

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 information 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

This is the last issue for the year 2005 and includes the usual sections on Regulatory Matters and Safety of Medicines. The article on nevirapine under Problems of Current Interest highlights the need to support improved access and use of medicines with matching patient-monitoring facilities. This has been an eventful year in pharmacovigilance. Rofecoxib, withdrawn towards the end of 2004, continued to occupy our interest with many debates and discussions on the lessons learnt and the way forward. Drug safety in children received a lot of attention and several initiatives are underway for establishing guidelines for the safe use of medicines in this vulnerable population. The 'donation' of expired medicines and poor quality devices such as contaminated syringes to tsunami hit regions highlighted the quality and safety issues in drug donation practices, calling attention to the expanding role for pharmacovigilance centres in promoting medicine safety. The year ended with a meeting of the WHO Advisory Committee on Safety of Medicinal Products which reviewed various issues on drug safety; the Committee's recommendations will be published early next year.

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Ibritumomab

Skin reactions warning added to labels

USA. Biogen Idec, in consultation with the United States Food and Drug Administration (US FDA) has written to health-care professionals that post-marketing reports of severe cutaneous or mucocutaneous reactions, some with fatal outcome, have been received for ibritumomab tiuxetan (Zevalin), a radio-immunotherapy approved for the treatment of non-Hodgkin's lymphoma. The product label has been updated with a boxed warning to reflect this information. Health-care professionals are advised that the potential risk of these reactions should be considered when using the ibritumomab tiuxetan (Zevalin) regimen. Patients experiencing a severe cutaneous or mucocutaneous reaction should not receive any further components of the regimen and should receive prompt medical evaluation.

Reference:

'Dear Health-care Professional' letter from Biogen Idec, October 2005
(<http://www.fda.gov>).

Morphine sulfate extended release capsules

Alcohol promotes rapid release

USA. Ligand Pharmaceuticals Inc. has strengthened the product label for morphine sulfate extended release capsules (Avinza) with the warning that patients should not consume alcohol while taking these capsules since alcohol could result in the rapid release and absorption of a potentially fatal dose of morphine. Additionally, patients are also warned not to use prescription or non-prescription

medications containing alcohol while on these capsules.

Reference:

'Dear Health-care Professional' letter from Ligand Pharmaceuticals Inc., October 2005 (www.fda.gov).

Pemoline

Withdrawn due to liver toxicity risk

USA. The US FDA has concluded that the overall risk of liver toxicity from pemoline (Cylert) outweighs the benefits of this drug indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). FDA is aware of 13 reports of liver failure resulting in liver transplant or death associated with pemoline use. A boxed warning was added to the label regarding the liver toxicity. This led to fewer prescriptions being written for pemoline (1/5 the earlier number). But, the FDA is of the opinion that the risk remains, particularly when considering the fact that one new case of pemoline-associated liver failure was reported even after the improved labelling intervention. The manufacturer (Abbott) of the proprietary version (Cylert) of the product discontinued its sales in May 2005. Subsequently, manufacturers of the generic versions have also agreed to stop sales and marketing of pemoline products. Health-care providers who currently prescribe pemoline products are advised to switch their patients to an alternative therapy.

Reference:

Alert. United States Food and Drug Administration, October 2005
(<http://www.fda.gov>).

Tamsulosin hydrochloride

Risk of Intraoperative Floppy Iris Syndrome (IFIS)

Canada. Ophthalmologists are being informed that a surgical condition known as IFIS could occur during phaco-emulsification cataract surgery in some patients previously (or currently) treated with alpha-1 adrenoceptor blocking agents such as tamsulosin hydrochloride (Flomax). The syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigating currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. Tamsulosin hydrochloride is used in the treatment of signs and symptoms of benign prostatic hyperplasia. The etiology of IFIS is not very clear at present. In the meantime, Health Canada is advising that in order to minimize the potential consequences of IFIS during phacoemulsification surgery, planned measures such as iris hooks, iris dilator rings etc. should be considered in male patients who have previously received (or, are currently receiving) tamsulosin hydrochloride treatment.

