

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.

*Quality Assurance and Safety:
Medicines, PSM-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 Collaborating Centre for
International Drug Monitoring
Stora Torget 3,
753 20 Uppsala, Sweden
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>.*

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NEWS & ISSUES

The New Year started on a busy note with two global meetings in February: the fifth meeting of the Advisory Committee on Safety of Medicinal Products (ACSoMP), 25-27 February 2008, and a meeting organized by WHO (HIV Department and the Department of Medicines, Policy and Standards), together with the Forum for Collaborative HIV Research, on case definitions, toxicity grading and laboratory diagnosis of adverse events related to antiretroviral (ARV)-use. Recommendations or relevant information from these meetings will be included in subsequent issues of the newsletter.

In this issue, as always, we bring you the latest regulatory decisions and safety updates for medicinal products along with information from the seventeenth meeting of the Global Advisory Committee on Vaccine Safety held in Geneva, 12-13 December 2007.

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Aprotinin**Programme for special access**

Worldwide. Bayer temporarily suspended the marketing of aprotinin (Trasylol) worldwide until final data from the Canadian BART trial (Blood conservation using antifibrinolytics: a randomized trial in high-risk cardiac surgery patients) are available. Health Canada, the United States Food and Drug Administration (US FDA) and other regulatory authorities have been interested in working with the company to develop a programme for the use of aprotinin during the product's temporary marketing suspension. Under such a programme, physicians would be able to request aprotinin for treatment of certain surgical patients with an established medical need. Currently, aprotinin is approved for prophylactic use to reduce perioperative bleeding in patients undergoing cardiopulmonary bypass during coronary artery bypass graft surgery and who are at an increased risk for blood loss and blood transfusion requirement. Bayer, in consultation with Health Canada, has developed a process to make aprotinin available for high-risk patients where the physician believes use of aprotinin is warranted and falls within the current approved indication. The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK has announced that limited supply of aprotinin to individual patients will be permitted under 'Special' regulations. The MHRA plans to issue further guidance following completion of the Europe-wide

review of the product's benefits and risks.

Reference:

Reactions weekly 1181 p. 2; 8 December, 2007.

Atorvastatin**Advice relating to interactions and risk of hemorrhagic stroke**

UK. Health-care professionals are being informed that:

- atorvastatin levels may increase when administered with drugs that inhibit its metabolism (via cytochrome P450 CYP3A4 inhibition), with an increase in the risk of side-effects; alternative non-interacting therapies should be considered if possible, and if not, then the lowest possible dose of atorvastatin must be used or atorvastatin should be stopped temporarily, if the interacting drug is only being used for a short period; and when given with certain specific drugs, atorvastatin dose should not exceed 10mg (with cyclosporine), 20mg (with clarithromycin) and 40mg (with itraconazole);
- evidence from a recent study suggests that patients with recent haemorrhagic or lacunar stroke (without coronary heart disease) may have an increased risk of haemorrhage stroke when treated with 80mg atorvastatin daily.

The product label for atorvastatin (Lipitor) has been updated with the above information.

Reference:

'Dear Health-care professional' letter from Pfizer Limited,

3 December 2007
(www.mhra.gov.uk).

Bio-identical hormone replacement therapy**No medical evidence about safety, effectiveness**

USA. Seven pharmacy operations in the US that prepare so called 'bio-identical hormone replacement therapy' (BHRT) have received warnings from the US FDA that there are no medical evidence for the safety and effectiveness of these products. The US FDA is concerned that these false and unfounded claims will mislead women and health-care professionals. The pharmacy operations claim that these BHRT drugs, which contain hormones estrogen, progesterone and estriol, are superior to FDA-approved menopausal therapy drugs and that they prevent or treat serious diseases, including Alzheimer's disease, stroke, and various forms of cancer. The US FDA states that these compounded drugs (BHRT) are not approved and that the Agency's warning does not target pharmacists who practice traditional pharmacy compounding (which involves preparing a drug for an individual patient in response to a valid prescription).

Reference:

FDA News. US FDA, 9 January 2008
(www.fda.gov).

