

WHO PHARMACEUTICALS NEWSLETTER



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

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

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News & Issues

Previous issues had warned readers of specific safety concerns with products such as gatifloxacin and infliximab. In this issue we bring you information on new or reinforced regulatory recommendations for these and other products along with safety information on others - or do we mean 'toxicity' information? In the feature article Professor Marcus Reidenberg writes 'We should not say drug safety when we mean drug toxicity'. What are your views on this? Do we need to be a bit more candid and avoid 'newspeak'? E-mail us your comments for a full discussion and we will publish them in the next issue of the newsletter.

The WHO International Working Group for Drug Statistics Methodology got together 22-23 March 2006 in Oslo, Norway for its 19th meeting. The Working Group meets twice a year and advises the WHO Collaborating Centre for Drug Statistics Methodology on the development and maintenance of the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) for drugs. There is some concern that the work of the Centre and the usefulness of the ATC/DDD system as a tool for drug utilization research are not well known in some parts of the world. We wish to address this gap and plan to include articles and other appropriate information on the ATC/DDD in future issues of the newsletter. In the meantime, if you wish for any specific information on the subject, write to us and we will do our best to help.

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Adalimumab, Etanercept, Infliximab Linked to HBV reactivation

Canada. Manufacturers of the anti-TNF α (anti tumour necrosis factor alpha) products etanercept (Enbrel), adalimumab (Humira) and infliximab (Remicade) have issued a 'Dear Health-care Professional' letter and a public communication, both endorsed by Health Canada, advising of a possible association between use of these drugs and reactivation of hepatitis B virus (HBV) infection (1,2). In the letter, Amgen Canada (for Enbrel), Abbott Laboratories (for Humira) and Schering Canada Inc. (for Remicade) advise that HBV reactivation has been reported very rarely in patients with chronic HBV infection receiving these drugs; less than one adverse event per 10 000 treated patients has been reported cumulatively, with one report originating from Canada (1). According to the companies, clinically active HBV infection occurred after a latency period of three weeks to 20 months after starting treatment. They point out that as the majority of patients were receiving other immunosuppressives, a direct causal relationship between anti-TNF α therapy and HBV relapse may be difficult to establish. Where patient outcome information was provided, most patients improved after receiving antivirals or stopping anti-TNF α therapy, but fatal outcomes have also occurred. The companies advise that patients at risk for HBV infection should be evaluated for previous evidence of HBV infection before starting anti-TNF α therapy. Furthermore, patients identified as chronic HBV carriers should be monitored for signs and symptoms of active HBV infection during treatment and for several months after

stopping treatment. The Canadian Product Monographs for these products (Enbrel, Humira and Remicade) are being revised accordingly. In the communication, the companies say that patients who experience any symptoms of HBV infection should contact their doctor immediately, and warn that symptoms may occur several months after initiating anti-TNF α therapy (2).

References:

1. 'Dear Health-care Professional' letter from Amgen Canada, Abbott Laboratories Limited and Schering Canada Inc., 13 January 2006 (<http://www.hc-sc.gc.ca>).
2. Public Communication from Amgen Canada Inc., Abbott Laboratories Ltd and Schering Canada Inc., 18 January 2006 (<http://www.hc-sc.gc.ca>).

Atomoxetine New warnings recommended

UK. Conclusions from an Europe-wide review on the health risks and benefits of atomoxetine (Strattera) highlighted that, overall, the balance of benefits and risks of (Strattera) remains positive in the treatment of attention-deficit hyperactivity disorder, but it was also concluded that warnings regarding seizures and abnormal heart rhythm risks should be added to the product information for the drug, according to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) (1). It was further concluded that prescribers should be reminded that (Strattera) should only be started by, and under the supervision of, a specialist, and that the current warning in the product information regarding the risk of suicidal thoughts and behaviour, and liver disorders, reflects the available data accurately, says the MHRA (1). The Patient Information Leaflet is to be updated and new advice is being issued to

doctors, states the agency.