Reference:

'Dear Ophthalmologist' letter from Boehringer Ingelheim (Canada) Ltd., 14 October 2005
(<http://www.hc-sc.gc.ca>).

Estrogen / progestin weekly patch

Higher levels of estrogen than birth- control pills

USA. According to the US FDA, a weekly contraceptive skin patch (Ortho Evra) that releases ethinyl estradiol (an estrogen hormone) and norelgestromin (a progestin hormone), exposes women to higher levels of estrogen than most birth control pills. Since the patch is changed once a week, it decreases the risk of pregnancy associated with the typical birth control pills when a woman might miss one or more daily doses. However, this advantage should be considered in the light of the risks due to exposure to a higher level of estrogen with the patch. Women are advised to talk to their physician to see if the patch is the right birth control option for them.

Reference:
FDA News. United States Food and Drug Administration, 10 November 2005
(<http://www.fda.gov>).

Factor VIII (FVIII) recombinant products

Risk of inhibitor development in previously treated patients

Europe. Recombinant factor VIII (FVIII) products are used for the prevention and treatment of bleeding in patients with haemophilia A. One of the major challenges in the treatment of haemophilia is the development of an antibody against factor VIII (also called an 'inhibitor'), leading to poor bleeding control in these patients. The risk of inhibitor

development is higher in haemophilia A patients than in patients with mild or moderate disease. Although the occurrence of inhibitors in previously treated patients should be seen as a natural response of the immune system to a foreign protein, the development of inhibitors in multi-transfused and stable previously treated patients (PTPs) may be due to the characteristics of an individual FVIII product. According to the European Medicines Agency (EMA), post-marketing monitoring has revealed a higher number of cases of inhibitors in PTPs treated with recombinant FVIII products than would be expected from experience with plasma derived FVIII products. On the basis of available data for all currently authorized recombinant FVIII products, the Committee for Medicinal Products for Human Use (CHMP) could neither assess the true incidence of inhibitor development, nor differentiate the risk of inhibitor development in PTPs among recombinant FVIII products. The EMA has therefore issued a statement with the following points:

- Inhibitors in PTPs have been reported for all recombinant FVIII products.
- On the basis of current data, it is not possible to quantify and compare the risk between recombinant FVIII products. Additional studies are needed.
- Patients should continue therapy and follow the recommendations of their physicians.
- If bleeding is not controlled with usual doses, patients should consult their physician immediately.

The EMA advises that a workshop is planned in the first quarter of 2006 to review current knowledge on FVIII products and inhibitor development, to discuss standardization of

requirements, definitions and methods used in pre- and post-marketing studies with PTPs and previously untreated patients for FVIII products.

Reference:
Public Statement. European Medicines Agency (EMA), 18 October 2005
(<http://www.emea.eu.int>).

Liqiang 4 dietary supplement

Presence of glyburide

Canada. Health Canada is warning consumers that 'Liqiang 4 dietary supplement capsules' contain glyburide, a prescription drug used to treat type 2 diabetes. The supplement could thus have life-threatening consequences in diabetics and in individuals with low blood sugar if used without medical supervision. Liqiang 4 capsules, promoted for use in the control of diabetes, are not approved for sale in Canada. However, consumers could probably buy them through mail-order or over the Internet. Consumers are advised to immediately stop using these products and to seek medical attention, especially if they are currently being treated with anti-diabetic drugs.

Reference:
Advisory. Health Canada, 25 October 2005
(<http://www.hc-sc.gc.ca>).

