WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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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This Newsletter is also available on our Internet website: http://www.who.int/medicines

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Contents

No. 6, 2007

This is the last newsletter for this year. There are two feature items in this issue that readers may find interesting: one is a summary of recommendations from the working groups at the thirtieth meeting of the national pharmacovigilance centres that was held in October this year, in Argentina. The other is a summary of events leading to, and scientific basis for the decision to suspend nimesulide in Ireland.

We wish all our readers a very healthy and happy year ahead.

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TABLE OF CONTENTS

Aprotinin

Temporary suspension while awaiting review of BART-study mortality data

Worldwide. Following consultation with Health Canada, the United States. Food and Drug Administration (US FDA), the German Federal Institute for Drugs and Medical Devices (BfArM), and other health authorities, Bayer has temporarily suspended marketing of Trasylol® (aprotinin), a drug used to control bleeding during heart surgery. This action follows the recent termination of a clinical study in Canada (Blood conservation using antifibrinolytics: a randomized trial in a cardiac surgery population (BART) clinical study), the preliminary interim data analysis from which indicated an increase in all-cause mortality in patients receiving aprotinin (Trasylol) compared to the other study drugs. The study was designed to compare aprotinin to epsilon-aminocaproic acid and tranexamic acid in decreasing the occurrence of massive bleeding associated with high-risk cardiac surgery. Data are now being collected from centres throughout Canada and a final data analysis will be undertaken by BART trial investigators. Further actions that may be undertaken in response to the analysis of that information will be made public.
During this temporary marketing suspension, Bayer Inc. in consultation with regulatory authorities have developed a process to make aprotinin available for high-risk patients where the practitioner is of the opinion that aprotinin is required and falls within the current approved indication.

References:

1. Communication from Bayer Healthcare Canada, 5 November 2007 (www.bayerhealth.ca)
2. Drug Safety Update, Volume 1(5): December 2007 (www.mhra.gov.uk)

Carisoprodol

Suspended due to greater risks than benefits

Europe. The European Medicines Agency (EMEA) has issued a press release recommending the suspension of the marketing authorization for all medicinal products containing carisoprodol. The Agency made this recommendation following a review by the Committee for Medicinal Products for Human Use (CHMP) which concluded that the risks of these medicines are greater than their benefits. The CHMP has assessed all available information on the safety of carisoprodol-containing products and has concluded that there is evidence for carisoprodol associated risk of abuse or addiction as well as intoxication and events related to psychomotor impairment. The CHMP undertook this assessment following plans made for the products' withdrawal from the Norwegian market due to new information available on the above adverse events. Carisoprodol is a centrally acting muscle relaxant, which is used mainly for the treatment of acute lower back pain. The EMEA advises that due to the risk of withdrawal symptoms, patients should not stop carisoprodol treatment prior to seeking advice from their doctor. Any switch to a new medication should be made gradually and under medical supervision.

Reference:

Press Release. EMEA, 16 November 2007 (www.emea.europa.eu)

Desmopressin

Risk of hyponatraemia and seizures; intranasal formulations no longer indicated in PNE

USA. The US FDA is warning that certain patients, including children treated with the intranasal formulation of desmopressin for primary nocturnal enuresis (PNE), are at risk for developing severe hyponatraemia that can result in seizures and death. Desmopressin intranasal formulations (marketed as DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimate Nasal Spray) are no longer indicated for the treatment of PNE and should not be used in hyponatraemic patients or patients with a history of hyponatraemia. The Agency advises that PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatraemia. The US FDA has requested manufacturers to update the prescribing information for desmopressin.

Reference:

FDA Alert. US FDA, 4 December 2007 (www.fda.gov)

Eltroxin tablets

New formulations that should not be halved or crushed

New Zealand. GlaxoSmithKline New Zealand is advising that since July 2007, a new formulation of levothyroxine (Eltroxin®) (also known as thyroxine) 50 mcg and 100 mcg tablets has been available in the country. These reformulated tablets are no longer scored and should not be halved, so patients who require a dose of 25mcg daily must instead be prescribed one 50mcg tablet to be taken every second day. It is also recommended by the manufacturer that, due to lack of data on crushing the tablets, these tablets should only be prescribed to patients who are

able to swallow the tablets whole. These tablets should be taken on an empty stomach, preferably before breakfast.

Reference
Prescriber Update, 28(1):6, November 2007 (www.medsafe.govt.nz).

Erythropoiesis stimulating agents

Labels to address risks to cancer and chronic kidney failure patients

USA, Australia. Labels for erythropoiesis-stimulating agents (ESAs) will now include information on the evidence of risks that these agents pose to patients with cancer and patients with chronic kidney failure. The ESAs available in the USA include darbepoetin alfa (Aranesp), and epoetin alfa (Epogen, Procrit). These are indicated in the treatment of certain types of anaemia. For patients with cancer, the new boxed warnings emphasize that ESAs caused tumour growth and shortened survival in patients with advanced breast, head and neck, lymphoid and non small-cell lung cancer when they received a dose that attempted to achieve a haemoglobin level of 12 grams per deciliter (g/dL) or greater. For patients with chronic kidney failure, the new boxed warning states that ESAs should be used to maintain a haemoglobin level between 10 g/dL to 12 g/dL. There are study results that show that maintaining higher haemoglobin levels in patients with chronic kidney failure increases the risk of death and other serious conditions. The new labelling provides specific instructions for dosage adjustments and haemoglobin monitoring for chronic kidney failure patients who do not respond to ESA treatment with an adequate increase in their haemoglobin levels. Additionally, the new boxed warnings clarify that ESAs should only be used in patients with cancer when treating anaemia specifically caused by chemotherapy and not for other causes of anaemia; and that ESAs should be discontinued once the patient's chemotherapy course has been completed.
Health-care professionals have been notified of similar label updates in Australia. The three ESAs currently available in Australia are erythropoietin alfa (Eprex), erythropoietin beta (NeoRecormon), and darbepoetin alfa (Aranesp). They are approved for the treatment of anaemia associated with chronic renal failure and with the treatment of certain malignancies in Australia.

