

Regulatory and Safety Matters

Troglitazone withdrawn

United States of America — The Food and Drug Administration has requested Parke-Davis/Warner-Lambert, the manufacturer of troglitazone (Rezulin®) to remove the product from the market. This action has been taken subsequent to a review of safety data which compared the risk benefit of troglitazone with rosiglitazone (Avandia®, Smith-Kline Beecham) and pioglitazone (Actos®, Takeda/Eli Lilly).

Troglitazone was indicated for the treatment of type 2 diabetes mellitus. When considered as a whole, the pre-marketing clinical data and post-marketing safety data from troglitazone indicated that continued use of troglitazone poses an unacceptable risk to patients as compared to similar alternative diabetes drugs.

Patients using troglitazone should not discontinue taking troglitazone but are urged to contact their physicians for information on alternative treatments.

Reference: *HHS News*, P00-8. 21 March 2000.

Cisapride and cardiac effects

United States of America — The manufacturer of cisapride has announced that it will stop marketing the product (Propulsid®; Janssen) in the USA with effect 14 July 2000. This effective date is intended to provide adequate time for patients and physicians to decide on treatment alternatives. Cisapride is a prescription drug indicated for severe night-time heartburn in patients with gastro-oesophageal reflux disease who do not adequately respond to other therapies.

Patients who already take the drug are encouraged to consult their doctors about other treatment options. The company will continue to make the drug available only to patients who meet specific clinical eligibility criteria under a limited-access protocol.

Continuing reports of heart rhythm disorders and deaths have been associated with cisapride in

people taking certain other medications or with underlying conditions known to be risk factors. A recent analysis of 270 cases of adverse events (including 70 fatalities) revealed that approximately 85% of these cases occurred in patients with identifiable risks.

Reference: *FDA Talk Paper*, T00-14, 23 March 2000.

Cisapride: changes to labelling

United States of America — Prior to the subsequent withdrawal of cisapride (Propulsid®) from the US market referred to above, the manufacturer had announced changes to the labelling and patient medication guide following reports of serious cardiac arrhythmias including ventricular fibrillation, torsades de pointes, and QT prolongation.

Between July 1993 and May 1999 more than 270 cases were reported, with 70 fatalities. Approximately 85% of these cases occurred in patients with known risk factors including the administration of other drugs which cause QT prolongation, inhibited liver enzyme metabolism or depleted serum electrolytes.

Cisapride is contraindicated in patients taking certain macrolide antibiotics, antifungals, and protease inhibitors, anti-arrhythmics, antidepressants and other agents such as grapefruit juice. The revised package insert contains full prescribing information.

Reference: Dear Doctor letter dated 24 January 2000 from Janssen Pharmaceutica Research Foundation.

Cisapride: updated warning issued

New Zealand — Strict controls are in place on the use of cisapride, which is indicated for severe gastro-intestinal conditions. In New Zealand, cisapride can only be prescribed by a physician on a specialist's recommendation, thereby minimizing the possibility of the drug being prescribed to people most at risk of known side effects. However, an updated warning has been circulated to physicians giving information on the reports received in the USA.

The National Centre for Adverse Reactions Monitoring has received 19 reports of adverse effects since 1991. None of these were fatal and only one case involved cardiac disturbance.

Reference: *Medsafe Media Release*, 24 March 2000.

St John's wort: recommendations for use

France — Following the recent publication of several papers describing significant interactions between St John's wort (*Hypericum perforatum*) and digoxin, theophylline, indinavir, ciclosporin, certain oral anticoagulants, antidepressants and oral contraceptives, the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSPS) has made the following recommendations:

1. Patients not yet taking St John's wort:

- patients being treated with antiretroviral agents, and particularly indinavir (Crixivan®), for HIV infection should not take St John's wort in view of the risk of decreased efficacy of the treatment.
- patients being treated with antidepressants should not take St John's wort concomitantly because of the risk of adverse reactions (restlessness, nausea, gastric disturbance).
- women taking oral contraceptives should not take St John's wort concomitantly because of the risk of a diminution in the contraceptive effect.
- in general, St John's wort should not be taken concomitantly with any other medicinal treatment in view of the risk of a drug interaction which could result in a reduction in the efficacy of the medicines.

