

Regulatory Matters

Alendronic acid-induced oesophageal ulcers

United States of America — Alendronic acid is the first non-hormonal therapy to be approved in a number of countries for the treatment of osteoporosis in postmenopausal women; it is also indicated for the treatment of Paget disease.

Since introduction of the product onto the market, the manufacturer has received a number of case reports of oesophagitis and oesophageal ulceration where patients have presented with retrosternal pain, and difficulty or pain in swallowing.

As a result, the manufacturer has circulated a letter to doctors and other health professionals stating that oesophageal reactions have been reported that are of a greater severity than those observed during controlled clinical trials. The manufacturer has duly revised the package labelling and patient insert to emphasize that reactions such as oesophageal erosion, ulceration or oesophagitis may be avoided or reduced by carefully following the instructions for use as set out in the new recommendations.

Each tablet should be swallowed with a full glass of plain water immediately on rising in the morning and at least 30 minutes before the first food, beverage or medication of the day. Patients should be instructed not to lie down for at least 30 minutes after taking the tablet, and not to take the drug at bedtime or before rising for the day.

Source: From the FDA. *Journal of the American Medical Association*, 278: 1534 (1996).

Oral contraceptives containing desogestrel or gestodene: updated position statement

European Union — The Committee for Proprietary Medicinal Products (CPMP) held a meeting in April 1996 to discuss further the risks of thromboembolism associated with combined oral contraceptives containing desogestrel or gestodene. In addition to the previous statement published in October 1995 (1) the following position statement has now been issued by the CPMP.

Venous thromboembolism is a serious but rare risk associated with the use of oral contraceptives. Because this complication is rare it is difficult to study, and estimates of its incidence are not precise.

All studies hitherto presented to the CPMP indicate that the risk for venous thromboembolism is higher in users of desogestrel or gestodene-containing oral contraceptives than in users of levonorgestrel-containing oral contraceptives. The impact of biases and confounders on the difference still cannot be fully evaluated.

Data from studies of haemostatic factors indicate differences between levonorgestrel-containing oral contraceptives (so-called second generation) and desogestrel or gestodene-containing oral contraceptives (so-called third generation), but these are of unknown clinical relevance as yet.

The requested pooled analyses of acute myocardial infarction have not yet been performed and currently available data do not allow a conclusion that desogestrel or gestodene-containing oral contraceptives have an advantage over levonorgestrel-containing oral contraceptives in this respect.

There is no evidence that from a public health point of view the other major benefits or risks (e.g. reliability of contraception) are different from desogestrel or gestodene-containing oral contraceptives. For the individual there may, however, be benefits in quality of life.

Factors other than the "generation" of pill used, such as heredity and immobilization, also have an important role for the occurrence of venous thromboembolic events.

To further evaluate to what extent biases and confounding factors have contributed to the difference in risk of venous thromboembolic events in users of desogestrel or gestodene-containing oral contraceptives and levonorgestrel-containing oral contraceptives respectively, and to clarify whether there are differences in effect on myocardial infarction rates, the CPMP will request further analysis of the data presented, and carefully keep the ongoing studies under review.

The previous message to doctors/users is still relevant and in addition doctors/users are reminded of the following:

- Discontinuation of oral contraceptives should be seriously considered in situations that are associated with an increased risk of venous thromboembolic events, such as immobilization, major trauma or major surgery.
- Due to the vague symptomatology of many venous thromboembolic events, discontinuation of oral contraceptives should be considered in cases of suspected thrombosis in patients on oral contraceptives, while diagnostic interventions are being pursued.
- In cases of an uncertain diagnosis of venous thromboembolic events, alternative contraceptive strategies should be discussed with the patient, since the event may represent a first signal of oral contraceptive-associated thrombophilia.

Source: Position statement of the CPMP on oral contraceptives containing desogestrel or gestodene. CPMP/374/96, EMEA, 17 April 1996.

Temazepam now a controlled drug

United Kingdom — The Secretary of State for Health has announced that temazepam, a short-acting benzodiazepine, is to be transferred from schedule 4 of the Misuse of Drugs Regulations 1985 to schedule 3, which will mean tighter controls on its availability. These measures are being taken in an attempt to prevent misuse (1). It is also announced that gel-filled capsules of the drug will no longer be prescribed on the National Health Service.

Liquid-filled temazepam capsules have been widely abused on the illicit drugs market, the liquid gel lending itself to intravenous administration. This formulation was replaced in the United Kingdom by tablets and capsules containing semi-solid gel, which it was considered difficult to inject. In spite of this there has still been evidence of abuse (2).

The rescheduling means that:

- Simple possession of the drug without authority will be an offence;
- Import and export of the drug are required to be licensed;
- Temazepam will become subject to a set of safe custody requirements, and the drug will be kept in locked controlled-drug cabinets;
- Additional documentation will be required when a person other than a doctor supplies the drug, and will require persons who are not already authorized to possess, supply or produce schedule 3 drugs to obtain an appropriate written authority;
- Supply on prescription will be more carefully undertaken; and
- Containers in which the drug is supplied will be suitably marked.

