

Regulatory Matters

Acetylsalicylic acid

Chile — The Institute of Public Health has decided, having regard to the apparent relationship between use of acetylsalicylic acid and Reye's syndrome, that all pharmaceutical products containing acetylsalicylic acid should carry a warning on the label that the drug should not be given to children under 12 years of age with febrile viral diseases except on the advice of a doctor.

Reference: Resolution No. 01042 of 2 February 1987, Ministry of Health, Santiago, Chile.

Acipimox

Australia — The Drug Evaluation Committee has refused registration of acipimox capsules, 150, 250 mg (Olbetam®: Farmitalia, Carlo Erba) indicated for the treatment of hypertriglyceridaemia either with or without hypercholesterolaemia, because more information is needed on clinical benefit and safety, bioavailability should be determined, additional pharmacokinetic data should be provided, the mechanism of action should be described, and more information on carcinogenicity should be provided.

Reference: Report of the 129th Meeting of the Australian Drug Evaluation Committee, 19 June 1987.

Alkylpoly(oxyethylene) sulfates

Federal Republic of Germany — The Federal Health Office has requested all pharmaceutical manufacturers to indicate which of their licensed products contain alkylpoly(oxyethylene) sulfate detergents and the maximum concentration of dioxan in parts per million (milligrams per kilogram) that is liable to occur as an impurity in these products.

Alkylpoly(oxyethylene) sulfates are used as detergents largely but not exclusively in externally-

applied products. When ethylene oxide is used in their synthesis, they may contain several hundred parts per million of dioxan. This compound, administered to rats at a concentration of 1 per cent in drinking water, has induced hepatic and renal necroses within five months in a high proportion of the animals. Occasional animals have also developed hepatomas and carcinomas of the nasal cavity.

Reference: *Deutsche Apotheker Zeitung*, 127: 831 (1987).

Amantadine

United States of America — The Food and Drug Administration has informed WHO that the product information on preparations containing the antiviral and anti-parkinsonism compound amantadine (Symmetrel®: Dupont) has been amended. Because of reduced renal clearance and resultant higher plasma levels in patients over 65 years of age, the recommended dose for elderly patients with parkinsonism has been reduced from 200 mg to 100 mg daily.

Reference: Letter to WHO from United States Food and Drug Administration dated 21 July 1987.

Antihistamines

Belgium — The General Pharmaceutical Inspectorate of the Ministry of Public Health and Environment has informed WHO that the approved information relating to products containing H1-antihistamines must warn against their administration to children aged less than one year because their sedative effect may be associated with episodes of sleep apnoea. Products containing a phenothiazine antihistamine will be formally contraindicated for this reason in children under one year, except on medical advice.

Reference: Letter to WHO from the General Pharmaceutical Inspectorate of the Ministry of Public Health and Environment, Brussels, Belgium, 18 June 1987.

Federal Republic of Germany — The Committee of Experts on Prescription of Drugs has advised that antihistamine products indicated for vomiting during pregnancy should be dispensed only on medical prescription. Antihistamines labelled for other indications should mention pregnancy as a contraindication. The Committee has concluded that the safety of antihistamines during pregnancy has not been adequately demonstrated. It notes, in particular, that epidemiological studies have suggested that intra-uterine exposure to some antihistamines is associated with an increased risk of neonatal pyloric stenosis.

Reference: *Bundesgesundheitsblatt*, 30:186 (1987).

Anti-inflammatory proteolytic enzymes

Philippines — The Bureau of Food and Drugs of the Department of Health has informed WHO that pharmaceutical products containing anti-inflammatory proteolytic enzymes, including papain, lysozyme, trypsin and streptokinase, have been withdrawn from the market on grounds of lack of efficacy. Manufacturers and distributors were required to recall all stocks by 30 October 1987.

Reference: Letter to WHO from the Bureau of Food and Drugs, Ministry of Health, Manila, Philippines, dated 2 June 1987.

Bupivacaine-containing anaesthetics

Sweden — The National Board of Health and Welfare has refused to approve two local anaesthetic preparations containing bupivacaine at a concentration of 7.5 mg/ml (Marcain® injection fluid and Marcain Adrenalin® injection fluid: Astra) on the grounds that the risk of adverse effects exceeds the potential benefit.

