

# Regulatory and Safety Matters

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## **Pneumococcal vaccine: recommendations for use**

**United States of America** — The Federal Advisory Committee on Immunization Practices has recommended administration of pneumococcal vaccine during the 2000–2001 flu season. The vaccine has a demonstrated effectiveness of almost 70% in preventing infections and can be given at the same time as influenza vaccine (1).

Infection with *Streptococcus pneumoniae* is one of the most common causes of death in the United States, mainly in the elderly. It accounts for approximately 50 000 cases of bacteraemia, 3000 cases of meningitis, up to 175 000 hospitalizations from pneumonia and 7 million cases of otitis media yearly.

The vaccine is recommended for persons aged 65 years or older; persons 2–64 years of age with chronic cardiovascular disease, pulmonary disease or diabetes, including immunocompromised individuals, those suffering from sickle cell disease or splenectomy, or ethnic groups such as Native or Alaskan Americans.

Children under 2 years of age and children up to 59 months of age who are at high risk of infection (such as those in day care, with frequent acute otitis media, etc.) should receive the pneumococcal vaccine, Prevnar® which was licensed in February 2000 (2). The vaccine is the first multivalent conjugate pneumococcal vaccine for children under 2 years of age and is administered in 4 shots. Most children over 2 years of age will only need one dose of the vaccine.

### **References**

1. CDC Office of Communications Press Release, [www.cdc.gov](http://www.cdc.gov), 22 June 2000.
2. *HHS News*, P00-3, 2000.

## **Valaciclovir: neuropsychiatric reactions**

**Australia** — Valaciclovir is an antiviral prodrug of aciclovir used in the treatment of herpes infections.

The Adverse Drug Reactions Advisory Committee has received 69 reports of minor reactions including headache, nausea, rash, dizziness. However, 13 more severe neuropsychiatric reactions have been reported and include hallucination, confusion, delirium, ataxia, dysarthria, convulsions, psychosis and stupor. Of these, all but one occurred in patients with chronic renal failure or age-related renal impairment. Although this is consistent with the product information physicians should be made aware of the possibility of these risks.

**Reference:** *Australian Adverse Drug Reactions Bulletin*, 19: 2 (2000).

## **Zanamivir: revisions to labelling**

The manufacturer of zanamivir (Relenza® Glaxo-Wellcome Inc.), has circulated an important warning on revisions to the safety labelling of the product, which was approved in 1999 for the treatment of uncomplicated acute illness due to influenza virus.

The warning describes reports of bronchospasm and decline in lung function in some patients and states that zanamivir is not recommended in patients having underlying airways disease, such as asthma or chronic obstruction pulmonary disease. Fatal events have been reported and information has been added on allergic-like reactions including the potential for masking of serious bacterial infections which may present as influenza-like symptoms. New animal toxicity data have also led to a change in the information on use in pregnancy.

**Reference:** Letter from Glaxo Wellcome, July 2000 available from US Food and Drug Administration on <http://www.fda.gov/medwatch/safety/2000/relenz.htm>

## **Celecoxib: adverse reaction reports**

**Australia** — Since October 1999 the Adverse Drug Reaction Advisory Committee has received 919 reports of suspected adverse reactions to celecoxib the first in the class of COX-2 inhibitors to be marketed. In 869 reports, celecoxib was the only suspected drug. Commonly, minor gastrointestinal reactions have been reported but there have also been cases of other more serious reports including gastrointestinal ulcers and bleeding.

There have also been 9 reports of acute renal failure or worsening of chronic renal failure. In these reports the patients were elderly or taking both an angiotensin converting enzyme (ACE) inhibitor or diuretic at the time celecoxib was started. Other types of reactions appear to be rashes/urticaria; allergy; peripheral oedema; dizziness and headache.

**Reference:** *Australian Adverse Drug Reactions Bulletin*, 19: 2 (2000).

### Olanzapine: serious reactions

**Canada** — Olanzapine, an atypical antipsychotic, was first marketed in July 1996 for treatment of schizophrenia and related psychotic disorders. A total of 153 reports of suspected adverse drug reactions associated with olanzapine have so far been received by the Canadian Adverse Drug Reaction Monitoring Programme.