Meningococcal vaccine

Reports of Guillain- Barré Syndrome

USA. Five cases of Guillain-Barré syndrome (GBS) have been reported in the United States following the administration of the meningococcal conjugate vaccine A, C, Y and W-135 (trade name Menactra), manufactured by Sanofi Pasteur. It is not known yet

whether the adverse events were caused by the vaccine. GBS is a serious neurological disorder that can occur, often in healthy individuals, either spontaneously or after certain infections. GBS typically causes increasing weakness in the legs and arms that can be severe and require hospitalization. Meningococcal infection, which the vaccine (Menactra) prevents, is a major cause of bacterial meningitis, affecting approximately 1 in 100,000 people annually. The infection can be life threatening: 10-14 percent of cases and 11-19 percent of survivors may have permanent disability. Dr Jesse Goodman, the Director of the FDA's Center for Biologics Evaluation and Research, advises that at the present time there are no changes in recommendations for vaccination; individuals should continue to follow their doctor's recommendations. The FDA is not able to determine if any or all of the cases were due to vaccination. The current information is very preliminary and the two agencies are continuing to evaluate the situation. The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body reporting to WHO, reviewed this issue at its thirteenth meeting in Geneva, 1-2 December 2005. The committee's findings will be published in the next issue of the Weekly Epidemiological Record.

Reference:

FDA News. United States Food and Drug Administration, 30 September 2005 (<http://www.fda.gov>).

Menze Qianweishu slimming herbs capsule

Found to contain sibutramine

Hong Kong. The Department of Health (DH) has warned the public not to buy or consume a slimming product 'Menze Qianweishu slimming herbs capsule' since laboratory tests have revealed that the product contains sibutramine. Sibutramine can increase blood pressure and heart rate. Sibutramine containing products can therefore only be sold on a doctor's prescription, under the supervision of a pharmacist. Consumers are advised to immediately discontinue using the product, discard any unused portions of the product or return them to the importing company in Hong Kong.

Reference:

Communication from the Department of Health (Leader Sheet), Chinese Medicine Division, Government of Hong Kong, 12 August 2005.

Methadone Cardiac vigilance recommended

New Zealand. Prescribers are advised that methadone, used in the treatment of opioid dependence and for analgesia in moderate to severe pain, may cause QT prolongation and *torsades de pointes*. Higher doses, concomitant QT interval-prolonging agents and the presence of other risk factors for QT prolongation may predispose patients to the development of potentially fatal arrhythmias with methadone. ECG monitoring is recommended with methadone doses > 150 mg/day and in patients with either risk factors for QT prolongation or symptoms that may be attributable to arrhythmia. If

QT prolongation occurs, specialist advice should be sought regarding discontinuing or reducing the dose of methadone. There have been two reports of arrhythmia in patients taking methadone in New Zealand. At present there are 282 reports of heart rate and rhythm disorders associated with methadone in the WHO adverse drug reactions database.

Reference:

Prescriber Update Articles. Medsafe, November 2005 (<http://www.medsafe.govt.nz>).

Nimodipine Serious events due to IV use of oral formulations

Canada. Bayer Healthcare, in collaboration with Health Canada, is advising health-care professionals that inappropriate IV administration of the contents of oral nimodipine (Nimotop) 30 mg capsules has been temporally associated with serious, life-threatening or fatal adverse events. In a letter to hospital chiefs of medical staff, directors of extended care facilities and directors of nursing homes, Bayer Healthcare states that the contents of nimodipine (Nimotop) capsules must not be administered by way of injection into an IV line or other parenteral routes, and that if the capsule cannot be swallowed by the patient, the contents should be extracted into a syringe and emptied into the patient's naso-gastric tube then washed down with 30 mL of normal saline. Bayer says that it is working with Health Canada to update the monograph of nimodipine (Nimotop) with regard to drug administration.

Reference:

'Dear Health-care Professional' letter from Bayer Healthcare, 21 September 2005 (<http://www.hc-sc.gc.ca>).

Oseltamivir

Safety update

Europe. The European Medicines Agency (EMA) has issued a Press Release following reports of alleged suicide in two young boys treated for influenza. In the release the agency notes that:

- oseltamivir (Tamiflu) has been approved in the European Union for the treatment of influenza in children between 1 and 13 years of age and for the prevention and treatment of influenza over 13 years and adults;
- so far no causal relationship has been identified between the use of oseltamivir (Tamiflu) and psychiatric symptoms such as hallucination and abnormal behaviour;
- psychiatric events during oseltamivir (Tamiflu) treatment are difficult to assess because of the presence of concurrent medications and because influenza itself can precipitate psychiatric symptoms, particularly in children and in the elderly.

The Committee for Medicinal Products for Human Use (CHMP) has asked the marketing authorization holder (Roche) to provide a cumulative safety review of all available data on serious psychiatric disorders, including all case reports with a fatal outcome involving oseltamivir use. The EMA will make a statement on the outcome of this evaluation.

Reference:

Press release. European Medicines Agency (EMA), 17 November 2005 (<http://www.emea.eu.int>).

Nevirapine and serious liver adverse reactions: implications for fixed dose combinations

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Nevirapine belongs to the class of non-nucleoside reverse transcriptase inhibitors (NNRTI's) and is one of the recommended drugs in the WHO first-line antiretroviral (ARV) regimens for the treatment of adult and adolescent HIV patients (1). Nevirapine has been associated with severe liver toxicity in some cases. The product label has been revised several times over the last couple of years to include more information on liver toxicity associated with long-term nevirapine use; health-care providers and patients have been warned about the appropriate use of ARV triple combination therapy containing nevirapine (2).

The package insert for Boehringer Ingelheim's proprietary version of nevirapine (Viramune[®]) includes the warning that unless clinical benefit outweighs risk, nevirapine therapy is not recommended for women with CD4+ cell counts >250 cells/mm³ or in men with CD4+ cell counts >400 cells/mm³ (3). It is, however, likely that many clinicians are unaware of this issue and continue prescribing without discrimination, thereby jeopardizing the safety of HIV patients. An additional concern might be that other companies marketing nevirapine may not yet have included a similar warning.

Liver toxicity (2)

Both clinically symptomatic and asymptomatic liver toxicity are observed with the use of nevirapine, either as a single dose treatment to reduce mother-to-child transmission or in combination with other HIV drugs. The symptoms of nevirapine liver toxicity may be misleading: a rash, a fever or flu-like symptoms. Any of these symptoms may be associated with elevated liver enzymes. On the other hand, patients may be asymptomatic before the onset of rapidly progressive liver failure and death. Nevirapine liver toxicity typically occurs after only a few weeks of dosing and may progress to liver failure despite monitoring of laboratory tests, which is not characteristic of other antiretrovirals. Conversely, if a patient has not experienced liver toxicity within the first 3-4 months of treatment with a nevirapine-containing regimen, the risk of subsequent liver toxicity is low.

Females and patients with higher CD4+ cell counts are at increased risk of liver toxicity. Females have a three fold higher risk of symptomatic nevirapine liver toxicity than males, and females with CD4+ cell counts > 250 cells/mm³ have a 12 fold higher risk of symptomatic liver toxicity than females with CD4+ cell counts < 250 (11% vs. 0.9%). Males with CD4+ cell counts > 400 cells/mm³ have a five fold higher risk of symptomatic liver toxicity than males with CD4+ cell counts < 400 (6.3% vs. 1.2%). The product information from Boehringer Ingelheim (as mentioned above) is thus consistent with these observations.

Nevirapine-related deaths due to symptomatic liver toxicity, including some in HIV-infected pregnant women, have been reported to the Food and Drug Administration Medwatch programme in the United States (2). Serious and fatal liver toxicity have also been reported to the World Health Organization (WHO) Adverse Drug Reaction database, Vigibase. (see Table 1).

PROBLEMS OF CURRENT INTEREST

Table 1. Number of reports in Vigibase for nevirapine and WHO-ART* preferred terms belonging to the System Organ Class 'Liver and biliary disorders'.

Adverse Drug Reaction	No. of reports in total	No. of reports with fatal outcome	No. of reporting countries
ALPHA-FETOPROTEIN INCREASED	11	1	1
BILIRUBINAEMIA	64	5	9
CHOLANGITIS	1	0	1
CHOLECYSTITIS	3	0	3
CHOLELITHIASIS	2	0	2
COMA HEPATIC	18	4	2
GALLBLADDER DISORDER	5	1	1
GAMMA-GT INCREASED	29	1	7
HEPATIC CIRRHOSIS	10	5	1
HEPATIC ENZYMES INCREASED	26	0	12
HEPATIC FAILURE	77	23	7
HEPATIC FUNCTION ABNORMAL	170	8	11
HEPATIC NECROSIS	25	5	4
HEPATITIS	198	18	13
HEPATITIS CHOLESTATIC	49	1	6
HEPATITIS CHRONIC ACTIVE	1	0	1
HEPATITIS INFECTIOUS	2	0	1
HEPATITIS VIRAL	11	2	3
HEPATOCELLULAR DAMAGE	51	6	7
HEPATOMEGALY	23	3	3
HEPATORENAL SYNDROME	31	19	3
HEPATOSPLENOMEGALY	7	2	2
JAUNDICE	84	2	11
LIVER FATTY	16	5	3
PORPHYRIA	1	0	1
SGOT INCREASED	83	6	6
SGPT INCREASED	85	6	6

* WHO Adverse Reaction Terminology

In addition, Vigibase contains reports of increased hepatic enzymes, hepatocellular damage and hepatitis with a combination product containing stavudine, nevirapine and lamivudine.

Globally, NNRTI-based regimens are the most widely prescribed combinations for initial therapy. In spite of the potential for serious and life-threatening liver toxicity and skin rashes with nevirapine, it remains an important part of the HIV treatment regimen for many HIV-infected individuals worldwide. It is a potent NNRTI with demonstrated clinical efficacy when administered in appropriate combination regimens. The hepatotoxicity however, makes it less suitable for treating patients who use other hepatotoxic drugs such as rifampicin. On the other hand, nevirapine may be the best choice in women of childbearing potential or who are pregnant.

Fixed dose combinations (FDCs)

Nevirapine is also available as a Fixed Dose Combination (FDC) with two other drugs, lamivudine and stavudine. FDCs simplify treatment and drug management issues, improve adherence of health-care workers to treatment standards, decrease errors in drug administration, simplify drug forecasting, procurement, distribution and stocking because fewer items and lower volumes are necessary, and reduce the risk of misuse of single drugs. Due to these advantages the use of FDCs is likely to increase, particularly in countries with limited health-system infrastructures. However, since CD4 testing facilities are not always available in these settings, there is a real danger of indiscriminate use of FDCs containing nevirapine also in those individuals who may be at real risk for hepatotoxicity.

Conclusion

Health professionals responsible for the management of HIV-infected persons are advised that significant liver toxicity may develop if a nevirapine-containing regimen is initiated in patients with relatively high CD4+ cell counts. This adverse effect is linked to the chemical composition of the drug and hence, will likely develop regardless of whether the drug is formulated separately or as part of a FDC. It remains important to improve laboratory testing facilities in locations where antiretroviral therapy is distributed to identify and manage this and other possible adverse effects.

References

1. *Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach*. Geneva, World Health Organization, 2003.
2. *FDA Public Health Advisory for nevirapine (Viramune)*. United States Food and Drug Administration, 19 January 2005 (<http://www.fda.gov/cder/drug/advisory/nevirapine.htm>).
3. http://www.boehringer-ingenheim.com/hiv/prod/downloads/Viramune_Product_Mono_April2005.pdf

Twenty-eighth Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring

Observations from Working Group Exercises

The Twenty-eighth Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring was held from 26 to 29 September 2005, in Geneva, Switzerland. In this meeting, working group exercises focused on several key issues in pharmacovigilance including:

- how pharmacovigilance centres react to high profile (drug) withdrawals
- pharmacovigilance in public health programmes
- reporting adverse events following immunization (AEFI)
- reporting and learning from patient safety events
- developing an international taxonomy for patient safety events
- the relevance of the International Classification of Diseases (ICD) in pharmacovigilance.

In the previous issue of the newsletter we summarized the discussions from the first three of these exercises. We now report the key conclusions from the remaining three:

Reporting and learning from patient safety events

The World Health Assembly in 2002 urged member countries to focus on patient safety. Pharmacovigilance (PV) centres currently focus mainly on drug safety issues and are often questioned as to how effective these actions have been in ensuring patient safety. Generally, people are aware that medication errors do occur; however, they may not make the connection that pharmacovigilance centres *already provide* a system to monitor and analyse the occurrence of these errors. Understanding this link would help to understand the role of PV centres in promoting health care, with the patient as the ultimate beneficiary. The working group agreed that there is a necessity to have a system in place to escalate local reports of medication errors to an international level, so that signals can be identified and strategies and remedial actions implemented in a global sense.

In placing the focus on patient safety, there is a need to:

- make a clear distinction between medication errors and adverse drug reactions;
- develop a standardized system to collect and collate reports of medication errors;
- standardize key words in order to facilitate effective analysis of collected data.

Existing adverse drug reaction (ADR) reporting forms/systems in countries may not be suitable for capturing data on medication errors. In addition, getting reports on medication errors could be difficult due to medico-legal implications. Patients have to be educated to take responsibility for their medications, whilst emphasizing that unavoidable ADRs can and will occur. A thorough analysis would identify possible root causes for the reported errors. Strategies would have to be developed and implemented to minimize recurrence of errors. It must be realized that the greater focus on patient safety, with all its implications, would entail expansion and extension of the current services and functions of the national pharmacovigilance centres.

The working group concluded that it is best to commission a pilot project of a limited number of countries, to study the feasibility for pharmacovigilance centres to shift the focus on to patient safety, with the particular emphasis on capturing medication errors and not only restricted to collecting ADR reports. As a first step, the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden could produce a draft protocol for the study and may concentrate on a particular area, e.g. parenteral infusions. Several countries have expressed a strong interest in participating in the pilot study to investigate the role of pharmacovigilance centres in promoting patient safety.

Developing an International Taxonomy for Patient Safety

Growing concerns among a number of countries about patient safety have led WHO to call for a concerted international effort to understand and prevent adverse events in health care. At present the studies and incident monitoring systems that report patient safety data, with a few exceptions, differ in the way they define, count, and track adverse events. The lack of standardized nomenclature and taxonomy for patient safety events have confounded the development of appropriate and sustainable solutions to the many patient safety related problems. In order to facilitate the global exchange and dissemination of information among users of incident reporting systems, it is necessary to adopt a common patient safety terminology and to collect standardized patient safety data that are conducive to processing and classification. The working group arrived

at the opinion that the United States Joint Commission on Accreditation of Healthcare Organizations' (JCAHO's) scheme for Patient Safety Event Taxonomy can serve as a starting point. The group examined the five primary categories: impact, type, domain, cause, and prevention and mitigation and, agreed that further categories may be needed for developing countries. The group considered that a patient safety event taxonomy should be incident rather than patient based. It was noted that a patient safety event taxonomy goes beyond, and is broader than, medication adverse events. It covers policy and practice, procedures and everything that happens to the patient. The group concluded that an International Patient Safety Event Taxonomy (IPSET) will enhance pharmacovigilance activities and promote patient safety worldwide and recommended that this be developed.

The relevance of the WHO Classification systems (in particular, the International Classification of Diseases, ICD) in pharmacovigilance

Several national centres participating in the WHO Programme for International Drug Monitoring use ICD-10 or 9 for recording indications and concomitant morbidity. However, there are limitations to the use of the ICD. It cannot be used to code ADRs as it is not suitable for symptoms, the section for drugs (Y40-59) is not compatible with the Anatomical, Therapeutic, Chemical (ATC) classification and special indications, e.g. anaesthesia, cannot be coded.

Suggestions from the workshop were as follows:

- An ICD drug classification should be compatible with the ATC if it is to be used.
- For special indications the UMC should assign temporary codes and negotiate new codes with the ICD team on behalf of national centres.
- Temporary codes should be integrated into Vigibase Online.
- A mapping exercise should be undertaken to identify common elements. There should be mapping between WHO-adverse reaction terminology (WHO-ART) and ICD 10/11.

As a related recommendation, the group stated that since industry codes are in MedDRA (medical dictionary for regulatory activities) and most national centres use WHO-ART (WHO adverse reaction terminology), a back-mapping of WHO-ART to MedDRA would be useful to avoid manual re-coding by national centres.