No. 3, 2008

NEWS & ISSUES

This issue has been delayed considerably on account of some of our support staff leaving the unit, and due to teething difficulties with an all new global resource management system in WHO. But things are slowly getting back on track and we apologize for the inconvenience to our readers. Some of the information in this issue may be a bit old but we thought it would be useful to record them nevertheless, as a way of archiving the information for your future reference. Thank you for your continuing interest.
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Conventional antipsychotics
Boxed warnings on fatalities in elderly patients

USA. The United States Food and Drug Administration (US FDA) is requiring manufacturers of conventional antipsychotics to add Boxed Warnings about the increased risk of death in elderly patients treated for dementia-related psychosis. The FDA based this requirement on recent studies together with earlier evidence for atypical antipsychotics, that both atypical and conventional antipsychotics have an increased risk of death in elderly patients with dementia-related psychosis.

Manufacturers of antipsychotics are being asked to update labelling so that all drugs have the same warnings.

The FDA advises health-care professionals that:
- antipsychotics are not approved for treatment of dementia-related psychosis
- physicians who prescribe antipsychotics to elderly patients with dementia-related psychosis should discuss the increased mortality risk with their patients, patients’ families and caregivers.

Reference:

Becaplermin
Boxed warning added about increased cancer risk

USA. The US FDA has added a boxed warning to the label of 0.01% becaplermin gel (Regranex) regarding the increased risk of cancer mortality in patients who have used three or more tubes of the product. Becaplermin is mainly used to heal wounds in patients with diabetes. This action follows the Agency's review of safety data from a retrospective study showing a five-fold increased risk of cancer mortality in patients exposed to three or more tubes of becaplermin (see WHO Pharmaceuticals Newsletter No. 2, 2008). The US FDA cautions health-care professionals to carefully weigh the risks and benefits of treating patients with becaplermin.

Reports in WHO ICSR database:
Total 58 reports, 2004 – 2008 all from USA:
Melanoma malignant 1
Adenocarcinoma NOS 1
Pulmonary carcinoma 1
Skin hypertrophy 55

Reference:

Epoetins
Warning for use in cancer patients

Europe. European Medicines Agency (EMEA) has recommended updating the product information for epoetin-containing medicines with a new warning for their use in cancer patients stating that blood transfusion should be the preferred method of correcting anaemia in patients suffering cancer.

Epoetin-containing medicines are indicated in patients with chronic renal failure and for the treatment of anaemia in symptomatic patients with non-myeloid tumours receiving chemotherapy. New data from studies that show an increased risk of tumour progression, venous thromboembolism and shorter overall survival in cancer patients who received epoetins compared to patients who did not receive them.

Reference:

Etanercept
Label to indicate risk of infections in children

USA. The US FDA’s Dermatologic and Ophthalmic Drugs Advisory Committee is recommending that labelling for Amgen's etanercept (Enbrel) include warnings that use of the agent in paediatric patients may lead to moderate to severe infections and can result in death.

The committee recommended the following labelling changes:
- Under the ‘Adverse Reactions in Patients with Juvenile Idiopathic Arthritis’ section, the wording should be changed to reflect that use of etanercept therapy in the paediatric population may lead to moderate to severe infections and can result in serious outcomes, including death and hospitalisation.
- In the same section, the list of serious adverse events reported in the postmarketing period should be updated to include macrophage activation syndrome, malignancies, diabetes mellitus and systemic lupus erythematosus.

Reference:
Etoricoxib
Risk of cardiovascular side effects

Europe. The European Medicines Agency (EMEA) recommended that the product information for etoricoxib-containing products should be updated concerning the risk of cardiovascular side effects.

Etoricoxib is a non-steroidal anti-inflammatory drug (NSAID). It is currently indicated to relieve the symptoms of osteoarthritis, rheumatoid arthritis and pain and signs of inflammation associated with acute gouty arthritis. In addition, an application is currently under evaluation to extend the indication of the etoricoxib-containing medicine Arcoxia to treat ankylosing spondylitis.

In the evaluation of etoricoxib concerns were raised over the cardiovascular safety of etoricoxib-containing medicines when used to treat ankylosing spondylitis at a dose of 90 mg once a day. These concerns also extended to the treatment of rheumatoid arthritis which is used at the same dose.

The Committee for Medicinal Products for Human Use (CHMP) recommended updating the existing contraindication in patients with hypertension that is not adequately controlled to state that patients whose blood pressure is persistently above 140/90 mmHg and has not been adequately controlled should not take etoricoxib.

Reference:

Fluoroquinolones
Boxed warning against increased risk of tendinitis and tendon rupture

USA. US FDA notified healthcare professionals that a BOXED WARNING and Medication Guide are 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.

Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in those over age 60, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy. Physicians should advise patients, at the first sign of tendon pain, swelling, or inflammation, to stop taking the fluoroquinolone, to avoid exercise and use of the affected area, and to promptly contact their doctor about changing to a non-fluoroquinolone antimicrobial drug. Selection of a fluoroquinolone for the treatment or prevention of an infection should be limited to those conditions that are proven or strongly suspected to be caused by bacteria.

Reference:

Moxifloxacin
Hepatic reactions - restriction in use in upper respiratory infections

Europe. EMEA has concluded that moxifloxacin-containing medicines for oral use should only be prescribed in the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis and community acquired pneumonia when other antibiotics cannot be used or have failed. The Agency also recommended strengthening the warnings for oral moxifloxacin medicines. The reason is increased risk of hepatic reactions.

The EMEA’s Committee for Medicinal Products for Human Use (CHMP) has reviewed all available information on the safety of moxifloxacin-containing medicines for oral use, following concerns over their liver safety when used for acute bacterial sinusitis, acute exacerbation of chronic bronchitis and community-acquired pneumonia. The CHMP concluded that the benefits of oral moxifloxacin medicines continue to outweigh its risks. However, due to safety concerns, mainly related to an increased risk of adverse hepatic reactions, the CHMP recommended restricting their use in these indications.

The CHMP also recommended that the warnings of oral moxifloxacin-containing medicines be strengthened.

Reference:

Label changes for use in pregnancy
Risks and benefits highlighted

USA. The US FDA has proposed extensive changes to labelling for prescription medications, including biological products, to better inform patients of the risks and benefits of drugs that are used during pregnancy and breastfeeding. Drug labelling would be required to outline the potential risks and benefits of the medication for both the mother and the foetus, and how these risks may vary throughout the course of the pregnancy.

Reference:
medicines should be strengthened concerning the risk of diarrhoea, heart failure in women and older patients, severe skin reactions and fatal liver injury.

Reports in WHO ICSR database: Moxifloxacin (terms with more than 15 reports)

Hepatic enzymes increased 57
SGOT increased 26
SGPT increased 25
Hepatic failure 18
Hepatic function abnormal 35
Hepatitis 32
Hepatitis cholestatic 17
Hepatocellular damage 18
Bilirubinaemia 23
Jaundice 54

(See also WHO Pharmaceuticals Newsletter No. 2, 2008, for reports of multifocal leukoencephalopathy).


Pegvisomant-somatostatin analogues
Increased risk of hepatic enzyme elevations

Canada. Pfizer, in consultation with Health Canada, has issued a 'Dear Healthcare Professional' letter advising of an increased risk of hepatic enzyme elevations in patients receiving the anti-growth hormone pegvisomant (Somavert) in combination with a somatostatin analogue, such as octreotide. Pfizer advises health-care professionals that baseline serum ALT, AST, total bilirubin and ALP levels should be obtained prior to pegvisomant initiation and routinely monitored during the course of treatment. If a patient develops liver test elevations of 3−5 times the upper limit of normal (ULN), pegvisomant may be continued, but liver tests should be monitored weekly. If a patient develops liver test elevations of > 5 times the ULN, transaminase elevations of > 3 times the ULN with any increase in total bilirubin, or signs or symptoms of liver injury, pegvisomant should be immediately discontinued. If liver injury is confirmed, pegvisomant should be permanently discontinued. The Canadian product monograph will be updated to include this new information.

Reference: Bristol-Myers Squibb Medical Imaging. Updated safety information on DEFINITY (Rm) (Perflutren Injectable Suspension) and serious adverse cardiopulmonary reactions. Internet Document, 23 May 2008 (www.hc-sc.gc.ca).

Norfloxacin
Restricted use in urinary infections

EMEA. The CHMP has concluded that the marketing authorisations for oral norfloxacin-containing medicines, when used in the treatment of acute or chronic complicated pyelonephritis (kidney infection), should be withdrawn because the benefits of these medicines do not outweigh their risks in this indication. This is based on the fact that the efficacy has not been adequately demonstrated for this type of infection.

In current practice, this disease is usually treated using either injectable antibiotics, or other fluoroquinolones taken by mouth or given by injection. The recommendation of the CHMP does not have an impact on the use of oral norfloxacin-containing medicines in other types of infection.


Perflutren injectable suspension
Warning section to be revised

Canada. Bristol-Myers Squibb Medical Imaging has issued a 'Dear Healthcare Professional' letter, in consultation with Health Canada (HC), advising of changes to the safety information for the contrast medium perflutren injectable suspension, (Definity).