Olanzapine was reported as a suspected drug in 22 deaths including suicide, overdose, neuroleptic malignant syndrome, arrhythmia, myocardial infarction, heart failure, pneumonia, sepsis, sudden death, mesenteric thrombosis, and choking.

Eleven reports of haematological reactions described leukopenia, granulocytopenia, neutropenia, pancytopenia or anaemia. In 5 of the 11 cases, the patient had a history of similar problems when taking the chemically related drug, clozapine. A history of clozapine-induced leukopenia may be a risk factor for haematological reactions to olanzapine.

Neuroleptic malignant syndrome was reported in 11 cases of which 2 were fatal. Health care professionals should be aware of the signs and symptoms of this syndrome which includes fever, sweating, muscle rigidity, altered mental state, irregular heart rate or blood pressure or heart rhythm. Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents.

Adverse drug reactions of a similar nature have previously been reported in this journal (2).

#### References

1. *Canadian ADR Newsletter*, 10(3): 2 (2000)
2. *WHO Drug Information*, 13(3):171 (1999).

### Infliximab approved for rheumatoid arthritis

**European Union** — The European Commission has granted marketing authorization for infliximab, (Remecade®) for use in combination with methotrexate in the reduction of signs and symptoms of rheumatoid arthritis in patients with active disease. The product should only be used when the response to disease-modifying antirheumatic drugs, including methotrexate alone, has been inadequate.

The ability of infliximab to neutralize tumour necrosis factor (TNF)-alpha, a proinflammatory mediator, represents a treatment advance in reducing the swelling and inflammation associated with the disease. The approval was based on findings from ATTRACT, one of the largest clinical trials to be carried out in patients with advanced rheumatoid arthritis. Results from the trial demonstrate that infliximab was generally well tolerated. The most common adverse events included upper respiratory tract infections, headache, nausea, sinusitis, rash and cough. The incidence of infusion reactions was below 5%. It is estimated that 2.5 million people in Europe are affected by rheumatoid arthritis.

Infliximab is also approved for the treatment of Crohn disease.

#### Reference:

1. Communication from Johnson & Johnson at <http://www.jnj.com> 29 June 2000.
2. European Agency for the Evaluation of Medicinal Products. Listing of medicinal products granted a community marketing authorization under the centralized procedure, June 2000.
3. *Pharmaceutical Journal*, 265: 10 (2000).

### Tenecteplase: the first "clot buster"

**United States of America** — The Food and Drug Administration has approved tenecteplase for the reduction of mortality associated with acute myocardial infarction. The product is a single-bolus thrombolytic agent having the potential to simplify heart attack treatment by offering physicians the fastest administration of a thrombolytic to date. It is possible to administer within five seconds and in one dose, which is evaluated in relation to the weight of the patient.

Tenecteplase works by stimulating the body's own clot-dissolving mechanism by activating plasminogen, a naturally occurring substance secreted by endothelial cells in response to injury to the artery walls. Tenecteplase activates plasminogen, which converts into plasmin and breaks down the fibrin mesh that binds the clot together. The clot is then dissolved, restoring blood flow to the heart.

As with all thrombolytics, the most significant adverse events observed in clinical trials with this product include intracranial haemorrhage and stroke. The effects of the drug are currently under investigation in four ongoing clinical trials, involving more than 9000 patients, which have been designed to evaluate various heart attack regimens in combination with other agents.

Tenecteplase (TNKase®, Genentech) is a bioengineered recombinant DNA-derived version of naturally-occurring tissue plasminogen activator (TPA). The product will be provided in a needleless injection system kit.

**Reference:** Genentech, <http://www.genentech.com> 2 June 2000.

### **Bupropion: a new approach to smoking cessation**

**United Kingdom** — Bupropion, (Zyban®) the first non-nicotine prescription medicine for use as an aid to smoking cessation has been launched. It acts as a dopamine and noradrenaline reuptake inhibitor to break the cycle of addiction: dopamine is implicated in craving and noradrenaline in withdrawal symptoms. Clinical trials involving 1500 patients (1) showed bupropion to be twice as effective as nicotine replacement therapy. The results also showed that 30% of subjects were not smoking after one year compared to 16% using nicotine replacement therapy patches.