Reference:
1. MedWatch Alert. US FDA, 8 November 2007 (www.fda.gov).
2. Australian Adverse Drug Reactions Bulletin, 26(6): 22-23, 2007.

Lumiracoxib

Suspended in the United Kingdom due to risk of liver damage

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has suspended the license for lumiracoxib (Prexige) due to the safety concerns about possible liver damage for patients. UK joins Australia, Canada and others in this decision (see WHO Pharmaceuticals Newsletter No. 5, 2007). Lumiracoxib, used to treat painful symptoms of osteoarthritis of the knee and hip, was first made available in the UK in December 2005. In August 2007, following analysis of data available at that time, the MHRA introduced new prescribing restrictions (contraindications) for patients with current or previous liver problems, and additional requirements for blood tests before and during lumiracoxib treatment for all other patients. The Commission on Human Medicines (CHM) has now reviewed the latest worldwide data on the safety of lumiracoxib which show an increase in the number of cases of serious liver reactions that have occurred with the licensed 100 mg dose; in some cases the reactions were associated with short-term use (less than one month). In the light of these latest data, the CHM has advised that previous measures could not be relied upon to guarantee patient safety and has therefore recommended a suspension of the products. Patients taking lumiracoxib are advised to make an appointment to see their doctor at the next convenient opportunity.

Reference:
Press Release. MHRA, 19 November 2007 (www.mhra.gov.uk).

Mycophenolate mofetil

Revised as Category D drug, to reflect risk of fetal harm

USA. US FDA has notified transplant specialists and other health-care professionals that the prescribing information for mycophenolic acid has been revised. Mycophenolate mofetil (CellCept) is an immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants. It is administered in combination with cyclosporine and corticosteroids. The US FDA is advising that there is now definite post marketing evidence of increased risk of first trimester pregnancy loss and congenital malformations, especially external ear malformations, facial abnormalities including cleft lip and palate, anomalies of the distal limbs, heart, oesophagus, and kidney associated with the use of this drug during pregnancy. In post marketing data (collected from 1995 to 2007) on 77 women exposed to systemic mycophenolate mofetil during pregnancy, 25 had spontaneous abortions and 14

had a malformed infant or fetus. The pregnancy category for this product has now been changed from Category C (risk of fetal harm cannot be ruled out) to Category D (positive evidence of fetal risk). Within one week of beginning mycophenolate mofetil therapy, women of childbearing potential should have a negative serum or urine pregnancy test. In addition, women of childbearing potential (including pubertal girls and peri-menopausal woman) taking this product must receive contraceptive counselling and use effective contraception. Health-care professionals and patients should be aware that mycophenolate mofetil reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. Additionally, the Agency advises that a patient who is planning a pregnancy should not use this product unless she cannot be successfully treated with other immunosuppressant drugs. Health-care professionals should discuss the risks and benefits of mycophenolate mofetil as well as alternative immunosuppressant therapy with the patient. The risks and precautions described above also apply to the mycophenolic acid delayed-release tablets (Myfortic).

Reference:
Medwatch Alert. US FDA, 27 November 2007 (www.fda.gov).

Rosiglitazone

Revised prescribing information due to adverse cardiac events

Canada (1). GlaxoSmithKline Inc. has written to health-care professionals that there are new restrictions on the use of rosiglitazone-containing products (AVANDIA®, AVANDAMET® and AVANDARYL™) indicated in the treatment of type 2 diabetes. These restrictions follow the Health Canada assessment of adverse event reports, published articles and other available information on congestive heart failure, myocardial infarction and related events associated with the use of these products. According to the new restrictions:

- rosiglitazone is no longer approved as monotherapy for type 2 diabetes except when metformin use is contraindicated or not tolerated.
- rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated.
- treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure

Health professionals are also reminded that;

- rosiglitazone is not indicated for use with insulin. This combination is associated with an increased risk of heart failure.
- rosiglitazone is not indicated for triple therapy (that is, therapy with rosiglitazone in combination with both metformin and a sulfonylurea). Increases in congestive heart failure and other fluid retention-related events have been reported in patients receiving rosiglitazone as part of triple therapy.

When adequate glycaemic control is not obtained through diet and exercise plus monotherapy, then rosiglitazone can be used in dual therapy, as follows: use in combination with metformin; or when metformin is contraindicated or not tolerated, use in combination with a sulfonylurea. Rosiglitazone can be added to (not substituted for) the monotherapy agent.

Health Canada is advising patients to talk to their doctors about the risks of continuing rosiglitazone therapy if they have underlying heart disease, or are at high risk of heart attack or heart failure.