Reference: *Information från Socialstyrelsens läkemedelsavdelning*, 12: 52 (1987).

Butalbital (combination product)

Luxembourg — Following discussion with the Bureau for Drug Registration, the manufacturer of an analgesic combination preparation containing

butalbital + propyphenazone + caffeine (Optalidon®: Sandoz) has agreed to reformulate the product to exclude the barbiturate component.

Reference: Communication to WHO from the Bureau for Drug Registration, Luxembourg, 11 June 1987.

Calcitonin

France — The Ministry of Health has approved an extension of the indications for synthetic salmon calcitonin (Calsyn 50®: Rorer-Armour-Montagu) to include cyclical treatment of vertebral osteoporosis when fluorides are contraindicated or not tolerated; and for preventing bone resorption during prolonged immobilization. It was previously approved for treatment of Paget's disease, hypercalcaemia, familial hyperphosphataemia and some other dystrophic bone diseases, such as Sudeck's atrophy.

Reference: *La Revue Prescrire*, 7: 308 (1987).

Ceftriaxone

United States of America — The Food and Drug Administration has approved an extension of the indications for ceftriaxone (Rocephin®: Roche) powder for injection 0.25, 0.5, 1, 2 and 10 g/ampoule, for surgical prophylaxis in patients undergoing vaginal and abdominal hysterectomy.

Reference: FDA Drug and Device Product Approvals, 10 (5-6), (1987).

Cell therapy

Federal Republic of Germany — The Federal Health Office has provisionally suspended the registration of all injectable preparations used in the practice of "cell therapy" on the grounds that serious and sometimes fatal reactions have been associated with these products, which have not been demonstrated to possess any therapeutic effect.

The reported adverse effects comprise allergic manifestations, shock, and delayed reactions involving the central nervous and respiratory systems. Moreover, the possibility of contamination of these preparations with human viral pathogens including Visna-Maedi virus and scrapie virus

cannot be excluded, even when they are derived from healthy animals.

The agency emphasizes that it lacks a mandate to restrict the use of "fresh cell" suspensions prepared by the prescriber for immediate administration to the patient, but it sets on record its concern regarding the safety of these products.

Reference: Bundesgesundheitsamt, Pressebericht 6 August 1987.

Cimetidine

France — The Ministry of Health has approved a high-dose cimetidine tablet (800 mg) for the acute treatment of benign peptic ulcer that can be adequately controlled by a single nightly dose.

Reference: *La Revue Prescrire*, 7: 69 (1987).

Clometacin

France — Following reports of hepatitis, in some cases fatal, associated with the use of the peripherally-acting analgesic clometacin (Duperan®: Cassenne Laboratories), the Ministry of Health has ordered the withdrawal of a long-acting tablet formulation containing 325 mg. A 100 mg tablet will remain available labelled: "Strictly reserved for the treatment of acute pain". It is recommended that treatment should not extend beyond 10 days and should not be repeated.

Reference: *La Revue Prescrire*, 7: 273-274 (1987).

Cyclophosphamide

United States of America — Under its orphan drugs programme, the Food and Drug Administration has approved the use of cyclophosphamide (Cytoxan®: Bristol) for the treatment of biopsy-proven minimal-change nephrotic syndrome in children. The preparation is available as tablets of 25 and 50 mg, and powder for injection 0.1, 0.2, 0.5, 1.0 and 2.0 g/ampoule.

Reference: *FDA Electronic Bulletin Board*, 28 May 1987.

Cyproterone acetate

Australia — The Drug Evaluation Committee has approved an extension of the indications for cyproterone acetate (Androcur®: Schering) tablets 50 mg, for treatment of inoperable prostatic carcinoma in patients in whom primary hormonal manipulation has failed or who are at risk from cardiovascular disease or who do not tolerate estrogen therapy.

Reference: Report of the 129th Meeting of the Australian Drug Evaluation Committee, 19 June 1987.

Dantrolene

United States of America — The Food and Drug Administration has approved an extension of the indications for dantrolene sodium (Dantrium®: Norwich) powder for injection 20 mg/ampoule, to include prophylactic therapy of malignant hyperthermia.