Carbamazepine

SJS/TEN more common in patients with HLA-B*1502

USA. Risk of carbamazepine-related Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) is significantly increased in patients positive for the HLA-B*1502 allele, according to the US FDA. This information has been added to the product label and in the revised boxed warning. The Agency says that the HLA-B*1502 allele occurs exclusively in patients with Asian ancestry including South Asian Indians. Screening for this allele should be performed for most patients of Asian ancestry before carbamazepine initiation and the drug should not be started in those who test positive for HLA-B*1502 allele unless the expected benefit clearly outweighs the increased risk. SJS and TEN risk may also be increased in patients who test positive for HLA-B*1502 and receive other antiepileptic drugs that have been associated with these disorders. Despite the risk being low in patients who test negative for this allele, SJS and TEN can still develop in this group, says the Agency. In more than 90% of carbamazepine recipients, SJS and TEN develop within the first few months of drug initiation; therefore, the risk is low in patients who test positive for HLA-B*1502 allele but have been receiving carbamazepine for more than a few months.

Reports in WHO Individual Case Safety Reports (ICSR) database:

Toxic epidermal necrolysis 45 (1997 – 2007)

Stevens Johnson syndrome 1180 (1969 - 2007).

Reference:

FDA Alert. US FDA, 12 December 2007 (www.fda.gov).

Edetate disodium

Fatalities due to medication errors or unapproved use

USA. The US FDA has issued a Public Health Advisory about important safety information concerning the use of edetate disodium (marketed as Endrate and generic products). The Agency advises that adults and children have died after receiving edetate disodium instead of edetate calcium disodium, or when edetate disodium has been administered for 'chelation therapies' and other uses not approved by the US FDA. The Agency notes that, because edetate disodium and edetate calcium disodium have very similar names and are commonly referred to as only 'EDTA', they are easily mistaken for each other. The US FDA is currently reviewing the benefit/risk profile of edetate disodium, and has issued important safety considerations to be observed in the interim. In particular, the US FDA recommends that hospitals evaluate their need to stock edetate disodium in their pharmacies. The Agency also advises that adults and children who receive treatment for lead poisoning should only be given the edetate calcium sodium form of 'EDTA'. Other recommendations include that the abbreviation 'EDTA' should not be used when

prescribing or dispensing an order for either of these drugs, and prescribers should consider including the indication for use on prescribing orders.

Reference:

Public Health Advisory. US FDA, 16 January 2008 (www.fda.gov).

Ethinylestradiol/norelgestromin birth control patch

Label to include risk of VTE

USA. The US FDA has approved additional changes to the label for the ethinylestradiol/norelgestromin transdermal contraceptive patch [Ortho Evra Contraceptive Transdermal (Skin) Patch] to include the results of a new epidemiological study that found that users of the birth control patch were at higher risk of developing serious blood clots, also known as venous thromboembolism (VTE) than women using oral contraceptive pills. The patch was studied in women aged 15-44. These recent findings support an earlier study that also said that women in this group were at higher risk for VTE (see WHO Pharmaceuticals Newsletter No. 5, 2006). The Patch releases ethinyl estradiol (an estrogen hormone) and norelgestromin (a progestin hormone) through the skin into the blood stream. Women using the product will be exposed to about 60 per cent more estrogen than if they were using typical birth control pills containing 35 micrograms of estrogen.

Increased levels of estrogen may increase the risk of side effects, including VTE.

Reference:

FDA News. US FDA, 18 January 2008 (www.fda.gov).

Lumiracoxib

Withdrawn

New Zealand. Lumiracoxib [Prexige] has now been withdrawn from the New Zealand market (see WHO Pharmaceuticals Newsletters Nos. 5 and 6, 2007 for withdrawals in other countries.) Medsafe, the medicines and medical devices safety authority in New Zealand has reviewed the latest safety data for lumiracoxib and found reports of liver damage associated with prolonged use of low-dose lumiracoxib. The Agency has advised current lumiracoxib users to stop taking the drug and to consult their doctor if they develop nausea, vomiting, stomach pains, loss of appetite, yellowing or pruritus of skin, or dark urine.

Reference:

Reactions weekly, 1184: 4, 12 January 2008.