UK (2). According to the MHRA a Europe-wide review of available data for the safety and efficacy of thiazolidinediones (the class to which rosiglitazone belongs) has resulted in revised prescribing information for this class of antidiabetic drugs. The revised prescribing information emphasizes that the benefits of rosiglitazone (and piaglitazone) for treatment of type 2 diabetes continue to outweigh the risks but that rosiglitazone should be used in patients with ischaemic heart disease only after careful evaluation of every patient's individual risk; and that rosiglitazone, combined with insulin should be used only in exceptional cases and under close medical supervision.

(See WHO Pharmaceuticals Newsletter No. 4, 2007 for related message from US FDA).

References:
1. Dear Health-care Professional letter from GlaxoSmithKlne Inc, 1 November 2007 (www.hc-gc.sc.ca).
2. Drug Safety Update, Volume 1(5), December 2007 (www.mhra.gov.uk).

Cefepime

Reports of death being investigated

USA. The US FDA has issued an early communication(1) about the ongoing review of new safety data and the request for additional data to further evaluate the risk of death in patients treated with cefepime. An article in the May 2007 issue of The Lancet Infectious Diseases (2) raised the question about increased mortality with the use of cefepime, a broad spectrum B-lactam antibiotic currently approved for the treatment of a variety of infections due to susceptible strains of microorganisms. The article describes higher all-cause mortality in patients treated with cefepime compared to other B-lactam antibiotics. The US FDA advises that until the evaluation is completed, health-care professionals who are considering the use of cefepime should be aware of the risks and benefits described in the product's prescribing information and the new information from this meta-analysis.

References:

1. Early Communication. US FDA, 14 November 2007 (www.fda.gov).
2. Lancet Infectious diseases, 7:338-348, 2007.

Clozapine

Constipation could be fatal

New Zealand. According to doctors PM Ellis (Wellington School of Medicine), RM McLean and M Harrison-Woolrych (Intensive Medicines Monitoring Programme (IMMP), University of Otago), gastrointestinal effects due to clozapine can have fatal consequences. Clozapine is an atypical antipsychotic that is effective for the treatment of resistant schizophrenia. It causes agranulocytosis in up to 1% of patients and regular monitoring of neutrophil counts is mandatory throughout treatment. In New Zealand one death from agranulocytosis has been reported to the IMMP. In contrast, four deaths from complications of severe constipation have been reported with the drug. Clozapine-induced constipation may be associated with serious effects such as intestinal obstruction, bowel perforation and toxic megacolon. The four deaths reported to IMMP demonstrate that these effects can be fatal. The authors note that although many anticholinergic drugs are known to cause dysmotility, clozapine has a much more potent effect through its interaction with multiple receptors, (including anticholinergic and serotonergic receptors) affecting gastrointestinal activity. This action is exacerbated by co-prescription of anticholinergic agents such as benztropine and tricyclic antidepressants. The IMMP reminds health professionals that the gastrointestinal effects of clozapine are potentially serious. Awareness of this issue may prevent life-threatening complications. Patients should be asked about bowel function and dietary advice should be provided if needed.

Reference:

Prescriber Update, 28(1):7, November 2007 (www.medsafe.govt.nz).

Glitazones

Fluid retention, cardiac failure and macular oedema

New Zealand. The Centre for Adverse Reactions Monitoring (CARM) in New Zealand has received reports of peripheral oedema, pulmonary oedema, pleural effusion and exacerbation of cardiac failure with pioglitazone and rosiglitazone. Dr Ruth Savage, Medical Assessor, New Zealand Pharmacovigilance Centre warns that glitazone antidiabetic drugs (example, pioglitazone, rosiglitazone used in type 2 diabetes) can cause dose-related but severe fluid retention, which is more likely to occur when these drugs are used in combination with insulin or sulphonylureas. Consequences include new or worsening cardiac failure and macular oedema. Pioglitazone and rosiglitazone are contraindicated in patients with NYHA Class III and IV heart failure, and not recommended in patients with symptomatic heart failure. Dr Savage advises that patients taking glitazones need to be informed of possible symptoms, and monitored for fluid retention and associated complications. If signs or symptoms develop, prescribers should stop or reduce the dose of glitazone. According to Dr Savage, reports of fluid retention leading to oedema and related conditions made up the greatest proportion of adverse reactions to glitazones reported to the WHO Global Individual Case Safety Reports (ICSR) database, Vigibase, until December 2006. In the cases reported to CARM, one patient was admitted to hospital with oedema extending from the legs to the chest while taking pioglitazone 15 mg daily. Another developed oedema of the legs and abdomen, and shortness of breath on exertion three weeks after starting rosiglitazone 4 mg daily. There was no evidence of cardiac failure. He recovered with furosemide treatment and discontinuation of rosiglitazone.

Reference:

Prescriber Update, 28(1):8-10, November 2007 (www.medsafe.govt.nz).

Inhaled long-acting beta agonists

Risk of serious asthma exacerbations

New Zealand. Medsafe (1) is drawing prescribers attention to published evidence (2, 3) that long-acting beta agonist (LABA) inhaled bronchodilators (including salmeterol and eformoterol) might increase the risk of serious asthma exacerbations, including life-threatening episodes, particularly in patients who do not use a concomitant inhaled corticosteroid. Physicians are reminded of the following:

- LABAs should not be used as monotherapy or first-line treatment for asthma; a LABA should be added to asthma treatment only if an appropriate dose of an inhaled corticosteroid does not provide adequate control.
- Patients should be warned not to stop or reduce corticosteroid therapy without medical advice, even when symptoms improve.
- LABA therapy should not be initiated, or the dose increased, in patients with significantly worsening or acutely deteriorating asthma.
- Patients should be advised to seek medical attention immediately if their asthma deteriorates suddenly.
- A reassessment of therapy should be undertaken if asthma worsens despite regular use of a LABA and an inhaled corticosteroid.