It is recommended that bupropion be used alone since combining with nicotine replacement therapy may raise blood pressure. This possibility needs further investigation. Side effects to date have been mild and transient with the most common reports being insomnia, dry mouth and headache. No dependency has so far been demonstrated. A support programme is also provided by the manufacturer (2).

### **References**

1. *New England Journal of Medicine*, **340**: 685 (1999).
2. *Pharmaceutical Journal*, 265: 9 (2000).

### **Doxorubicin for ovarian cancer**

#### **European Union/United States of America** —

The Committee for Proprietary Medicinal Products (CPMP) has recommended approval of pegylated liposomal doxorubicin hydrochloride (Caelyx®) for the treatment of advanced ovarian cancer in women who have failed first-line platinum-based therapy (1). The application proposes that Caelyx® be administered intravenously once every four weeks for as long as the disease does not progress and the patient continues to tolerate treatment. The product has previously received centralized marketing authorization in the European Union for the treatment of AIDS-related Kaposi sarcoma and extensive mucocutaneous or visceral disease (2).

In the USA, doxorubicin (Doxil®) was approved in 1999 (under an accelerated review process designed to address urgent unmet needs) to treat metastatic ovarian cancer in women whose disease is refractory to paclitaxel and platinum-based chemotherapy. The product is a liposomal formulation of doxorubicin, using a novel targeted delivery system to help evade recognition and uptake by the immune system. This allows liposomes and their pharmaceutical content to circulate in the body longer (3).

Ovarian cancer is the second most common gynaecological cancer in the USA; an estimated 25 200 cases were diagnosed in 1999 and approximately 35 000 new cases are diagnosed in the European Union every year. Between 55 to 75% of women relapse within two years.

### **References**

1. Publication of CPMP opinions at <http://www.eudra.org/humandocs/humans/opinion.htm> June 2000.
2. Schering Plough, company news on line. <http://www.schering-plough.com> (3 July 2000).
3. Alza corporation. <http://www.alza.com> (3 July 2000).

## Linezolid: the first oxazolidone antimicrobial approved

**United States of America** — The Food and Drug Administration has approved linezolid, (Zyvox®), the first antibacterial drug of the new oxazolidinone class to treat infections associated with vancomycin-resistant *Enterococcus faecium*, including cases with bloodstream infection. Other indications are treatment of hospital-acquired pneumonia, complicated skin and skin structure infections, including cases of methicillin-resistant *Staphylococcus aureus*, community-acquired pneumonia and uncomplicated skin and skin structure infections.

Vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* infections are a particular problem in hospitalized or immunocompromised individuals. Since 1989 there has been a rapid increase in the incidence of methicillin-resistant *Staphylococcus aureus* infections. These organisms are often resistant to multiple antibiotics and limited therapeutic options are available to patients.

The most frequently reported side effects attributed to linezolid in clinical studies were headache, nausea, diarrhoea and vomiting. The most important laboratory test change was a decrease in platelet counts. Linezolid may interact with other drugs, including over-the-counter cold remedies containing pseudoephedrine or phenylpropranolamine and cause an increase in blood pressure.

Due to concerns about appropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with linezolid in an outpatient setting. The manufacturer anticipates that linezolid will be used principally in hospitals or institutional care settings.

Worldwide licensing is intended by the manufacturer, and an application has also been submitted in the United Kingdom (2).

### References

1. *FDA Talk Paper*, T00-17 (2000).
2. *Pharmaceutical Journal*, **264**: 284 (2000).

## Guidance for adverse reactions labelling

**United States of America** — The Food and Drug Administration has issued a draft guidance for the development of the adverse reactions section of labelling for human prescription drugs and biologics. The document, which was published in June, is the first in a series of guidances for industry that are intended to make the labelling more consistent and helpful to prescribers and patients.