Modafinil

Life-threatening skin and other serious hypersensitivity reactions

Canada. Shire Canada Inc. has issued a 'Dear Health-care Professional' letter to advise of new warnings regarding modafinil (Alertec) and severe skin reactions, serious hypersensitivity reactions and psychiatric adverse effects. The Product Monograph has been updated

to advise that modafinil can cause life-threatening skin and other serious hypersensitivity reactions. It states that severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have occurred in both adults and children receiving modafinil. Furthermore, angioedema, anaphylactic reaction and multi-organ hypersensitivity reactions, involving at least one fatal case, have been reported in association with the drug. The revisions also include warnings that modafinil is not approved for use in paediatric patients, and can cause psychiatric symptoms. Patients are advised to stop taking modafinil and seek medical attention immediately if they experience a skin rash, sores in the mouth, blisters and skin peeling, swelling of the face, eyes, lips, tongue or throat, difficulty swallowing or breathing, or a hoarse voice.

Reports in the WHO ICSR database:

1997 - 2007

<i>Allergic reaction</i>	<i>6</i>
<i>Anxiety</i>	<i>41</i>
<i>Nervousness</i>	<i>46</i>
<i>Depression</i>	<i>33</i>
<i>Insomnia</i>	<i>45</i>
<i>Somnolence</i>	<i>43</i>
<i>Dermatitis exfoliative</i>	<i>1</i>

Reference:

'Dear Health-care Professional Letter' from Shire Canada Inc. 18 December 2007 (www.hc-sc.gc.ca).

Nonoxynol 9 OTCs

To include warning about lack of protection against HIV and other STDs.

USA. The US FDA has directed manufacturers of over-the-counter (OTC) stand-alone vaginal contraceptive and spermicidal products containing the chemical ingredient nonoxynol 9 (N9) that these products should have a warning that N9 does not provide protection against infection from HIV or other sexually transmitted diseases (STDs). Stand-alone spermicides include gels, foams, films or inserts containing N9 and are used for contraception. The US FDA also requires that the labels for these products warn that N9 can irritate the vagina and rectum, which may increase the risk of contracting HIV/AIDS from an infected partner.

Reference:

FDA News. US FDA, 18 December 2007 (www.fda.gov).

Rosiglitazone

New warnings and contraindications in Europe

Europe. The European Medicines Agency (EMA) has recommended updating the product information for rosiglitazone-containing antidiabetic medicines with the following:

- a new warning that the use of rosiglitazone in patients with ischaemic heart disease and/or peripheral arterial disease is not recommended;
- a new contraindication stating that

rosiglitazone must not be used in patients with an acute coronary syndrome, such as angina or some types of myocardial infarction. When rosiglitazone was first introduced in the European Union in 2000, it was contraindicated in patients with a history of cardiac failure (see WHO Pharmaceuticals Newsletter No. 3, 2007). The current updates are the result of a re-assessment of the benefits and risks of rosiglitazone and pioglitazone (another antidiabetic medicine) in 2007. A boxed warning on the risks of heart failure was added for all thiazolidine class of antidiabetic drugs (which includes rosiglitazone) in the US in 2007 (see WHO Pharmaceuticals Newsletter No. 4, 2007).

Reference:

Press Release. EMEA, 24 January 2008 (www.emea.europa.eu).

Sargramostim

Liquid formulation withdrawn due to increasing adverse reaction reports

USA. Bayer Healthcare Pharmaceuticals is withdrawing the liquid formulation of sargramostim (liquid Leukine), a recombinant human granulocyte-macrophage colony-stimulating factor (rhu GM-CSF) used to help prevent infection in certain types of cancer therapy. The manufacturer notes that there has been an increase in the spontaneous reports of adverse reactions associated with the product (liquid

Leukine) ever since the liquid formulation was changed to include edetate disodium (EDTA). Health-care professionals are requested to immediately stop using the liquid sargramostim (liquid leukine) and to return any unused vials. Bayer is assuring health professionals that it will establish a special access program for the currently marketed lyophilized sargarmostim (lyophilized Leukine, 250mcg) which does not contain EDTA. Bayer will reformulate liquid sargramostim (liquid Leukine), to eliminate EDTA from the formulation.

Reference:

'Dear Health-care Professional' letter from Bayer HealthCare Pharmaceuticals, 23 January 2008 (www.fda.gov).