(See WHO Pharmaceuticals Newsletter No.1, 2006 for related information from the US FDA.)

References:

1. Prescriber Update 28(1):3-4, November 2007 (www.medsafe.govt.nz).

2. Nelson HS et al. The Salmeterol Multicentre Asthma Research Trial – A Comparison of Usual Pharmacotherapy for Asthma or usual Pharmacotherapy Plus Salmeterol. Chest 129:15-26, 2006.

3. Salpeter SR et al. Meta-analysis: Effect of Long-Acting Beta-Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths. Annals of Internal Medicine, 144:904-912, 2006.

Quinolone antibiotics

Tendon disorders

New Zealand. Medsafe, New Zealand's Medicines and medical devices safety authority, is reminding prescribers of the risk of tendon disorders, such as tendonitis, tendon rupture and tendinopathy, associated with the use of quinolone antibiotics. The Agency notes that the onset of these adverse effects can occur as early as the first few hours after the initial dose and as late as six months after treatment. Patients should be advised to inform their prescriber immediately of symptoms suggestive of tendon disorders, such as oedema, erythema, and sharp pain, particularly with walking and palpitation. According to the Agency of the 104 cases of tendon disorders reported so far to New Zealand's Centre for Adverse Reactions Monitoring (CARM), 69% involved quinolones, mainly ciprofloxacin, norfloxacin and enoxacin. Prescribers are cautioned to be vigilant when prescribing quinolones to patients already receiving steroid therapy, those with renal insufficiency or who are elderly as these risk factors are known to increase the likelihood of quinolone-associated tendon disorders.

Reference:

Prescriber Update, 28(1):3, November 2007 (www.medsafe.govt.nz).

Tramadol

Seizures and serotonin syndrome

New Zealand. Tramadol is a centrally-acting analgesic indicated for moderate to severe pain. It stimulates opioid receptors, and inhibits noradrenaline and serotonin reuptake. Seizures and serotonin syndrome are amongst the more commonly reported serious adverse reactions attributed to tramadol in the CARM and in the WHO Global Individual Case Safety Report (ICSR) database.

Serotonin syndrome: The CARM database holds three reports of serotonin syndrome occurring in patients taking tramadol. In each case serotonin syndrome occurred after extra serotonergic medicine was taken as follows: tramadol dose increased in a patient taking tramadol, paroxetine and thioridazine; tramadol added to long-term treatment with amitriptyline and high-dose fluoxetine (60mg daily); citalopram recommenced after patient started tramadol. In the latter case, the tramadol was commenced in hospital where the patient's history of citalopram use was not recorded. Symptoms and signs of serotonin syndrome include at least three of the following: agitation, ataxia, increased sweating, diarrhoea, fever, hyperreflexia, myoclonus, or shivering. The syndrome usually occurs after initiating or increasing the dose of a serotonergic medicine. Medicines known to cause serotonin syndrome include antidepressants (such as selective serotonin reuptake inhibitors (SSRIs), mirtazapine), antiparkinson agents (amantadine, bromocriptine etc), migraine therapy (dihydroergotamine, sumatriptan), and other agents such as bupropion, carbamazepine etc.

Seizures: Tramadol can induce seizures especially at high doses. In the last five years, tramadol has been the most commonly implicated medicine in reports of seizures to CARM. A total of ten reports were received up to December 2006, involving eight females and two males with an age range of 15 to 49 years. Seizures have been reported in patients receiving tramadol at recommended dose levels. However, reports to CARM indicate that high doses, co-prescribed medicines and a history of epilepsy may increase the likelihood of seizures with tramadol. Other medicines or history of seizures may further increase seizure risk with tramadol. In the CARM reports, three patients were taking a tricyclic antidepressant (TCA) as well as tramadol. One was also taking an antipsychotic medicine, and one an SSRI. Two of these patients experienced seizures when the dose of tramadol was increased.

Prescribers are reminded that seizures can occur with tramadol, particularly if high doses are used, when tramadol is used with other serotonergic medicines or with medicines that lower the seizure threshold. Physicians should prescribe the lowest effective dose of tramadol and avoid its use in patients with a history of seizure disorders. In patients with risk factors for seizures or serotonin syndrome, it may be prudent to consider other analgesics instead of tramadol.

***Reference**:*
Prescriber Update, Volume 28(1):11-12, November 2007.

Warfarin

Potential for interactions

New Zealand. It is well recognized that warfarin interacts with many medicines and foods such as cranberry juice, resulting in elevated International Normalized Ratio (INR) values and thus increasing the risk of bleeding in some patients (1-2). Evidence is accumulating that warfarin might interact with herbal products or complementary and alternative medicines as well (3). In New Zealand, there have been eight reports received by CARM involving warfarin interactions with complementary and alternative medicines. These included St John's Wort (*Hypericum perforatum*); ginger; aloe vera and manuka honey; creatine; glucosamine with chondroitin; and a product containing *L. acidophilus* and *B. bifidum*. The most common reaction was increased INR (seven cases); but epistaxis occurred in one patient. Medsafe warns that despite an absence of good evidence of a causal association for all of these interactions, the potential consequences are significant, so health professionals and patients should be aware of possible harm. More frequent INR monitoring is warranted in patients who take, stop or start any complementary and alternative medicine while on warfarin. Health professionals are encouraged to report suspected reactions or interactions to CARM so that more information can be gathered about complementary and alternative medicines.