Existing requirements which apply to schedule 4 drugs, such as keeping of records of the quantities produced, imported and exported, will remain in effect.

References

1. Communication from the Home Office, London, United Kingdom, 16 April 1996.
2. Martindale — *The extra pharmacopoeia*. Royal Pharmaceutical Society, London. Thirty-first edition. 1996.

HIV protease inhibitors and spontaneous bleeding

France — The Medicines Agency has reported 9 cases of haematoma in haemophilic patients with AIDS who are being treated with the HIV protease inhibitors indinavir, zidovudine and zalcitabine. An inquiry is in progress (1). It should be noted that factor VIII infusion in these patients has had to be increased since the beginning of treatment.

United States of America & Canada — The FDA has learned of 15 case reports of spontaneous bleeding episodes in HIV-positive patients with haemophilia receiving protease inhibitors in Europe. Of these cases, 11 have involved haematomas and 5 haemarthroses. None involved serious injury or death. The majority of patients, who are on multiple drug therapy, have continued taking the HIV protease inhibitors despite the bleeding event. No events have been reported within the United States. To date, there is no conclusive evidence to establish that this class of drugs is the cause of spontaneous bleeding episodes. However, the FDA

will continue to keep close watch on the situation since the three products in question have been given marketing approval under the FDA's accelerated approval mechanism for treatment of life-threatening illness.

The FDA and manufacturers of the products in question recommend that health-care providers monitor haemophiliac patients for spontaneous bleeding episodes whenever any protease inhibitors are used as part of HIV treatment. However, patients with haemophilia and HIV infection who are currently on protease inhibitor therapy should not discontinue treatment, but consult with their health care providers if they have any concerns (2).

The Canadian Health Protection Branch is also closely monitoring the situation and, in addition to the above-mentioned cases, has received a report of one Canadian patient affected by spontaneous bleeding. HPB states that all of the reports involved patients with haemophilia and advanced HIV infection who were receiving multiple drug treatment. Clinical studies using HIV protease inhibitors have not so far reported an increased incidence of either bleeding or coagulation abnormalities in patients with or without haemophilia (3).

References

1. Notice from Medicines Agency, France dated 20 June 1996.
2. Letter to US health-care providers from the Department of Health & Human Services, sent on 17 July 1996.
3. Notice to health care providers in Canada sent by the Health Protection Branch on 18 July 1996.

Terbinafine: surprising number of reports

Australia — Terbinafine is a new antifungal drug with activity against infections due to dermatophytes and *Candida albicans*. The product was first marketed in Australia in late 1993, and since that time the Adverse Drug Reactions Advisory Committee (ADRAC) has received 168 reports documenting a total of 323 suspected adverse reactions. ADRAC is concerned by the number and nature of these reports, considering that the drug is often used for minor conditions and for a prolonged period.

There are two prominent groups of adverse reactions. Those involving the gastrointestinal tract, which include taste perversion or loss, and those involving the skin, suggestive of hypersensitivity or photosensitivity. So far, ADRAC has received 2 reports describing suspected neutropenia and one case of agranulocytosis. Finally, there are 11 reports of adverse hepatic reactions.

While all the above reactions are mentioned in the product information, careful prescribing and close monitoring must be encouraged.

Source: *Australian Adverse Drug Reactions Bulletin*. Volume 15, number 1, 1996.

Withdrawal of topical products containing gentamicin

Malaysia — In view of the fact that long-term use of topical antibiotics can lead to development of hypersensitivity and widespread use can lead to a risk of emergence of resistant strains, the Drug Control Authority has withdrawn marketing of topical cream or ointment products containing gentamicin. Out of 28 products available for topical use in Malaysia, 16 contained gentamicin as the sole active substance, while the other 12 preparations were combinations of gentamicin with a corticosteroid.

Source: *Newsletter of the Drug Control Authority of Malaysia*, 10: 4 (1996).

Emergency contraceptives recommended for over-the-counter (OTC) use?

New Zealand — The Medicines Classification Committee (MCC) has recommended that emergency contraceptive tablets be sold by pharmacists over-the-counter. These will be supplied in a special pack which contains instructions approved by the Ministry of Health. Meanwhile, the recommendation cannot be implemented until approval has been given by the Cabinet to amend the Medicines Regulations.

Source: *New Zealand Prescriber*. Update No. 12, July 1996.

Conjugated estrogens and generic pharmaceuticals

United States of America — Natural conjugated estrogens excreted by pregnant mares are used for estrogen replacement to treat symptoms of the menopause and allied disorders such as postmenopausal osteoporosis, atrophic vaginitis, kraurosis vulvae and atrophic urethritis. Discussion is now centred on which active hormonal ingredient contributes to the effectiveness and safety of the brand product, Premarin®, Wyeth Ayerst, and which of these components should be included in the generic version of the product.