ACE inhibitors and angiotensin II receptor antagonists

Not for use in pregnancy

UK. The MHRA advises that angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists that are licensed for various indications including hypertension, should not be used at any stage of pregnancy. In addition, use in women who are planning pregnancy should be avoided unless absolutely necessary, in which case the potential risks and benefits should be discussed. The Agency has based this advice on US cohort study results that noted an increased risk of congenital anomalies with ACE inhibitors and on the fact that there are some case reports of congenital anomaly after exposure to angiotensin II receptor antagonists.

Reference:
Drug Safety Update
Vol. 1(5): 9, December 2007
(www.mhra.gov.uk).

Amlodipine

Reports of photosensitivity

The Netherlands. As on 31 May 2007, there were three reports of amlodipine (Norvasc) associated photosensitivity in Lareb, the national pharmacovigilance centre in Netherlands. In these cases, the time to reaction onset ranged from hours to two weeks. Patient outcome was reported in one case, with the woman recovering after amlodipine withdrawal.

Photosensitivity is not listed in the Dutch Summary of Product Characteristics for amlodipine.

Reports in the WHO ICSR database:
87 reports of photosensitivity associated with amlodipine use.

Reference:
Reactions weekly 1186 p. 3; 26 January, 2008.

Articaine-containing local anaesthetics

Reports of sensory disturbances

Finland. The Finnish National Agency for Medicines has received 84 reports of adverse reactions to dental local anaesthetics up to the end of October 2007. Of these, 52 involved products containing articaine and epinephrine (adrenaline) and listed 82 different reactions. Sensory disturbances were the most commonly reported adverse reaction (n = 12) followed by nausea or vomiting (11), urticaria or other rash (9), anaphylaxis (8) and palpitations (8). The sensory disturbances comprised numbness or paraesthesia involving the face, lips or tongue. These symptoms were not reported in association with other dental local anaesthetics.

Reference:
TABU: Drug Information from the National Agency for Medicines, Finland, 6: 58-59, 2007.

Bisphosphonates

Reports of musculoskeletal pain

USA. The US FDA has advised health-care professionals not to overlook the possibility of severe and sometimes incapacitating musculoskeletal pain in patients receiving bisphosphonates. The association between bisphosphonates and severe musculoskeletal pain, if overlooked, can delay diagnosis and prolong pain and/or impairment, necessitating analgesic use. The severe musculoskeletal pain may develop within days, months or years after bisphosphonate initiation. According to the US FDA, this severe musculoskeletal pain is different than the acute phase response characterized by chills, fever, bone pain, muscle pain and arthralgias that sometimes accompanies initial bisphosphonate exposure. The Agency advises that bisphosphonates could be discontinued if severe pain symptoms occur; prescribers should consider the risks and benefits of bisphosphonate use and patients should immediately contact their doctor if they develop severe musculoskeletal pain during bisphosphonate treatment.

Reports in WHO ICSR database (from 1988-2006):
25 reports of similar reactions from Canada and USA.

Reference:
FDA Alert. US FDA,
7 January 2008
(www.fda.gov).

Cetirizine, levocetirizine

Linked to arthralgia

The Netherlands. The Pharmacovigilance Centre, Lareb has received seven reports of arthralgia associated with the use of cetirizine (Zyrtec) or levocetirizine [Xyzal] up to 1 March 2007. Four reports involved cetirizine and three involved levocetirizine. Arthralgia is not listed in the Dutch Summary of Product Characteristics for either agent.

Reports in the WHO ICSR database: 54 reports of arthralgia associated with cetirizine and five reports associated with levocetirizine.

Reference:

Reactions Weekly 1186 p. 3; 26 January, 2008.

Clonidine

Reports of weight gain

The Netherlands. The Pharmacovigilance Centre Lareb has received six reports of weight gain associated with clonidine use up to 1 June 2007; four of these involved children. The time to reaction onset ranged from one month to one year. Outcomes were detailed for two patients; both lost weight after a reduction in the clonidine dosage. Weight gain is not listed in the Dutch Summary of Product Characteristics for either brandname or generic clonidine.

Reports in the WHO ICSR database: 28 reports of

clonidine-associated weight gain.

Reference:

Reactions Weekly 1186 p. 4; 26 January, 2008.

