

Regulatory Matters

Losartan and irbesartan: similar in advantage to ACE inhibitors

Australia — The Adverse Drug Reaction Advisory Committee (ADRAC) has reviewed reports associated with the angiotensin II receptor antagonists losartan and irbesartan since their introduction in 1997 for the treatment of hypertension. By November 1998, 230 reports had been received for losartan and 133 reports for irbesartan. Skin reactions such as rash or pruritus, and neuropsychiatric disturbances such as insomnia, depression, confusion, nightmares and agitation, were most common. There were also 37 reports of cough with similar clinical characteristics as those seen with use of angiotensin converting enzyme (ACE) inhibitors. Likewise, angioedema with swelling of the neck, face and tongue were reported as well as hepatic dysfunction and hyperglycaemia.

The findings strongly suggest that patients having experienced these reactions while using ACE inhibitors may not benefit from changing medication to the recently introduced angiotensin II receptor antagonists.

Reference: *Australian Adverse Drug Reactions Bulletin*, 18 (1): 2 (1999).

Variations in troglitazone assessments

Japan and United Kingdom — The regulatory status of the diabetes drug, troglitazone (Rezulin®), has been reviewed in previous issues of this journal (1).

Troglitazone continues to be marketed in Japan as well as in 12 other countries (2). In the United Kingdom, it was voluntarily suspended by the company in December 1997 after only two months on the market, as a result of reports of serious hepatic reactions. A licence variation application with new prescribing criteria and advice on monitoring of liver function tests was subsequently submitted to the Medicines Control Agency but was rejected because the drug was not considered to have a favourable risk benefit profile (3).

United States of America — The Food and Drug Administration has estimated that the risk of acute liver failure may be as high as 1 in 758 patients taking troglitazone, and that 1 in 1800 patients may develop acute liver failure when taking the drug for six months. As a result of advice from the Advisory Committee on Endocrinologic and Metabolic Drugs, the FDA has considered four options in dealing with the situation: continue to monitor closely the number of cases of liver failure; shorten the time interval for monitoring of liver enzymes; limit use to patients with normal liver function tests; or eliminate one or more indications, such as monotherapy (4).

The following changes reflect the FDA's subsequent decision concerning the labelling and recommended use of troglitazone:

- Troglitazone is no longer indicated for use as initial single agent therapy.
- Transaminase levels should be tested before treatment and at monthly intervals thereafter.
- Each prescription of troglitazone will be accompanied by an information data sheet to be provided to the patient.
- Troglitazone is indicated for use in combination with a sulfonylurea and metformin in diabetes patients who are not adequately controlled with these two drugs alone. (5)

The case of troglitazone has demonstrated that, although considerable progress has been made in the harmonization of regulatory requirements for ICH (International Conference on Harmonization) countries — practical interpretation still differs when evaluated on a case by case basis.

References

1. *WHO Drug Information*, 12(1): 13 (1998) and 12(2): 81–82 (1998).
2. *Pharma Japan*, 164: 3, 1999
3. *The Pharmaceutical Journal*, 262: 424 (1999).
4. FDA. Endocrinologic and Metabolic Drugs Advisory Committee, 10 May 1999. <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3499t1>
5. *FDA Talk Paper*, T99-28, 1999.

Zolpidem and zopiclone: dependence

Germany — The Medicines Commission has issued a warning on the dependence potential of the short-acting benzodiazepine agonist hypnotics zolpidem and zopiclone in patients with a history of dependence to benzodiazepines.

The Medicines Commission and the Federal Institute for Drugs and Medical Devices have together received reports of 572 suspected adverse reactions. These included 28 cases of dependence, 16 of withdrawal symptoms and 9 cases of abuse. Some 41 million defined daily doses (DDDs) of zolpidem have been prescribed annually.

In addition to the German reports, WHO's International Drug Monitoring Programme in Uppsala has received reports of 13 cases of abuse, 71 cases of dependence and 36 cases of withdrawal syndrome associated with zolpidem. Zopiclone has been associated with 6 reports of abuse, 13 of drug dependence and 9 cases of withdrawal syndrome. Some 22 million defined daily doses (DDDs) of zopiclone were prescribed in 1997 (1). As previously reported in this journal, caution should be exercised when prescribing hypnotics (2).

References

1. Data presented at the Ninth International Conference of Drug Regulatory Authorities (ICDRA), Berlin, April 1999.
2. *WHO Drug Information*, 12(1): 8 (1998).

Etanercept and sepsis

United States of America — The Food and Drug Administration has advised physicians of reports of serious life-threatening infections, including sepsis, in patients using etanercept. Many of the cases occurred shortly after initiation of treatment although clinical studies did not show an increase in serious infections in patients.

Etanercept is a new genetically-engineered protein first approved in November 1998 for the treatment of moderate to severe rheumatoid arthritis not responding to other treatment. Etanercept inhibits the action of tumour necrosis factor, a component of the body's natural defence against serious infection.

Because of the new reports, the warning related to sepsis has been extended to include patients with

active, chronic or localized infection. It is recommended that patients who develop a new infection while being treated should be monitored closely. Physicians should be cautious in prescribing etanercept to patients with a history of recurring infections, or underlying conditions such as advanced, poorly-controlled diabetes.