Reference: FDA Drug and Device Product Approvals, 10 (5-6), (1987).

Dantron

Norway — Following the lead of Riker, the major manufacturer of the anthraquinone laxative, dantron, all manufacturers in Norway have discontinued production of this substance. High dosages are reported to have produced positive results in some mutagenicity tests, and to have induced hepatic carcinoma in rodents. There is no evidence to suggest that products containing dantron have induced cancer in man. Existing stocks were consequently not recalled to avoid the undue public anxiety that would have resulted from an immediate sales embargo.

Reference: *Nytt fra Statens legemiddelkontroll*, 3: 6 (1987).

Dihydroergotamine mesilate + heparin sodium + lidocaine hydrochloride

United States of America — The Food and Drug Administration has approved an extension of the indications for dihydroergotamine mesilate +

heparin sodium + lidocaine hydrochloride (Embolex®: Sandoz), injection fluid 0.5 mg + 5,000 IU + 7.46 mg per 0.7 ml, for the prevention of post-operative deep venous thrombosis and pulmonary embolism in total hip replacement surgery.

Reference: FDA Drug and Device Product Approvals, 10 (5-6), (1987).

Flunitrazepam

The Netherlands — Following reports in the lay press and subsequent Parliamentary questions about severe paradoxical aggression alleged to result from the abuse of the benzodiazepine sedative flunitrazepam (Rohypnol®: Roche), particularly when administered in combination with other psychoactive agents, the manufacturer was requested by the Board for the Evaluation of Medicines to revise the product information. The updated version, which accords with the prevailing guidelines for benzodiazepine products especially regarding precautions and warnings, became operative with immediate effect.

Emphasis is now accorded to the potential of benzodiazepines to induce dependence and withdrawal symptoms. The latter commonly present as headache, anxiety and sleep disturbances. In severe cases, however, depersonalization, hypersensitivity to light and sound, hallucinations and epileptic episodes have occurred. Prescribers are thus warned that treatment should never be abruptly withdrawn.

Paradoxical aggression is described as being more frequent in children and elderly persons and administration to children should be discouraged.

The recommended dosage has been reduced in all circumstances to 2 mg per day. Previous proposals provided for a daily dose of up to 6 mg per day for non-ambulatory patients.

The company has also advised pharmacists and doctors of the need for prudence in prescribing and dispensing the product in order to ensure it is not channelled to drug addicts. Its use in excessive dosage in combination with other psychoactive drugs is reported to have resulted in agitation, aggression and criminal behaviour with subsequent amnesia.

Reference: Information provided to WHO from Hoffmann-La Roche B.V., Mijdrecht, Netherlands, 16 September 1987.

Fluvoxamine

Iceland — The Committee on Pharmaceuticals has refused to approve for registration the anti-depressant fluvoxamine (Fevarin®: Ferrosan) on the grounds that animal experiments have shown teratogenicity and a potential to cause renal damage; studies on dependence liability in monkeys are lacking; and it has not been demonstrated clinically that this product holds any advantage over other antidepressants already available.

Reference: Notification from the Committee on Pharmaceuticals, Reykjavik, Iceland, 2 February 1987.

Glyceryl trinitrate

Australia — The Drug Evaluation Committee has approved the extension of the indications for glyceryl trinitrate (Suscard®: Astra) buccal tablets 1, 2, 2.5 and 5 mg, for acute angina and short-term or situational angina prophylaxis.

Reference: Report of the 129th Meeting of the Australian Drug Evaluation Committee, 19 June 1987.

Herbal products

Canada — The Expert Advisory Committee on Herbs and Botanical Preparations of the Health Protection Branch of the Ministry of Health and Welfare has set out comprehensive proposals for the control of herbal products within Canada.

It has concluded that most herbs currently on the market are safe when used according to instructions. However, those that are pharmacologically active should be restricted to medicinal use for the treatment of specific conditions. The following warning labelling is proposed for food products containing pharmacologically active herbs to alert sensitive individuals to possible untoward effects, as follows: "Caution. This [herb or preparation] may pose a risk to health for individuals who [stating the contraindicated condition]."