In a 'Dear Colleague letter' (2), Professor Gordon Duff, from the Commission on Human Medicines, highlights the following new prescriber advice:

- (Strattera) has been associated with QT-interval prolongation and should be used cautiously in patients with congenital, acquired or a family history of QT prolongation; this risk could be increased if (Strattera) is given concomitantly with drugs that inhibit cytochrome P450 2D6, or cause QT-prolongation or electrolyte disturbances.
- (Strattera) is associated with a risk of seizures and should be used cautiously in patients with a seizure history, and discontinuation should be considered in patients with developing seizures or increased seizure frequency. Due to the risks of suicidal thoughts and behaviour, and severe hepatic liver injury, prescribers are reminded that patients should be monitored for signs of suicidal thoughts or behaviour, or depression, and referred for treatment if needed, and that (Strattera) should be discontinued in patients with laboratory evidence of liver injury or jaundice, says Professor Duff.

References:

1. Press Release. UK Medicines and Healthcare Products Regulatory Agency, 17 February 2006 (<http://www.mhra.gov.uk>).
2. Duff G. Strattera (atomoxetine) - conclusions of risk: benefit review. UK MHRA Commission on Human Medicines, 16 February 2006 (<http://www.mhra.gov.uk>).

Bevacizumab Label to include information on PLS

USA. In response to two reports of bevacizumab (Avastin)-related reversible posterior leukoencephalopathy syndrome (PLS) published in the *New England Journal of Medicine*, Dr Hal Barron from Genentech, USA, has advised that the bevacizumab (Avastin) package insert will be updated. Genentech has agreed that the patients in the two reports meet the clinical criteria for reversible PLS. The company is investigating one additional case and is currently reviewing the global safety database for cases that have reversible PLS-associated clinical signs and symptoms. Genentech advises that it is important for physicians to be aware of the symptoms and signs of reversible PLS and of its association with hypertension; hypertension is a known bevacizumab (Avastin)-associated adverse reaction, and has been included in the package insert since the drug was approved in 2004. Genentech plans to update the package insert with a description of reversible PLS and with a recommendation to discontinue bevacizumab in the event of reversible PLS diagnosis. Appropriate actions will be implemented outside of the US by Roche, Genentech's corporate partner.

Reference:

Barron H. Reversible posterior leukoencephalopathy syndrome and bevacizumab. Reply. *New England Journal of Medicine*, 2 March 2006, 354: 982.

Bosentan Label to indicate liver adverse effects

USA. Cases of hepatotoxicity have been reported to Actelion Pharmaceuticals and, as a result, the US labelling for bosentan (Tracleer) has been

changed, according to a 'Dear Health-care Professional' letter issued by the company; health professionals are also being reminded of the importance of continued monthly liver function testing in bosentan recipients. According to Actelion, in one of the reported cases, a patient started to experience gradual increases in baseline ALT levels after about one year of starting bosentan and, after another nine months of treatment, she had markedly elevated levels of aminotransferase and bilirubin; furthermore, after bosentan was stopped, her bilirubin levels continued to increase and her AST and ALT levels remained elevated. The company believes that this case emphasizes the need to continue monthly monitoring for the duration of therapy, and to adhere to the recommended dosage adjustment and monitoring guidelines described in the labelling for the product.

Reference:

'Dear Health-care Professional' letter from Actelion Pharmaceuticals US, Inc., 1 March 2006 (<http://www.fda.gov>).

Gatifloxacin Reinforced warnings in Canada, labelling changes in US

Canada, USA. Health Canada has advised patients with diabetes mellitus (DM) against the use of gatifloxacin (Tequin), due to concerns about blood glucose disorders (1) while the United States Food and Drug Administration (US FDA) has advised labelling changes for gatifloxacin (Tequin) in the US following continued serious reports of hyper- and hypoglycaemia (2).

Health Canada's advice against gatifloxacin use in patients with DM is based on recommendations from Bristol-Myers Squibb. Health Canada is

currently reviewing the revised product information for gatifloxacin (Tequin) and, in the meantime, has recommended alternative therapies for patients with DM. Doctors who prescribe gatifloxacin (Tequin) to patients without DM have been recommended by the manufacturer to take enhanced precautions, and undertake medical monitoring, particularly in patients with risk factors, including patients who are aged ≥ 75 years, have kidney disorders or receive diabetes drugs, says Health Canada. (See WHO Pharmaceuticals Newsletter No. 1, 2006 for previous warnings from Health Canada).