There have been worldwide reports of serious cardiopulmonary reactions, including fatalities, occurring during, within 30 minutes of, and up to several days after administration. As of March 31 2008, there had been one case in Canada of a fatal cardiopulmonary adverse reaction.

The product monograph for Definity is being updated. The warning section will be revised to include guidelines for close monitoring of patients with pulmonary hypertension or unstable cardiopulmonary conditions, during and for at least 30 minutes after administration.

The revised product monograph will include a statement about adverse drug reactions occurring during post marketing use.

Reports in WHO ICSR database: Perflutren

Circulatory failure 1 (USA)
Fibrillation cardiac 1 (USA)

Reference: Bristol-Myers Squibb Medical Imaging. Updated safety information on DEFINITY (Rm) (Perflutren Injectable Suspension) and serious adverse cardiopulmonary reactions. Internet Document, 23 May 2008 (www.hc-sc.gc.ca).
**Rotavirus gastroenteritis vaccine**

**Additional safety studies required**

**USA.** Approving GlaxoSmithKline's (GSK's) oral, live attenuated, human rotavirus vaccine (Rotarix) the US FDA exercised its new authority (Food & Drug Administration Amendments Act (FDAAA), 27 September 2007) to require a postmarketing safety study (1). On 3 April 2008, the Agency approved Rotarix for the prevention of rotavirus gastroenteritis in infants (2). The approval was based on clinical data from nearly 75 000 infants participating in trials conducted in North and South America, Europe, Asia and Africa.

The US FDA considers analyses of spontaneous postmarketing adverse events insufficient to assess potential serious risks. Consequently, GSK is required to conduct a US-based postmarketing observational study of Rotarix to assess the potential serious risk of intussusception and other serious adverse effects (start June 2009; final report by March 2012).

**Reports in WHO ICSR database:**

<table>
<thead>
<tr>
<th>Intestinal obstruction</th>
<th>(2001-2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3</td>
</tr>
<tr>
<td>France</td>
<td>1</td>
</tr>
<tr>
<td>USA</td>
<td>118</td>
</tr>
</tbody>
</table>

**References:**

1. Rotarix Product Approval Information, US FDA, 3 April 2008 ([www.fda.gov](http://www.fda.gov)).
Abacavir and abacavir-containing medications
Serious hypersensitivity reactions

USA. The US FDA informed health-care professionals that serious and sometimes fatal hypersensitivity reactions caused by abacavir therapy are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*5701. Abacavir is an anti-HIV medicine and is a nucleoside reverse transcriptase inhibitor (NRTI). The US FDA reviewed data from two studies that support a recommendation for pre-therapy screening for the presence of the HLA-B*5701 allele and the selection of alternative therapy in positive subjects. Genetic tests for HLA-B*5701 are available and all patients should be screened for the HLA-B*5701 allele before starting or restarting treatment with abacavir or abacavir-containing medications. Development of clinically suspected abacavir hypersensitivity reactions requires immediate and permanent discontinuation of abacavir therapy in all patients, including patients negative for HLA-B*5701.

Reference:

Abacavir and abacavir-containing medications
Risk of myocardial infarction

Canada. GlaxoSmithKline (GSK), in consultation with Health Canada, has issued a ‘Dear Healthcare Professional’ letter, regarding the potential increased risk of myocardial infarction (MI) in HIV patients treated with abacavir-containing products (Ziagen, Kivexa and Trizivir). GSK has provided Health Canada with recent findings of a study (1) which suggested an increased MI risk in HIV-infected patients treated with abacavir-containing products. The letter says that available data does not allow a definite conclusion about the association between abacavir use and an increased MI risk at this time. GSK recommends that physicians discuss the potential risks and benefits of abacavir with their patients and that the overall benefit-risk profiles of abacavir should be considered, particularly in patients with pre-existing serious cardiovascular diseases. The letter states that "at this time, Health Canada has undertaken the review of this safety data and will advise Canadians if further risk measures are deemed necessary". (See WHO Pharmaceuticals Newsletter No. 2, 2008 for related information).

Reports in WHO ICSR database:
Myocardial infarction (1999 – 2008) 46

Reference:

Clozapine
Increased cardiovascular risks

New Zealand. New Zealand’s Medsafe has issued a prescriber update regarding the association of clozapine with increased risks of myocarditis and cardiomyopathy. Clozapine is an atypical antipsychotic used for the management of schizophrenia. 25 cases of clozapine-associated myocarditis and 17 cases of clozapine-associated cardiomyopathy were reported between March 2000 and November 2007 in New Zealand. Two patients died. Clozapine has been associated with myocarditis and, to a lesser extent, cardiomyopathy. Myocarditis generally occurs 1–2 months after the initiation of clozapine. It is not a common adverse event, but affects relatively young people, is not necessarily dose-related, and can be fatal. Cardiomyopathy...
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usually has a later onset, after about nine months of treatment. Of the patients with myocarditis, the median age was 30.5 years. In 80% of these cases, the duration of treatment to reaction onset was one month.