A separate system of registration is proposed for herbs and botanical preparations and a review procedure is under consideration that will require marketed products to meet specifications contained in a "standardized drug monograph". The format of

these monographs has yet to be settled but they will include reference to ingredients listed quantitatively and identified by the part of the plant as required; labelled and advertised claims; cautionary or warning statements; quality assurance with respect to both good manufacturing practice and identification of ingredients. Combination products will be accepted only if they are justified on sound therapeutic principles.

It is further proposed that claims for all products, whether sold as food or drugs, be based upon reliable supporting data, including citations in standard herbals when this information has not been superseded by more recent research. Labelled claims must be readily understandable by consumers, and ingredients must be identified both by the Latin binomial name of the plant from which they are derived and by an optional common name which may be more informative to the consumer.

The existing 'Code of Practice: General Principles of Food Hygiene for Use by the Food Industry of Canada' is applicable as a general, voluntary guideline on the manufacture of these products.

Reference: *Health Protection Branch Information Letter No. 726, 13 August 1987.*

Ibuprofen

Canada — The Expert Advisory Committee on Ibuprofen of the Health Protection Branch, Ministry of Health and Welfare, has recently published a report on the prescription status of ibuprofen.

It is concluded that the available 200 mg formulation of ibuprofen is a more effective analgesic in dysmenorrhoea and dental pain than the 325 mg formulation of acetylsalicylic acid. It is recognized that ibuprofen is associated with the same range of adverse effects as other nonsteroidal anti-inflammatory agents but it is regarded as safe as or safer than acetylsalicylic acid in the dose recommended for non-prescription use (see also, however, p. 46). No conclusion is offered concerning its safety relative to paracetamol. However, it is noted that elderly patients may be at increased risk when treated with ibuprofen, and that insufficient information is available to establish its safety either in children under 12 or in pregnant women.

The Committee thus proposes that ibuprofen 200 mg be available to adults from pharmacies without

prescription on the understanding that the pharmacist will personally advise customers on its use at the time of sale.

The maximum recommended dose is 200-400 mg every 4 hours, not exceeding 1200 mg in 24 hours. Labelled indications are restricted to temporary relief of menstrual pain, toothache, and minor aches and pains in muscles, bones and joints.

Required warnings on retail containers include the following:

"Do not take this product if you are allergic to products containing acetylsalicylic acid (ASA) or other salicylates."

"Consult your physician before taking this drug if you have peptic ulcer, hypertension, heart failure or any other serious disease, or if you are pregnant or taking any prescribed drug."

"Consult your physician if the pain for which you are treated requires continued use for more than 5 days."

"Do not give to a child under 12 years of age."

In addition, manufacturers of these products will be required to provide assurance that they will conduct post-marketing research to establish any risks associated with the proposed over-the-counter availability of ibuprofen, and provide information on sales volume in order to assess the impact of this decision on patterns of analgesic use. At the same time the Health Protection Branch is requested to re-examine the implications of the continued availability of acetylsalicylic acid as a non-prescription drug.

Reference: *Health Protection Branch Information Letter No. 720, 27 March 1987.*

Interferon alfa-2a

Australia — The Drug Evaluation Committee has approved interferon alfa-2a (Roferon®: Roche) specifically and exclusively for the treatment of hairy-cell leukaemia. Registration was refused for AIDS-related Kaposi's sarcoma and malignant melanoma on grounds of inadequate data.

Reference: Report of the 128th meeting of the Australian Drug Evaluation Committee, 24 April 1987.

Interleukin-2

United States of America — In the light of encouraging preliminary reports, the Food and Drug Administration has authorized the National Cancer Institute to extend its investigational use of interleukin-2, either alone or in combination with lymphokine-activated killer cells, to treat advanced melanomas and renal cancers that are not amenable to other therapy.

Reference: HHS News P87-12, Food and Drug Administration, 7 May 1987.

Ipratropium bromide

France — The approved indications for the bronchodilator agent ipratropium bromide (Atravent®: Boehringer Mannheim) have recently been extended to include symptomatic treatment of seromucous rhinorrhoea in non-infected obstructive non-allergic or allergic rhinitis. Use in children under 15 years of age is contraindicated.