The labelling changes for gatifloxacin (Tequin) in the US include a stronger warning on hyper- and hypoglycaemia, a contraindication for use in diabetic patients, and data to identify other risk factors for high and low blood sugar levels, including concomitant glucose-altering medications, older age and renal impairment (2). The US FDA says that it will continue to monitor gatifloxacin's (Tequin's) safety to ensure that the drug's benefits outweigh the risks.

References:

1. Public Advisory. Health Canada, 16 February 2006 (<http://www.hc-sc.gc.ca>).
2. 'Dear Health-care Provider' letter from Bristol-Myers Squibb Company, 15 February 2006 (<http://www.fda.gov>).

Hydroxycarb- amide Label to include information on cutaneous vasculitis

USA, Canada. Bristol-Myers Squibb Company has advised that the labels for hydroxycarbamide preparations (Hydrea and Droxia in the US (1); Hydrea in Canada (2)) have been updated to include information on cutaneous

vasculitic toxicities occurring in patients with myeloproliferative disorders. The Warnings and Adverse Reactions sections of the labels have been updated to say that there have been reports of cutaneous vasculitic toxicities, including gangrene and vasculitic ulcerations, associated with hydroxycarbamide therapy in patients with myeloproliferative disorders, and that the toxicities occurred most often in patients who had received, or were receiving, interferon therapy. Bristol-Myers Squibb recommends that hydroxycarbamide be discontinued, should cutaneous vasculitic ulcerations develop. The Precautions and Dosing and Administration sections have been revised to warn that the drugs should be handled with care to decrease the risk of exposure, and that gloves should be worn when handling the bottles. In addition, the Precautions section of one of the products (Hydrea) now advises that, as elderly patients may be more sensitive to hydroxycarbamide, and are more likely to have reduced renal function, they may require a lower dose regimen.

References:

1. *Communication from Bristol-Myers Squibb, 20 January 2006* (<http://www.fda.gov>).
2. *'Dear Health Professional' letter from Bristol-Myers Squibb Canada, 1 March 2006* (<http://www.hc-sc-gc.ca>).

Ximelagatran Withdrawn due to adverse liver effects

UK. AstraZeneca has decided to withdraw the anticoagulant melagatran / ximelagatran (Exanta™) from the market. This is based on new patient safety data of serious liver injury in a trial (EXTEND trial) examining the use of the product in extended venous thromboembolism (VTE) prophylaxis in orthopaedic surgery (OS) up to 35 days

post-operatively. The ongoing clinical trials will be discontinued and patients switched to other treatments. AstraZeneca estimates that approximately 400 patients are currently being prescribed the drug for short-term prevention of VTE following OS. The company advises that it is important that patients do not stop melagatran / ximelagatran (Exanta™) treatment without consulting their doctor. Regulatory files in OS and other indications in the US, Europe and elsewhere will now be withdrawn. The new patient report indicates a potential risk of severe liver injury, with an observation of rapid onset of signs and symptoms in the weeks following the end of the 35 days treatment. AstraZeneca is advising that no new patients should be commenced on melagatran / ximelagatran (Exanta), and that doctors should consider switching current recipients to an alternative anticoagulation while taking the patient's circumstances into account and ensuring uninterrupted anticoagulation.

Reference:

AstraZeneca Press Release, 14 February 2006
(<http://www.astrazeneca.com>).

Aprotinin

Reports of serious cardiovascular, cerebrovascular and kidney effects

USA, Canada. The US FDA has issued a Public Health Advisory, warning doctors and patients that the results of two studies have linked aprotinin (Trasylol) injection with an increased risk of serious adverse effects such as kidney disorders, myocardial infarction (MI) and stroke in patients undergoing artery bypass graft surgery. According to the advisory, the agency is evaluating the results of these studies more closely, along with other scientific literature and reports to the US FDA Medwatch programme to determine whether labelling changes or any further actions are required. Meanwhile, the Agency advises healthcare providers to monitor patients carefully for toxicity, especially to their kidneys, heart or central nervous system (CNS), and report any adverse events promptly to Bayer, the drug manufacturer, or via Medwatch. Furthermore, the Agency advises that physicians should consider limiting use of aprotinin to situations where the clinical benefit of reduced blood loss is essential to the medical management of the patient and outweighs the potential risks. In Canada, Bayer HealthCare has written to health professionals that it is working with Health Canada and worldwide regulatory authorities to evaluate and analyse the data from the two studies as well as other available reports, to address questions regarding product safety and to identify any further action.

