

Regulatory Matters

Acitretin: avoidance of pregnancy

European Communities — The Committee for Proprietary Medicinal Products has announced that chromatographic analysis of blood samples taken from patients receiving the orally-administered retinoid, acitretin (Neotigason®: Hoffmann-La Roche), which has recently been introduced in several countries of the European Economic Community, suggests that it may be partially metabolized to its analogue, etretinate.

Acitretin, which is prescribed for severe psoriasis, was anticipated to eventually supersede etretinate. Both compounds are potential teratogens but, because acitretin has a considerably shorter serum half-life, a relatively short period of contraception was considered adequate to avert a drug-induced congenital deformation during a subsequent pregnancy. Pending the results of further analyses, the Committee recommends that:

- the product information should advise patients that an effective method of contraception should be maintained during treatment and for 2 years thereafter.
- a warning should be included in the summary of product characteristics that patients should not donate blood during treatment or for 1 year thereafter.

As a result of this finding, the product licence for acitretin has been suspended in France. It remains registered in Belgium, Denmark, Luxembourg, the Netherlands and Portugal. In each of these countries strenuous efforts have been made to advise all women of child-bearing age who have already used the product of the need to observe a prolonged period of contraception.

Source: Committee for Proprietary Medicinal Products. Pharmacovigilance Opinion No. 9 — Acitretin (Neotigason®), Commission of the European Communities, 14 December 1990.

Anabolic steroids: enhanced control measures

Canada — The Health Protection Branch of the Ministry of Health and Welfare is proposing the application of additional controls on the distribution and sale of androgenic-anabolic steroids following publication of a report recently prepared by a commission of inquiry. This body concluded that abuse of these substances is fast spreading throughout all echelons of sport into high schools.

Only licensed dealers will be permitted to import, export or distribute these products which, henceforth, will be dispensed only on the prescription of a veterinarian or medical practitioner. Licensed dealers, pharmacists, veterinarians and medical practitioners will be required to maintain records and provide reports upon request. The distribution of anabolic steroid implants suitable only for veterinary use will not be affected.

Source: *Information Letter No. 790*, 9 January 1991, Health Protection Branch, Health and Welfare, Canada.

Paediatric antidiarrhoeal preparations withdrawn

Peru — The Director of the Drug Registration Office of the Ministry of Health has informed the World Health Organization that it proposes to withdraw from the market all paediatric preparations containing diphenoxylate, streptomycin, hydroxyquinolones and kaolin/pectin intended for the symptomatic control of diarrhoea (1). Paediatric formulations of analogous products containing loperamide have already been withdrawn.

These actions have been taken following reports of fatal paralytic ileus among children in Pakistan who were treated for acute diarrhoea with loperamide drops (2). The manufacturer subsequently withdrew this formulation worldwide and the syrup formulation was additionally withdrawn in Pakistan.

Other countries that have recently announced similar decisions include:

Libyan Arab Jamahiriya — withdrawal of paediatric products containing either diphenoxylate, loperamide, clioquinol or pectin (3).

Mexico — withdrawal of paediatric products containing either diphenoxylate or loperamide (4).

References

1. Communication to WHO from the Director of Drug Registration, Ministry of Health, Lima.
2. Bhutta, T.I., Tahir, K.I. Loperamide poisoning in children. *Lancet*, **335**: 363 (1990).
3. Communication to WHO from the General People's Health Committee Secretariat, Libyan Arab Jamahiriya, 22 May 1990.
4. Communication to WHO from the Director-General of Drug Registration, Ministry of Health, Mexico, 28 November 1990.

Beclobrate: risk of hepatitis

Switzerland — The Intercantonal Office for Control of Medicines has announced the withdrawal of the antihyperlipidaemic agent, beclobrate, following two reported cases of fatal hepatitis associated with its use. Both patients had taken other derivatives of fibric acid previously without incident. Despite prompt withdrawal of treatment both patients died of rapidly progressive hepatic failure within 3-4 weeks.

Source: Communication to WHO from the Intercantonal Office for Control of Medicines, 24 September 1990.

Canthaxanthin: disallowed as an active ingredient

Ireland — The National Drugs Advisory Board has recommended that no pharmaceutical product containing canthaxanthin as an active ingredient should be considered for registration (1).

Canthaxanthin is a highly lipid-soluble synthetic carotenoid. It is not converted into vitamin A in man and, after ingestion, it can persist in detectable quantities for many months in the plasma (2). In countries where it is used as a food additive, it is

ingested in small amounts in the diet. It is used, in particular, to enhance the colour of the yolks of chicken eggs and the flesh of rainbow trout. More recently, it has been incorporated in larger quantities in orally administered skin-tanning preparations (3, 4).

The most widely recognized adverse effect attributed to canthaxanthin is a retinopathy resulting from deposition in the retina (5-9). Characteristic golden-yellow deposits appear around the macula. Itching, urticaria and, very rarely, hepatitis have also been reported and overdosage has been associated in at least one patient with fatal aplastic anaemia (10).

References

1. National Drugs Advisory Board, Dublin. Annual Report for 1989 (published in December 1990).
2. Gunson, H.H., Merry, A.H., Britton, G., Stratton, F. Detection of carotenoids in blood donors taking Orobronze: a cautionary note. *Clinical and Laboratory Haematology*, **6**: 287-292 (1984).
3. A 'suntan' in capsules — Orobronze. *Drug and Therapeutics Bulletin*, **21**: 57 (1983).
4. Lober, C.W. Canthaxanthin — the 'tanning' pill. *Journal of the American Academy of Dermatology*, **4**: 660 (1985).
5. Boudreault, G., Cortin, P., Corriveau, L.A. et al. Canthaxanthine retinopathy, I: Clinical study in 51 consumers. *Canadian Journal of Ophthalmology*, **18**: 325-328 (1983).
6. Cortin, P., Boudreault, G., Rousseau, A.P. et al. Retinopathy due to canthaxanthine, II: Predisposing factors. *Canadian Journal of Ophthalmology*, **19**: 215-219 (1984).
7. Rousseau, A.P. Canthaxanthine deposits in the eye. *Journal of the American Academy of Dermatology*, **8**: 123-124 (1983).
8. Ros, A.M., Leyon, H., Wennersten, G. Crystalline retinopathy in patients taking an oral drug containing canthaxanthine. *Photodermatology*, **2**: 183-185 (1985).
9. Daiker, B., Schiedt, K., Adnett, J.J., Bermond, P. Canthaxanthine retinopathy: an investigation by light and electron microscopy and physicochemical analysis. *Archives of Clinical and Experimental Ophthalmology*, **225**: 189-197 (1987).
10. Bluhm, R., Branch, R., Johnston, P., Stein, R. Aplastic anaemia associated with canthaxanthin ingested for 'tanning' purposes. *Journal of the American Medical Association*, **264**: 1141-1142 (1990).

Counterfeit drugs: remedial measures

Ethiopia — Concerned by reports of the unlawful entry of counterfeit and other illicit drugs into the country, the Ministry of Health has placed dealers on notice that:

- all retailers who sell pharmaceuticals and medical supplies to the public should obtain their supplies ONLY from importers and/or distributors approved and licensed by the Ministry of Health.
- all retailers should keep as part of their records all receipts/invoices of supplies of pharmaceuticals, which should be made available at the request of inspectors delegated by the regulatory authority.
- all retailers are required to dispense to patients, at all times, full doses of over-the-counter and prescription drugs; wholesale dispensing of drugs by retailers is strictly prohibited.

Source: Communication to WHO from the Ministry of Health, Addis Ababa, 1 February 1991 with a copy of the Circular Notice to retail outlets.

Glafenine: withdrawal on grounds of safety

Belgium — The General Inspectorate of Pharmacies has withdrawn the marketing authorization for all pharmaceutical products containing the analgesic, glafenine. (1)

The action has been taken following a large number of reports of adverse effects associated with the use of glafenine. These include allergic responses: anaphylactic shock, acute tubulo-interstitial renal insufficiency and immuno-allergic hepatitis. The agency has concluded that these reactions constitute an untoward hazard and that other, safer products are available.

Within the past year, the competent authorities in three other European countries — **France** (2), **Italy** (3) and **Switzerland** (4)— have each implemented administrative measures and issued advice to doctors aimed at restricting the availability and curbing the use of glafenine.

Sources:

1. Communication to WHO from the General Inspectorate of Pharmacies, Ministry of Public Health, Brussels, dated 11 January 1991.
2. Communication to WHO from the Ministry of Solidarity, Health and Social Welfare, Paris, dated 5 January 1990.
3. *Bolletino d'Informazione sui Farmaci*, **14** (2): 3 (1990).
4. Communication to WHO from the Intercantonal Office for Control of Medicines, Bern, dated 25 January 1991.

Metipranolol eyedrops: granulomatous anterior uveitis

United Kingdom — In consultation with the Medicines Control Agency the manufacturer has withdrawn all eyedrops containing the beta-adreno-receptor antagonist, metipranolol. The decision results from reports of low-grade granulomatous anterior uveitis associated with its use.

Notwithstanding extensive use of these products elsewhere, only two such cases are known to have been reported outside the United Kingdom. The formulation marketed in the UK differs from that supplied to other countries in that the preparation is sterilized by irradiation in the final container. The manufacturer is investigating the possible relevance of this factor in the determination of this adverse effect.

Source: Communication to the World Health Organization from Smith & Nephew Pharmaceuticals Ltd dated 18 February 1991.

Organ extracts: dangers of allergenicity and infection

Norway — The Medicines Control Board has decided that no organ extract of human and animal origin, regardless of whether it is derived from apparently healthy or diseased tissue, may be lawfully dispensed (1). A pre-existing ban is now extended to include preparations previously exempted from control, including homoeopathic and anthroposophic preparations labelled as containing the prescribed agent at a dilution of less than one in one million. The Board considers that the use of organ extracts carries an inherent and unaccept

able risk of transmission of infection and induction of allergy, whereas no therapeutic effect has been scientifically documented. The Board may still issue an exemption in special circumstances provided that adequate documentation is provided on the safety of the extract.

An analogous decision has been taken by the Medical Products Agency in **Sweden** which has refused an application for registration of an injectable calf thymus extract for the treatment of diseases resulting in impaired cellular immune responses (2). It considered that the active ingredients were inadequately specified and that the toxicological and clinical properties of the product had not been evaluated.

Sources

1. *Nytt fra Statens legemiddelkontroll*, 4: 21 (1990).
2. *Information från Läkemiddelsverket*, 1 (3): 150 (1990).

Propaphenone: fatal dysrhythmias

Japan — The Pharmaceutical Affairs Bureau has amended the approved data sheet for the antidysrhythmic agent, propaphenone, in the light of reports that ventricular tachycardia and ventricular fibrillation supervened in 5 treated patients, 3 of whom died.

Doctors have been advised to prescribe propaphenone only for patients who cannot be treated with other antidysrhythmic drugs or who are unresponsive to them. It is contraindicated in patients with congestive heart failure or severe atrioventricular or sinoatrial block.

Source: Pharmaceutical Affairs Bureau, Ministry of Health and Welfare. *Information on Adverse Reactions to Drugs*, No. 104, September 1990.

Trolamine: concerns regarding potential carcinogenicity

Switzerland — The Intercantonal Office for Control of Medicines has restricted the use of the emulsifier, trolamine (triethanolamine), in pharmaceutical products because it has been shown, under certain circumstances, to be converted in the stomach into carcinogenic N-nitrosamines. It is no longer permitted in medicinal products intended for internal

use, and the following restrictions now apply to its incorporation in products intended for external use:

- trolamine used for this purpose should not contain more than 50 ppb N-nitrosamines, expressed as 2,2'-(nitrosoimino)diethanol.
- the concentration of trolamine in the finished product may not exceed 2.5 per cent w/w.
- the amount of N-nitrosamines in the finished product must be below detection level.
- companies must demonstrate compliance with these rules by presenting results obtained with a validated method of analysis.

The same requirements apply to the manufacture of products for parenteral use, except that no formal limit is applied to the concentration of trolamine in the finished product.

Source: *Bulletin mensuel de l'Office Intercantonal de Contrôle des Médicaments*, p.760, November 1990.

Urocanic acid: discontinuation of use in sunscreens

Australia — Urocanic acid has been withdrawn from use in sunscreens and cosmetic products at the request of the Federal Bureau of Consumer Affairs. A review recently undertaken on its toxicological properties has shown that it has an immunosuppressive effect in animals. Moreover, there is no evidence that it protects against skin cancers induced by ultraviolet light. Indeed, it has been shown to induce tumours in mice exposed to ultraviolet radiation and croton oil.

Source: Communication from the Therapeutic Goods Administration, dated 6 February 1991.

Urokinase: not for embolic stroke

Japan — The Pharmaceutical Affairs Bureau has advised doctors that it has received 22 reports of haemorrhagic cerebral infarction in patients with stroke who were under treatment with the antithrombotic enzyme, urokinase. The agency has called for the product information to be amended to emphasize that it should be used in the treatment of

stroke only when the condition results from cerebral thrombosis. Use of urokinase should be avoided, the Agency advises, in the management of patients with cerebral embolism having regard to the considerably greater risk of haemorrhagic infarction in this situation.

Source: Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Tokyo. *Information on Adverse Reactions to Drugs*, No. 101, March 1990,

Water-soluble gums: danger of oesophageal obstruction

United States of America — The Food and Drug Administration is proposing to amend the labelling

of laxatives, dietary aids and other over-the-counter drug products containing water-soluble gums as active ingredients. This regulation will embrace products containing such substances as guar gum, karaya gum, plantago seed (psyllium), tragacanth, and xanthan gum. Cases of oesophageal obstruction and asphyxia have been reported as a consequence of the rapid expansion of these ingredients as they absorb water during their passage through the oesophagus. A warning is proposed that the product should not be used by persons who have difficulty in swallowing and that every dose should be washed down with liberal amounts of water.

Source: *United States Federal Register*, 55 (210): 45782-45785 (1990).