2. Patients under treatment must not discontinue taking St John's wort without medical advice.

Although St John's wort has been promoted as a treatment for mood disorders and is available as a food supplement, it is not approved as a medicine in France.

Reference: Communiqué from the Agence Française de Sécurité Sanitaire des Produits de Santé, 1 March 2000.

Northern hemisphere influenza vaccine

World Health Organization — The composition of the vaccine for the November 2000–April 2001 influenza season in the Northern hemisphere has been determined and communicated to vaccine manufacturers.

- an A/Moscow/10/99(H3N2)-like virus
- an A/New Caledonia/20/99(H1N1)-like virus
- a B/Beijing/184/93-like virus+

WHO strongly recommends the use of vaccine as an effective preventive measure against this potentially fatal disease. Even in those cases when the vaccine does not fully protect against the disease, severity of illness and frequency of serious complications are reduced.

Specific vaccine viruses used in each country should be approved by the national control authorities. National public health authorities are responsible for recommendations regarding use of vaccines. All WHO recommendations are published and communicated to public health authorities, national control authorities and influenza vaccine manufacturers. Updated epidemiological information is available on <http://www.who.ch/emc/flu/indexhtm> and the geographical information system, Flunet, at <http://oms.b3e.juu.fr/flunet>.

Reference: Recommended composition of influenza virus vaccines for use in the 2000–2001 season. *Weekly Epidemiological Record*, 75: 61–65 (2000).

Nicotine replacement therapy

New Zealand — The Government has announced measures to improve access to nicotine replacement therapies. These may now be sold through smoking cessation clinics run by medical practitioners, nurses, pharmacists or psychologists. Previously, they could only be obtained from pharmacies or on a doctor's prescription.

The Government has taken a strong stance on smoke-free policies and improving access to smoking cessation therapies.

Reference: *Medsafe Media Release*, 15 March 2000.

Anorectic agents: suspension of marketing authorization

France — As a result of recommendations made by the Committee on Proprietary Medicinal Products (CPMP), the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSPS) has announced that it will shortly suspend marketing authorization for medicinal products containing the anorectic agents amfepramone, clobenzorex, fenproporex and mefenorex. These products have been dispensed through hospital prescription since 1995 because of their implication in the occurrence of arterial pulmonary hypertension.

The Agency suspended marketing authorizations for fenfluramine and dexfenfluramine in 1997 due to the unacceptable risk of cardiac valvulopathies.

Reference: La Revue Prescrire Vol. 19, No. 199, October 1999.

Insulin cartridges: leakage risk

European Union — The European Agency for the Evaluation of Medicinal Products (EMA) has issued a warning on the risk of leakage during use of recombinant human insulin cartridges (Insuman Infusat®; 100 IU/ml solution for injection in cartridges of 3.15 ml). Insufficient supply of insulin has led to reports of hyperglycaemia with hospitalization in four cases.

The marketing authorization holder, Aventis Pharma, recently informed the EMA of 15 reports concerning leakage of cartridges used for semi-synthetic insulin. Faulty cartridges should be returned via the pharmacy or medical pump centre.

Reference: EMA Public Statement on Insuman Infusat® 100 IU/ml solution for injection in cartridges of 3.15 ml (insulin human), 14 February 2000.

Zimox®: trade name duplication and risk of errors

Islamic Republic of Iran — The Tehran Drug and Poison Information Centre has informed the World Health Organization that a combination product containing the anti-Parkinson drugs carbidopa and levodopa is being imported into Iran from Greece with the trade name Zimox®. Zimox® is also the name of a product well known to contain the anti-

biotic amoxicillin and is cited in reference books such as Martindale and Index Nominum.