References:

1. *Public Health Advisory. United States Food and Drug Administration, 8 February 2006* (<http://www.fda.gov>).

2. *'Dear Health-care Professional' letter from Bayer HealthCare, February 2006* (<http://www.bayerhealth.ca>).

Benzocaine

Mouth and throat use linked with methaemoglobinaemia

USA. The US FDA has issued a Public Health Advisory to highlight that the use of benzocaine sprays (including Cetacaine, Hurracaine and Topex) in the mouth and throat has occasionally been linked with methaemoglobinaemia, a potentially life-threatening condition. The agency also advises that the Veterans Health Administration has announced the decision to cease benzocaine spray use for the local numbing of mouth and throat mucous membranes for minor surgical procedures or tube insertion.

The US FDA warns that methaemoglobinaemia has occurred when benzocaine sprays were used for a longer duration or more frequently than recommended. The agency suggests the following points for consideration when using benzocaine sprays in the mouth or throat:

- Patients with breathing problems, or who smoke, are at greater risk for methaemoglobinaemia-related complications.
- The use of products with different active ingredients (e.g. lidocaine) may be beneficial in patients with a greater tendency for elevated methaemoglobinaemia levels, such as children aged less than four months and older patients with certain in-born defects.
- Patients should receive the minimum dosage required to reduce methaemoglobinaemia risks.
- Patients who receive benzocaine sprays should

be carefully monitored for methaemoglobinaemia.

- Blood analysis for methaemoglobinaemia should be done using a co-oximeter.
- A change to chocolate-brown blood colour may be a danger sign.
- Patients with suspected methaemoglobinaemia should be promptly treated.

The US FDA advises that it has received adverse event reports of symptoms probably indicating methaemoglobinaemia associated with the use of benzocaine sprays, but that these reports had been received over a period of many years and that this event is uncommon. The US FDA reports that it is reviewing available safety information for these products, but is not planning to remove them from the market at this time.

Reference:

Public Health Advisory. United States Food and Drug Administration, 10 February 2006 (<http://www.fda.gov>).

Ergot derivatives

Reports of fibrotic complications

Australia. Fibrotic complications, including pericarditis, and pleural or retroperitoneal fibrosis, are important potential adverse reactions associated with the use of ergot derivatives such as cabergoline, bromocriptine and pergolide, according to the Australian Adverse Drug Reactions Advisory Committee (ADRAC). Since the beginning of their marketing in 1997 until December 2005, ADRAC has received 86 reports of suspected adverse reactions associated with cabergoline. Fifteen of those reports have described pneumonitis, or pleural or pulmonary fibrosis/effusion, and the time of onset varied from a few days

to over three years. Most of the reports described pleural effusion or fibrosis, or both, and eight of the patients recovered, two were improving, and the remaining five had not recovered by the time the report was submitted. ADRAC says that there have been no reports of fibrotic complications associated with low-dose cabergoline (Dostinex) used for lactate suppression and hyperprolactinaemia treatment, and that all ergot derivatives can cause fibrotic changes. Prescribers should be aware of the possible fibrotic changes associated with long-term use of ergot derivatives, including cabergoline, pergolide and bromocriptine, and should instruct patients to report cough or dyspnoea, says ADRAC.

Reference:

Australian Adverse Drug Reactions Bulletin, February 2006, 25(1): 3.

Fluoroquinolones Interactions with warfarin

Australia. The Australian Drug Reactions Advisory Committee (ADRAC) has received reports of interactions between fluoroquinolones and warfarin. ADRAC has received reports of interactions between warfarin and ciprofloxacin (9 reports), norfloxacin (11) or moxifloxacin (1); one report involved both ciprofloxacin and norfloxacin. With the exception of one patient, who had vaginal bleeding, coagulation disorders were detected during laboratory investigations for other patients. Eight patients had an International Normalized Ratio (INR) of more than seven. In one patient, INR increased from a baseline value of 2 to > 10, four days after moxifloxacin initiation and, two days after moxifloxacin and warfarin discontinuation and treatment with vitamin K, the INR had decreased to 1.2. ADRAC advises health professionals to

consider the possibility of interactions between fluoroquinolones and warfarin, and to monitor INR when the drugs are used concomitantly. (Interactions involving fluoroquinolones and warfarin have also been reported in Canada; see WHO Pharmaceuticals Newsletter No. 5, 2004).