References

1. Committee on Safety of Medicines. Interaction between warfarin and cranberry juice: new advice. Current problems in pharmacovigilance 30:10, 2004 (www.mhra.gov.uk)
2. Suvarna R, Pirmohamed M, Henderson L. Possible interaction between warfarin and cranberry juice. British Medical Journal 327(1749):1454, 2003.
3. Myers SP. Interactions between complementary medicines and warfarin. Australian Prescriber 25(3):54-56, 2002.
4. Prescriber Update, 28(1):4-5, November 2007.

Thirtieth annual meeting of representatives of national centres participating in the WHO Programme for International Drug Monitoring, 10-13 October 2007: recommendations from working groups

There were eight breakout sessions at the recently concluded annual meeting of pharmacovigilance centres in Buenos Aires, Argentina. Below is a summary of recommendations and discussion points from the working groups at these sessions.

Proposal on opening the database: which fields to be open to the public?

The objective of this working group was to:

- collect information on experiences in providing data from ADR databases to third parties
- get an overview on national legal requirements with regard to data privacy
- give preliminary recommendations and make some practical proposals on
  (i) how to be transparent with regard to safety data, and
  (ii) how to protect strictly and effectively data privacy.

It was reported that requests for information are received by all 12 national centres represented at the working group but not all have procedures available for dealing with these requests. If available, some are only general, others are restrictive, or very elaborate and sophisticated reflecting daily practices and needs of the respective centre.

Interested third parties are physicians, researchers (epidemiologists), lawyers, individuals as well as patient organizations or the general public, media, and politicians. Third parties have different interests and have queries ranging from very basic information (number of reports; number of fatal cases) to more detailed information, e.g. for specific rare Adverse Drug Reactions (ADRs), signals, or comparative data. Agencies need to be more open in response to these questions and to be more transparent in their decision-making processes.

It was concluded that information from ADRs in databases should be given to interested third parties, but the answers should be tailored to the individual/organization requesting the data, and that data privacy should be rigorously respected according to national legislation. It was recommended that rules and procedures be established to deal with third party requests to remove multiple conflicting information. A caveat paper should be applied in sharing information. To maintain data privacy, narratives should never be given to third parties, but can be given to the market authorization holder. Alternatively, the third party can be asked what specific fields they want to have. Doctors often want summaries instead.

Discussion: LAREB (Netherlands) has opened their database on its website for information to the general public (www.lareb.nl). Information is restricted to age groups rather than specific ages (a specific age could be an identifier). The key point about making information available is that it gives confidence to the public.

(The above recommendations will be discussed further at subsequent meetings of the WHO Programme.)

Proposal to open access to the Signal Document

A signal document is a publication of potentially interesting pharmacovigilance signals by the Uppsala Monitoring Centre Review Panel. It is based on information derived form the WHO global individual case safety reports (ICSR) database, the Vigibase. It is distributed to a restricted audience of national pharmacovigilance authorities.

The objective of this working group was to determine whether to expand access to the signal documents and if so, to determine what the distribution should be and how this will impact the safety of the end user.

Advantages of opening access to the signal document is that it reaches a wider audience, provides greater transparency, increases public confidence in pharmacovigilance, contributes to scientific research, and gives feedback to the reporters. Disadvantages include misinterpretation of information and creating unnecessary scares. It was agreed upon by the group to increase access to signal, but it is important to describe how the reports are collected, how a signal is detected and how the results should be interpreted. A solution proposed is that all signals should be published in the same journal, that marketing authorization holders should be allowed to make a comment and that the national centres

should be notified in advance. Signals could be graded as weak or strong to better assess impact. The impact could be measured by the increase in number of reports or increased number of research following signals.

(The above recommendations will be discussed further at subsequent meetings of the WHO Programme.)

How to get information from and to end-users (patients)

This working group concentrated on the questions: Why do we need to involve consumers as partners in pharmacovigilance? How to involve them as reporters, advocates, and fund raisers or in promotional activities, training and data collection? What sort of reporting mechanisms would best work for patients? How to empower patients with information: what they need to know, when and how quickly they need to know, and why? What are the best practices of getting information to patients? Should national centres submit reports from patients to the WHO global individual case safety reports database at the Uppsala Monitoring Centre (UMC)?

It was agreed that there is a need to involve consumers/patients in pharmacovigilance. Concerns regarding reporting by patients include the quality of reports from patients, whether there is too much noise, incomplete information, sources of information to the patients (e.g. internet sites), and patients' access to their prescribers.

International experience indicated that patients are advised to report to their physicians, or to go to their pharmacists, or some patients report directly to national centres. Some national centres are not interested in accepting reports from patients/consumers, while some may accept from special interest groups. In developing countries, patients need the assistance of health professionals with their reports. An Information Hotline is available in some countries. EudraVigilance does not accept reports from patients; all reports must be medically confirmed.

Consumers/patients have rights and are acknowledged as end users. By involving patients, it is hoped to improve compliance, and by accepting patient reports one gets another view of patient safety. Mechanisms for reporting by patients must be suitable. Empowering patients with information is an opportunity for National Centres to provide information, and can also be a public health role. There was almost unanimous agreement in this working group that consumer reports accepted by the National Centres should be reported to the UMC.