To date, no clear risk factors have been identified for clozapine-associated myocarditis and cardiomyopathy. Pre-treatment cardiovascular screening is recommended. Medsafe says that, in patients where myocarditis is suspected, clozapine should be withheld and the patient urgently referred to a cardiologist. If myocarditis is confirmed, clozapine should be discontinued. If myocarditis is ruled out, other possible diagnoses, such as cardiomyopathy, should be considered.

(See WHO Pharmaceuticals Newsletter No. 3, 2007 for reports of clozapine-associated myocarditis received in Australia).

Reference:
Prescriber Update
29(1): 10-12 May 2008
(www.medsafe.govt.nz)

Fluorescein
Reports of anaphylactic reactions

Netherlands. The Netherlands Pharmacovigilance Centre (Lareb) has received four reports, concerning two events of anaphylactic reactions associated with fluorescein use up to 31 August 2007. Fluorescein is a colouring agent used in diagnostic procedures.

The two events involved a 49-year-old man and a 56-year-old woman who experienced anaphylactic reactions after administration of fluorescein for angiography; the woman subsequently died.

Reports in WHO ICSR database:

Fluorescein
Total 131 reports from 17 countries (1979 – 2008)
Anaphylactic reaction 13
Anaphylactic shock 78
Anaphylactoid reaction 40

Reference:

Fluticasone propionate
Reports of haematoma

Netherlands. The Netherlands Pharmacovigilance Centre (Lareb) has received 12 reports of haematoma associated with the use of medications containing fluticasone propionate up to 3 September 2007. A further six cases of purpura associated with the use of inhaled fluticasone propionate were reported in this period.

Nine cases involved inhaled salmeterol/fluticasone propionate, three involved fluticasone propionate nasal spray or nasal drops (Flixonase), and one involved inhaled fluticasone propionate (Flixotide).

While haematoma, purpura and ecchymosis are listed in the Summary of Product Characteristics (SPC) of nasally acting or inhalation corticosteroid preparations containing beclometasone or budesonide, these adverse reactions are not listed in the SPC for fluticasone propionate preparations.

Reports in WHO ICSR database:

Fluticasone propionate/Salmeterol xinafoate
Total 30 reports from 7 countries, 2000 – 2008
Purpura 17
Purpura allergic 1
Haematoma 12

Reference:
Inhaled and intranasal fluticasone propionate and haematoma, Lareb, May 2008 (www.lareb.nl).

Nitrofurantoin
Reports of hepatotoxicity

Australia. Following two reports of submassive hepatic necrosis associated with nitrofurantoin to the Adverse Drug Reactions Advisory Committee (ADRAC), a review of hepatic adverse events with this drug was conducted. According to ADRAC, the Australian Therapeutic Goods Administration (TGA) has received 637 reports of adverse events associated with nitrofurantoin up to April 2008, which included 17 reports of death. Of the 637 reports received, 119 were reports of hepatobiliary reactions, including 32 serious cases; seven cases were fatal. Other reports included jaundice (4), hepatitis (13) or hepatic failure (2). In seventeen of the serious cases, nitrofurantoin was the only suspected drug. The majority of reports involved women aged more than 50 years, who were taking nitrofurantoin 50–200 mg/day for acute urinary tract infections (UTIs; 11), recurrent UTIs (11), or as prophylaxis (10). (Nitrofurantoin is used to treat urinary tract infections.)

Reports in WHO ICSR database:

Nitrofurantoin – Liver disorders
Totally 1683 reactions
(1968 – 2008)
Death in connection with liver disorders 23
Hepatic function abnormal 319
Hepatic failure 47
Hepatic necrosis 25
Hepatocellular damage 54
Coma hepatic 7

Reference:

Reports in WHO ICSR database:

Somavert – pegvisomant coreported with octreotide - liver disorders
Cholelithiasis 1
Hepatic enzymes increased 2
both reports from DEU

Reference:

Pioglitazone
ADR update

Netherlands. Up to 9 October 2007, the Netherlands Pharmacovigilance Centre (Lareb) received 57 reports involving 77 ADRs associated with the oral anti-diabetic drug pioglitazone. Of these reports, two concerning the same patient were filed by two marketing authorization holders. The reported ADRs involved only one report of cardiac failure and no reports of myocardial infarction.

