fluoroquinolones (Tendon disorder, Tendinitis, Tendon rupture and Tenosynovitis).

Reference:
Australian Adverse Drug Reactions Bulletin 27:18-19, 2008 (www.tga.gov.au)

Icodextrin

Warnings of dangerous drug-device interaction

USA. The US FDA has highlighted the interaction between icodextrin (Extraneal) and point-of-care glucose monitoring devices that do not use test strips specific for glucose. The Agency says it has continued to receive adverse event reports, including fatalities, related to the interaction.

The strips noted to be associated with the interaction are those that use the reagents glucose dehydrogenase pyrroloquinolinequinone or glucose-dye-oxidoreductase (such as FreeStyle and Accu-Chek).

As icodextrin is broken down into maltose *in vivo*, using test strips that are not specific for glucose can show falsely elevated blood glucose readings in patients receiving the drug. This in turn can lead to the inappropriate

administration of insulin, which can cause hypoglycaemia, coma and death. Falsely elevated readings can also mask true hypoglycaemia, which may then go untreated.

The US FDA urges health-care providers and patients to read the package insert for test strips, or consult the manufacturer of the device and test strip, in order to determine the glucose methodology for any system used for glucose monitoring of patients treated with icodextrin. The Agency also notes that the drug-device interaction, which was identified before icodextrin approval, is described in the labelling, and that the manufacturer has undertaken several safety measures.

Reference:
Drug Safety Newsletter 1(4):49, 2008 (www.fda.gov).

Lenalidomide

US FDA reports SJS/TEN cases

USA. The US FDA has announced that it has received 14 reports of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) related to lenalidomide (Revlimid). The adverse events cover the period from the drug's approval in December 2005 to 23 January 2008.

Typically, patients presented with a rash involving the arms and/or legs, or the whole body; bullous or vesicular eruptions were present in some cases. All 14 cases required medical intervention. Ten patients were receiving lenalidomide for multiple myeloma and three for myelodysplastic syndrome, both of which are approved indications; one patient was receiving the drug for an unapproved indication, myelofibrosis. Nine of the 14 patients improved or recovered, six after receiving systemic corticosteroids. Death was reported in three cases. Two patients died 12 and eight days post-admission, respectively. Although no cause of death was given for the first patient, there was a diagnosis of SJS at the time of death; in the second case, progression of multiple myeloma was the cause of death. The third case involved a patient diagnosed with TEN after completing a fourth cycle of lenalidomide (21-day cycle); the rash resolved five days post-admission but the patient died 30 days post-admission from progression of multiple myeloma.

Reports in WHO Global ICSR database, VigiBase:

Lenalidomide

Totally 3909 reports:
Stevens Johnson syndrome 2
Epidermal necrolysis 10
(all reported from USA).

Reference:
Drug Safety Newsletter 1(4):43, 2008 (www.fda.gov).

Levothyroxine

High number of adverse reaction reports with new formulation

New Zealand. Medsafe is investigating adverse reactions associated with a new formulation of levothyroxine sodium (Eltroxin by GlaxoSmithKline). This follows the unusually high number of adverse reaction reports received by the country's Centre for Adverse Reactions Monitoring (CARM).

CARM received 746 adverse reaction reports, which affected approximately 1% of all recipients. Typical adverse reactions included symptoms that occur after use for several weeks or months that can be attributable to thyroid dysfunction (e.g. headache, weight gain, lethargy, alopecia, insomnia, palpitations), symptoms reported shortly after patients change brands of levothyroxine (e.g. eye pain, conjunctivitis, headaches, visual disturbance) and allergic reactions.
Medsafe investigated adverse reactions patterns in other countries supplying the new formulation (e.g. Germany, The Netherlands, and Singapore). These countries have not experienced the same increase in adverse events seen in New Zealand. Medsafe also contacted all 83 countries participating in the WHO adverse reactions monitoring programme and found no increased in adverse reactions.

Reference:
Media Conference Information, Medsafe, 11 September 2008 (www.medsafe.govt.nz).

Mefloquine

Antimalarial associated with pneumonitis

US. The US FDA has received 13 reports of pneumonitis associated with mefloquine. The cases involved patients aged 4–68 years, nine of whom were female.