Reference:

Australian Adverse Drug Reactions Bulletin, February 2006, 25(1): 2.

Methyl-1- testosterone Reports of serious health risks

Canada. Health Canada is warning against the use of (methyl-1-testosterone; Andro Technologies) M1T due to potentially serious health risks such as liver disorders and hardening of the arteries. The agency also warns against the use of any other supplements containing methyl-1-testosterone promoted for use as a legal steroid and body building supplement. The agency advises that, in Canada, methyl-1-testosterone is a controlled substance and there are no authorized methyl-1-testosterone-containing products on the Canadian market. To date, Health Canada has received one report of serious liver toxicity involving M1T as the suspected causative agent. The agency has notified the Canada Border Services Agency to detain any shipments of products containing M1T.

Reference:

Public Warning from Health Canada, 6 February 2006, (<http://www.hc-sc.gc.ca>).

Nimodipine Warning against intravenous use of capsules

USA. Bayer and US FDA notified health-care professionals of changes to the prescribing information for nimodipine (Nimotop), including a boxed warning to notify prescribers about medication administration errors with nimodipine. Nimodipine is approved for oral administration to improve neurological outcome after subarachnoid haemorrhage. When administered intravenously or parenterally, it can cause serious adverse events, including death. Nimodipine must not be administered intravenously or by any parenteral route

Reference:

'Dear Health-care Professional' letter from Bayer HealthCare, February 2006, (www.fda.gov).

Pegaptanib Allergic reactions reported

Canada. There have been rare post-marketing reports of hypersensitivity or allergic reactions associated with pegaptanib (Macugen), according to Health Canada-endorsed safety information issued by Pfizer Canada Inc. (1,2). Pegaptanib is indicated for the treatment of subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration, and is administered once every six weeks by intravitreal injection. Pfizer says that the hypersensitivity reactions, which included anaphylaxis and angioedema, were observed within several hours of patients receiving the procedure, and ranged from mild to severe. The company states that no direct relationship to pegaptanib (Macugen) or to other factors has been established in these cases, and

that there have been no Canadian reports of such reactions. According to Pfizer:

- patients who are allergic to pegaptanib, or to other components or products used in the injection procedure, should not receive pegaptanib (Macugen);
- prior to the pegaptanib injection procedure, the medical history of the patient should be evaluated for hypersensitivity reactions;
- ophthalmologists should be aware of potential hypersensitivity reactions associated with pegaptanib, and monitor their patients accordingly; if necessary, they should use appropriate procedures to treat these reactions.

Pfizer is working with Health Canada to revise the Canadian labelling for pegaptanib (Macugen) to reflect this post-marketing experience.

Reference:

'Dear Ophthalmologist' letter, from Pfizer Canada Inc., 12 January 2006 (<http://www.hc-sc.gc.ca>).

Rosiglitazone Reports of parotid gland enlargement

Canada. Health Canada has received five case reports of parotid gland enlargement suspected of being associated with rosiglitazone (Avandia) use. The reports involved four women and one man, aged 53–72 years (age not stated in one case), with adverse reaction onset (n = 4) ranging from six to eleven months after rosiglitazone initiation. Some of the reports indicated a complex medical history and multiple concomitant medications. Four of the patients had bilateral parotid gland enlargement; one patient had parotid gland enlargement to five times its normal size. In three cases the

reaction was reported as painless. One patient also experienced submandibular gland swelling and, in another patient, parotiditis was considered as a differential diagnosis. Patient outcomes on rosiglitazone withdrawal were: improvement in one week (n = 1), gradual resolution over four months (1) and not yet recovered (1); the outcome was not stated in the remaining two reports.

Reference:

Canadian Adverse Reaction Newsletter January 2006, 16(1): 3.