The Food and Drug Administration has asked the manufacturer to perform additional studies to assess the risk of serious infection related to etanercept.

Reference: *FDA Talk Paper*, T99-22, 1999.

Clozapine and gastrointestinal obstruction

United Kingdom — The Medicines Control Agency has received 20 spontaneous adverse reaction reports describing gastrointestinal obstruction associated with clozapine, an antipsychotic used to treat resistant schizophrenia. Three of the reported cases were fatal.

The reaction is thought to be due to the anticholinergic properties of clozapine, in particular when used in conjunction with other medications with anticholinergic effects such as tricyclic antidepressants, antiparkinsonian agents and other antipsychotics. Patients with a history of colonic disease or previous bowel surgery may have a higher risk of this reaction.

Reference: *Current Problems in Pharmacovigilance*, 25: 1 (1999).

Orlistat for obesity

United States of America — The Food and Drug Administration has approved orlistat, a new drug for the treatment of obesity. This is the first in a new class of nonsystemically-acting anti-obesity drugs known as lipase inhibitors. Orlistat acts in the gastrointestinal tract by breaking down dietary fats into smaller molecules that can be absorbed by the body. In this way, absorption of fat is decreased.

During treatment, patients should be on a nutritionally balanced, reduced calorie diet that contains not more than 30% of calories in fat. Orlistat is indicated for patients with a body mass index of 30 or more. Because orlistat reduces the absorption of some fat-soluble vitamins and beta carotene, pa-

tients should take a supplement that contains fat-soluble vitamins and beta carotene.

Reference: *FDA Talk Paper*, T99-9, 1999.

Trovafloxacin and alatrofloxacin: CPMP recommends suspension

European Union — Reports of serious hepatic events concerning the recently-approved fluoroquinolone antibiotics, trovafloxacin (Trovan®, Turvel®) and the intravenous formulation, alatrofloxacin (Trovan IV®, Turvel IV®), have led to the suspension of the marketing authorization in member countries of the European Union.

Since February 1998, 152 documented cases of serious hepatic events have been reported, including 9 cases in which patients died or required a liver transplant. A review shows that in 35% of cases the events were accompanied by a hypersensitivity reaction and occurred between 1 and 60 days after initiation of treatment, suggesting that onset and severity of events are unpredictable (1).

The Committee for Proprietary Medicinal Products (CPMP) is of the opinion that Trovan®, Turvel®, Trovan IV® and Turvel IV® can no longer be safely administered in normal clinical usage, and has recommended that the marketing authorizations for trovafloxacin and alatrofloxacin be suspended. Existing supplies are to be withdrawn (2).

Patients are advised to contact their physician immediately, but should not stop taking the product until their treatment regimen has been reviewed.

Physicians are requested not to prescribe trovafloxacin and to review treatment of patients currently taking alatrofloxacin with a view to switching to alternative antibiotics or discontinuing treatment.

Reference:

1. Trovan/Trovan IV/Turvel/Turvel IV (trovafloxacin/alatrofloxacin). Serious, severe and unpredictable liver injuries. *EMEA Press Release*. EMEA/15770/99.
2. Trovan/Trovan IV/Turvel/Turvel IV (trovafloxacin/alatrofloxacin). Recommendation to suspend the marketing authorization in the European Union, London, 11 June 1999. EMEA/17438/99.

Trovafloxacin and alatrofloxacin: FDA reports reservations in use

United States of America — Following reports of rare but serious liver injuries leading to cases where patients died or required a liver transplant, the Food and Drug Administration has issued a health advisory to physicians concerning use of the antibiotics, trovafloxacin and alatrofloxacin.

Physicians are informed that trovafloxacin and alatrofloxacin should be reserved for use only in patients meeting the following criteria:

- Patients who have at least one of several specified infections such as nosocomial pneumonia, or complication intra-abdominal infections which are serious or life- or limb-threatening;
- Patients who begin their therapy in inpatient health care facilities;
- Patients for whom the physician believes that, even given the new safety information, the benefit of the product outweighs the potential risks.

Therapy should, in general, not continue beyond 14 days and should be discontinued if the patient experiences any clinical signs of liver dysfunction.

The FDA is taking this action to reduce the potential risk from this product while preserving the clinical option of an effective broad-spectrum antibiotic for serious or life-threatening infections. Revised labelling will be approved shortly.

Reference: *FDA Talk Paper*, T99-26, 1999.

Control of misoprostol

Brazil — Following a report in this journal concerning abortifacients on free sale in Brazil (1) the Secretariat of Public Health has provided the following clarification and has informed us that marketing of an illegal abortion kit containing misoprostol and methotrexate has not been reported to the authorities in Brazil.

In 1985, the Brazilian Government approved and registered the drug Cytotec® containing misoprostol as the active ingredient. The product was indicated for the treatment and prevention of gastric and duodenal ulcers and a warning stated that it

should not be used in pregnant women, since it could cause abortion or adverse effects on the fetus.