Five patients took mefloquine to treat malaria, six took the

drug for malaria prophylaxis while the indication for two patients was unknown. The median time from first receiving mefloquine to the onset of respiratory symptoms was two days.

Patients were hospitalized with respiratory diagnoses such as diffuse interstitial pneumopathy, pneumonitis and dyspnoea/lung infiltration. Seven patients exhibited bilateral lung infiltrates on X-ray, bronchoalveolar lavage fluid from two patients revealed increased eosinophils and neutrophils, and lung biopsy showed an autoimmune interstitial alveolitis in one patient. A four year-old girl died after developing pneumonitis. Ten patients recovered fully following the cessation of mefloquine. Five patients showed improvement with corticosteroid therapy. One patient underwent mefloquine rechallenge and developed severe pneumonitis. Antibiotic therapy was ineffective in many cases, suggesting an immune-mediated rather than an infectious cause.

Reports in WHO Global ICSR database, VigiBase:

Mefloquine

Pneumonitis 5 reports, Pneumonia 6 reports.

Reference:
Drug Safety Newsletter 1(4): 41-43, US FDA, 2008 (www.fda.gov).

MHRA receives further ADR reports with varenicline

UK. In July 2008, the UK MHRA issued advice with regard to the risk of suicidal thoughts and behaviour in association with varenicline. The Agency has announced that since that time, it has received further reports of suspected adverse events in association with the drug.

The MHRA says that, up to 29 Sept 2008, there have been 3541 reports of suspected adverse reactions received via the UK Yellow Card Scheme for varenicline. Alongside psychiatric reactions, sleep disorders and GI reactions were the most commonly reported adverse effects. The MHRA highlights that depression or depressed mood and suicidal ideation are the most frequently reported psychiatric disorders in association with varenicline. (See previous issues of the *WHO Pharmaceuticals Newsletter* for information related to mood changes with varenicline by the US FDA (*No,1, 2008*) and by Health Canada (*No. 3, 2008*)

***Reference**:*
Drug Safety Update 2(4): 2-3, November 2008 (www.mhra.gov.uk)

Paracetamol

Debate on paracetamol-asthma link

UK. The Commission on Human Medicines has said that there is no strong evidence that paracetamol use in infancy can cause asthma. This follows a review of a study published in *the Lancet* that explored the link between paracetamol use in infancy and the risk of asthma, rhinoconjunctivitis, and eczema in children aged six/seven years. The results suggested an association between asthma and paracetamol.

The Commission had a number of concerns over the study's conclusion. One concern was the possibility that use of paracetamol in infancy reflected treatment of a true underlying cause of asthma such as a viral illness, which necessitated the administration of an antipyretic. Another was the fact that paracetamol was the only available analgesic in many regions of the world so that the study comparison is between use of analgesics in infancy or not, rather than between the use of paracetamol or not. The commission also said that the study did not consider the effect of parental choice of analgesic, which may be based on the parents' own asthmatic status and their consequent avoidance of a non-steroidal anti-inflammatory drug.

The Commission on Human Medicines is a committee of the UK's MHRA and the review was carried out by its Pharmacovigilance Expert Advisory Group.

Reference:
Drug Safety Update 2(4):9, November 2008 (www.mhra.gov.uk).

Phenytoin

Caution against use in HLA-B*1502-positive patients

The US FDA is advising health-care professionals to consider avoiding phenytoin (marketed as Dilantin, Phenytek and generics) and fosphenytoin (marketed as Cerebyx and generics) as alternatives to

carbamazepine in patients positive for the HLA-B*1502 allele.
Recently, the US FDA communicated an increased risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) associated with carbamazepine in patients with this particular allele (see *WHO Pharmaceuticals Newsletter No. 1, 2008*). The allele occurs almost exclusively in patients with Asian ancestry. Now the Agency is investigating preliminary data regarding a possible increased risk of SJS/TEN from phenytoin in this demographic group. Any such association is also applicable to the drug fosphenytoin. As with carbamazepine, the available data suggest that the risk for serious skin reactions with phenytoin appears to be greatest in the first few months of therapy. At this point, there is insufficient data to recommend testing for the HLA-B*1502 allele in Asian patients prior to commencing phenytoin.

Reference:
FDA Alert, US FDA, 24 November 2008 (www.fda.gov).