The draft guidelines emphasize the need to focus the adverse reactions section on drug safety information that is important to prescribing decisions, and to convey this in a format that is clear, easy to find and consistent across different drugs and drug classes. The guidance suggests that the adverse reaction section be limited to information that can be helpful in treating, monitoring and advising patients. Long and exhaustive lists of every reported adverse event, including those that are infrequent or minor, should be avoided.

*Guidance for Adverse Reactions Labeling*, Food and Drug Administration is available on: [www.fda.gov/cder/guidance/1888dft.htm](http://www.fda.gov/cder/guidance/1888dft.htm).

**Reference:** *FDA Talk Paper*, T00-30 (2000).

## Legislation adopted in Europe on orphan drugs

**European Union** — In a bid to encourage the pharmaceutical industry to invest in developing treatments for diseases which are rare or not economically viable, legislation has been adopted to stimulate new treatment options for patients. Pharmaceutical companies may now apply to the European Agency for the Evaluation of Medicinal Products (EMA) to designate orphan medicinal products. Under the new legislation, companies will be able to request reductions in fees for market authorizations and for alterations to the approval after registration. Companies whose products are granted orphan drug status will be entitled to a 10-year period of market exclusivity.

The prospect of obtaining a 10-year period of market exclusivity for orphan medicinal products in the European Union will provide a strong incentive for sponsors. Pharmaceuticals intended to treat

diseases which may have a high prevalence in developing countries, but which are classified as rare in the European Union, such as malaria, may also be designated as orphan medicinal products. A Committee, which includes representatives of patient organizations, has been created to evaluate whether a potential medicine meets the criteria of an orphan drug.

Similar legislation was adopted in the United States in 1983, where the application of tax incentives for companies proved to be effective. However, tax incentives are not possible in the European Union due to the absence of a centralized system of taxation.

**Reference:** European Commission Press Release. *Commission takes measures to help rare disease patients.* <http://www.eudra.org> 27 April 2000.

### More drug safety measures planned in Japan

**Japan** — The Ministry of Health and Welfare will propose new drug safety measures, including standardization of safety measures. The Ministry will continue to study ways to improve drugs and medical devices that are liable to be misused or confused with other products, including ways to improve postmarketing surveillance. Among these measures is the standardization of warning labels and rules for product naming. A proposal has also been submitted which will oblige manufacturers to conduct intensive monitoring of their products shortly after launching.

**Reference:** *Pharma Japan*, 1704: 11 (2000).

### "Street drug alternatives" are not dietary supplements

**United States of America** — The Food and Drug Administration has made a review of 140 reports of adverse drug reactions linked to the use of dietary supplements containing ephedrine alkaloids. The FDA has called for additional information before proposing limits to the dosing level and duration of use (1).

In addition to these actions, the Agency has issued a *Guidance for Industry on Street Drug Alternatives* in response to the proliferation of various products promoted as alternatives to illicit street drugs. These products, which are intended to affect psy-

chological states are generally labelled as containing herbals, vitamins, minerals or amino acids. Given their intended use, the FDA does not consider street drug alternatives to be dietary supplements. Street drug alternatives are therefore considered as unapproved and misbranded drugs that are subject to regulatory action, including seizure and injunction (2).

#### References

1. US Food and Drug Administration. *Dietary supplements containing ephedrine alkaloids: docket update, availability.* <http://www.fda.gov/OHRMS/DOCKETS/98fr> 31 March 2000.
2. US Food and Drug Administration. *Guidance for Industry on Street Drug Alternatives.* <http://www.fda.gov/OHRMS/DOCKETS/98fr.040300d.txt> 31 March 2000.

### Tamsulosin: syncope now reported

**Japan** — Tamsulosin was marketed in 1993 for dysuria due to prostatic hypertrophy. Based on reports received during the first phase of postmarketing surveillance, hypotension was added to the precautions section of the labelling in 1994. Cases of syncope/unconsciousness were also cited with reference to case reports from other countries.

Five cases of syncope/unconsciousness due to orthostatic hypotension associated with the use of tamsulosin have since been reported in Japan.