(In 2000 the product labelling for pioglitazone was revised in Japan to include information on adverse cardiac events associated with pioglitazone; see WHO Pharmaceuticals Newsletter No. 4, 2000)

Reports in WHO ICSR database:

Pioglitazone
Total 4273 reports from 22 countries (2000 – 2008)
Cardiac failure 405
Cardiac failure left 14

Myocardial infarction 74

Reference:
Update on reports of pioglitazone, Lareb, May 2008 (www.lareb.nl)

Rimonabant
Reports of serious ADRs

UK. Spontaneous reports of depression, psychiatric disorders, hypoglycaemic reactions, paranoia, rash, tremor and headache associated with the anti-obesity drug rimonabant (Acomplia) have been reported to the UK MHRA, according to an article in Drug Safety Update (1). A total of five fatal ADR reports have been received up to 9 May 2008. According to the agency, the total number of ADR reports with rimonabant during this period in the UK was 720. The fatal ADR reports comprised two cases of myocardial infarction, one case of sudden death, one case of infection (fungal pneumonia) and one case of suicide (2). Up to the end of January 2008, 673 ADR reports (1971 individual reactions) with rimonabant were received in the UK. Of these, 423 were serious and four reports had a fatal outcome. The most commonly reported ADRs were psychiatric disorders (44%), CNS disorders, gastrointestinal disorders, general disorders and skin and subcutaneous disorders; these ADRs are labelled in the Summary of Product Characteristics. The most common psychiatric reactions were depression, related mood disorders and associated symptoms. Hypoglycaemic reactions, paranoia, rash, tremor and headache, which are not in the product information, were identified as new safety signals based on spontaneous cases reported.

(According to the European Medicines Agency (EMEA) rimonabant (Acomplia) is contraindicated in patients with ongoing major depression or who are being treated with antidepressants because of the risk of psychiatric adverse effects; see WHO Pharmaceuticals Newsletter No.4, 2007.)

References:

Reports in WHO ICSR database:

Total 58 reports from ARG, CHE, DEU,FIN, NOR
Headache 5
Tremor 2
Hypoglycaemia 3
Paroniria 4
Depression 27
Other psychiatric disorders 136

Risperidone, pipamperone
Reports of epistaxis

Netherlands. As at 30 August 2007, the Netherlands Pharmacovigilance Centre (Lareb) had received 12 and 11 reports of epistaxis (nosebleeds) associated with the use of the antipsychotic drugs risperidone and pipamperone, respectively. The majority of reports involved children aged 5–14 years. Epistaxis is not listed in the Dutch Summary of Product Characteristics for either risperidone or pipamperone. However, the adverse reaction is listed in the American SPC for risperidone (incidence 0.1%–1%).

Reports in WHO ICSR database:

Risperidone
(1994 – 2008)
Epistaxis 79, from 11 countries

Pipamperone

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Epistaxis 13.

Reference:

Salbutamol
Dental caries associated with use in children

Netherlands. The Netherlands Pharmacovigilance Centre (Lareb) has received five reports of dental caries associated with the use of salbutamol (Albuterol) up to 5 September 2007. The five cases involved four boys and one girl aged 5–9 years who developed dental caries while receiving salbutamol, which is a beta-2 agonist used to treat asthma. While well-described in the literature, dental caries are not listed in the SPC for the antiasthmatic drug sodium cromoglicate nasal spray.

Reports in WHO ICSR database:
Total 10 reports.

Reference:

Statins
High-dose associated with muscle disorders

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) continues to receive reports of myositis/rhabdomyolysis in situations where treatment with HMG-CoA reductase inhibitors (statins) has been initiated at an inappropriately high dose.

By late 2007, the Australian Therapeutic Goods Administration (TGA) had received 5846 adverse reaction reports that implicated a statin. Of these reports, almost one third were of muscle disorders such as myopathy, myalgia, myositis or rhabdomyolysis. When severe, the muscle disorders were associated with myoglobinuria and, in extreme cases, renal failure.

ADRAC reminds prescribers that statin treatment should be initiated at the lowest possible dose. The dose may then be titrated, if necessary, according to lipid levels. Patients receiving statins should be monitored for adverse reactions, especially for any symptoms of muscle disorders.

Reference:

Salbutamol
Dental caries associated with use in children

Statins
High-dose associated with muscle disorders

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ADRAC reminds prescribers that statin treatment should be initiated at the lowest possible dose. The dose may then be titrated, if necessary, according to lipid levels. Patients receiving statins should be monitored for adverse reactions, especially for any symptoms of muscle disorders.