The Centre is concerned about the potential for error that could result from this duplication of trade names. Information has been forwarded to the national drug authorities in order to avoid preventable mistakes in the dispensing of Zimox®, and an announcement has also been circulated to health professionals.

The Centre urges pharmaceutical companies to establish beforehand whether the names chosen for their products have not already been used.

Reference: Communication from the Tehran Drug and Poison Information Centre, 24 November 1999.

Benzbromarone and hepatitis

Japan — Following reports of eight cases of fulminant hepatitis related to use of benzbromarone, the Ministry of Health and Welfare in Japan has requested all manufacturers to revise the labelling to include a warning of hepatic dysfunction and to circulate a letter to health professionals.

Benzbromarone, which is indicated for gout, is marketed as 13 products by 10 companies. As reflected in the revised labelling, liver function tests should now be performed periodically and for at least six months after the start of administration. Patients should receive an explanation of the risk of hepatic dysfunction and should consult the physician immediately in the event of anorexia or general malaise. Contraindications for this condition have also been added.

Reference: *Pharma Japan*, Number 1689, 20 March 2000.

Nevirapine: severe cutaneous reactions

France — Nevirapine, a non-nucleoside reverse transcriptase inhibitor was first launched in Europe in 1998 for use in HIV infection. Although attention was drawn to the possibility of serious cutaneous reactions and hepatic complications through a warning notice and information to prescribers, fatal outcome reports continue to be received.

Between November 1997 and November 1999, the Agence Française de Sécurité Sanitaire des

Produits de Santé (AFSSPS) has received 16 reports of cases of Stevens-Johnson syndrome and 14 cases of Lyell syndrome, of which 5 were fatal. It was noted that in many cases the manufacturer's recommendation to initiate treatment with a half-dose had not been respected.

During the same period, 44 cases of hepatic complications were also reported. The Agency has drawn attention to the need for care and recommended that liver function tests should be carried out at two-weekly intervals during the first two months of treatment. A letter has been circulated to health care professionals giving details of warnings and contraindications.

Reference: *La Revue Prescrire*, Number 205, April 2000.

FDA cannot regulate tobacco industry

United States of America — The Supreme Court has ruled that the Food and Drug Administration (FDA) lacks the power to regulate tobacco. In 1996, the FDA decided that it could regulate tobacco in the light of new evidence that demonstrated the industry's intention to feed consumers' nicotine habits.

In the 5 to 4 ruling, the judges said that Congress had not given the FDA the authority to regulate tobacco. The Court agreed that tobacco use, particularly among children and adolescents, poses perhaps the single most significant threat to public health in the United States. However, it said that regulations on tobacco were the responsibility of Congress.

The FDA's antismoking initiative would have required retailers to check the identification of cigarette buyers under the age of 27 and would have prohibited cigarette vending machines except in bars and other adult-only places.

Reference: *News. British Medical Journal*, 320: 894 (2000).

New Internet website: information for consumers

United States of America — The Food and Drug Administration has announced the establishment of an Internet website to provide information on buying prescription drugs and medical products on-line.

This initiative is part of an action plan to increase public awareness of the health, economic and legal risks of on-line sales of prescription drugs and medical products.

The website is located at: <http://www.fda.gov>

Information is available on consumer protection, FDA enforcement practices, advice on identifying health fraud and general questions about Internet drug sales. Consumers who suspect that a website is illegally operating can fill in an electronic complaint form.

Reference: *HHS News*, P99-33 (1999).

Cyber warnings for drug sales via the Internet

United States of America — In recent weeks the Food and Drug Administration has issued letters via the Internet to operators of non USA-based internet sites that offer to sell on-line prescription medicines that may be illegal. The letters inform the operators about the laws governing prescription drug sales within the USA, with an explanation of the statutory provisions that govern interstate commerce of drugs and a warning that future shipments of the products may be automatically detained and subject to refusal of entry.