In 1991, the Government adopted restrictive measures with the objective of prohibiting misuse. Sale was limited to prescription-only through pharmacies.

In 1998, the following restrictive measures were decided:

- Medicinal products containing misoprostol can only be used in authorized hospitals.
- Distribution of free samples of medicines containing misoprostol is prohibited.

Reference:

1. *WHO Drug Information*, 12(4): 240 (1998).
2. Communication to WHO from the National Institute of Public Health, Brazil, dated 9 February 1999.

Paracetamol: further warning

Sweden — The Medical Products Agency has strengthened warnings on the labelling, package inserts and product information of paracetamol preparations in order to avoid severe adverse reactions, including liver damage.

The product information must now indicate that higher than recommended doses carry a risk of severe liver damage. The product should not be used without a medical prescription if the user has alcohol problems or liver disorders, or if taking concomitant medications which also contain paracetamol.

Reference: *Info från Läkemedelsverket*, 1: 1999.

Metamizole sodium withdrawn

Yemen — The Supreme Board of Drugs and Medical Appliances has withdrawn all formulations of metamizole sodium because of the potential to cause anaphylactic shock and agranulocytosis.

Reference: Communication to WHO from Ministry of Health, Yemen dated 17 December 1998.

Ginkgo biloba suspended

Germany — The Federal Institute for Drugs and Medical Devices has extended the suspension of the marketing authorization for a dry extract of *Ginkgo biloba* for parenteral infusion because of reports of anaphylactic reactions including shock, fever, leucocytosis and cardiac arrhythmia, which in some cases were life-threatening.

Reference: Communication to WHO from the Federal Institute for Drugs and Medical Devices dated 10 December 1998.

Home test for hepatitis C

United States of America — The Food and Drug Administration has approved the first over-the-counter blood collection kit for testing for antibodies to hepatitis C virus (HCV), the most common blood-borne infection and a major cause of liver damage in the USA. It is spread through contact with infected blood and is responsible for 8000–10 000 deaths annually.

The kit does not require a prescription and can be mailed to a designated laboratory for analysis. Results are available anonymously by telephone. As part of the test, the manufacturer provides a telemedicine service which offers education and counselling about HCV and, if desired, referral to a physician.

Reference: *FDA Talk Paper*, T99–20, 1999.

Urokinase: possible transmission of infectious agents

United States of America — The Center for Biologics Evaluation and Research has issued a warning letter to all health care providers concerning urokinase (Abbokinase®), a treatment for pulmonary embolism, coronary artery thrombosis and intravenous catheter clearance. This recommends that Abbokinase® be reserved only for those situations where a physician has considered alternative treatment and has determined that the use of Abbokinase is critical to the care of a specific patient in a specific situation.

This action was taken subsequent to inspections of Abbott Laboratories and its supplier of human

neonatal kidney cells. The kidney cells used in the manufacture of this product were harvested post-mortem from human neonates from a population at high risk for a variety of infectious diseases, including tropical diseases. Although some efforts were made by the supplier to screen and test mothers, neonate donors and kidney cells, these measures were not consistently or reliably performed.

Prior to use in the manufacture of Abbokinase®, the human kidney cells were harvested, stored and handled in a manner which may have permitted contamination with infectious agents. Nor has the viral inactivation process used on currently available lots of the product been fully validated for viral inactivation.

Reference: Letter to health care providers, Center for Biologics Evaluation and Research, 25 January 1999.

Astemizole voluntarily withdrawn

United States of America — The Food and Drug Administration has announced that the manufacturer of the antihistamine, astemizole (Hismanal®), has decided to voluntarily withdraw the drug from the market given the overall risk benefit profile of the drug.

Reference: *FDA Talk Paper*, T99-29 (1999).

Polygeline: hypotension

Germany — In collaboration with the manufacturer, The Federal Institute for Drugs and Medical Devices has issued a notification for a batch recall of the plasma expander, polygeline, after an increased number of reports of hypotension were received.

Some of these reports described a rapid fall in blood pressure after administration of polygeline but a definitive relationship has not been established. The manufacturer has initiated a precautionary recall worldwide until the issue is clarified.

Reference: Rapid Alert from the Federal Institute for Drugs and Medical Devices, Berlin, 26 February 1999.

Northern hemisphere influenza vaccine 1999–2000

The composition of the vaccine for 1999–2000 (northern hemisphere influenza season) has been published and communicated to vaccine manufacturers by WHO. The vaccine will contain the following three components:

- An A/Sydney/5/97 (H3N2)-like virus
- An A/Beijing/262/95 (H1N1)-like virus
- A B/Beijing/184/93-like virus (the most widely-used vaccine is B/Harbin/7/94) OR
A B/Shangdong/7/97-like virus

Decisions on the most appropriate B component should be made by national control authorities on the basis of local epidemiological data.

These three strains were chosen because influenza A(H3N2), A(H1N1) and influenza B viruses continued to circulate widely during the 1998–1999 influenza season.

The specific vaccine viruses used in each country should be approved by the national control authorities. National public health authorities are responsible for recommendations regarding the use of vaccines.