Reference:

Strontium ranelate
ADR update

Australia. To date, 47 reports of suspected adverse drug reactions related to strontium ranelate (Protos) have been reported in Australia, according to ADRAC. Strontium ranelate is a bone formation stimulant used in the treatment of postmenopausal osteoporosis.

Of these 47 reports, 16 reports involved rash, one accompanied by eosinophilia and one by fever. ADRAC has also received a report of severe cholestatic hepatitis associated with eosinophilia, pruritus and rash in a 62-year-old woman. According to ADRAC, clinical trials have shown an increased incidence of venous thromboembolism in patients receiving strontium ranelate, compared with those receiving placebo. Three cases of deep venous thrombosis and one of superficial vein thrombosis have been reported after 1–4 months of treatment; however, two of these patients had risk factors for venous thromboembolism.

ADRAC has advised patients to stop treatment and seek medical advice at the first appearance of rash during strontium ranelate treatment. Once stopped, strontium ranelate should not be restarted.

(See WHO Pharmaceuticals Newsletter No. 1, 2008 for reports of severe allergic reactions associated with strontium ranelate in the UK.)

Reference:

TNF antagonists
Review of lymphoma and other cancer risks in children

USA. FDA has issued an early communication about its ongoing safety review of tumour necrosis factor (TNF) antagonists. The agency is investigating a possible relationship between the use of these drugs and development of lymphoma and other cancers in children and young adults; currently, infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira) and certolizumab pegol (Cimzia) are the four TNF antagonists available in the US. The FDA is investigating about 30 reports of cancer submitted between 1998 and April 2008. These reports involved patients who received TNF antagonists along with other immunosuppressants for Crohn's disease, juvenile rheumatoid arthritis or other diseases when they were aged ≤ 18 years. The Agency has advised parents, caregivers and healthcare providers of children receiving TNF antagonists to be aware of the possible risk of lymphoma and other cancers.

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Reports in WHO ICSR database:

**Etanercept**
Total 6 reports:
- Leukaemia granulocytic 1
- Eye neoplasm 1
- Lymphoma malignant 1
- Ovarian cyst 1
- Renal carcinoma 2

**Infliximab**
Total 7 reports:
- Leukaemia granulocytic 1
- Hepatic neoplasm malignant 1
- Lymphoma malignant 3
- Thrombocythaemia 2

Reference:
Media Release, US FDA, 4 June 2008 ([www.fda.gov](http://www.fda.gov)).

**Varenicline**
Serious neuropsychiatric adverse events

Canada. Pfizer Canada has issued a Health Canada-endorsed Dear Healthcare Professional letter informing health-care providers about postmarketing reports of serious neuropsychiatric adverse events associated with use of varenicline (Champix) for smoking cessation.

From April 2007, when varenicline was introduced in the Canadian market, to 30 April 2008, Health Canada has received 226 reports of neuropsychiatric adverse events; a total of 708,534 prescriptions were filled for the drug during this time period. The reported adverse events included depression, agitation, behavioural changes, hostility, suicidal ideation, suicide and worsening of pre-existing psychiatric illness.

Pfizer has advised health-care professionals:
- to alert families and caregivers of varenicline recipients about the need to monitor for neuropsychiatric symptoms;
- to instruct patients to stop taking varenicline and contact their healthcare provider immediately if they develop depressed mood, agitation, hostility, behavioural changes, suicidal ideation or suicidal behaviour;
- to ‘diligently monitor’ varenicline recipients with concomitant or previous psychiatric conditions.

Reference:

**Risk evaluation and mitigation studies (REMS)**

USA. Under the FDAAA (see rotavirus vaccine story on page 8), the US FDA can now require risk evaluation and mitigation strategies (REMS) for new products if it determines such schemes are necessary to ensure that the benefits of a drug outweigh the risks. Notably, the FDA can withhold product approval until REMS are in place.

Reference: ([www.fda.gov](http://www.fda.gov))

**FDA Sentinel Initiative**

The US FDA has proposed a Sentinel Initiative that will improve patient safety and quality of medical care by increasing the Agency’s capacity to monitor the postmarketing use of a medicinal product. The initiative has been described as a move from "reactive dependence on voluntary reporting of safety concerns to proactive surveillance of medicinal products on the market". The Sentinel Initiative includes development of a new electronic system that will enable the US FDA to gather information from various sources to identify possible postmarketing adverse events. The system will use information from existing electronic claims and medical records data sources maintained by participating private and government entities. Federal agencies and academic researchers will be able to use claims data from the Medicare prescription drug programme.