Reference: *FDA Talk Paper*, T00-8 (2000).

Triax®: a harmful product sold on the Internet

United States of America — The Food and Drug Administration has warned consumers not to purchase or consume the product Triax Metabolic Accelerator®, containing the active ingredient tiratricol.

The product is marketed as a dietary supplement for weight-loss purposes. However, the Food and Drug Administration has determined that it contains an unapproved new drug containing triiodothyroacetic acid, a potent thyroid hormone which can cause serious health problems, including heart attacks and stroke. Several individuals have reported abnormal thyroid function test results while using Triax® and have experienced severe diarrhoea, fatigue, lethargy or profound weight loss.

Reference: *FDA Talk Paper* T99-52 (1999).

Illegal products on the market

United States of America — The Food and Drug Administration (FDA) has taken legal action to protect consumers against unproven claims for drugs promoted as treatments for cancer and other diseases.

Such unapproved drugs include: *BeneFin*, produced from shark cartilage and promoted as a treatment for cancer; *SkinAnswer*, a glycoalkaloid skin cream advertised for treatment of skin cancer; and *MGN-3*, a rice-bran extract promoted as a treatment for cancer and HIV.

Reference: *FDA Talk Paper*, T99-56 (1999).

Epoetin alfa: inappropriate practices compromise product sterility

United States of America — An outbreak of 21 episodes of bacteraemia or pyrogenic reactions has been reported in patients receiving epoetin alfa (Epogen®, Amgen) at a dialysis unit. A recent investigation has revealed that unused portions of epoetin alfa remaining in single dose preservative-free vials were collected and pooled into common vials for use in other patients. These practices were linked to extrinsic bacterial contamination.

Health care professionals are warned that once a syringe has entered a single-dose vial, the sterility of the product can no longer be guaranteed. Multiple entries should not therefore be made into single-dose vials and residual medication from two or more vials should not be pooled.

Reference: Letter from Amgen at www.fda.gov/medwatch

Propylene glycol and amprenavir

United States of America — The manufacturer of amprenavir (Agenerase®, Glaxo Wellcome) has issued a warning concerning a potential risk associated with the amount of propylene glycol present in the oral solution formulation. Amprenavir is a protease inhibitor indicated for the treatment of HIV infection in combination with other antiretroviral agents in patients 4 years of age and older.

Propylene glycol is metabolized by an enzyme pathway which does not attain equivalent adult activity until 12 to 30 months of age. Infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole are not able to adequately metabolize and eliminate propylene glycol, leading to its accumulation.

Although no reports have been received of serious injury or death, potential safety concerns exist due to the high propylene glycol content of amprenavir. It is therefore advisable to use amprenavir capsules or other protease inhibitor formulations in preference to the oral solution in those patients at risk.

Reference: Letter from GlaxoWellcome Inc. at www.fda.gov/medwatch

Trastuzumab: pulmonary reactions

United States of America — The manufacturer of trastuzumab (Herceptin®, Genentech) has warned of 62 postmarketing reports of serious adverse events related to the use of their product indicated for the treatment of breast cancer. To date, 25 000 women have been treated with trastuzumab which the FDA approved in 1998.

Adverse events include hypersensitivity reactions (anaphylaxis), infusion reactions, and pulmonary events (adult respiratory distress syndrome). A total of 15 fatal outcomes were reported. In the majority of patients the symptoms occurred with the first dose of trastuzumab or within 12 hours of infusion. Most patients with fatal outcome had significant pre-existing pulmonary compromise secondary to intrinsic lung disease and/or malignant pulmonary involvement.

Such patients should be treated with extreme caution. Any patients experiencing symptoms should be discontinued immediately and be closely monitored until complete resolution of symptoms. Patients should also be informed of the possibility of delayed severe reactions.

Reference: Letter from Genentech dated 3 May 2000 at www.fda.gov/medwatch