Focusing on current concerns around direct-to-consumer advertising of pharmaceuticals, the group made a unanimous recommendation, to prohibit direct-to-consumer advertising.

Identifying risks in special populations – women and children

The objective of this working group was to ascertain which populations are at risk and why they are vulnerable. It was also intended to discuss the needs for preventive systems to be in place.
For pregnant and lactating women there are few data from clinical trials on the safety of medicines. Women may be exposed inadvertently and there is a lack of information/education/guidance in resource-limited settings. Use of pregnancy registries could be useful. It should be identified who would compile such a registry. Intensive monitoring systems could lead to creating registers, or the collection of all congenital abnormalities, stillbirths, birth defects, etc. could create a "congenital abnormalities" register.

For women of childbearing age there is a need to educate health professionals, the general public and the media. Establishment of medical information centre may be useful for inadvertent exposure.
Children are vulnerable because they have unique physiological features and handle drugs differently. Extrapolation of adult data to children is often not appropriate nor backed by solid evidence. In resource poor settings, children are often malnourished and conditions such as marasmus, kwashiorkor are common. Mostly medicines used in children are off-label use, although there are now some clinical trials in children. There are few formulations specific to children and dosage in children is often inaccurate. There are often few reports in children, hence, it is difficult to know the true extent of ADRs. Global networking and sharing of information, or pooling of data could contribute to the knowledge. Poison Centres are often a source of information for ADRs in children. An essential medicines list for children should be established. The WHO has published a booklet promoting safety of medicines in children. At the forthcoming International Conference of Drug Regulatory Authorities (ICDRA), a pre-meeting session will focus on issues of medicines for children.

Patient safety: extending the scope of pharmacovigilance centres

The objectives of this working group were to consider the role of pharmacovigilance centres in relation to medication error, to discuss current and proposed reporting formats, to address terminology/reporting issues and to consider recommendations to progress work carried out to date.

The existing roles of pharmacovigilance centres in monitoring medication errors (ME) need to be expanded and the ability to detect cases of ME increased. Limitations of existing systems include terminology and presentation of information. Pharmacovigilance centres are mostly not ready for root cause analysis and clinical response to corrective actions in terms of speed.

A proposal for a combined ADR and ME report form needs to be discussed further. There are areas which can be identified for focused analysis, e.g. anticoagulants, anti-diabetics, beta-blockers, digoxin, or which concentrate on patients presenting with allergy (angioedema/anaphylaxis) that may be due to ME.

It was recommended that:
- national centres interact with relevant national bodies to ensure integration of activities related to ME
- national centres complete and return questionnaires to facilitate a comprehensive overview of data to complete the pilot project
- the UMC develops a web-page for ME activities, with links to relevant documents
- a special ad-hoc meeting takes place to further progress activities
- co-operation continues with the World Alliance for Patient Safety

Communication and Crisis Management in Immunization and Other Health Programmes

This working group session was designed to solicit various countries' experience and gain some of the best practices in crisis management that could serve as an outline for development of a WHO technical document which shall be part of the WHO crisis management strategy for vaccine safety crisis. If problems are not addressed, the loss of credibility to government programmes can be damaging to public health.

Shared experiences of some countries on crises covered impact of rumours, role of the media, perception of disasters, coincidental adverse events following immunization (AEFI), anti-vaccine lobby, interpretation of science, premature withdrawal or suspension of a product which can fuel misinformation.

The identified needs for national centres were the desire to create guidelines or Standard Operating Procedures (SOPs) and protocols to predict, prepare and plan for future events. These protocols should for example cite identified communication list (who should receive explanatory messages), and the roles that each one should play to address a communication crisis and who are the trusted opinion leaders that need to be recruited to help manage this crisis, and some communication materials developed targeted according to the expected audience. Training and drills were deemed necessary which includes key skills like process management and communication skills balanced with science.

In dealing with potential groups that are considered 'activists' against a public health programme, the working group suggested that it is important to consider the context of culture and allow equal opportunities for these activist groups to articulate their concerns. When explaining the facts of a crisis, compassion and empathy were cited as critical components of a credible messenger.

Some of the reasons that contributed to the creation of a crisis were that science, while not an exact discipline at times, does contribute to conflicting results, hence, perceived as poor or weak. Thus when scientists become unequivocal and unwilling to communicate the facts appropriately, the society becomes mistrusting. Other factors for crises include political pressures, religious agendas and unresolved issues that turn into recurrent debates.

The method of communication should consider culture and context and should target various levels from global to community in such a manner as to build partnership with many stakeholders. Social marketing is a tool to sell to the community.

At this workshop lessons learned were to:
- be prepared for the crisis all the time
- learn to deal with different perceptions and to understand the audience
- build trust and credibility and to be recognized in the community even before the crisis
- have effective media communication systems
- be honest, transparent, credible, quick in clarifying any misinformation

- show empathy and compassion when there is a tragedy even if this is unrelated to the product or the program
- choose a spokesperson who is kknown, familiar, trusted and trained
- learn from other countries' experience

It was proposed that a course on communication techniques should be considered at next year's annual meeting.