Chromic-phosphate-P-32

Leukaemia risk in children prompts warning

US. Chromic-phosphate-P-32 suspension (Phosphocol P 32) use may increase the risk of leukaemia in certain situations, according to a 'Dear Healthcare Provider' letter issued by Mallinckrodt Inc.

The company reported that two children with haemophilia, aged 9 and 14 years developed acute lymphocytic leukaemia about 10 months after receiving intra-articular Phosphocol P 32 injections (total doses 0.6 and 1.5 mCi); this route of administration is not approved by the US FDA.

The Phosphocol P 32 package insert now contains a Warnings statement that details the above information, and an Adverse Reactions statement that reports that leukaemia in children has been identified during postmarketing experience. An additional Adverse Reactions statement highlights that radiation injury to the bladder, caecum and small bowel following Phosphocol P 32 administration into the peritoneal cavity has also been identified.

Reference:
'Dear Health-care Provider' letter from Covidien, Mallinckrodt Inc., 29 August 2008 (www.fda.gov).

Rituximab

Fatal PML case reported

US. Genentech and Biogen Idec have informed health-care professionals about a case of fatal PML in a patient with rheumatoid arthritis who received rituximab (Rituxan).

The patient was diagnosed with JC virus infection with resultant fatal PML approximately 18 months after receiving the last dose of rituximab in a long-term safety extension clinical study. Nine months before PML development, the patient had received chemotherapy and radiotherapy for oropharyngeal cancer. Before rituximab initiation, he had received methotrexate, steroids and a tumour necrosis factor inhibitor; methotrexate and steroids were also given during and after rituximab treatment.

Fatal PML following off-label use in systemic lupus erythematosus has been previously reported in some patients (see *WHO Pharmaceuticals Newsletter No. 1, 2007*). The package insert Warning section on PML has previously noted reports of PML in patients with hematologic malignancies and autoimmune diseases for which rituximab is not approved.

Reports in WHO Global ICSR database, VigiBase:

Rituximab

Progressive multifocal leukoencephalopathy 46 reports (AUT 1, DEU 3, ITA 6, NLD 1,USA 35).

Reference:
Media Release, US FDA, 11 September 2008 (www.fda.gov).

Venlafaxine

Updates on safety information regarding overdose

Canada. The manufacturers of all extended-release (XR) venlafaxine products have issued a 'Dear Healthcare Professional' letter and a Public Communication, both endorsed by Health Canada, to

advise of new safety information regarding venlafaxine XR overdose.

Venlafaxine is an antidepressant belonging to the class of medicines known as serotonin and noradrenaline reuptake inhibitors (SNRIs). Retrospective studies suggest that venlafaxine overdose may be associated with an increased risk of death, compared with other SSRIs. Also, reports of fatal acute overdoses have been received detailing venlafaxine doses as low as approximately 1 g. Therefore, health-care providers are advised to prescribe venlafaxine XR in the smallest quantity of drug in order to reduce the risk of overdose. Increased risk of behavioural and emotional changes has been observed with venlafaxine and, health-care providers, patients, caregivers and family should be vigilant for such changes. This safety information will be incorporated into the dosage section of all Canadian Product Monographs for venlafaxine XR products.
(See *WHO Pharmaceuticals Newsletter No. 4, 2006* for warnings, restrictions in use and measures to minimize risks of overdose in the UK.)

Reference:
Public Communication, Health Canada, 23 Oct 2008 (www.hc-sc.gc.ca).

Europe and USA to join forces on new therapies and drug safety

The EU and the USA have affirmed their commitment to regulatory cooperation in the areas of advanced-therapy medicines and nanotechnology-derived medicines, as well as on the exchange of pharmacovigilance information. This builds on achievements made previously in areas such as oncology, vaccines, orphan medicines and paediatric medicines (See *WHO Pharmaceuticals Newsletter No. 4, 2007*). Notable progress has already been made on implementing the Transatlantic Administrative Simplification initiative since its launch in November 2007, particularly in the areas of inspections, qualification of biomarkers, paediatrics and advanced-therapy medicines.

Reference:
EMEA, 7 October 2008 (www.emea.europa.eu).

FEATURE

Drotrecogin alfa – Thrombosis?

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Introduction
Drotrecogin alfa (activated) is a recombinant form of human activated protein C that has anti-thrombotic, anti-inflammatory and profibrinolytic activities. It is used mainly in intensive care medicine as a treatment for severe sepsis (sepsis associated with acute organ dysfunction). It is to be administered in multiple slow infusions, as a rule, in the dose of 24 µg/kg/hour for four days.[1]

Sepsis is a complex illness involving both infection and inflammation when the body's response, instead of being localised to the site of infection, is systemic, occurring throughout the body. This "overreaction" to the infection may result in organ damage and is more dangerous than the initial infection itself.[2]

Patients who die during episodes of sepsis are more likely to have coagulation defects, including lower levels of circulating antithrombin III and protein C. The latter is a vitamin K-dependent anticoagulant protease. In sepsis, protein C deficiency appears before the onset of observable indicators of septic shock. The administration of an exogenous analogue might be able to modulate the patient's response during sepsis.[1,3]

Among the known adverse reactions of drotrecogin alfa, the only serious one observed in clinical trials was bleeding events.[3,4]

Description of the new ADR reports
Thirteen non-duplicate reports of thrombotic events in septic patients treated with drotrecogin alfa were reported to VigiBase, the database of the WHO Collaborating Centre for International Drug Monitoring, in the period 2002 to 2007. There were 12 reports from the USA and one from the UK. The reports are summarised below:

1. A General Practitioner (GP) described a 66-year-old male who developed thrombosis after administration of drotrecogin alfa. No details were reported.

2. A 72-year-old male was treated with drotrecogin alfa for three days. On the second day of the treatment, pulmonary haemorrhage and thrombosis were observed. The type of the reporter was not disclosed.

3. A 34-year-old male was treated with drotrecogin alfa for six days in 2002. The concomitant medication comprised antibiotics as well as paracetamol and hydrocodone bitartrate. The report, sent by a GP, specified thrombosis, multiple organ failure and gangrene as adverse effects, the onset appeared eight days after the termination of treatment.

4. A 66-year-old male was treated with drotrecogin alfa for three days. The concomitant medication comprised paracetamol, codeine, atenolol, lorazepam, triamcinolone, propofol, dopamine, levofloxacin, morphine, famotidine, salbutamol, metoclopramide, diazepam, midazolam, thiamine, piperacillin-tazobactam combination and heparin. Their dosage and other treatment date were missing. The adverse reactions observed on the last day of the drotrecogin treatment were deep venous thrombophlebitis and thrombosis.

5. A pharmacist described a 45-year-old female who was administered drotrecogin alfa for four days. The concomitant medication comprised dopamine and norepinephrine. The adverse effects described were intestinal ischaemia, decreased prothrombin level and thrombosis.

6. A pharmacist described a 72-year-old male treated with drotrecogin alfa for four days. The concomitant medication comprised sodium bicarbonate, pantoprazole, norepinephrine, vasopressin, paracetamol, dopamine, amiodarone, vancomycin and piperacillin-tazobactam combination. The adverse reactions described were anaemia, discoloured faeces and thrombosis.

7. A 68-year-old male was administered drotrecogin alfa for five days. The concomitant medication comprised cefotaxime, clarithromycin, amiodarone for two days, hydrocortisone for eight days and lorazepam for two days. One day after the termination of the drotrecogin treatment the patient developed thrombosis.

8. A pharmacist described an 86-year-old male who was treated with drotrecogin alfa for two days. No concomitant medication was reported. The life threatening adverse reactions comprised hypotension, gastro-intestinal haemorrhage and thrombosis. Positive dechallenge was also observed.

9. A physician reported the case of a female treated with drotrecogin alfa who developed thrombosis. No details were disclosed.

10. A pharmacist described a 63-year-old female treated with drotrecogin alfa for three days. The concomitant medication comprised ranitidine, azithromycin, ceftriaxone, dopamine and norepinephrine. The adverse reactions reported were increased blood chloride and urea, hypernatraemia, hypokalaemia, hyperglycaemia, peripheral oedema, thrombocythaemia and thrombosis. The dechallenge seemed to be negative. No further information was provided.

11. A physician described a 70-year-old female treated with drotrecogin alfa for two days. The reported adverse effects were rash, jaundice, rectal disorders, bacterial infection, peritonitis and thrombosis.

12. An "other health professional" reported the case of a 29-year-old female treated with drotrecogin alfa for two days. The concomitant medication comprised norepinephrine and dobutamine. The adverse reactions were haemorrhage and thrombosis.

13. A physician reported a 30-year-old female who was administered drotrecogin alfa (no other information was available). The adverse reaction was thrombosis.

Evaluation of the reports

Six of the thirteen reports do not mention concomitant medication. Because of the clinical situation in which drotrecogin is used, it is almost certain that other medicines were coadministered. Thus, it is possible that some concomitantly used but undisclosed medicine might have contributed to the adverse effect.

Seven reports (3, 4, 5, 6, 7, 10 and 12) describe a range of concomitant medications. According to European Summaries of Product Characteristics (SPCs) of these medicines as well as an international database,[5] only propofol (administered in a single case) has a recognised, although very rare adverse effect of thrombophlebitis.[6]

Signal assessment

On the basis of the pharmacologic properties of drotrecogin alfa its administration is unlikely to lead to thrombosis. On the contrary, drotrecogin use is frequently associated with bleeding, related to its antithrombotic and profibrinolytic properties.[1] In a Phase III placebo controlled clinical trial, the incidence of thrombotic events was similar in the drotrecogin and placebo arms.[4] This was confirmed by an analysis of results from combined clinical trials: when compared with placebo, patients in the active treatment arms experienced numerically fewer thrombotic events, although the difference was not statistically significant.[7]

Thrombosis frequently occurs in patients with severe sepsis.[7] Disseminated intravascular coagulation (DIC) may develop in 30-50% of patients with severe sepsis and septic shock, especially when caused by Gram-negative bacteria. The mortality of sepsis is correlated with the development and severity of DIC.[8] Protein C serves as an important anticoagulant compensatory mechanism. The cytokines produced in sepsis incapacitate the protein C pathway. One of the critical mediators of DIC is the release of a transmembrane glycoprotein, Tissue Factor. This is released in response to exposure to cytokines or endotoxin and plays a major role in the development of DIC in septic conditions. For this reason, drotrecogin alfa is recommended in the therapy of DIC.[8,9] Additionally, a retrospective subgroup analysis of a clinical trial demonstrated a lower mortality rate among patients treated with drotrecogin alfa who met the criteria for DIC.[10]

Hence the conclusion is that, in these spontaneous reports, a manifestation of the underlying disease was reported as a possible adverse drug reaction. This hypothesis is further supported by the following:

- The clinical manifestations of DIC are extremely variable.[9] The pathological processes involved deplete the body of its platelets and coagulation factors, and so paradoxically may lead to both thrombus formation and haemorrhage;
- Septic patients are generally treated in intensive care units but the adverse effect reporters (if disclosed) were mostly GPs, pharmacists and "other health professionals", possibly not possessing first-hand information;
- On consulting the WHO database, it can be seen that other reports to drotrecogin alfa between 2002 and 2007 specified various haemorrhages (the well-known adverse effects of drotrecogin alfa), as well as 43 reports of DIC itself.

Conclusion

In thirteen reports of thrombosis associated with the use of drotrecogin alfa, retrieved from VigiBase, it appears likely that the reported thrombotic events represent a manifestation of the underlying disease process (severe sepsis), rather than an adverse reaction to any administered medicine. This analysis underlines the importance of considered assessment of all reported adverse drug reactions data.

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Orlistat: First centrally approved drug to win EU OTC switch

Europe. The EMEA has recommended that the anti-obesity drug orlistat (Alli) be granted over-the-counter status. This is the first time that the status of a centrally authorized medicine in the EU has been switched from prescription-only to non-prescription. The switch was part of an extension of the marketing authorization, when the drug's owner, Glaxo Group Limited, applied for a lower dose capsule (60 mg) with a new classification as a non-prescription medicine. Orlistat (60 mg) is used in conjunction with dieting to treat overweight patients who have a body mass index of 28 or above. According to the EMEA, when assessing a request to switch the marketing authorization status, it looks in particular at the safety profile of the medicine, at the quality and usefulness of the information provided to patients and at the likelihood that patients will use the medicine correctly.

Reference:

EMEA, 23 October 2008 (www.emea.europa.eu).