**Reference:** *Pharmaceuticals and Medical Devices Safety Information*, 159, 22 March 2000.

### Dapsone hypersensitivity syndrome

**Singapore** — A 22-year-old serviceman on an overseas training exercise in Brunei, received 100 mg dapsone and 12.5 mg pyrimethamine (Maloprim®) weekly as antimalarial chemoprophylaxis.

Two weeks later, he developed fever which was resolved by taking paracetamol but was followed by sudden onset of pruritus on both hands. Pruritic papular rash appeared on hands and feet and progressed to the trunk. Fever returned with chills, left cervical and right inguinal lymphadenopathy and hepatosplenomegaly. Maloprim® was discontinued. On admission to hospital he was afebrile and had bilateral periorbital swelling. The arms, legs and trunk were covered by an erythematous

popular rash and petechiae on the feet. The skin had begun to exfoliate. After four days' treatment with oral prednisolone and hydroxyzine he recovered.

**Reference:** *Singapore Adverse Drug Reaction News*, Volume 2 (1), March 2000.

## Kava extract linked to hepatitis

**Switzerland** — The Inter-cantonal Office for the Control of Medicines has received information on a case of hepatitis following administration of Kava extract (*Piper methysticum*). Physicians and pharmacists are reminded that symptoms such as fatigue, loss of appetite or nausea indicate hepatic reactions and a need to stop taking Kava extract. Patients should be warned to watch for such signs and consult a physician if they appear (1).

Since 1998, six Kava products have been marketed in Switzerland for the treatment of anxiety and nervousness. Several other cases of adverse reactions have been reported and include 9 spontaneous reports of hepatic reactions (8 women and one man). One report (2), on an ethanolic Kava extract describes severe hepatitis after 6 months intake of 60 mg Kava-lactones, while rechallenge induced recurrence of symptoms 14 days later. This represents one case in 170 000 treatment regimens of an average duration of 30 days. Delay of symptoms varies between 3 weeks and 4 months, although one case was reported two years later.

In three cases, clinical symptoms of hepatitis included icterus denoting a decrease in prothrombin time. In four cases where a biopsy was practised, cellular necrosis, inflammatory reaction and eosinophilia were observed, denoting an immunological reaction.

### References

1. Communications de l'OICM. *Bulletin des médecins suisses*, 1335–1338 (2000).
2. Strahl, R. *Deutsche Medizinische Wochenschrift*, 123: 1410–1414 (1998).

## Gene therapy and patient protection

**United States of America** — The Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have announced two initiatives to

strengthen safeguards for individuals enrolled in clinical studies involving gene therapy.

### **The Gene Therapy Clinical Trial Monitoring Plan**

will require that sponsors of gene therapy trials routinely submit monitoring plans to the FDA. These plans will be reviewed and modifications sought if warranted. Surveillance and inspections of clinical trials will be carried out to assess whether the plans are being followed and if monitoring is adequate to identify problems. The experience and training of the monitors will also be addressed. Conferences will be convened for investigators in order to enhance the conduct of gene therapy trials.

A series of **Gene Transfer Safety Symposia** will be organized quarterly by the NIH and FDA to enhance patient safety through the sharing and analysis of medical and scientific data from gene transfer research. The symposia will include topics such as: monitoring of safety data, cardiovascular complications of vector administration, good clinical practice in research, cell and gene therapy guidance for product development, quality control and assurance, entry criteria and informed consent for participants.

The FDA is requesting manufacturers to provide additional information on cell banks, viral banks and other products for use in clinical studies. Quality control data will also need to be produced on each lot of products either produced by the manufacturer or used by them in clinical trials.

Action has also been taken to achieve greater adherence by researchers to existing requirements. These include:

- a series of site visits to NIH-funded institutions to review institutional compliance with a range of NIH rules, regulations and guidelines relevant to gene transfer research, conflict of interest and invention reporting.
- a review of institutional policies and procedures to ensure compliance with NIH guidelines. NIH is also contacting investigators to ensure they have reported all serious adverse events to the NIH.

A website and database will be created to provide public access to data on gene transfer research as of October 2000.

**Reference:** *HHS News*. New initiatives to protect participants in gene therapy trials, 7 March 2000.