Desmopressin

Reminder to stay alert to symptoms of hyponatraemia

UK. Desmopressin is a synthetic analogue of vasopressin and is approved for various indications including treatment of primary nocturnal enuresis (PNE), nocturia associated with multiple sclerosis when other treatment has failed etc. It is available in nasal, oral (tablet or melt) and injection formulations. The PNE indication was recently removed from all desmopressin nasal spray products because of an increased risk of hyponatraemia compared with the oral formulation (see WHO Pharmaceuticals Newsletter No. 3, 2007). However, health-care professionals are warned to remain vigilant for signs and symptoms of hyponatraemia associated with the use of all desmopressin formulations, particularly the melt formulation. In mild cases, the symptoms may include anorexia, headache, nausea or vomiting; in more severe cases, the symptoms may include muscle cramps and weakness, confusion, convulsions, or coma.

Reference:

Drug Safety Update Vol. 1(6): 6, January 2008 (www.mhra.gov.uk).

Dosulepin

Measures to reduce risk of fatal overdose

UK. Dosulepin is a tricyclic antidepressant medicine and has a small margin of safety between the therapeutic dose and potentially fatal doses. The UK MHRA advises that use of dosulepin in new patients should be avoided. Where necessary, only specialist-care prescribers should start treatment in dosulepin-naïve patients and they should limit the amount issued per prescription. Every year up to 200 people in England and Wales commit suicide or fatally overdose with dosulepin. Since November 2007, pack sizes have been limited and the packaging made safer to limit the potential for fatal overdose with products that contain dosulepin.

Reference:

Drug Safety Update, Vol. 1 (5): 7, December 2007 (www.mhra.gov.uk).

Ethinylestradiol/ norelgestromin transdermal patch

MI and thromboembolic adverse reactions

Canada. Transdermal ethinylestradiol/norelgestromin (Evra) is a hormonal contraceptive system containing 6mg of norelgestromin and 0.6mg of ethinyl estradiol per patch. Since the product was first introduced in the Canadian market in 2004, Health Canada has received 16 cases of thromboembolism and one of myocardial infarction (MI) suspected of being

associated with the product. Two of the 17 cases had a fatal outcome. Hormonal contraception is one of the known risk factors for venous thromboembolism (VTE). Other risk factors include prolonged immobility, major surgery, family history of VTE, increasing age, smoking and obesity (see page 2 for latest update in the USA).

Reference:

Canadian Adverse Drug Reaction Newsletter, Vol. 18(1):3, January 2008.

Fentanyl transdermal patches

Reminder about safe use

USA. The US FDA has issued a second safety warning concerning fentanyl transdermal patches, prompted by continuing reports of death and life-threatening adverse events after either inappropriate prescribing or incorrect use by patients. The Public Health Advisory, similar to that first issued in July 2005 (see WHO Pharmaceuticals Newsletter No. 3, 2005) emphasizes that fentanyl patches are only for patients who are opioid-tolerant and have chronic pain that is not well controlled by other analgesics. The transdermal opioid should not be used to manage sudden, occasional or mild pain, or short-term postoperative pain. Also, both prescribers and patients using fentanyl patches should be aware of the signs of fentanyl overdose. The Agency is also asking Johnson & Johnson, (manufacturer of the Duragesic fentanyl patch), and all manufacturers of

generic fentanyl transdermal patches to update their product information and to develop a medication guide for patients.

*Reports in the WHO ICSR database (1991 - 2007):
Death - 1367 (by transdermal or topical use).*

Reference:

Public Health Advisory. US FDA, 21 December 2007 (www.fda.gov).

Fluconazole

Fixed drug eruption

The Netherlands. Lareb has received five reports of fixed drug eruption associated with fluconazole capsules between 1996 and 2002. Time to reaction onset ranged from within hours to two years.

*Reports in the WHO ICSR database:
17 reports of fixed drug eruption associated with fluconazole use.*

Reference:

Reactions weekly 1186 p. 4; 26 January, 2008.