Reference: *La Revue Prescrire*, 7: 114 (1987).

Metoclopramide

United States of America — The Food and Drug Administration has approved an extension of the indications for metoclopramide (Reglan®: Robins) injection fluid 10 mg/ml, for the prevention of post-operative nausea and vomiting.

Reference: FDA Drug and Device Product Approvals, 10 (5-6) (1987).

Mucopolysaccharide polysulfuric acid esters

Federal Republic of Germany — The Federal Health Office is planning to withdraw from the market two injectable preparations containing mucopolysaccharide polysulfuric acid esters (Arteparon®, Arteparon Forte®: Luitpold-Werk) that are indicated for the treatment of arthroses. It is claimed that their efficacy has never been adequately demonstrated and that both

products have been associated with a variety of adverse effects including exacerbation of damage to the treated joint, allergic phenomena and anaphylactic shock.

Reference: Bundesgesundheitsamt Pressebericht, 15 July 1987.

Nabilone

United States of America — The Drug Enforcement Administration of the Department of Justice has placed nabilone (Cesamet®: Lilly) under Schedule II of the Controlled Substances Act. This implies that only licensed persons may handle the substance and products containing it, and that registers must be kept of all handling and storage. It will be available only on prescription. Nabilone, a synthetic substance closely related to dronabinol, is used for the clinical treatment of emesis in cancer therapy. It is considered to have a high potential for abuse which could result in severe psychological or physical dependence.

Reference: *Federal Register*, 52 (66): 11042-3 (1987).

Oral contraceptives: revised patient package insert

United States of America — The Food and Drug Administration proposes to revise the requirements for patient package inserts for oral contraceptive drugs. The proposed changes are intended to simplify the content and format of the insert, to render it more comprehensible and to provide for more timely updating of the information.

Instead of listing specific items, the text will contain general categories of information, thus making it easier for manufacturers to introduce updated information. Further changes to simplify updating and to allow greater flexibility in the text include elimination of the requirement for a separate summary patient insert which may now be combined with the detailed patient package insert into a single leaflet. Printing specifications will no longer be stipulated and distributors will be free to adopt whatever method they choose for distribution of patient package inserts — which under current requirements must accompany the drug product — provided that all persons in the distribution chain

receive an adequate number of inserts to meet their responsibilities.

The package insert is required to contain the following information:

1. The name of the drug.
2. Summarized information regarding the effectiveness of oral contraceptives in preventing pregnancy, contraindications to their use, and a statement of the associated risks and benefits.
3. A more discursive statement regarding the effectiveness of oral contraceptives.
4. Information that the patient should provide to the prescriber before taking the drug.
5. A listing of medical conditions that deserve special consideration when oral contraceptives are prescribed and about which the patient should inform the prescriber.
6. A warning regarding serious adverse effects of oral contraceptives.
7. A boxed warning concerning the risks associated with cigarette smoking and oral contraceptive use.
8. A listing of other serious adverse reactions and potential safety hazards that may result from the use of oral contraceptives.
9. Information on precautions the patients should observe while taking oral contraceptives, including:
 - (i) A listing of activities and drugs, foods, or other substances the patient should avoid because of known, clinically significant interactions with oral contraceptives.
 - (ii) A statement of risks to the mother and unborn child from the use of oral contraceptives before or during early pregnancy.
 - (iii) A statement concerning excretion of the drug in human milk and associated risks to the nursing infant.
10. A statement concerning possible adverse effects which may help the patient evaluate the benefits and risks arising from the use of oral contraceptives.
11. A statement of possible benefits associated with oral contraceptive use.
12. Information on how to take oral contraceptives properly: what to do when a dose is forgotten or when a patient becomes pregnant after discontinu-

ing use; the dangers of using the product for other conditions and of giving it to others; the possibility that the patient's pharmacist or practitioner may have a more technical leaflet about the drug product which the patient may ask to review.

Reference: *Federal Register*, 52 (76): 13107 (1987).