Two estrogen ingredients — estrone sulfate and equilin sulfate — have been regarded as Premarin's main active substances. Despite the company's petition, the contribution made to the product's safety and effectiveness by the remaining estrogens (which include estrogen-8, 9-dehydroestrone sulfate — delta-8-DHES) has been questioned by generic companies. The US Food and Drug Administration has prepared a document entitled *Preliminary analysis of scientific data on the composition of conjugated estrogens*, and has included this as part of the public docket for the petition. A *Federal Register* notice providing an opportunity for public comment on this preliminary analysis will soon be published.

Reference: FDA Talk Paper, T96-73, 1996.

Chlormezanone withdrawn following skin reactions

France — In agreement with the French Medicines Agency, the manufacturers of chlormezanone-containing products (Trancopal®, Trancogesic®, Sanofi Winthrop and Alinam®, Therabel Lucien Pharma) have decided to stop marketing the product and recall batches immediately (1). The decision was based on findings of a recently published multicountry case-control study on the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis (2). Based on these developments, Sanofi Winthrop has decided to withdraw the drug worldwide (3).

Chlormezanone is a mild tranquillizer with muscle-relaxant properties and a sedative effect which has been available since the 1960s in a single formulation, and later in combination with either analgesics or nonsteroidal anti-inflammatory drugs.

It is generally used as adjunctive therapy for the treatment of lumbago, torticollis or pain caused by minor injuries.

Results of the study show that the incidence of Stevens-Johnson syndrome is estimated at 1 to 6 cases per million person-years and toxic epidermal necrolysis at 0.4 to 1.2 cases per million person-years. Although these conditions are rather infrequent, they may kill or severely disable previously healthy people and they are frequently associated with drug use. When skin detachment is very extensive, prognosis is poor, with death rates of 30 to 40 per cent. Documentation of a causal relationship with medication requires widespread population studies because of the low frequency of disorders. This explains the fact that drugs may have been used for many years before such data on adverse reactions become available. The present study began in 1989 and included about 120 million people in France, Germany, Italy and Portugal.

The continued reporting and monitoring of adverse drug reactions has once again proven crucial in the benefit/risk assessment of treatment. Whenever safer alternative drugs or therapy become available, older therapies are subject to reassessment. The present withdrawal should thus be appreciated as a sign of improvement and appropriateness of available treatment.

References

1. Agence du Médicament. *Pharmacovigilance*. 14 October 1996.
2. Roujeau, J.C., Kelly, J.P., Naldi, L. et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *New England Journal of Medicine*, 333: 1600-1607 (1995).
3. *SCRIP*. No. 2176, p. 16. 1996.

Marketing authorization of fixed combination medicinal products

European Union — The Committee for Proprietary Medicinal Products (CPMP) has approved guidelines for submission of an application for marketing authorization of fixed-dose combination medicinal products. The guidance comes into effect for European Union countries in October 1996.

Pharmaceutical companies submitting an application are now required to justify the particular

combination of active substances proposed. Fixed-combination products will only be considered acceptable if the proposed combination is based on valid therapeutic principles.

For any individual fixed combination, it is necessary to assess the potential advantages in a clinical setting against possible disadvantages in order to determine whether the product meets the requirements of efficacy and safety.

Potential advantages of fixed combinations should include one of the following:

(a) An improvement of the benefit/risk assessment due to:

1. Addition or potentiation of therapeutic activities of their substances, which results in:

- a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile; or
- a level of efficacy above the one achievable by a single substance with an acceptable safety profile.

2. The counteracting by one substance of an adverse reaction produced by another.

(b) A simplification of therapy which improves patient compliance. (When it is the only claim, it would be restricted to a particular situation such as non-prescription products).

Disadvantages of fixed combinations include:

- the fact that even a combination which meets the needs of the average patient is unlikely to be ideally adjusted for the needs of each individual patient; and

- the addition of the different adverse reactions specific to each substance.

The guideline points out that fixed combinations, in principle, may not be considered rational if the duration of action of the substances differ significantly. This may not apply where it can be shown that the combination is clinically valid despite differences in this respect, i.e. if one substance is intended to enhance absorption of the other or where the substances are intended to exert their effects successively.

Each substance of the fixed combination must have a justified action. The inclusion of a substance to counteract an adverse reaction of another substance may be considered justified, but only if the adverse reaction is a serious or commonly occurring one. However, the inclusion of a substance intended to produce unpleasant adverse effects as a means of preventing abuse is undesirable. It is considered that substances having a critical dosage range or a narrow therapeutic index are inappropriate for inclusion in fixed combinations.

The guideline goes on to discuss indications, drug interactions and dosage levels of each of the substances, and the need for pharmacodynamic and pharmacokinetic studies, and clinical trials to prove efficacy and safety of fixed combinations. It also points out that safety studies in animals should be conducted, but may not be required if all the substances concerned have been extensively used in humans in identical or very similar combinations and if their safe long-term use has been well documented.

Reference: European Agency for the Evaluation of Medicinal Products. *Note for guidance on fixed combination medicinal products*. CPMP/EWP/240/95.