Gadolinium-containing contrast agents

Risk of nephrogenic systemic fibrosis

Australia. A strong association has been recognized between the development of nephrogenic systemic fibrosis (NSF) in those with serious renal impairment and the use of gadolinium containing contrast agents used to enhance the quality of magnetic resonance imaging

(MRI) (see WHO Pharmaceuticals Newsletter No. 2, 2007). The Therapeutic Goods Administration in Australia (TGA) has received one report of NSF in association with a gadolinium containing contrast agent. The patient had pre-existing renal impairment. NSF usually presents as reddened or darkened patches, papules, or plaques, accompanied by swelling and thickening of the skin on extremities. The disorder may affect organs (liver, lungs, muscle and heart) leading to fatal outcome. Australian Guidelines on the use of gadolinium-containing contrast agents are being developed. Before referring patients for contrast MRI, doctors are advised to ensure that the procedure is warranted, to screen patients for renal dysfunction, and to make sure that the patient is not pregnant since the fetus is considered at high risk for NSF.

Reference:

Australian Adverse Drug Reactions Bulletin, Vol. 27(1): 2, February 2008 (www.tga.gov.au).

Gardasil

Safety update

Europe. Gardasil is a vaccine approved in the European Union (EU) for the prevention of cervical cancer and other diseases caused by human papillomavirus (HPV) types 6, 11, 16 and 18. The EMEA has received reports of sudden, unexpected deaths of two young women in EU who had previously received

Gardasil. In both cases the cause of death could not be identified and a causal relationship could not be established between the deaths and the administration of Gardasil. At present the Agency is of the opinion that the benefits of the vaccine continue to outweigh the risk but they will closely monitor the safety of Gardasil for additional information that might impact the benefit-risk profile of the product.

Reference:

Press Release. EMEA, 24 January 2008 (www.emea.europa.eu).

Glucosamine

Interaction with warfarin

Australia. The TGA in Australia has received 12 reports suggesting an interaction between warfarin and glucosamine. Most of the cases described changes in the international normalised ratio (INR) after patients previously stable on warfarin started taking glucosamine. The INR fell slightly in two of the cases but in 10 others the INR value increased. Potentiating effect of glucosamine on warfarin activity is also reported in the WHO Individual Case Safety Reports (ICSR) Database, the Vigibase. The mechanism of this interaction is unknown. ADRAC recommends that patients taking warfarin should have their INR assessed within a few days and no later than two weeks after commencing or changing the dose of a complementary medicine.

Reference:

Australian Adverse Drug Reactions Bulletin, Vol. 27(1): 3, February 2008 (www.tga.gov.au).

Imiquimod

Severe adverse reaction reported

The Netherlands. Up to 6 March 2007, the Netherlands Pharmacovigilance Centre Lareb received eight reports, involving 23 adverse drug reactions, related to imiquimod use. Of these, four reports involved severe skin reactions with super infections, reactivated viral infections, secondary infection, open wounds and haemorrhage. The other reported adverse drug reactions included syncope, pruritus, flu, headache, flu-like symptoms, malaise, leucocytosis and lymphadenitis with fever.

Reference:

Reactions weekly 1186 p. 4; 26 January, 2008.

Intravenous immune globulin

Myocardial infarction, cerebrovascular and thrombotic reactions

Canada. Over the last 10 years, Health Canada has received reports of cerebrovascular and cardiovascular (CV) adverse reactions (ARs) suspected to be associated with the use of intravenous immune globulin (IVIG). Between October 1997 and July 2007, the Agency received ten reports of stroke (reported as stroke, cerebral infarction, mini stroke or

cerebrovascular accident), four reports of myocardial infarction, six reports of thrombosis (reported as thrombosis, deep venous thrombosis or thrombophlebitis), two reports of pulmonary embolus, and one report of transient ischaemic attack suspected of being associated with IVIG use. Overall, 21 patients aged 28–88 years were involved; age was not reported for one of the patient and two patients developed more than one AR. The suspected products included Gammagard S/D, Gamimune N and Gamunex/IGIVnex; specific IVIG brand was not stated in three reports. Time to reaction onset varied according to the event. Nine of the ten strokes developed within a day after IVIG administration, whereas one stroke developed after three days. Three of the four myocardial infarctions developed during IVIG infusion, whereas the fourth developed after nine days. Transient ischaemic attack developed within a day, pulmonary embolism developed within 11 days and thrombosis developed within two weeks of IVIG administration. Stroke was fatal in one patient and resulted in persistent sequelae in four patients.

Reports in WHO ICSR database:

Gamimune and Gamimune-N (Reports 1988 - 2006)
25 reports of similar reactions from Canada and USA.
Gamunex (Reports 2005 - 2006)

6 reports of similar reactions from Canada, Germany and USA.

Gammagard (Reports 1992 - 2007)

81 reports of similar reactions from Canada and USA.

Reference:

Canadian Adverse Drug Reaction Newsletter, Vol. 18(1): 1, January 2008.

Methylthioninium chloride (methylene blue)

CNS toxicity with serotonergic drugs

UK. Methylthioninium chloride (methylene blue) is approved for the management of methaemoglobinaemia and is given either intravenously or by mouth. It is also used as a visualizing agent in surgical procedures although this is not an approved indication. The MHRA has received two reports of Central Nervous System (CNS) toxicity when intravenous methylthioninium was used as a visualizing agent for parathyroid or thyroid surgery. The MHRA notes that there are 27 other reports of CNS toxicity in literature when this product was used as a visualizing agent; in all but one case the patients were also receiving serotonergic drugs (such as selective serotonin reuptake inhibitor or SSRIs, bupropion, buspirone etc). CNS toxicity became apparent within a few hours of parathyroid or thyroid surgery, when the patients were recovering from anaesthesia. Health-care professionals are advised to:

- carefully assess the need for iv methylthioninium for visualization in surgical procedures;
- avoid methylthioninium in patients who have been treated recently with serotonergic drugs;
- to use the minimum possible dose of iv methylthioninium if it cannot be avoided, and to observe patients closely for CNS effects up to four hours after administration.

Reference:

Drug Safety Update Vol. 1(6) : 5, January 2008 (www.mhra.gov.uk).

Pregabalin

Reports of hypersensitivity reactions

Australia. Pregabalin is an anticonvulsant medicine used to relieve neuropathic pain. Hypersensitivity reactions to pregabalin comprise 13% of pregabalin-associated adverse event reports in the ADRAC database, according to the Agency. A range of symptoms were reported among a total of 22 patients, including 14 females and eight males. The reactions reported in the cases include anaphylaxis, and seven reports of allergic skin rash. The remaining reports included angioedema of the tongue, mouth, eyelids, lips, face or upper airway, with severe and widespread angioedema leading to difficulty in breathing. Of the 22 cases, 14 involved pregabalin as the only suspected drug; six women developed symptoms within hours of the first dose of pregabalin. A total of four

patients received emergency treatment, which involved adrenaline and/or parenteral steroids, and oral or IM antihistamines. Three patients exhibited skin reactions, which were confirmed by a positive dechallenge and pregabalin rechallenge. Information regarding histories of atopy or other allergies was deemed insufficient to draw conclusions about the predictive value of such histories among these patients.

Reports in the WHO ICSR database (2003 – 2007)

<i>Allergic reaction</i>	14
<i>Allergy</i>	1
<i>Anaphylactic reaction</i>	5
<i>Oedema peripheral</i>	129
<i>Drug hypersensitivity syndrome</i>	2
<i>Rash</i>	68
<i>Urticaria</i>	19
<i>Face oedema</i>	33

Reference: *Australian Adverse Drug Reactions Bulletin Vol. 26(6): 23 December 2007.*

Strontium ranelate
Risk of severe allergic reactions

UK. The MHRA advises that there is a risk of severe allergic reactions, including drug rash and eosinophilia systemic symptoms (DRESS) with strontium ranelate used in the treatment of osteoporosis. The reaction could also affect liver, kidneys and lung. Symptoms usually resolve when treatment is discontinued and with corticosteroid therapy. But recovery is often slow and there is a risk of symptoms returning during recovery.

Patients who develop a rash should stop taking strontium and should consult their physician immediately. Health-care professionals are advised not to re-start strontium once treatment has been stopped.

Reference:

Drug Safety Update
Vol. 1(5): 15 December 2007
(www.mhra.gov.uk).