Reference:
Media Release, US Department of Health and Human Services, 22 May 2008 ([www.hhs.gov](http://www.hhs.gov)).
Review of Oseltamivir Reports in Vigibase is reassuring but vigilance for hepatic and skin disorders recommended

Report from the WHO Collaborating Centre for International Drug Monitoring, Sweden.

Introduction

The antiviral agent oseltamivir is a selective inhibitor of influenza virus A and B neuraminidase. It is indicated for the treatment and prophylaxis of influenza virus infection types A and B although vaccination is preferred for prophylaxis. It should be commenced early in the course of illness to achieve maximum benefit. The WHO has recommended its use for treating Avian influenza A (H5N1) (1).

In 2007 the Uppsala Monitoring Centre (UMC) undertook a review of the international adverse reaction reports attributed to oseltamivir in the WHO Global Individual Case Safety Report Database, Vigibase, as well as the relevant literature and product information. This review did not identify any clearly defined signals of unsuspected serious adverse reactions not already in the product information or regulatory authority alerts, the latter concerning neuropsychiatric reactions.

Reports of serious skin disorders

Reports of Stevens Johnson Syndrome and toxic epidermal necrolysis had been reported in Vigibase. These disorders are listed under adverse reactions in product information for Tamiflu® (oseltamivir) but with causality not established (2). The Vigibase reports did not provide additional information on causality.

Oseltamivir and reports of hepatic disorders

Despite the lack of a clear signal, reports in Vigibase of serious hepatic disorders occurring in association with oseltamivir use were of concern. Reports of hepatic failure, hepatic necrosis, hepato-renal syndrome, jaundice and bilirubinaemia were statistically disproportionate to the background data. Product information for oseltamivir (Tamiflu®) indicated that hepatitis and abnormal liver function tests had been identified during post-marketing experience and that it was not possible to establish a causal relationship with oseltamivir exposure.

Patient Characteristics

At the time of the review Vigibase held 770 reports for oseltamivir. There were 46 non-duplicated reports of hepatic reactions including reports of hepatic failure and necrosis. Numbers of males and females affected were similar and the age range was 18 to 88 years apart from two infants aged 12 months.

Duration of oseltamivir use

Data provided in 25 reports showed patterns of use duration and reaction onset. Overall oseltamivir was used for one to five days in 17 patients. The longest periods of use were 8 days and 19 days. Onset of hepatic manifestations occurred up to one week after oseltamivir was discontinued in 16 patients.

Hepatic reactions to medicines usually become evident between five and ninety days after first exposure (3). For this reason eight patients with onset one to two days after first exposure and one patient for whom onset was 120 days after exposure were excluded from further analysis.

Dechallenge and Rechallenge

No reports had valid dechallenge or rechallenge data.
Hepatic failure, hepatic necrosis and serious hepatocellular reactions

Five reports of hepatic failure and/or hepatic necrosis were identified that contained information on time to onset from first exposure that was appropriate for drug-induced hepatotoxicity. Oseltamivir was the only medicine considered suspect in two of these reports.

There were no reports of cholestatic hepatitis occurring within five and ninety days of oseltamivir use. There were five reports of hepatocellular damage but these were poorly documented in terms of exposure duration and other medicines were often co-suspect. The originals of eight reports of jaundice and/or bilirubinaemia together with elevated hepatic enzymes or hepatitis were requested from the countries of origin in order to identify serious hepatocellular reactions that are likely to progress to hepatic failure (4). Three such reports were obtained. Two of these patients progressed to the hepatic failure group described above. The third patient had not taken other suspect medicines, only low dose paracetamol.

Thus oseltamivir appeared to be the most likely causal medicine in two reports of hepatic failure and one serious hepatocellular reaction.

It is of note that one patient with hepatic failure had pre-existing renal failure and was taking the maximum recommended daily dose of oseltamivir.

Causality

While oseltamivir appeared to be the most likely causal medicine in three reports of the most serious suspected hepatic reactions no details of investigations for other potential causes, eg viral studies, were provided. The other reports of serious hepatic disorders could not readily be assigned a causality classification.

There are difficulties in assigning causality to hepatic reports with oseltamivir for the following reasons:

1. Prodomal symptoms of hepatic disorders may mimic influenza symptoms.
2. Dechallenge data is largely unhelpful as oseltamivir has usually been discontinued before the reaction is evident.
3. If patients have influenza symptoms they are likely to take other medicines that can be hepatotoxic eg nonsteroidal anti-inflammatory medicines and paracetamol.
4. A number of patients were also taking antibiotics as well as oseltamivir and many of these were also potentially hepatotoxic.