Complementing spontaneous reporting with other methodologies, e.g. Cohort Event Monitoring (CEM)

The aim of this working group was to determine how national pharmacovigilance centres could expand their reporting systems to include cohort event monitoring (CEM) and to discuss the special requirements in CEM such as developing an events dictionary. CEM methodology is flexible; it builds cohorts by various means (prescription records, public health programmes, and other health records. It should be included in pharmacovigilance training. CEM has many additional needs in the area of terminology, because CEM uses terms that are never reported or rarely used in spontaneous reporting. Such terminology has to be in the context of local culture and programmes. A complete dictionary of 'adverse events' with a hierarchical structure should be developed. The working group proposed to map WHO-ART and the events dictionary developed by New Zealand's Intensive Medicines Monitoring Programme (IMMP), to update WHO-ART correspondingly, with provisions on ongoing maintenance in accordance with progress in medical sciences, and to have the terminology available within a data management tool such as the Vigiflow (see www.who-umc.org). A data management tool such as Vigiflow should be adapted to receive reports from CEM.

Complementing spontaneous reporting with other methodologies: stimulated passive reporting

Stimulated passive reporting (SPR) has been used in South Africa (SA) as a way of encouraging reporting of ADRs due to antiretrovirals. The objective of this working group was to determine whether SPR could be used as a methodology to improve spontaneous ADR reporting. The general consensus was that SPR was not a methodology per se, but could be used to encourage spontaneous reporting of ADRs. Advantages of SPR are that it could be used to suit country and/or product specific needs, to encourage spontaneous reporting of ADRs, and to increase awareness and culture of reporting. It could be effective if used appropriately to complement existing pharmacovigilance activities/systems. Disadvantages of SPR are that it does not necessarily increase the quality of reporting, it can limit reporters to reporting specified ADRs only and it does not determine incidence of ADRs and may limit information for signal generation.

Nimesulide: national and EU review and regulatory outcome

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Nimesulide is a non-steroidal anti-inflammatory drug (NSAID), with weak Cox-2 selectivity, which was first authorized in Italy in 1985 and is currently marketed in more than 50 countries worldwide. In common with other NSAIDs, a potential for hepatotoxicity associated with Nimesulide was identified and in view of concerns regarding this risk, experience with use of nimesulide was closely monitored by a number of countries, with articles published in national bulletins to highlight the issues among healthcare professionals. In addition, the product information was updated on a number of occasions to include strengthened warnings regarding the risk of hepatotoxicity.

In April 2002, in accordance with European legislative provisions, a formal referral procedure was initiated to review the benefit/risk profile of systemic nimesulide products across European Union (EU) Member States, following suspension of the national marketing authorisations in Finland and Spain due to concerns regarding hepatotoxicity. Following its assessment of the data at that time, the Committee for Proprietary Medicinal Products (CPMP) concluded that the benefit/risk profile of nimesulide for systemic use remained positive subject to a number of restrictions, including limiting the maximum daily dose to 100 mg twice a day for as short a duration as possible, limiting its use to the treatment of acute pain, osteoarthritis and dysmenorrhoea, contra-indicating its use in patients with hepatic disorders and the inclusion of warnings relating to the risk of serious hepatic reactions. The CPMP Opinion was endorsed by the European Commission in April 2004 and the product information was subsequently amended in line with the legally binding European Commission Decision.

On 9 May 2007, the Irish Medicines Board (IMB) received new data provided by representatives from the Irish National Liver Transplant Unit, based on a retrospective review of all cases of fulminant hepatic failure (FHF) of unknown cause (non-A, non-B, non-paracetamol overdose) transplanted at the unit from January 1994 until February 2007. Of the 29 evaluable cases of FHF included in the review, nine patients had recently commenced taking a nonsteroidal anti-inflammatory drug (NSAID) and of these, six were taking nimesulide. The treating clinician considered nimesulide as the probable cause of FHF in five of the six cases and a possible cause in the remaining case, based on the Naranjo scoring system. Two patients died following transplantation. The transplant cases occurred predominately in females (5/6) and the age range was from 23 to 61 years. The duration of use was reported as ranging from one week to four months. The data presented suggested that the development of FHF in association with nimesulide is unpredictable in nature and that it is difficult to define an at-risk population.

A cumulative review of all spontaneous reports of adverse reactions associated with the use of nimesulide on the IMB's pharmacovigilance database identified a total of 53 hepatic adverse reactions since nimesulide was first authorized in Ireland in 1995, including nine cases of hepatic failure, four of which resulted in fatal outcomes.

These data, in conjunction with a comprehensive literature review, informed the IMB decision on 15 May 2007 to suspend the marketing authorisations for all nimesulide-containing medicinal products for systemic use in Ireland and to again refer the issue to the CHMP for further consideration. This referral was initiated under Article 107 of Directive 2001/83/EC, as amended, which requires that EU Member States, the Agency (EMEA) and the MAH must be notified of national regulatory action taken and in the case of suspension/revocation, for the CHMP to prepare an opinion on the issue.

The CHMP initially considered the new safety data from Ireland on the risk of fulminant hepatic failure associated with nimesulide, as well as data available from published literature at its May 2007 meeting. In addition, the innovator MAH, Helsinn Birex Ltd., attended this meeting to provide explanation. The CHMP concluded that the hepatic profile of nimesulide, since the time of the previous referral, should be reviewed in an expedited manner with an opinion issued in July 2007. France was appointed rapporteur with Belgium and Ireland as co-rapporteurs. The procedure required assessment of pharmacovigilance data from individual member states and the responses from the MAHs to the list of questions agreed by CHMP. At the June 2007 meeting of the CHMP, the timetable for the procedure was extended with an opinion scheduled for September 2007.

Data provided by other EU-Member States where nimesulide is authorized (excluding Ireland) identified a total of 206 hepatic-related adverse reactions associated with nimesulide reported in the period since the previous referral, from 12 of the 14 Member States where nimesulide is authorized, including 15 hepatic-related fatalities. Limited data were received from national liver transplant units, although a further six liver transplants associated with nimesulide were identified in Italy. Overall, these data confirm that

serious and unpredictable hepatic reactions to nimesulide, including fatalities, continue to occur in a sustained manner despite extensive warnings in the current product information.

A review of the data available from the EudraVigilance database also suggested a higher reporting of hepatobiliary disorders (cholestasis and jaundice, hepatic failure and associated disorders and hepatocellular damage and hepatitis NEC) for nimesulide than for the coxibs. These data also suggest that nimesulide is associated with a higher case-fatality rate for hepatocellular damage and hepatitis and for cholestasis and jaundice.

A review of the MAHs' sales data indicated that in the period since the 2002 referral, while sales and prescriptions in the EU have fallen overall by approximately 10%, there have been marked increases in sales, particularly in newly established markets (example Austria, Czech Republic). In France and Ireland the indications for use were expanded post-referral and marked decreases were noted in other member states, including Italy and Portugal. This suggests that prescribing and usage practices are influenced predominately by local factors, including marketing. The data also show that in the EU, nimesulide is increasingly prescribed for 'musculoskeletal' indications, particularly low back pain and arthritic conditions, which are likely to be associated with chronic use.

Specific analysis of the safety profile of nimesulide in the context of hepatic-related adverse reaction reports indicates a doubling of reporting in the last five years compared to the previous 17 years. The innovator MAH suggests this increase may be attributable to the reporting of old cases in the post referral period due to an increased awareness by health-care professionals of the risks associated with nimesulide. Serious hepatic adverse reactions, however, accounted for a higher proportion of hepatic reports in the post-referral period indicating that the increase in reporting rates following the referral is not solely attributable to reporting bias. Furthermore, in newly established markets there was an increase in hepatic adverse reaction reports with increasing exposure independent of the proceedings of, or the measures taken after, the Article 31 referral. This is despite market research undertaken by the innovator MAH suggesting that the majority of patients are now taking the recommended dosage of 200 mg daily for a period of less than 15 days. Of particular concern, the proportion of hepatic reactions that occur with short-term treatment has increased, with 39.8% and 28.9% of cases occurring within 15 and 7 days duration of therapy, respectively, clearly demonstrating that there is no 'safe' duration of use for nimesulide. The data also suggests that amendments to the product information arising from the referral resulted in a shift in the demographics of the cases of hepatic adverse reactions rather than any meaningful impact on the incidence of cases.

while some cases of hepatic failure associated with nimesulide have occurred in patients who either had pre-existing liver disease or in whom nimesulide was continued despite liver dysfunction, avoiding such potential cases is not straightforward. Firstly, because a portion of the cases occurred in patients who to all appearances were previously well and who had consumed the drug at therapeutic doses and, furthermore, were appropriately dechallenged at the time of presentation. Secondly, neither radiological imaging nor prior medical history would detect any evidence of underlying hepatic cirrhosis. Without microscopic evidence, therefore, a prescribing physician would assume a normal liver at the time of prescription of the drug. This illustrates the difficulty in real clinical situations in separating the potential 'high-risk' group of patients from the 'normal-risk' ones.

Recent literature supports the finding of the 2003 publication of Traversa et al of an increased risk of severe hepatotoxicity associated with nimesulide compared with other NSAIDs. Non-clinical data also supports the unpredictable nature of nimesulide's hepatotoxicity.

In conclusion, because of their common use, NSAIDs contribute significantly to the overall burden of drug-induced liver injury. However, the importance of any drug as a cause of liver injury lies not in the overall number of cases, but in the severity of some reactions. Based on the review of the data presented, nimesulide is a NSAID with a higher and less predictable risk of severe hepatotoxicity than other NSAIDs and the data available indicate that previous measures taken to mitigate this risk have had limited effect.

The Rapporteur's assessment reports were discussed at the September CHMP meeting and the innovator MAH gave an explanation to the CHMP on 18 September 2007 centred on the list of outstanding issues identified in relation to hepatotoxicity. In addition, the innovator MAH proposed measures to improve the benefit/risk profile of nimesulide and to assess how the impact of these measures could be monitored and assessed. For this purpose, a Risk Management Plan (RMP) was submitted, the main proposals of which are a review of epidemiological data; a non-interventional study in European transplant centres to characterize acute hepatic failure attributed to drug therapy and requiring liver transplantation, a monitoring activity to evaluate the effectiveness of risk communication and a survey to clarify the modes

of use of nimesulide in selected EU Member States to identify potential misuse, in particular dispensing without prescription.

Having considered the available data, the CHMP concluded that nimesulide is associated with an increased risk of hepatotoxicity. However, the magnitude of this increased risk was considered slight and as such, the CHMP considered that marketing authorisations could be maintained, subject to restriction and amendment. In reaching its conclusion, the CHMP also considered the gastrointestinal toxicity profile of nimesulide as compared to other NSAIDs, and the possible consequences of switching to other NSAIDs with a higher gastrointestinal risk.

On 20 September 2007, the CHMP adopted an opinion recommending maintenance of the Marketing Authorisations for nimesulide-containing medicinal products for systemic use, subject to restricted use, amendment of the product information and conditions for the Marketing Authorisations. A European Commission Decision on this opinion is awaited at this time.