Terbinafine

Reminder to use oral form only after adequate trial of topical therapy

Australia. Oral terbinafine (Lamisil) is approved for the treatment of fungal infections of the nails and skin (ringworm) that are not responsive to topical therapy. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) advises that a total of 722 adverse event reports were recorded in Australia up to January 2008 in connection with terbinafine (all dose forms), 70 describe hepatic reactions, and 61 implicated oral terbinafine as the sole suspected drug. Half of the reports documented onset of hepatic reaction within the first month and 80% within seven weeks. ADRAC is concerned that physicians might opt for oral form of therapy without any trial of topical therapy. ADRAC reminds prescribers that oral terbinafine can be associated with rare but serious and life threatening toxicities and that doctors prescribing oral terbinafine should first ensure that there is a clear indication for its use.

Reference:

Australian Adverse Drug Reactions Bulletin,
Vol. 27(1): 3, February 2008
(www.tga.gov.au).

Varenicline

Users cautioned to report behaviour and mood changes

USA. The US FDA has issued an alert to highlight important revisions to the prescribing information for varenicline (Chantix; Pfizer), a prescription smoking cessation therapy. The US FDA warns that post marketing experience reports record serious neuropsychiatric symptoms that have occurred in patients taking varenicline (Chantix). These symptoms include changes in behaviour, agitation, depressed mood, suicidal ideation, and attempted and completed suicide. In most cases the neuropsychiatric symptoms developed during varenicline (Chantix) treatment, but in others, symptoms developed after withdrawal of therapy. In addition to highlighting the above information on adverse effects, the Agency is in the process of developing a medication guide for patients.

Reference:

FDA Alert. US FDA,
1 February 2008
(www.fda.gov).

Seventeenth meeting of the Global Advisory Committee on Vaccine Safety Geneva, 12–13 December 2007

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body established in 1999 to respond, independently from WHO, promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance, held its seventeenth meeting in Geneva, Switzerland, on 12-13 December 2007. Issues discussed were: Guillain-Barré Syndrome and vaccination; the safety of immunization for immunocompromised individuals; yellow fever vaccine safety; hepatitis B vaccination and rheumatoid arthritis; the safety of the live 14-14-2 Japanese encephalitis vaccine; the safety of meningococcal B vaccines; and rotavirus vaccines and Kawasaki disease.

Information on some of the topics discussed follows:

Hepatitis B vaccination and rheumatoid arthritis

The Committee considered the potential association between hepatitis B vaccination and rheumatoid arthritis. Prior to previous discussions on this topic held in June 2006, the Committee had commissioned a comprehensive literature review. At this meeting, the Committee reviewed more recent information, particularly on genetic issues.

The Committee concluded, based on review of the limited data available, that there was no convincing evidence to support an association between hepatitis B vaccination and rheumatoid arthritis. The topic will be considered further if new findings become available.

Safety of meningococcal B vaccines

The Committee was presented with safety data relating to use of outer membrane vesicle-based meningococcal B vaccines in Cuba, France, New Zealand and Norway.

The Committee noted that several new meningococcal vaccines were being developed, at least one of which is closely related to the vaccine used in New Zealand. While affirming the importance of putting in place carefully-considered safety studies of these new vaccines, the Committee was reassured by the absence of evidence of an excess of serious adverse events following vaccination with existing meningococcal B vaccines.

Guillain-Barré Syndrome (GBS) and vaccination

GBS has occasionally been observed in temporal association with vaccination. This association has been considered as causal in GBS cases following administration of the vaccine against Swine influenza and vaccines against rabies which have been derived from rabbit brains and other nervous tissues. Cases of GBS have also been reported in temporal association with other vaccines, including seasonal influenza, tetanus, meningococcal conjugate and diphtheria-tetanus-pertussis vaccines. Thus far a causal relationship has not been established, other than for Swine influenza vaccine and the aforementioned rabies vaccines.

GACVS recommended large-scale studies of the incidence of GBS before and after immunization. All cases would need to be carefully ascertained and documented. Improved understanding of the pathogenesis of all forms of GBS will help in the determination of possible associations between GBS and immunization. Such studies would be particularly helpful for the investigation of such neurological adverse events following immunization with pandemic or pre-pandemic influenza vaccines.

The report of the meeting was published in the WHO Weekly Epidemiological Record on 25 January and has been posted on the GACVS web site at http://www.who.int/vaccine_safety/en/