Selegiline Confusion with brand name Salagen

USA. Several cases where confusion between the brand name Salagen and the generic drug name selegiline resulted in a medication error have been described recently by the Institute for Safe Medication Practices (ISMP), according to the USA FDA Patient Safety News. In the first case, a dentist prescribed Salagen (pilocarpine) 5 mg, but the nurse misheard the order and requested selegiline 5 mg from the pharmacy. In the second case, a pharmacist entered 'selegiline' into the computer instead of 'Salagen' due to the similar spelling of the two drug names. According to the US FDA's Patient Safety News, the ISMP advises that both the brand and generic drug names should be listed on prescriptions to minimize such errors.

Reference:

FDA Patient Safety News: Show #48, February 2006, (<http://www.fda.gov>).

We should not say 'drug safety' when we mean 'drug toxicity'

Professor Marcus M. Reidenberg, Weill Medical College of Cornell University, New York, USA

Some time between thalidomide phocomelia in the 1960's and the present time, the term "drug safety" has come to be used when "drug toxicity" or "adverse drug reaction" is meant. "Drug safety" misleads the average person. Safe means free from the possibility to cause harm. Clearly no medicine is free from the possibility to cause harm. When one says a drug is "safe", one is stating something that is not true. To illustrate this point, all drugs that were new molecular entities approved by the United States Food and Drug Administration (US FDA) between 1 July 2004 and 30 December 2005 were reviewed for their adverse or toxic effects as described in their labelling. One serious adverse effect of each is in table 1. In addition, the common side effects of nausea and vomiting were assessed because data in the labelling from controlled clinical trials were often presented so that quantitative comparisons could be made. These data show that nausea appeared to be caused by 15 drugs and vomiting by 14. For some drugs, nausea or vomiting was mentioned in the narrative of the labelling but no comparative data were given. For the others, nausea and vomiting were as common in patients given the comparator as it was in those given new drug or not mentioned at all in the labelling. Despite the limitations, these data show that many of the drugs approved by the US FDA during this recent 18 month period can cause nausea and vomiting, and nearly every one has at least one serious adverse effect. Not one is free from the possibility to harm.

US law does not require that a drug be absolutely safe. A drug must only be "safe for use under the conditions prescribed, recommended or suggested in the proposed labelling." (*Reference: US Code: Title 21, 355. New Drugs. See under (d)1.*). This implies that a risk-to-benefit evaluation is what should be done to evaluate the acceptability of the drug for marketing. Absolute safety is not required since it is not possible to have a medicine that is safe as the word is used in normal English usage.

When we speak or write about drug safety or indicate that a drug is "safe", we mislead the listeners or readers, possibly including doctors. They think the drug is risk-free when it really is not. In truth, the drug has adverse effects that, in the judgment of the US FDA, constitute an acceptable risk for an average patient who might benefit from the medicine.

The US FDA has an Office of Drug Safety with three divisions: Division of Risk Management, Division of Medication Errors and Technical Support, and Division of Surveillance, Research, and Communication Support (accessed 27 January 2006 at <http://www.fda.gov/cder/Offices/ODS>). Thus, drug safety in the US FDA means risk management, medication errors, and surveillance for adverse drug reactions. Would not Office of Drug Toxicity be a much more informative term for the general public than Office of Drug Safety?

The Medline Plus web site of the National Institutes of Health has a drug safety page (accessed on 13 February 2006 at <http://www.nlm.nih.gov/medlineplus/drugsafety>). It is all about adverse drug reactions and drug recalls. Adis Press has a journal titled "Drug Safety". The papers published in it are about drug toxicity and adverse drug reactions. The PhRMA web site has a paper titled "Medicine Safety: an Overview" on its web site (accessed 27 January 2006 at <http://phrma.org/actions>). Its first sentence is: "No prescription medication is absolutely safe and all pose some magnitude of safety and health risks."

In March 2005, the Senate Committee on Health, Education, Labor and Pensions held hearings examining the US FDA's process of "ensuring drug safety". "Ensuring drug safety" misleads the entire country since drug safety cannot be ensured! George Orwell, in his novel 1984, described Newspeak. "No word in the *B vocabulary* was ideologically neutral. A great many were euphemisms. Such words, for instance, as *joycamp* (forced-labour camp) or *Minipax* (Ministry of Peace, i.e. Ministry of War) meant almost the exact opposite of what they appeared to mean."

The substitution of "drug safety" for "adverse drug reactions" may have been started by some pharmaceutical companies in the past. But even a few members of the pharmaceutical industry are no longer using the term "drug safety" as the name of their programmes concerned with drug toxicity and adverse drug reactions in the post-marketing period. "Pharmacovigilance" is the new name for this activity. It appears to be as a euphemism for an adverse drug reaction programme. It is time for all of us to stop using Newspeak terms like "drug safety" when we mean drug toxicity or adverse drug reactions.

FEATURE

Table 1. Adverse Reactions to New Molecular Entities

<u>Date Approved</u>	<u>Proprietary Name</u>	<u>INN/FDA Established Name</u>	<u>Serious Adverse Reactions</u>	<u>Nausea</u>	<u>Vomiting</u>
29 July 2004	Campral	acamprosate	Suicidal ideation or attempt	N	N
03 August 2004	Cymbalta	duloxetine hydrochloride	Hypertension	Y	Y
11 August 2004	Pentetate	pentetate	Wheezing	Y	N
26 Oct. 2004	Fosrenol	Lanthanum carbonate	Dialysis graft occlusion	Y	Y
26 Oct. 2004	Amphadase	hyaluronidase	Angioedema	N	N
10 Nov. 2004	Omacor	Omega-3-acid ethyl esters	(none compared to corn oil)	?	?
18 Nov. 2004	Tarceva	erlotinib hydrochloride	infection	Y	Y
19 Nov. 2004	VESicare	solifenacin succinate	Colonic/intestinal obstruction	Y	N
23 Nov. 2004	Multihance	gadobenate dimeglumine	(none found)	Y	Y*
15 Dec. 2004	Lunesta	eszopiclone	Depression	N	N
16 Dec. 2004	Vision Blue	Trypan blue	Staining certain intraocular lenses	?	?
17 Dec. 2004	Macugen	pegaptanib sodium	Endophthalmitis	?	Y
22 Dec. 2004	Enablex	darifenacin hydrobromide	Acute urinary retention	N	N
28 Dec. 2004	Prialt	ziconotide	Syncope	Y	Y
28 Dec. 2004	Clolar	clofarabine	Febrile neutropenia	Y	Y
29 Dec. 2004	Vent avis	iloprost	Hypotension	Y	Y
30 Dec. 2004	Lyrica	pregabalin	Accidental injury	?	N
16 March 2005	Symlin	pramlintide acetate	Hypoglycaemia	Y	Y
16 March 2005	Mycamine	micalofugin sodium	Thrombophlebitis	N	N
29 March 2005	Baraclude	entecavir	None described compared to lamivudine	N	N
28 April 2005	Byetta	exenatide	Hypoglycaemia	Y	Y
15 June 2005	Tygacil	tigecycline	Septic shock	Y	Y
16 June 2005	Levemir	insulin detemir	Lipodystrophy	?	?
22 June 2005	Aptivus	tipranavir	Bronchitis	Y	Y
22 July 2005	Rozerem	ramelteon	Somnolence	N	N
19 August 2005	Nevanac	nepafenac	Increased bleeding of ocular tissues	?	?
30 August 2005	Increlex	mecasermin (rDNA origin)	Hypoglycaemia	?	Y
28 Oct. 2005	Arranon	nelarabine	Blood dyscrasia	Y	Y
02 Nov. 2005	Exjade	deferasirox	Increased blood creatinine	Y	Y

Y = Nausea or vomiting common or more frequent than placebo, N = Nausea or vomiting not more frequent than placebo
 ? = not mentioned in labelling, * = from Micromedex



MHRA Suspends Clinical Trial

The Medicines and Healthcare products Regulatory Agency (MHRA) has suspended a phase 1 clinical trial for a new product that is being developed to treat chronic inflammatory conditions and leukaemia, having been notified that six men involved in the first stages of a clinical trial have been admitted into intensive care. Eight men took part in this stage of the clinical trial; six were given the product and two were given a placebo. The MHRA has suspended the Clinical Trial Authorisation (CTA) for this trial with immediate effect and is reviewing the data submitted with the application for the CTA.

Reference: MHRA Press Release, 14 March 2006 (<http://www.mhra.gov.uk>).