Oral contraceptives

United States of America — The Food and Drug Administration has revised the text of the guidelines for the labelling of estrogen/progestogen combination oral contraceptives. The text will now include reference to several collateral benefits that accrue from their use including decreased incidence of iron deficiency anaemia, dysmenorrhoea, benign breast disorders, functional ovarian cysts and pelvic inflammatory disease, as well as a protective effect against the development of ovarian and endometrial cancer.

Reference: *Federal Register*, 52 (76): 13132-33 (1987).

Phenylpropanolamine

Federal Republic of Germany — The Federal Health Office has recommended that pharmaceutical products containing the sympathomimetic compound phenylpropanolamine should be subjected to prescription control. These products, which are approved as appetite suppressants and for symptomatic relief of the common cold, have induced hypertensive episodes in susceptible individuals particularly when they have been taken together with coffee, alcohol, antihistamines or neuroleptics. Pharmacists are requested to report any evidence of abuse of these products and doctors are advised to remain alert both to the possibility of abuse and adverse cardiovascular effects.

Reference: *Bundesgesundheitsblatt*, 30: 187 (1987).

Piroxicam

Iceland — The Committee on Pharmaceuticals has additionally approved the use of piroxicam (Felden®: Pfizer) for the treatment of dysmenorrhoea. Two new pharmaceutical forms have also

been approved: suppositories in strengths of 10 and 20 mg, and dispersible tablets 20 mg.

Reference: Notification from the Committee on Pharmaceuticals, Reykjavik, Iceland, 5 May 1987.

Rifampicin

France — The Ministry of Health has additionally approved the use of rifampicin (Rifadine®: Merrell-Dow) in combination with doxycycline for the treatment of brucellosis. The recommended dosage schedule is:

- 3 x 300 mg rifampicin in the morning before breakfast.
- 2 x 100 mg doxycycline with the evening meal.

Reference: *La Revue Prescrire*, 7: 210 (1987).

Saccharin

United States of America — In April 1977, the Food and Drug Administration proposed restrictions on the use of the sweetening agent saccharin because of its reported association with cancer in experimental animals. The FDA proposed to ban saccharin from processed foods but to permit its use as a table-top sweetener. However, in the face of public reaction to this proposal, US Congress enacted a law in November 1977 which prevented restrictive action by the FDA for a period of two years, except insofar as the labels of products containing saccharin should warn that: "Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals."

This provision has been extended several times since its initial enactment, and the moratorium is now scheduled to operate until 1 May 1992. The FDA comments that the use of saccharin has been diminishing notably since the introduction of aspartame.

Reference: FDA Talk Paper T87-38, 1 September 1987.

Sympathomimetic agents

Federal Republic of Germany — The Ministry of Health has announced that, as from 1 July 1987, it

will subject all pharmaceutical products containing metamfepramone, fencamfamin or prolintane to prescription control. This complements an earlier decision in which cathine (D-norpseudoephedrine), propylhexedrine and ephedrine were placed on prescription control, and it results from evidence of abuse of other sympathomimetic substances.

Reference: *Bundesgesundheitsblatt*, 30: 186 (1987).

Syringes and needles for parenteral injection: restricted use

France — In order to reduce illicit use of needles and syringes by drug addicts, the Government of France has issued new rules regarding sale and dispensing:

- Needles and syringes may only be sold by pharmacies and manufacturers of medical devices.
- The packaging must indicate these legal restrictions and carry the notice: "For once-only use" in clearly-readable characters, when appropriate.
- In general, dispensing is only permitted on medical prescription.
- However, individuals over 18 years of age may obtain syringes or needles without a prescription on presentation of proof of identity and a written request dated and signed by the purchaser indicating his name and address. A copy of the prescription or the request must be retained by the seller for one year.

Reference: *Textes législatifs et réglementaires. Bull. Ordre* 303: 741 (1987).

Ticlopidine

France — The Ministry of Health has approved an extension of the indications for ticlopidine (Ticlid®: Millot-Solac) to include prevention of peripheral or central vascular insufficiency in patients with atherosclerotic arteriopathy of the lower limbs. Previously it was indicated exclusively for prevention and correction of platelet abnormalities developing during chronic haemodialysis or surgery involving an extracorporeal circulation.

Reference: *La Revue Prescrire*, 7: 258-9 (1987).

Triazolam

Australia — In 1986 the Drug Evaluation Committee approved triazolam tablets 0.125 mg (Halcion®: Upjohn) for the treatment of insomnia. Higher strength tablets (0.25 and 0.5 mg) were not approved because of concern regarding the risk of adverse effects resulting from inappropriate use (1). The company's subsequent appeal against the rejection of the 0.25 mg dosage form has now been dismissed (2).

References

1. Report of the 123rd Meeting of the Australian Drug Evaluation Committee, 11 April 1986.
2. Report of the 127th Meeting of the Australian Drug Evaluation Committee, 27 February 1987.

Trimethoprim/sulfonamide combinations

Sweden — The National Board for Drug Control, acting in agreement with the major manufacturers, has restricted the approved indications for products containing trimethoprim and a sulfonamide by excluding the treatment of uncomplicated urinary tract infections.

Products containing trimethoprim + sulfamethoxazole are now indicated exclusively for treatment of the following infections when these are due to sensitive organisms that are unresponsive to either compound alone: pyelonephritis, urinary tract infection complicated by multiresistant bacteria, typhoid or paratyphoid fever, acute exacerbation of chronic bronchitis, chronic bacterial prostatitis, septicaemia, shigellosis, and infections caused by *Pneumocystis carinii*.

Accepted indications for products containing trimethoprim + sulfadiazine are limited to complicated and/or higher urinary tract infections due to bacteria sensitive to the combination but unresponsive to either compound alone.

The agency has taken this action in the light of a large number of reported adverse effects including sensitivity reactions, mucocutaneous syndrome, blood dyscrasias and hepatic disorders, some of which have been severe and even fatal.

Reference: *Information från Socialstyrelsens läkemedelsavdelning*, 12: 48 (1987).

Vincamine in herbal medicines

Federal Republic of Germany — The Federal Health Office has withdrawn 27 herbal preparations containing vincamine that were indicated for the treatment of commonly occurring disorders ranging from toothache to haemorrhoids. The withdrawal was effected on grounds of inadequate evidence of efficacy and the risk of blood dyscrasias.

Reference: Bundesgesundheitsamt Pressebericht 22 July 1987.

Vitamins

France — The Directorate of Pharmacy and Medicines of the Ministry of Health has informed WHO that, with certain exceptions, vitamin-based pharmaceutical products will no longer be reimbursed from insurance funds. The only such products that will continue to qualify are:

- monocomponent products containing retinol (vitamin A), cyanocobalamin (vitamin B12), ergocalciferol (vitamin D), or vitamin E;
- injectable forms of monocomponent products containing thiamine (vitamin B1) or pyridoxine (vitamin B6).

The latter, it is considered, are indispensable in the treatment of clinically important vitamin deficiency states.

Reference: Letter to WHO from the Directorate of Pharmacy and Medicines, Paris, France, 26 May 1987.

VETERINARY DRUGS

Detomidine

Sweden — The National Board of Health and Welfare has approved detomidine (Domitor Vet®: Läkefarmos) injection fluid 10 mg/ml, an alpha-adrenoreceptor agonist with a sedative and analgesic effect, to be used for sedation of horses or cattle in diagnostic and minor surgical procedures or during transport. Withdrawal period for slaughter: horses 7 days; cattle 4 days. Withdrawal period for milk: 3 days.

Reference: Letter to WHO from the National Board of Health and Welfare, Uppsala, Sweden, 5 August 1987.

Lasalocid sodium

Sweden — The National Board of Health and Welfare has approved lasalocid sodium (Avatec®: Roche) powder 15 per cent, to be mixed with feed. It is indicated for prophylaxis and treatment of coccidiosis in poultry. Withdrawal period prior to slaughter: 3 days.

Reference: *Information från Socialstyrelsens läkemedelsavdelning*, 12: 51 (1987).

Luprostiol

Sweden — The National Board of Health and Welfare has approved luprostiol (Prosolvin®: Intervet) injection fluid 7.5 mg/ml. It is indicated for oestrus synchronization, evoking oestrus, treatment of endometritis and pyometra in cows. Withdrawal period for milk: 1 day; prior to slaughter: 4 days.

Reference: *Information från Socialstyrelsens läkemedelsavdelning*, 12: 52 (1987).

Monensin

United States of America — The Food and Drug Administration has approved the use of a protein-mineral feed block containing 0.033 per cent monensin for increased weight gain in pasture cattle. Animals may require supplemental feed, and roughage must be available at all times. No other types of protein block should be administered concurrently. Effectiveness of the block in culled cows and bulls has not been established. Ingestion of monensin by horses and other equines has resulted in fatalities.

Reference: *Federal Register*, 52 (138): 27, 197-98 (1987).

Tiamulin

Sweden — The National Board of Health and Welfare has approved tiamulin (Tiamutin® vet.: Lövens) injection fluid 200 mg/ml for treatment of dysentery in pigs. A solution containing 125 mg/ml for addition to the drinking water is also available.

Its use is contraindicated in pregnant sows. Withdrawal period before slaughter: 14 days.

Reference: Letter to WHO from the National Board of Health and Welfare, Uppsala, Sweden, 5 August 1987.

Dispensing of veterinary products in pharmacies

France — The Central Council of Dispensing Pharmacists has reminded members that they should refrain from advertising or promoting veterinary drugs in direct mail journals, through window displays, by provision of free samples, or through introductory discount prices. Veterinary products should be dispensed by or under the direct supervision of a pharmacist. Anthelmintic and antibiotic drugs, which need to be administered with pertinent caution, should be provided in small quantities for specific cases. Antibiotics for group treatment of animals should only be dispensed on prescription. Vaccines should not be sold without prescription either for notifiable illnesses or when a declaration of vaccination is required for crossing a border or exhibiting an animal.

Non-veterinary personnel involved in animal breeding should have access only to products necessary for their profession, such as vitamin E and progesterone. The sale of hormones, including implantable products, without prescription is prohibited.

Reference: *Moniteur des Pharmacies et des Laboratoires*, 1766: 12 (1987).

Generic substances used in animal feeds

United Kingdom — The Licensing Authority of the United Kingdom has introduced new arrangements for the licensing of generic substances used in animal feeds.

Applicants must provide data on the quality of each product, its acceptability and stability in animal feeds and information on its safety and efficacy under the proposed conditions of use. Since standard withdrawal periods must appear on the product labelling, no residue data are needed.

Licensed products may be supplied for incorporation in animal feeds for the treatment of animal diseases only on veterinary prescription. The licence will carry no recommendation for use against specific conditions or in particular species, nor will they give any information as to the dosage.

Reference: MAIL (*Medicines Act Information Letter*), No. 49, March 1987.

Withdrawal periods for medicated animal feeds

United Kingdom — A joint statement has been issued by the Ministry of Agriculture, Fisheries and Food, the British Veterinary Society and the Royal College of Veterinary Surgeons, setting out guidelines for veterinary surgeons on the withdrawal periods before slaughter or consumption to be observed when prescribing medicinal feed additives when this period is not specified in the licence. The standard periods are:

- eggs (all species) 7 days
- milk (all species) 7 days
- meat: - poultry 7 days
- pigs 10 days
- other species 28 days
- fish 200 degree days (cumulative total of the water temperature in degrees Celsius on each day following the last treatment)

Reference: MAIL (*Medicines Act Information Letter*), No. 49, March 1987.

Oil-based veterinary vaccines

United Kingdom — In veterinary practice large numbers of animals may be vaccinated at one time, a practice that increases the risk of accidental self-injection by the operator.

The Committee on Safety of Medicines has decided that the label or carton of such vaccines should carry the following warning text for the information of the users, doctors and casualty units:

"To the User: If you inject yourself accidentally with this product, go AT ONCE to the nearest Accident and Emergency (Casualty) Department of a hospital and show the information printed below to the doctor (or nurse) on duty."

"To the Doctor: Accidental self-injection with this oil-based product can cause intense vascular spasm which may, for example, result in the loss of a digit. Expert, PROMPT surgical attention is required and may necessitate early incision and irrigation of the injected area, especially where there is involvement of finger pulp or tendon sheaths."

Reference: Committee on Safety of Medicines, *Current*