Items (1) and (2) describe problems that make it almost impossible to assign a “probable” rather than “possible” causality to hepatic reactions attributed to oseltamivir. However, one advantage is that the usual short duration of oseltamivir treatment means that more serious injury may be avoided in many cases, if the association is causal.

Most of these difficulties also apply when assessing causality of serious skin disorders following exposure to oseltamivir.

Summary and Recommendations

There are reports of hepatic reactions attributed to oseltamivir in Vigibase that are more serious than those described in the product information. Where identifiable the reports appeared to be predominantly of hepatocellular disorders. There is no clear evidence of causality because of difficulty in discriminating influenza and the early symptoms of hepatic disease, because of common concurrent use of other hepatotoxic medicines and because of the usual short duration of oseltamivir use.

There is a strong argument for the alternative explanations, listed under “causality”, for these reports particularly the likelihood that oseltamivir was used to treat prodromal symptoms of hepatic disease rather than influenza. However, given the potential widespread and unsupervised use of oseltamivir a cautious approach should be considered. This could involve

1. Alerting patients to the possibility of hepatic and serious skin reactions as well as other documented adverse effects, at the time of prescription, and
2. Discontinuation of oseltamivir with hepatic function testing where patients are slow to recover from presumed influenza, or relapse. Such testing would identify both those patients whose
hepatic disorder had not been diagnosed earlier because they were presumed to have influenza and those who are developing an adverse reaction to oseltamivir. Oseltamivir will not provide any benefit at this stage and discontinuation may avoid more serious outcomes.

3. Prompt discontinuation of oseltamivir if a serious skin disorder occurs.

Patients prescribed or already holding oseltamivir should also be advised to consult their medical attendant prior to taking this medicine if they develop renal impairment as they may need to take a reduced dose.

**References**


* Note from the Uppsala Monitoring Centre. There are now 918 reports for oseltamivir in Vigibase including three additional reports of hepatic reactions. These reports do not alter the conclusions and recommendations of this article.

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**Singapore reporting (2007)**

**Key features of the year’s reports**

In 2007, the Pharmacovigilance Unit of Singapore's Health Sciences Authority received 13,475 local spontaneous adverse drug reaction (ADR) reports. Of these, 1,740 ADR reports were reviewed and analysed. Of the reviewed reports,

- 42% were classified as serious.
- Most of the reviewed ADR reports were from healthcare professionals in public hospitals (50.6%).
- More ADRs were reported in females (57.6%) than in males.
- Chinese patients had the highest proportion of ADRs (61.6%), followed by Malays (12.5%) and then Indians (8.3%).
- Most of the reported ADRs occurred in patients between the ages of 30 and 69 years (62.6%).
- Most reports were associated with pharmaceutical medicines (96.9%).
- The top four drugs suspected of causing an ADR were diclofenac (4.4%), naproxen (4.0%), cotrimoxazole [trimethoprim/sulfamethoxazole; 3.6%] and metoclopramide (3.6%).
- Most of the reported ADRs were skin-related disorders (25.0%).

**Reference:**

Substantial increase in number of reports in 2007: EMEA

EMEA received 381,990 ADR reports in 2007, recording a more than 25% increase on the previous year.

- 40% of all 2007 ADR reports involved centrally authorised medicinal products.
- 63,393 reports involved investigational medicines – an increase of 18% from 2006.
- There were 762 suspected signals related to 139 intensively monitored medicines and 349 suspected signals related to 162 routinely monitored products.
- After further analysis, follow-up was required for 22% and 10% of signals from intensively and routinely monitored products, respectively.

A greater number of periodic safety update reviews were conducted in 2007 than the previous year (313/273).

Reference:

Valuing the patient's voice

Benefits of patients’ reports

Netherlands. ‘Patient reports contribute substantially to the reporting of ADRs, both in quantity and quality’ and can make a significant contribution to reliable pharmacovigilance, according to researchers in The Netherlands. Between April 2004 and April 2007, the Netherlands Pharmacovigilance Centre (Lareb) received 2522 reports directly from patients, concerning 5401 ADRs, and 10,635 reports from healthcare professionals, concerning 16,722 ADRs. Significant differences were noted in the categories of seriousness and outcomes reported by patients and by healthcare professionals. Patients reported a higher number of life-threatening ADRs (5.2% vs 2.7%) and disability (2.3% vs 0.4%), and reported non-recovery more frequently (35.4% vs 16.7%). ADRs such as weight gain, decreased libido and fatigue were among the most frequently reported ADRs by patients, probably reflecting the impact of these ADRs on quality of life.

Reference: