WHO Drug Information

WHO Drug Information provides an overview of topics relating to drug development and regulation that are of current relevance and importance, and will include the lists of proposed and recommended International Nonproprietary Names for Pharmaceutical Substances (INN). Its contents reflect, but do not present, WHO policies and activities and they embrace socio-economic as well as technical matters.

The objective is to bring issues that are of primary concern to drug regulators and pharmaceutical manufacturers to the attention of a wide audience of health professionals and policy-makers concerned with the rational use of drugs. In effect, the journal seeks to relate regulatory activity to therapeutic practice. It also aims to provide an open forum for debate. Invited contributions will portray a variety of viewpoints on matters of general policy with the aim of stimulating discussion not only in these columns but wherever relevant decisions on this subject have to be taken.

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The WHO Certification Scheme: performance and potential

During the Forty-first World Health Assembly held in Geneva in May of this year, several substantive amendments were introduced into the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (1). These bring within the ambit of the Scheme drug substances as well as finished dosage forms, and products intended for veterinary use as well as those for human use. They also require the competent authority in the exporting country to provide copies of all approved labelling and package inserts, as contained in the product licence, together with the date of their approval.

With the introduction of the WHO certification procedure in 1975, an international corollary was established to national systems of product registration. Importing authorities were provided not only with a means of obtaining authoritative confirmation of whether a product offered for export is licensed within the country of origin, but also with a declaration indicating whether or not the licence holder is operating in accordance with internationally accepted standards of manufacturing practice. The recent amendments do not impinge upon these basic objectives; nor are they an expression of any perceived weakness in the Scheme. Their purpose is to update and strengthen it in the light of contemporary developments and needs.

- The provision for exchange of approved product information reflects the more detailed attention that highly-evolved regulatory authorities are now directing to labelling, and the fundamental importance of precise prescribing instructions in face of the ever-rising number of registered products in circulation.

- The inclusion of veterinary products in the Scheme is a consequence of the public health implications of the now intensive use of pharmaceutical and biological products in animal husbandry, and particularly of the widespread routine use of growth-promoting substances to increase yields in food-producing animals.

- The extension of the Scheme to include drug substances as well as finished dosage forms reflects the steadily rising international commerce in these commodities. More countries are manufacturing and exporting them, while others are becoming more active in formulating finished products from drug substances imported in bulk.

The last of these factors, together with the emergence of generic manufacturing as an important market force in many countries, is contributing to an important restructuring of the industry. The competitive edge that these companies bring to trade in patent-expired products is welcomed by governments everywhere as a means of relieving the heavy burden of drug costs in the public sector. At the same time, regulatory authorities are confronted with the challenge of ensuring that the safety of patients is never unnecessarily placed at risk by allowing quality to be compromised in the interests of economy. Assurance has to be obtained, through prevailing inspection and registration procedures, that generic companies operate to the same exacting standards as their research-based counterparts, and that the products they produce match those of equivalent marketed products, not only in their compliance with specifications but in their stability, bioavailability and clinical performance. Each of these qualities is determined not only by the innate characteristics of the active ingredients but by the excipients that are used and the techniques that are employed in the formulation process. In essence, generic products need to comply not only with prevailing regulatory standards of quality, efficacy and safety; assurance is also needed that they are effectively interchangeable with equivalent products already available.

Hard necessity accentuates the appeal of low-priced generic products in the least affluent countries where orders for drugs are frequently put out to open tender in order to encourage competitive bidding. Drugs bought at discount in this way may represent a sound investment since reputable producers often need to clear their stocks of a particular product before manufacturing another batch. Many agents — or
brokers — are engaged in the legitimate business of buying and selling such stocks. However, the true origin of a product readily becomes obscured when it is traded through intermediaries and the assurances and safeguards conferred by the WHO Certification Scheme can no longer be provided. Once the “pedigree” of a product is lost, the door is open to inadmissible practices. Products that are close to, or already past, their expiry dates may be passed off as recently manufactured. They may not have been produced in accordance with internationally-accepted standards of practice, nor formulated with the skills and knowledge required to create an acceptably stable or bioavailable product. At worst, counterfeit or spurious drugs may be slipped into the distribution chain. Some of these are contrived as fair copies of the labelled product; others are substandard in various ways, while others do not even contain the active ingredients specified on the label.

The need for sustained vigilance in the regulation and certification of pharmaceutical products was emphasized formally during the World Health Assembly. It was decided, during debate, not only to highlight the importance of exchange of data on product stability within the context of the Certification Scheme, but also to request the Director-General “to initiate programmes for the prevention and detection of the export, import and smuggling of falsely-labelled, spurious, counterfeited or substandard pharmaceutical preparations” (2).

Effective controls cannot be implemented without cost, and hard-pressed governments will want assurance that they will not lead to overzealous pre-occupation with quality assurance, and that the necessary investment is immediately cost-effective. WHO consequently needs to set high priority on amassing information to establish the extent to which purchased products are subsequently found to be substandard and the implications that this has for the health of the patient population. It also needs to identify more securely those products that merit particular attention. Products that are potentially lifesaving and those that require the protection of a cold-chain need to be subjected to the most rigorous standards of quality assurance wherever they are used. It is less widely appreciated that products as ubiquitous and important as tablets of acetylsalicylic acid, paracetamol and ferrous sulfate require skilled and sophisticated formulation if they are to resist the rigours of climatic extremes throughout their labelled shelf-lives. More comprehensive and systematic information on the dimensions of the problem are needed and representative national quality control laboratories in a variety of countries are already collaborating in assessing stability and bioavailability characteristics of samples of multisource products containing selected substances that are available on their domestic markets.

Even with the information already available, a small national quality control laboratory, staffed with pharmacists or analysts of high integrity and competence, acts as a potent deterrent to negligent and criminal practice in drug procurement and distribution. However, analysis must be complemented by sound administrative control through licensing and certification. For imported products, certification is an inherent component of quality assurance. It cannot be discarded without risk. Admittedly it is a fallible process, but to reject it on these grounds is simply to surrender responsibility. The remedy is to identify and to investigate shortcomings as they arise. All Member States participating in the Scheme accept that the certifying authority should institute enquiries whenever any quality defect is detected that is "considered to be of a serious nature by the importing country, not attributable to local conditions and circumstances, and appearing after the introduction of a particular batch in the importing state”(3). The strength of the Certification Scheme derives from the rigour with which it is implemented. If it is used appropriately and if complaints are notified efficiently and investigated assiduously it will be given all the teeth that it needs to dispose of the apparently intract-able problems.

References


Towards a single pharmaceutical market for the European Community

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Following the ratification and entry into force of the Luxembourg Single Act, the twelve Member States of the European Community are now fully committed to the creation by 31 December 1992 of an area without internal frontiers in which the free movement of goods, persons, services and capital is ensured. The institutions of the Community are currently involved in a major programme of legislation consisting of more than 300 measures in order to achieve this objective. For the pharmaceutical sector, the Commission's White Paper on the Internal Market envisaged the adoption of ten legislative measures between 1985 and 1992, four of which have already been adopted and a further two are under consideration by the European Parliament and the Council of Ministers.

A substantial body of Community legislation has already harmonized the rules for authorizing new medicines within the Community. As long ago as 1965, it was laid down that the sole criteria for authorization should be the quality, safety and efficacy of the medicinal products concerned. In 1975, two further directives dealt in detail with the types of tests and trials necessary to demonstrate quality, safety and efficacy; with labelling and packaging requirements; and with the obligations of manufacturers. These directives were amended and updated in 1983 and 1986. In addition, a series of notes for guidance on the conduct of various types of tests and trials have been adopted.

Although the criteria for registration are harmonized, the actual assessment of applications and the final decision on individual products remains the responsibility of Member States. Two procedures for coordinating national decisions at Community level are available. The first procedure, a decentralized one, enables a company which has previously obtained marketing authorization in one Member State to apply for the extension of the authorization to cover two or more of the other Member States. If one or more of these countries objects to the product, the application is referred to a Community-level committee, the Committee for Proprietary Medicinal Products (CPMP). The second procedure involves the concerted assessment of new products from the moment an application is first made to any Member State. At the end of the procedure, the CPMP gives an opinion to the Member States on the acceptability of the drug concerned. In neither case is the opinion binding, but experience shows that opinions of the Committee can have a strong persuasive effect. In order to assist companies using these procedures the CPMP has prepared a notice to applicants which harmonizes the presentation of applications for national procedures. The harmonized Community format is also widely accepted by other European countries.

The central feature of the internal market programme is the establishment of a single assessment for new drug applications which will be valid throughout all twelve Member States. The Commission intends to present proposals to achieve this result, based on the experience acquired with these two procedures, in the autumn of 1989 and it has already begun consultations on the form that this might take. These proposals will also have to include provisions which have evolved within the Community to formalize the arrangements for drug monitoring and the withdrawal of unsafe or ineffective products.

In January 1988, the Commission presented a package of proposals to extend the scope of the Community directives to cover immunological products and medicinal products derived from human blood and radiopharmaceuticals, which are currently excluded. In addition, it proposes to rationalize the information given to patients about over-the-counter products; to improve guarantees of the quality of manufacture of pharmaceutical products by requiring compliance with the Community Guide to Good Manufacturing Practice; and to improve the provision of information about medicines to third-party countries.
Like many other countries, all the Member States are currently engaged in a review of the quality, safety and efficacy of the older medicinal products. In accordance with Community legislation, this review must be completed by May 1990, after which time officially-approved scientific information should be available for all conventional medicinal products on the Community market. Thereafter, the Commission intends to present proposals to harmonize the information given to doctors and patients about medicines and the conditions under which medicines are made available to patients (over-the-counter or prescription only).

Within the countries of Europe the cost of pharmaceutical products is largely covered by compulsory health insurance which is substantially funded from public sources. The public authorities of many Member States therefore intervene to influence price formulation or to restrict the range of medicinal products covered by these schemes. A Commission proposal to increase transparency of these national price control and reimbursement systems is seen as the first step towards tackling the complexities that they inevitably pose in relation to the creation of the internal market.

Finally, two directives adopted in 1981 regulate the authorization of veterinary medicinal products within the Community. Although inspired by the rules applicable to medicines for human use, these directives also contain provisions to ensure that foodstuffs from treated animals do not contain residues which might pose a risk to the health of consumers. The Commission will be presenting further proposals to update these directives and eliminate barriers to intra-community trade in veterinary medicines before the end of 1988.

As work towards the completion of the internal market proceeds, the European Community will increasingly be required to exercise its competences internationally. The Community supports the Revised Drug Strategy of the World Health Organization. Indeed, the latest Commission proposals to the Council expressly recognize the importance of the WHO Certification Scheme and cover the provision of approved product information to third-party countries. For the future, the Commission is determined to ensure that the Community plays a full and responsible role in international pharmaceutical affairs.
Reports on Individual Drugs

Acetylsalicylic acid in vascular disease

Twenty years ago acetylsalicylic acid (aspirin) was shown to impair thrombus formation by inhibiting platelet function (1). This could readily have been dismissed merely as a contributory factor to its potential to induce gastrointestinal haemorrhage. Instead, it has dramatically extended the therapeutic value of acetylsalicylic acid, which has now emerged as a potential life-saving agent in the treatment and prevention of intravascular thrombotic disease and particularly in the acute treatment and secondary prevention of myocardial infarction.

At first sight it appears surprising that definitive demonstration of the clinical value of acetylsalicylic acid in these conditions has only recently been obtained. Misgivings about the uncertain consequences of antiplatelet treatment, which might not only decrease the incidence of serious occlusive events, but also possibly increase the incidence of serious haemorrhagic sequelae, explains some of the initial reticence. Also at issue, however, was the daunting scale of the studies required: reliable prospective confirmation, for instance, of a 20 per cent treatment-related reduction in the immediate death rate associated with acute myocardial infarction requires a sample size of several thousand patients.

Several of the early trials were undertaken using conventional anti-inflammatory doses of acetylsalicylic acid (2). However, it is now known that doses as low as 40 mg daily, which carry a much decreased risk of gastrointestinal haemorrhage (3), produce the full antiplatelet effect within a matter of days (4). Indeed, even intermittent administration of such doses may well be adequate to inactivate platelet prostaglandin cyclo-oxygenase and thereby prevent the synthesis of the potent vasoconstrictor and platelet aggregating substance, thromboxane (5). Encouraging but non-conclusive evidence of benefit from doses of this order in patients with potentially responsive conditions including transient ischaemic attacks, occlusive stroke, unstable angina and myocardial infarction (2) has ultimately provided a basis of confidence needed to plan larger studies. It also enabled the field of investigation to be extended to the primary prevention of thrombotic vascular conditions in apparently healthy individuals and in the critical immediate management of acute myocardial infarction.

Primary prevention

Data derived from 25 randomized trials of antiplatelet therapy in the secondary prevention of vascular disease have recently been collectively reassessed to establish, in an admittedly approximate way, the overall effects of treatment (2). The results, which were derived from a cumulative sample of some 29 000 patients provide persuasive evidence that antiplatelet treatment can reduce the incidence of serious vascular events by about one quarter among patients at particular risk of vascular disease. Similar effects were obtained with high and low doses of acetylsalicylic acid, acetylsalicylic acid with dipyridamole, and sulfipyrazone. The results were comparably encouraging in patients with histories of either cerebral or cardiac disease, but it was conceded that the balance of risk and benefit might be less favourable for primary prevention among people at low absolute risk of occlusive disease if antiplatelet treatment produced even a small increase in the risk of cerebral haemorrhage.

Secondary prevention

In an attempt to settle this uncertainty, large studies of the prophylactic use of acetylsalicylic acid among apparently healthy doctors have now been completed in the United States of America (6) and the United Kingdom (7). The results, however, are inexplicably inconsistent. Those from the United States trial, which involved 22 000 individuals, suggest that sustained administration of acetylsalicylic acid is just as effective in primary as in secondary prevention of stroke. It appeared to decrease the incidence of non-fatal myocardial infarctions by approximately one-third. Indeed, interim results obtained two years before the planned termination of the study were judged to be sufficiently conclusive to warrant its foreclosure. Nonetheless, doubts have been expressed about the broader applicability of the findings because the cardiovascular
of acetylsalicylic acid do not appear to be nearly as
full report, but it has pointed out that the benefits
tient" (11). The United States Food and Drug Ad­
of acetylsalicylic acid for primary prevention should
be substantially increased when hypertensive
drugs could be administered by any health worker in
virtually any situation. In its report, the Steering
Committee that organized the trial concludes that "if
one month of low-dose aspirin were to be given to
just one million new patients a year — which is only
a fraction of the worldwide total with acute myocar­
dial infarction — then a few tens of thousands of
deaths, reinfarctions, and strokes could be avoided
or substantially delayed and these benefits could be

If, indeed, the difference in the outcome of these two
trials is artefactual, the cause will probably never
become apparent. One hypothesis is that the
dosage of acetylsalicylic acid used in the British trial
(500 mg daily as opposed to 325 mg on alternate
days in the US study) inhibited the synthesis not
only of thromboxane but also of the endothelial
vasodilator substance, prostacyclin (8). However,
dose-dependent responses have been sought, but
not found, in long-term secondary prevention
studies (2, 3). In these circumstances it is preferable
to focus attention upon the congruent findings
within the two trials. In neither study was treatment
associated with a reduction in overall vascular
mortality, although neither had the power to detect a
modest reduction with reasonable certainty. In both
studies an excess of disabling haemorrhagic strokes occurred in the treated group, although in the US study this was more than counterbalanced
by the reduced risk of myocardial infarction. The
excess was not significant in either study but it
remains disturbing. Acetylsalicylic acid has been as­
associated with a similar increase in intracranial haem­
orrhage in at least one other study (3) and any risk
could be substantially increased when hypertensive
individuals and other vulnerable groups are not ex­
cluded from the treated population (9, 10).

In a joint communication, the principal investigators
of the two studies have advised that the prescription
of acetylsalicylic acid for primary prevention should
remain a matter of judgement in which the physician
considers the "cardiovascular risk profile of the pa­
tient" (11). The United States Food and Drug Ad­
ministration has also expressed concern that wide­
spread use of acetylsalicylic acid without careful
patient selection could do more harm than good
(12). It reserves its position until it is able to evaluate
the full report, but it has pointed out that the benefits
of acetylsalicylic acid do not appear to be nearly as
dramatic as giving up smoking and should not be
used as a substitute for shedding excess weight,
lowering raised plasma cholesterol concentrations
or reducing high blood pressure.

Acute treatment of Infarction

Because of the apparent implausibility that small
doses of acetylsalicylic acid might be just as
beneficial in the acute treatment of myocardial in­
farction as its prevention the hypothesis was left
untested until recently (13). However, indisputable
evidence has now been obtained from a large ran­
domized trial involving 17,187 patients with acute
myocardial infarction admitted to 417 hospitals in 16
countries that early institution of fibrinolytic and anti­
platelet therapy can save many lives (14). Three
treatment schedules were compared with each
other and with a placebo control: a 1-hour intra­
venous infusion of 1.5 MU of streptokinase, 160 mg
of enteric-coated acetylsalicylic acid daily for one
month, and a combination of both active treatments.
The greatest benefit was obtained by patients
treated within four hours of the first symptoms.
Streptokinase alone reduced the 5-week vascular
mortality by 35 per cent (SD 6). For aspirin alone the
reduction was 25 per cent (SD 7) and, for the combi­
nation, it was 53 per cent (SD 8). The separate
effects of streptokinase and acetylsalicylic acid were
thus apparently additive.

Marked, but lesser benefit was obtained even for patients in whom treatment was delayed for 13 to 24
hours. The value of acetylsalicylic acid was particu­
larly well sustained in this group: not only did it
reduce the five week mortality by 21 per cent
(SD12), it also significantly reduced both non-fatal
reinfarction (1.0 per cent vs 2.0 per cent) and non­
fatal stroke (1.0 per cent vs 2.0 per cent). More­
ever, unlike streptokinase, it did not demonstrably
increase the risk of cerebral haemorrhage or
episodes of bleeding requiring transfusion. The
absolute benefits of streptokinase and acetylsali­
cylic acid were greatest among those at highest risk —
women, the elderly, hypotensive patients and
those with an anterior infarct or a previous episode
of infarction — but in no group within the sample
was treatment without value. Acetylsalicylic acid is
widely available in many developing countries, its
use does not require laboratory monitoring and it
can be administered by any health worker in
virtually any situation. In its report, the Steering
Committee that organized the trial concludes that "if
one month of low-dose aspirin were to be given to
just one million new patients a year — which is only
a fraction of the worldwide total with acute myocar­
dial infarction — then a few tens of thousands of
deaths, reinfarctions, and strokes could be avoided
or substantially delayed and these benefits could be
doubled if low-dose aspirin were continued for at least a few more years”.

References


Acetylsalicylic acid in pregnancy

United Kingdom — A call for a controlled clinical trial of low-dose acetylsalicylic acid in women with bad obstetric histories associated with severe fetal growth retardation is contained in a recent letter to the Lancet (1). Previous studies have indicated that acetylsalicylic acid may reduce the risk of pregnancy-induced hypertension (2, 3) and the authors present a series of 42 cases to support their claim that a broader spectrum of high-risk pregnancies is likely to benefit if the mother takes 75 mg daily from the first or second trimester until delivery. Nineteen of these women had a history of severe pregnancy-induced hypertension, 16 had systemic lupus erythematosus and 7 had a history of fetal growth retardation unassociated with these risk factors. Only 8 of 84 pregnancies previously recorded within the group had resulted in live births, but 35 of a total of 38 additional completed pregnancies within the group resulted in live births when acetylsalicylic acid was taken. All of the infants, save one, were born in good condition and none of the 34 survivors had clinical or ultrasonic evidence of intracranial haemorrhage.

The authors conclude that impaired uteroplacental circulation, preventable by antithrombotic therapy, was the underlying cause of many abortions and perinatal losses recorded in these patients. They caution, however, that larger doses of acetylsalicylic acid have been associated with an increased incidence of intraventricular haemorrhage among babies born at 32 to 34 weeks (4), and that even lower doses may block platelet thromboxane production and platelet aggregation (5). Notwithstanding these highly encouraging results, they advise against the indiscriminate use of acetylsalicylic acid until its benefits and safety have been properly evaluated.

References


References


Mycobacterium BCG: counting by firefly luciferase assay of bacterial ATP

Poland — Classical techniques for determining the number of culturable particles of Bacille Calmette-Guérin vaccine are slow and require complex media. However, investigators at the Vaccines and Sera Control Department, National Institute of Hygiene, Warsaw, are encouraged by results they
have obtained from a simpler and more rapid method involving extraction of adenosine triphosphate (ATP) from mycobacterial cells with n-butanol at room temperature and its subsequent assay by the luciferin-luciferase bioluminescent method. The correlation between extracted ATP and colony counts made on Ogawa medium by the classical method was impressively high (r=0.99).


**Vitamin A supplements and diarrhoea**

Inadequate dietary intake of vitamin A is estimated to result worldwide in about 10 million new cases of xerophthalmia among pre-school age children every year. Of these, about 500 000 progress to blindness. Nonetheless, prevalence rates, even for mild xerophthalmia, rarely exceed 10 per cent and, if adequate protective strategies are to be developed, more needs to be known about predisposing risk factors.

One possible factor is diarrhoea, which has long been recognized as associated with vitamin A deficiency. As yet, however, it remains uncertain whether either of these conditions is causally related to the other. It is clearly plausible that diarrhoea, by reducing food intake and intestinal absorption, may precipitate vitamin A deficiency, but it is also possible that vitamin A deficiency, by compromising immune mechanisms and increasing the risk of bacterial colonization of the intestine, may increase the risk of diarrhoea.

The evidence currently available fails to resolve the question, and priority is being accorded, within WHO's Diarrhoeal Diseases Control Programme, to assess, within randomized, double-blind, placebo-controlled trials, whether administration of vitamin A has an impact on diarrhoeal morbidity. It will be administered either at community level to all children at a dosage of 200 000 IU every 4 to 6 months, or on a selective basis to children already suffering from diarrhoea.


**Targeted vidarabine inhibits viral replication in chronic hepatitis B**

Italy — Encouraging experience in the use of vidarabine (adenine arabinoside) in chronic hepatitis B has recently been reported from Italy. At present, no effective treatment exists for this common and potentially fatal condition. Interferon alfa has been shown to have some effect in inhibiting the replication of the virus, but the response is inconsistent and the danger of inducing acute hepatic damage precludes its use in severely ill patients.

Preliminary studies now suggest that reduced doses of vidarabine, when selectively targeted to liver cells, may be more effective than interferon alfa in this regard. Vidarabine, in the amounts previously required, produced severe dose-dependent adverse reactions. However, by conjugating its monophosphate ester with lactosaminated human serum albumin, which selectively enters hepatocytes, the effective antiviral dose has been reduced by a factor of 3 to 6. Work is now planned to determine whether the immediate inhibitory effect on viral replication that has been convincingly demonstrated in five volunteer subjects without any apparent adverse effect is sustained in the longer term and whether the treatment also promotes seroconversion.


**Nitrites and tolerance**

United Kingdom — In recent years, in an attempt to provide nitrites in more convenient dosage forms, particularly for patients with chronic angina pectoris, manufacturers have introduced a variety of sustained-release preparations — both oral and transdermal. A recent commentary in the *Drug and Therapeutic Bulletin* points out that this convenience is all too readily offset by an attenuation of the therapeutic vasodilatory action. All nitrites very rapidly induce tolerance and this is liable to become clinically significant unless they are withdrawn or maintained at a subtherapeutic level for a continuous period of 8 to 12 hours every day.

Indeed, the results of a randomized placebo-controlled trial conducted on a sample of 427 men
with chronic stable angina have indicated that the continuous transdermal administration of glyceryl trinitrate from adhesive skin patches is without influence on either the anginal attack rate or on sublingual trinitrate consumption (2).

To assure sustained reliability of action in these products, the article in the Bulletin recommends that:

• the minimum effective dose be used.

• a formulation or dosage regimen be selected, and adjusted to each patient's needs, that provides for virtual or complete withdrawal of the drug for some 10 hours each day.

• When necessary, higher doses of beta-adrenoceptor blocking agents or calcium channel blocking agents be used to reduce the number and intensity of anginal attacks during the "low nitrate" hours.

It also emphasizes the need for advice along these lines to be included in the manufacturers' prescribing information.

References


Etretinate: retinal abnormalities

Federal Republic of Germany — A group of doctors has described four patients whose colour vision deteriorated during long-term treatment with etretinate. In one instance, rod sensitivity after dark adaptation was also impaired. It is suggested that visual function be monitored throughout treatment, and that pre-existing defects in colour vision or degenerative or dystrophic retinal disease should be considered either as a contraindication to etretinate therapy or as an indication for more intensive surveillance throughout the period of treatment.


Beta-blockers in post-infarction patients

The effect of long-term use of beta adrenoreceptor blocking agents in post-infarction patients has been studied in many trials over the past decade. Only in some of these has significant benefit been demonstrated, and few provide any indication as to whether postulated benefit is confined to specific subgroups of patients. This uncertainty arises, in large measure, because many of the trials were too small to demonstrate clinically important differences with reasonable certainty. An attempt has now been made to resolve these doubts by pooling data from nine major long-term secondary prevention trials.

One-year mortality data have been obtained in this way from an aggregate group of nearly 14 000 patients. The outstanding finding was that mortality was reduced by 24 per cent in the treated group, and that subgroups with high placebo mortality (and particularly patients with a history of previous infarction, angina pectoris, cardiac insufficiency or conduction defects) benefited most. Some benefit was also demonstrable among patients at lesser risk but in absolute terms it was small, and no such trend was evident in some of the individual studies. No evidence accrued to suggest that the sex of the patient, baseline blood pressure or the lag time before starting treatment influenced the final outcome. Nor was any clear difference shown between the performance of different beta adrenoreceptor blocking agents.


A role for methotrexate in rheumatoid arthritis?

The management of rheumatoid arthritis remains unsatisfactory because none of the currently-recommended drugs suitable for long-term use can be relied upon to prevent further progression of the disease. Gold injections, penicillamine and antimalarials have been estimated to relieve symptoms in only half the treated patients and their effect often wanes over time. The search for more effective new drugs remains intense and, in the meantime, clinicians have explored the potential of various immunosuppressive agents and antimetabolites to
relieve severe active disease unresponsive to conventional therapy. Over the past decade methotrexate, which is currently approved by most regulatory authorities only for neoplastic conditions and severe, uncontrolled psoriasis, has become widely used for this purpose but not without trepidation because long-term methotrexate therapy for psoriasis has been associated with cirrhosis.

A recent commentary on the results of three studies presented at this year's annual meeting of the American Rheumatism Association strikes a note of cautious optimism (1). Experience thus far indicates that sustained methotrexate therapy can reduce pain and improve joint mobility for an indeterminate period (2). Some patients have already been treated for more than four years (3), but it is not yet clear whether efficacy will diminish with time and whether methotrexate inhibits the progression of the disease or merely palliates the inflammatory response. Meanwhile, the information that is accumulating regarding safety is largely reassuring. Single or multiple hepatic biopsies have been taken from some 370 patients in the ongoing studies. Early fibrotic changes were frequently seen and, in some cases, there was suspicion that they were slowly progressive. However, in comparison with the lesions described in psoriatic patients, some of whom have developed clinically-evident cirrhosis within five years, they were mild. Given the pressing need to relieve the symptoms of many patients desperate to escape from a life overshadowed by chronic pain and disability, the American College of Physicians has felt justified in advising doctors in the USA that it is appropriate to use methotrexate in severe rheumatoid arthritis when gold injections and penicillamine fail to give adequate relief (4).

References


Halofantrine in falciparum malaria

Kenya; Malawi — Encouraging reports of the value of halofantrine hydrochloride in chloroquine-resistant falciparum malaria continue to appear. A recent issue of the Lancet contains details of studies conducted under the auspices of the Liverpool School of Tropical Medicine in the United Kingdom(1, 2).

In Malawi (1), treatment using a single dose of 16 mg/kg proved inadequate since the recrudescence rate of 38 per cent after two weeks was unacceptably high. However, when three doses of 8 mg/kg were administered at six-hour intervals, recrudescence occurred within 14 days in only 2 of 49 children. In both these patients, who were infants, all symptoms had disappeared and parasitaemia was significantly reduced. Although in vitro evidence of chloroquine resistance was not obtained within the context of the study, such strains were known to have high prevalence in the area.

Two separate trials using different dosages of halofantrine were also undertaken at separate locations in Kenya (2). The first involved 46 children with low-grade Plasmodium falciparum infections, half of which were caused by organisms with significant in vitro resistance to chloroquine. In this group two doses of 10 mg/kg given 6 hours apart cleared parasitaemia within two days and no recrudescence was demonstrated within 14 days. This result is regarded as comparable to that obtained with chloroquine in an area of full susceptibility. In the second trial, 3 doses of 8 mg/kg, given at six-hour intervals, were administered to 60 children with moderate to high parasitaemia. Over 80 per cent of these infections were chloroquine resistant, but treatment was highly effective and well tolerated in all cases. Although parasitaemia recurred in 9 of these children between 14 and 28 days after treatment, it is suggested that this could well have been due to reinfection since the study was conducted in an area of intense transmission.

References


Community administration of ivermectin

Sierra Leone — Before ivermectin became available for treatment of onchocerciasis on a routine basis, expectation was high that it would prove to be suitable for the mass treatment of whole communities in hyperendemic areas. Only if it can be administered in this way is it likely to contribute significantly to ongoing efforts to reduce the prevalence of the disease where the need is greatest.

Inevitably, the preregistration trials were conducted on selected patients treated in a hospital setting and supplementary information was required to determine its performance in more representative circumstances. Valuable insight into the degree to which a single dose of 100 to 200 micrograms/kg is tolerated under field conditions is contained in a recent account of a placebo-controlled study involving some 1250 people from six village communities in a hyperendemic area of Sierra Leone. Overall, about one-third of the treated patients (as opposed to 10 per cent of those receiving placebo) reported one or more adverse effects over the next three days and 5 per cent had to take time off work. One welcome incidental effect was that over ten per cent of the patients receiving ivermectin passed Ascaris worms in their stools, although this was not unexpected since ivermectin is well established as a broad-spectrum anthelmintic in veterinary medicine.

Because virtually all the other effects could reasonably be attributable to a Mazzotti reaction resulting from the death of microfilariae, they are likely to be much less troublesome on subsequent exposure wherever a regular and effective suppressive regimen can be instituted. Nonetheless, the authors of the study advise that, on the basis of this experience, a health worker should remain for several days in any community in which ivermectin is distributed.


Oral rehydration therapy and child mortality

Egypt — In 1977 the Ministry of Health began distributing oral rehydration salts to its clinics throughout the country. By 1980, evidence had already been obtained that where health care workers and mothers had been taught how to prepare and use these preparations effectively, diarrhoea-associated mortality among children aged 1 month to 5 years had been reduced by as much as 45 per cent.

On the basis of this experience a national programme directed to the control of diarrhoeal diseases was established:

- to promote training in oral rehydration therapy;
- to encourage local production of both oral rehydration salts and balanced, polyvalent intravenous solutions for the management of severe dehydration within a hospital setting; and
- to develop community awareness of the value of oral rehydration through the mass media.

The effect of this programme on infant and child mortality throughout Egypt is still being assessed through household surveys and analysis of civil registration data. Preliminary data, however, have recently been published for the areas previously studied in 1980. The outcome is highly encouraging. Better case management, both by mothers and health care workers, has been associated with a continued decline in mortality in children under five. Indeed, this decline has been accelerating since 1983, and it is most marked during those seasons of the year in which diarrhoeal diseases are most prevalent.


Effect of influenza immunization on mortality

United States of America — Several studies of the efficacy of influenza vaccine in elderly populations have now been published. The results have been varied and, in general, they have been based on retrospective surveys in which cases of influenza infection were identified solely on clinical grounds.

A further such study, recently reported in the Archives of Internal Medicine, is of particular interest since it was undertaken prospectively and all cases of influenza were confirmed serologically by demonstration of rising antibody titres in paired
serum samples. It was conducted in the winter of 1982 to 1983 in a home for the elderly in New York. All the occupants were offered influenza immunization before the annual outbreak of the disease. Of these, 181 elected to be immunized and 124 refused but, nonetheless, agreed to take part in the study. Overall, mortality was reduced by almost 60 per cent in the vaccinated group (13 of 181 compared with 22 of 124). Although the potential for important biases to influence a comparison determined by self-selection in an open, non-randomized study was admitted and examined, it was concluded that the difference was most reasonably attributable to the protective effect of the vaccine.

The epidemic, on this occasion, was caused by a strain of the H3N2 subtype of influenza A virus that was closely related to, but not completely identical with, the H3N2 strain included in the polyvalent vaccine. The authors speculate that, had these strains been identical, efficacy would probably have been even higher.

In reviewing other studies of vaccine efficacy in the elderly, the authors conclude that, although not all the criteria necessary for adequate assessment have always been observed, sufficient evidence now exists to show that vaccines containing the H3N2 subtype provide substantial protection against identical or related strains. Whether the same is true for H1N1 subtypes of influenza A and for influenza B is, in their view, still in need of direct confirmation.


First clinical study of a birth control vaccine

Since 1974, the World Health Organization has promoted the development of a contraceptive vaccine directed against human chorionic gonadotropin (hCG). The expectation is that such a vaccine might stimulate the production of antibodies that neutralize the luteotropic action of hCG and thus induce regression of the corpus luteum and possibly inactivate the hCG-producing cells of the peri-implantation blastocyst.

A considerable amount of preliminary work has been necessary to develop a preparation which has both adequate immunogenicity and the specificity necessary to avoid cross-reactive autoimmunity with the structurally-related luteinizing hormone produced in the anterior pituitary. The preparation, as it is now formulated, consists of a synthetic peptide antigen representing an aminoacid sequence contained within the beta subunit of hCG. This is conjugated to diphtheria toxoid to form a hapten-carrier complex which is dispersed in a saline-oil emulsion containing a water-soluble synthetic adjuvant. This formulation is effective in preventing pregnancy in baboons and it was approved for phase I trials, both in Australia and the United States of America, on the basis of toxicological and immunosafety studies undertaken in primates and other laboratory animals.

The first clinically-based investigation of the vaccine, conducted in Australia, has recently been reported in the Lancet. It was concerned, not with direct demonstration of an antifertility effect, but with an examination and assessment of the characteristics of the immune response in a group of thirty surgically-sterilized female volunteers. These were divided into five equal groups, and members of different groups received different doses of the vaccine in two intramuscular injections six weeks apart. The results are highly encouraging. Antibodies were generated in quantities likely to have an antifertility effect in all subjects and no serious adverse effects were detected over a six-month period of follow-up. Some women, however, complained of transient diffuse myalgia, but there is suspicion that they may have received a relatively unstable preparation that could well have resulted in over-rapid release of the peptide from the injection site.

Data already obtained in non-human primates indicate that, after the antibody titres wane, neither fertility nor pregnancy is demonstrably impaired, and plans are already in hand to conduct a phase II clinical trial in which dose-response patterns will be investigated in greater depth.

General Information

Poliomyelitis eradication by the year 2000 adopted as WHO goal

In May 1988 the Forty-first World Health Assembly declared WHO's commitment to the global eradication of poliomyelitis by the year 2000. The Assembly noted that this represents a fitting challenge to be undertaken now, on the Organization's fortieth anniversary, and an appropriate gift, together with the eradication of smallpox, from the twentieth to the twenty-first century.

The Assembly called for the eradication initiative to be undertaken in ways which strengthen the Expanded Programme on Immunization, helping that programme, in turn, to contribute to the development of the health infrastructure and of primary health care.

The first priority for action is to attain ongoing immunization coverage rates of at least 80 per cent as quickly as possible for a protective course of polio vaccine and all other vaccines included within national immunization programmes. By the year 2000 these rates should exceed 90 per cent, with immunization provided as a part of comprehensive maternal and child health services.

Improved surveillance is the second priority. Countries are asked to begin reporting by "district" (taken to be a major geopolitical area ranging from a few hundred thousand to a few million persons, depending on the country) even in the event of zero cases. Standardized case definitions are being proposed and countries reporting less than 10 cases per year are asked to identify whether they are associated with vaccine or wild virus, and, in the case of the latter, whether the cases are indigenous or imported.

Improved surveillance requires improved laboratory services for isolating and characterizing polio viruses. A global network of reference laboratories is being formed and these will be used to develop a fully-functioning system of national laboratories backed up by international reference laboratories by 1995.

Other priorities include developing and introducing new training materials for health professionals and information/educational materials for the public, and strengthening polio rehabilitation services and research and development.

The cost is expected to fall between US$100 and 500 million, compared with US$ 300 million for smallpox eradication. This cost estimate is over and above what is required to support routine national immunization programmes which now require some US$ 150 million per year in external support. During the decade of the 1990s, when full immunization coverage rates are attained and additional vaccines are added, this external support will need to grow to US$ 500 to 600 million per year.


Cost and benefit in cancer care

United Kingdom — A working group of cancer physicians, epidemiologists and health economists was convened recently with the support of the Cancer Research Campaign to consider what policies might be developed to optimize the management of cancer in the face of an aging population and limited resources for treatment.

According to a preliminary report in the British Medical Journal, the group concluded that the case for unfettered clinical freedom in the management of cancer can no longer be justified. It is wasteful of resources and sometimes harmful to the patient. Criticism was accorded, in particular, to the widespread use of expensive investigations that are unlikely to influence patient management and to the use of new and expensive cytotoxic or hormonal drugs when clear advantage over older and cheaper agents has not been established in controlled trials. The following recommendations were agreed and will form a basis for further action:

1. Guidelines defining appropriate and inappropriate care in cancer need to be established by an expert review panel for each tumour site.
2. Consensus statements should be distributed to the medical profession, be made available upon request to all interested bodies, and be re-evaluated and updated on a regular basis. The demand on resources of different treatments should be included in these reviews.

3. Action should be taken to establish consensus panels without delay. This will require the active support of both physicians and those agencies concerned with the delivery of care to patients with cancer.

4. Savings achieved by rationalization of cancer management should remain available for reallocation to other areas of cancer care.


Guidelines for drug donations

When drugs are donated, even with the best of intentions, more than goodwill needs to be at hand. The Christian Medical Commission of the World Council of Churches, sensitized over many years to the problems created by inappropriate voluntary aid to developing countries, has recently issued a series of practical guidelines for donors and recipients of pharmaceutical products.

Misunderstandings, which derive from uncertainties on the part of donors about the properties of pharmaceutical products, about health problems in general and about the structure of health services in developing countries are often compounded by lack of clear explanations from recipients about what is needed and a reticence to inform the donor when the wrong kind of assistance is provided. Too often, the result is that supplies are inappropriate, inadequately packaged and labelled, or virtually — if not totally — time-expired. Immediate improvement would occur, in the view of the Commission, if:

- donations were always restricted to drugs contained in National Drugs Lists or in the WHO Model List of Essential Drugs;
- adequate independent certification were always obtained through the WHO Certification Scheme to assure quality;
- care were taken to ensure that all supplies have an unexpired shelf-life of at least one year at the time of their arrival; and
- supplies were always delivered in large packages, at one strength and labelled with the international nonproprietary name (INN).

Even so, as the Commission points out, a financial contribution will, in many cases, be more appropriate than the delivery of drugs which are sometimes available locally at lower prices.

Reference: Christian Medical Commission, World Council of Churches, 1211 Geneva 20, Switzerland.

Physician dispensing: a conflict of interest?

United States of America — In recent years an apparent resurgence of physician dispensing has attracted considerable political and professional debate in the United States to the extent that legislation has been drafted which seeks to ban the practice except in emergency situations, in rural areas and community health clinics. The principle at issue, as defined by a public interest investigative group and published in a recent issue of the Market letter, is whether the dispensing physician, faced with a financial incentive to prescribe, is confronted with an inherent conflict of interest. This is the argument on which the American Pharmaceutical Association and others have formally challenged the practice. Those favouring it argue that there is advantage in the doctor dispensing directly to a patient whom he knows, and that there is an inconsistency in allowing a doctor to stock and administer injectable drugs and refuse him the right to dispense other treatments. The factual basis on which these positions have been adopted is recognized to be sparse: in the last analysis, however, it is acknowledged that it is of crucial importance to the standing and credibility of doctors that they should not be seen to be engaged, however virtuously, in any activity that risks bringing the ethics of their profession into question.

Biotechnology gains momentum in drug development

United States of America — The Pharmaceutical Manufacturers Association has recently completed a survey of biotechnology-derived drugs and vaccines under development within companies based in the United States. This indicates that nearly every major pharmaceutical company in the country is involved in this area of research, and that almost half the projects are directed to new cancer therapies. Of a total of 81 products, 67 are already undergoing clinical trials and marketing applications have been filed for 14.

Almost simultaneously, the US Office of Technology Assessment has provided a broader overview of the US biotechnology enterprise. Private industry's investment is estimated to approach US$ 2000 million annually. This is outstripped, however, by the contribution of the Federal Government which spends US$ 2700 million on basic and "generic applied" research. Unlike agricultural biotechnology, pharmaceutical development is, in general, considered to be attracting adequate investment, although some key areas — including research in protein chemistry and drug delivery systems — are identified as being underserved.

References

AIDS therapy: prospects reassessed

United States of America — The Pharmaceutical Manufacturers Association, in commenting on a recent Senate Committee hearing to assess the development and approval of experimental AIDS therapies, highlights the prediction of the Commissioner of the Food and Drug Administration, Dr Frank Young that "probably 90 to 95 per cent of AIDS drugs will fail" safety or efficacy standards and that only five or six new therapies will join zidovudine on the market before 1995.

Dr John Beary, representing the PMA, underscored the fundamental difficulty facing the research-based companies in their endeavours: viruses are intracellular parasites that use normal human processes for their own survival. Thus, medicines that destroy a virus often cause unacceptable toxicity to the human host because the patient's own cells may be destroyed as well. Moreover, because the AIDS virus incorporates its genes into the patient's own chromosomes life-long infection results. There is currently no technology for eliminating the cells that are infected, nor does a solution appear to be on the immediate horizon. Efforts are consequently being focused on preventive vaccines, on means of suppressing viral replication and of protecting the immune and central nervous systems.


Vaccine potency testing: information on laboratory facilities sought

Drug regulatory authorities in several countries have been contacted by the Biologicals Unit of the World Health Organization in order to obtain information on laboratory facilities which might be utilized in vaccine potency testing, especially for the measles and polio vaccines used in WHO's Expanded Pro-

gramme on Immunization. This is part of a new initiative to strengthen existing laboratories which, with minimal additional equipment and training, may have the ability to provide laboratory support for the Programme (for example, by retesting vaccines with suspected potency problems or by organizing serological studies) and for the global eradication of poliomyelitis. Those authorities which have not yet responded are urged to do so as soon as possible. The replies are essential to determine which laboratories are able to take part in this initiative.

Reference: Biologicals Unit, Division of Drug Management and Policies, World Health Organization, Geneva, Switzerland.
Antibiotic audit in a hospital setting

**New Zealand** — Virtually everywhere the costs of health care in the public sector threaten to outstrip available resources. Doctors are having to learn to become more cost conscious, they are having to conform to drug policies determined at institutional or national level, and they are having to accept scrutiny of their prescribing practices through a process of peer review. The results of such reviews are rarely published and this lends particular interest to a recent report of an audit on the use of antibiotics from a restricted list in a 650-bed general hospital in New Zealand. Seventy-three written justifications for prescribing these products were examined. Only half of these requests cited precise therapeutic indications; the remainder were for prophylactic use or empirical treatment.

Slightly over one-third of the total requests were judged to be inappropriate on the basis of the information available and, of these, the majority were for prophylactic use. Two faults were dominant. Firstly, prophylactic use, often to provide cover for plastic surgery, was frequently extended unnecessarily. Secondly, expensive third-generation cephalosporins were particularly subject to over-use, even in prophylactic situations in which they offered no tangible advantage over cheaper alternatives.

The authors conclude that the need for a written justification for the prescription of selected antibiotics is not apparently effective in reducing the incidence of inappropriate use below that reported from institutions without such requirements. However, their survey clearly establishes a need for an effective measure of control and it has prompted a revision of policy within the hospital concerned to require signed approval by the consultant-in-charge for continuation of each prescription for restricted antibiotics beyond 48 hours.


Child-resistant packaging and elderly patients

**Canada** — Many children continue to be poisoned each year from drugs taken inadvertently and the Canadian Medical Association has long recommended that prescription and nonprescription drugs that are hazardous to children be marketed in child-resistant packages. Regulations that standardize such packaging are now needed, in the view of the Association, but it suggests that normal closures for drug packages be available to elderly or disabled people who may have difficulty opening the package. When prescribing drugs in such cases, physicians should have the discretion to indicate that a normal package should be provided.


Drugs or psychotherapy in neurotic disorder?

**United Kingdom** — Neurotic disorders are the most common psychiatric conditions in clinical practice, yet basic disagreements still exist regarding their classification and management. The assumption is frequently made that different diagnostic entities require different treatments, although it is contested whether this has ever been adequately established. This orthodoxy has now been challenged by the results of a trial conducted under conditions closely representative of routine clinical practice that involved more than 200 outpatients attending inner-city out-patient clinics (1). Each was diagnosed as having either generalized anxiety, panic or dysthymic disorder on the basis of a structured clinical interview, and each was allocated randomly for a period of six weeks to one of five treatments: diazepam, dosulepin, placebo, cognitive and behaviour therapy or a self-help treatment programme. Within the admittedly low limits of sensitivity of the trial the effects of treatment were found to be independent of the original neurotic diagnosis. In particular, dosulepin, a typical antidepressant, was assessed as being equally effective after four weeks in all diagnostic groups and not only, as might have been expected, in blocking panic attacks.

Overall, the authors conclude that anxious and depressed patients, with the exception of those with severe to moderate depression or agoraphobia, are likely to gain comparable benefit from either simple psychological support or an antidepressant drug such as dosulepin, administered in low dosage. Diazepam showed no superiority over other treatments. Indeed, it became progressively less effective after four weeks, and its tendency to
induce habituation and dependence discounts it, in the authors' view, as suitable treatment in this group of disorders. (See also page 147).

However, the report of the trial has subsequently been criticized (2, 3) on a variety of grounds regarding the selection of patients, the choice of treatments, the dosages employed and the duration of therapy. It certainly draws far-reaching conclusions on the basis of limited evidence. Nonetheless, if it provides an effective stimulus for further critical and larger-scale investigations of the management of neurosis, it will have rendered valuable service.

References


Transfer of topically-applied drugs

France — Doctors from the Rouen Regional Centre for Drug Monitoring report two cases of adverse effects caused by transfer of topically-applied drugs by close bodily contact:

- a woman who developed facial hair growth when her husband used a testosterone cream for hypo­gonadism; and

- a man who developed gynaecomastia when his wife started applying an estrogen-containing cream for menopausal symptoms.

Similar examples of transfer of systemically-active substances, including glyceryl trinitrate ointment, have been cited previously and the authors suggest that doctors should be alert to this possibility with all topically-applied preparations.


Bioequivalence of generic drugs

United States of America — A report recently presented to the Food and Drug Administration by its Bioequivalence Task Force concludes that there is a "remarkable lack of hard evidence" to substantiate claims of bio-inequivalence among generic drugs approved for use within the United States of America. However, the group makes several recommendations regarding the evaluation of generic products and suggests minor changes in the statistical tests used to establish bioequivalence. It also points to the need for doctors and pharmacists to allay potential confusion by explaining to patients that equivalent products produced by different manufacturers may differ in colour or shape.

Copies of the complete report can be obtained from the Food and Drug Administration, Dockets Management Branch (HFA-305), 5600 Fishers Lane, Rockville, Maryland 20857, USA.


Importation ban on skin-lightening soaps and creams

Nigeria — According to a recent announcement in *Pharmanews*, the Government has banned importation of some 30 medicated soaps and bleaching creams containing either salts of mercury or more than 2 per cent of hydroquinone. These products are often used by dark-skinned persons to lighten the complexion. Local manufacturers were directed to withdraw or reformulate them in May 1986 on the grounds that they were "dangerous to health". The additional measures, which also include penal sanctions against anyone who displays, advertises or offers these articles for sale, are considered necessary in the face of continued availability of products allegedly manufactured in Europe and the Americas.


Accelerated availability of new drugs for serious conditions

United States of America — Sensitized to the plight of patients with AIDS, the US Government
has made provision for the Food and Drug Administra-
tion to allow — under specified conditions — more extended use of drugs that show promise in the treatment of life-threatening or other serious conditions, but have not yet been formally approved for marketing.

This provision applies only when:

• no comparable or satisfactory alternative treatment therapy exists to treat the defined target population of patients;

• the drug is either being subjected to — or has been investigated in — controlled clinical trials, and remains under active development;

• a reasonable basis already exists for concluding the drug may be effective in the circumstances proposed and that it poses no undue risk; and

• satisfactory assurances are supplied that the drug will be used in an appropriate manner, in accordance with an agreed protocol, and that records will be maintained to generate additional data on its safety in use.

It is envisaged that the commercial sponsor will normally seek the required permission to use a drug in this way by applying for a "treatment IND" (treatment investigational new drug application). In some cases the Food and Drug Administration may limit such use to physicians already engaged in the clinical development of the product. However, provision is also made for individual investigators to file applications. The Food and Drug Administration has assured sponsors that they would ordinarily not be expected to provide such information involuntarily to an individual, but "there may be unusual circumstances in which this will not prove to be the case".

To date, five drugs have been made available under these provisions:

• Trimetrexate for \( P. \) \textit{carinii} pneumonia for certain AIDS patients.

• Cytomegalovirus immune globulin for attenuation of primary cytomegalovirus infection associated with renal transplantation.

• Ifosfamide and mesna for germ cell cancer when both first-line and salvage chemotherapy have failed.

• Selegiline, a selective inhibitor of enzymes that inactivate dopamine, as an adjunct to standard antiparkinsonism drugs in patients unresponsive to treatment.

• Clomipramine for treatment of severe incapacitating obsessive-compulsive disorder, a condition for which there is currently no approved drug therapy.

References


Task force on counterfeit drugs

Nigeria — The Ministry of Health has announced the creation of a standing task force on counterfeit drugs that is charged to search out substandard products, and to serve as a focus for exchange of information among the peoples and governments of the West Africa sub-region.

In a complementary move, the West African Pharmaceutical Federation has recently convened an International Training Seminar on Pharmaceutical Quality Assurance to underscore the necessity of instituting good manufacturing practices in all pharmaceutical production units. This, it emphasizes, is not only an essential safeguard to patients' well-being, but a mandatory prerequisite to the development of a thriving drug export market.

Regulatory Matters

Drugs for Human Use

Antibiotics: final monograph for over-the-counter topical products

United States of America — Within the context of its review of over-the-counter products, the Food and Drug Administration has issued definitive rules on the conditions for marketing topical antibiotic drug products that are labelled to help prevent infection in minor wounds, cuts, abrasions and burns.

Antibiotics accepted for this use either as single ingredients or in combination include bacitracin, chlorotetracycline, tetracycline, neomycin, polymyxin B and oxytetracycline. Gramicidin, an ingredient in several widely-available products of this class, was found not to be effective in this context and will no longer be accepted.

The Agency decided to allow continued marketing of preparations containing one or more of these antibiotics in combination with local anaesthetics on the understanding that the indications will be limited to “first aid” for the temporary relief of pain or discomfort in minor wounds, cuts, scrapes and burns.

References

Buprenorphine: reduced dosage

Sweden — Following reports of respiratory depression in patients receiving the analgesic buprenorphine either sublingually or parenterally, as recently reported in the Lancet (1), the National Board of Health and Welfare has decided to decrease the recommended sublingual dose to 0.2 - 0.4 mg every 6 to 8 hours (2). Doctors were reminded that buprenorphine is approved only for relief of post-operative pain for periods not exceeding 6 to 7 days.

References

Cianidanol: definitive withdrawal

Switzerland — The Intercantonal Office for Drug Control has informed WHO that the marketing licence for products containing the immunomodulatory agent cianidanol, specifically indicated for treatment of chronic and acute hepatitis B, has been withdrawn. No further appeal against the decision is allowed and existing stocks were to be recalled by 30 June 1988.

Cianidanol was withdrawn worldwide in 1985 by the manufacturer after four fatal cases of agranulocytosis had been associated with its use. Subsequently, it was readmitted onto the Swiss market with severely restricted indications.

Reference: Communication to WHO from the Office Intercantonal de Contrôle des Médicaments, 1 July 1988.

Clomipramine: approved for obsessive compulsive disorders

United States of America — The Food and Drug Administration has approved the use of clomipramine exclusively for the treatment of obsessive-compulsive disorder, a psychiatric disease characterized by acute anxiety produced from internally
Driven thoughts and impulses, sometimes preventing the patient from performing simple but necessary tasks and interfering with day-to-day functioning. Approval is given under the terms of an investigational new drug protocol, implying that the manufacturers may distribute the drug free of charge directly to the physicians of eligible patients, pending the submission of an application for marketing authorization. (See also p.139).


Clomethiazole: revised product information

Federal Republic of Germany — The Federal Health Office has decided, having reviewed reports of relevant adverse reactions, that the approved information for products containing the sedative clomethiazole should contain a reference to its association with cases of circulatory and respiratory depression, cough, stomach pains, and burning sensations in the neck and nose.

For parenteral preparations, an additional statement is required to indicate that equipment for aspiration, artificial ventilation and tracheotomy must be readily available when the drug is administered, and that cyanosis, erythema, localized thrombophlebitis and hypotension may supervene if it is injected too rapidly.

Use of these preparations is now contraindicated in children under 10 years of age and in all patients with suspected hypersensitivity.


Diclofenac: revised product information

Federal Republic of Germany — The Federal Health Office has decided, having regard to reported adverse reactions, that the approved information for products containing the nonsteroidal anti-inflammatory agent diclofenac should indicate that cases of haemolytic anaemia have been associated with their use.


Diltiazem: hypersensitivity warning

Federal Republic of Germany — The Federal Health Office has decided, having regard to reported adverse reactions, that the approved information for products containing the antidysrhythmic agent diltiazem should indicate that dermal hypersensitivity reactions, including cases of erythema multiforme, have been associated with the use of these products.


Expiry dates: proposed amendment to the food and drug regulations

Canada — Expiry dates are currently required by statute only on the labels of vitamins, antibiotics, and products that cannot be assured to maintain their purity, potency or physical characteristics for at least 3 years from the date of manufacture.

The Health Protection Branch is now recommending that this requirement be extended to all registered pharmaceutical products: and that the proposal becomes effective within one year from the date of adoption of the amendment.

Further requirements for tamper-resistant packaging

United States of America — In 1982, following the discovery in a retail outlet of paracetamol capsules criminally contaminated with cyanide, the Food and Drug Administration required that the packaging of all cosmetics and, save in exceptional instances, all over-the-counter drug products should be designed in such a way that illicit access to the contents cannot be obtained without demonstrably damaging the container (1). The Agency now proposes to amend the existing regulations to require that hard gelatin capsules are supplied in packages incorporating at least two tamper-resistant features, or one such feature when the capsules themselves are sealed in a tamper-resistant manner (2).

References

Heat-treated factor VIII: restricted use

Sweden — In the light of evidence that factor VIII preparations heat-treated at 60°C may still be capable of transmitting HIV infection, the National Board of Health and Welfare has decided that such products may henceforth be administered only to individuals known to be HIV-positive.


Human blood and blood products: testing for HIV antibody

United States of America — The Food and Drug Administration has issued a final rule that each unit of human blood and any component extracted from human blood intended for use in preparing a biological product should be tested and demonstrated to be negative by an approved test for antibody to human immunodeficiency virus. The rule applies to all human blood and blood components, including products not currently subject to licensing requirements such as material used for in vitro diagnostic procedures.


Isoniazid/protonamide/dapsone: hepatic toxicity

Federal Republic of Germany — The Federal Health Office has decided, on the basis of reported adverse reactions, that the approved product information for a combination product containing isoniazid + protonamide + dapsone, indicated within the Federal Republic of Germany for the treatment of mycobacterial infections should bear the warning that hepatic disturbances, occasionally life-threatening, may occur. Monitoring of liver function is recommended at least monthly and treatment should be discontinued if clinical or biochemical evidence of dysfunction is detected.


Isotretinoin: restricted use

United States of America — The retinoic acid derivative, isotretinoin, is approved for use in the United States only for severe recalcitrant cystic acne. The labelling and other product information for both doctors and patients stress that it must not be taken by pregnant women because of its potential to cause birth defects.

Despite these warnings, 62 cases of birth defects in infants exposed in utero to isotretinoin have already been reported to the Food and Drug Administration, and there are strong grounds for believing that additional cases have occurred. The Food and Drug Administration has consequently announced a series of additional measures based on advice received from its Dermatological Drugs Committee (see WHO Drug Information Vol. 2, No. 2, page 72) intended to eliminate, as far as is feasible, the use of this product during pregnancy:

- labelled warnings to the patient will be strengthened to stress that there is an extremely high risk (one in four, or greater) of congenital deformity if isotretinoin is taken during pregnancy, and this statement will be accompanied by a photograph of...
an infant with a characteristic isotretinoin-induced deformity.

- Warnings to the doctor will state that the product should be prescribed only by physicians who have special competence in the diagnosis and treatment of severe acne and who understand the risk of teratogenicity, and that its prescription for women of childbearing potential is contraindicated unless the patient:
  - has severe, disfiguring cystic acne recalcitrant to standard therapies;
  - is reliable in understanding and carrying out instructions;
  - is capable of complying with mandatory contraceptive measures;
  - has received both oral and written warnings of the hazards of pregnancy, has acknowledged these in writing and has provided signed, informed consent to treatment; and
  - has had a pregnancy test with a negative result within two weeks of initiating therapy.

Therapy must not be initiated until the second or third day after the start of the next normal menstrual period, and monthly pregnancy tests are recommended.


**Isoxicam: marketing suspension extended**

**Federal Republic of Germany** — The Federal Health Office has extended the suspension of the marketing authorization for the nonsteroidal anti-inflammatory agent isoxicam until 31 March 1989 in order to give the manufacturers the opportunity to investigate further the causes of the severe skin reactions that were the basis for this action.

Reference: *Deutsche Apotheker Zeitung, 128: 24 (1988).*

**Nifedipine: sublingual absorption ineffective**

**Federal Republic of Germany** — In the light of information from the Netherlands that sublingual absorption of the calcium channel blocking agent nifedipine is negligible (1), the Federal Health Office has requested that the product information be changed to explain that in acute angina pectoris or hypertensive crisis the capsule should be bitten and its contents immediately swallowed with water and NOT kept for some time in the mouth as was originally recommended (2, 3).

References


**Nontherapeutic ingredients: disclosure on labelling**

**Canada** — The Health Protection Branch is proposing an amendment to the Food and Drug Regulations that will require qualitative disclosure of all nontherapeutic ingredients on the labelling of all drug products.

The proposal applies to all substances that enter into the formulation of a product, including colours, flavouring agents and components of the delivery system, such as capsule shells. In order to assist consumers in identifying products to which they may be sensitized it is recommended that these substances be identified by names used in current editions of standard reference books.

It is intended, in the case of products available without prescription, that this information should be displayed on the outer label or, when this is impracticable, in the accompanying labelling. In the case of prescription drugs it may be provided either on the packaging or in the accompanying prescribing information.

Reference: *Health Protection Branch Information Letter No. 733, (1988).*
Prenylamine: worldwide withdrawal

Following reports of cases of polymorphic ventricular tachycardia, the United Kingdom Committee on the Review of Medicines has refused to renew the marketing licence of products containing the calcium channel blocking agent prenylamine, indicated for the treatment of angina pectoris. A similar decision has since been taken by the Federal Health Office of the Federal Republic of Germany. The manufacturer has informed the World Health Organization that it has decided to withdraw the product worldwide from the market by 31 March 1989.


Somatropin: possible link with leukaemia

Federal Republic of Germany — The Federal Health Office is aware of 9 cases of leukaemia that have been reported in patients receiving somatropin for pituitary dwarfism. Only one of these has occurred in the Federal Republic of Germany. Five cases have been notified from Japan where a preliminary epidemiological investigation has raised suspicions that the incidence of leukaemia could be increased by a factor of 10 in the population of patients receiving this form of replacement therapy. Thus far, most of the cases have arisen in patients receiving pituitary-derived material, but doctors are advised to notify any case of leukaemia that occurs in a patient that has received any preparation of somatropin or a derivative.

References

Ranitidine: revised product information

Federal Republic of Germany — The Federal Health Office has decided, on the basis of adverse reaction reports, that the approved information for products containing the anti-ulcer H2-receptor blocking agent ranitidine should indicate that they have been associated with cases of reversible thrombocytopenia, leukopenia, agranulocytosis, pancytopenia (sometimes with bone marrow dysplasia), and reversible visual disturbances.


Spironolactone: restricted indications

United Kingdom — The Committee on Safety of Medicines has decided, on the basis of carcinogenicity studies in rodents, that products containing spironolactone should no longer be indicated for the treatment of essential hypertension and idiopathic oedema.

The approved indications are now restricted to cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, the diagnosis and treatment of primary hyperaldosteronism, and congestive heart failure.


Revised requirements for synthetic packaging materials

Federal Republic of Germany — The Federal Health Office now requires that manufacturers of pharmaceutical products must provide it with details of the composition of any synthetic packaging materials that come into direct contact with the product, including plasticizers used to render plastic materials flexible and other auxiliary agents. Data should also be submitted to justify the use of these substances and to indicate the extent to which they may be leached into solution. (See also page 150).


Sulfadoxine/pyrimethamine: revised product information

Federal Republic of Germany — The Federal Health Office has decided, having regard to
reported adverse reactions, that the approved information for combination antimalarial products containing sulfadoxine + pyrimethamine should indicate that the use of the preparation has been associated with allergic pulmonary reactions with interstitial infiltration that resulted in cough, severe respiratory distress and fever.


**Tiabendazole: under prescription control**

**United Kingdom** — The Department of Health and Social Security has subjected preparations containing the anthelmintic drug, tiabendazole, to prescription control having regard to concern about teratogenicity demonstrated in animal studies. The product information will now warn that it should not be used by women of child-bearing potential unless pregnancy has been excluded.


**Tretinoin: prohibition in cosmetics**

**Federal Republic of Germany** — Having regard to its teratogenic potential, the retinoid tretinoin is no longer accepted as an ingredient in cosmetic products. The decision became operative on 29 March 1988, but manufacturers have been allowed one year from that date to clear their stocks. Previously, tretinoin was allowed in a concentration of 0.001%.


**Triazolam: restrictive measures**

**Federal Republic of Germany** — The Federal Health Office has decided to withdraw the registration of tablets containing triazolam 0.5 mg, having regard to reports of dose-related adverse psychotropic reactions. At the same time the approved product information for tablets containing 0.25 mg has been amended to stress that triazolam should only be used for short-term treatment of sleep disturbances. Use during pregnancy and lactation is contraindicated and it is emphasized that particular caution is required in treating patients with depressive or suicidal tendencies. The section on adverse effects is now required to indicate that anterograde amnesia, anxiety, confusion and depressive states are occasionally associated with treatment, and that dosage should immediately be reduced should ataxia or disturbances of speech or vision occur. A warning to the patient not to drive or operate heavy machinery during treatment is also required.


**Drugs for Veterinary Use**

**Carcinogenicity testing: safety standards for new veterinary drugs**

**United States of America** — The Food and Drug Administration has announced stricter safety standards for new veterinary drugs intended for administration to food-producing animals. The safety data contained in any marketing application for a proposed animal drug that is potentially carcinogenic must now include a method to test food products derived from the treated animal. The method must be suitable for use by the Food and Drug Administration and the Department of Agriculture in checking the meat, fat, liver or kidneys of the animals after slaughter, as well as milk and eggs for human consumption.

The test is required to be sufficiently sensitive to demonstrate that a maximum lifetime risk of one in a million — a risk that is essentially zero — is not exceeded. This standard is considered to provide better protection than the previously-used residue limit of up to two parts per billion because it will have regard to the potency as well as the amount of the carcinogen detected. The acceptability of the test will be assessed in the light of:

- tests in laboratory animals for carcinogenicity and other evidence of toxicity;
• data indicating how the drug is metabolized in the treated animal; and
• the length of time the drug and metabolites remain in the animal's body.


Cefoperazone: registration refusal

Norway — The Medicines Control Authority has refused the registration of the cefalosporin antibiotic, cefoperazone, indicated for the treatment of mastitis in dairy cows, because it considers that use of the product is not medically justified.


Cefuroxime: approved for use in cattle

Iceland — The Committee on Pharmaceuticals has approved the use of the broad spectrum cefalosporin antibiotic, cefuroxime, for the treatment of bacterial infections in milk cattle, particularly those caused by Staphylococcus aureus resistant to other antibiotics. Withdrawal periods are three days for milk, and one day for slaughter.


Chloramphenicol: prohibited in food-producing animals

Canada — The Health Authorities have prohibited the use of the antibiotic chloramphenicol in animals intended for consumption as food or for production of food including milk and eggs.


Fenbendazole: extension of indications

United States of America — The Food and Drug Administration has extended the approved indications for the use of fenbendazole in medicated feeds to include use in cattle at a dose of 5 mg/kg body weight for the treatment of various worm infections. It should be given as the sole ration for one day, and should not be administered within 13 days of slaughter. It may not be used in dairy cattle of breeding age.


Halofuginone + bacitracin methylenedisalicylate approved

United States of America — The Food and Drug Administration has approved a combination product containing the coccidiostatic agent, halofuginone, hydrobromide (2.72 g per ton) + the polypeptide antibiotic bacitracin methylenedisalicylate (10 to 50 g per ton) for the prevention of coccidiosis in broiler chickens caused by Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. nivati and E. maxima, and for improved feed efficiency. Treatment should be withdrawn five days before slaughter. It should not be used in laying hens, and contact with skin, eyes and clothing should be avoided.


Maduramicin approved

Sweden — The National Board of Health and Welfare has approved maduramicin powder 10 mg/g, for prophylaxis against coccidiosis in broiler chickens.

Monensin approved

Sweden — The National Board of Health and Welfare has approved monensin powder 10% to be mixed in the feed for prophylaxis against coccidiosis in chickens.


Parvovirus vaccine approved

Sweden — The National Board of Health and Welfare has approved a parvovirus vaccine prepared from inactivated swine parvovirus (strain NADL-2) for active immunization of infected swine.


Sulfadimidine: carcinogenicity in rodents

United States of America — The National Pork Producers Council has requested its members voluntarily to suspend use of the veterinary antibiotic, sulfadimidine, until the Food and Drug Administration has completed an evaluation of a toxicological study undertaken in mice in which thyroid carcinomas developed in some highly-dosed animals.

The Center for Veterinary Medicine of the Food and Drug Administration has called for any additional information manufacturers may possess on the safety of the drug, and for its use to be discontinued at least 15 days before slaughter.


Sulfadimidine: residues in milk

United States of America — A small-scale survey carried out by the Food and Drug Administration has disclosed low levels of sulfadimidine in a number of samples of cow's milk. Sulfadimidine is an antibiotic which is not approved for use in dairy cattle during lactation. The Agency states that the very low concentrations found do not represent a health hazard for the consumer since they are unlikely to induce hypersensitivity reactions even in people allergic to sulfonamides.

Action is being taken to prevent further use of sulfadimidine in milk-producing cows by validating a new, more effective and more sensitive testing method and by informing veterinarians and dairy farmers of the existing concern about its use.

The National Conference on Interstate Milk Shipments, representing the country's milk agencies, has requested the Food and Drug Administration to consider banning the drug for veterinary use. The Board's current monitoring network will be used to investigate the presence of sulfadimidine in bulk milk and to establish a study committee to examine methods to control the use of antibiotics by dairy farmers.


Trichophyton verrucosum vaccine approved

Sweden — The National Board of Health and Welfare has approved a live vaccine, LTF-130, prepared from Trichophyton verrucosum, for active immunization against ringworm disease in cattle.

Advisory Notices

Amsacrine: new preparation recommended with lactic acid as solvent

Sweden — Recent toxicological studies have shown that the solvent $N,N$-dimethylacetamide, which is used to dilute the antileukaemic drug amsacrine, induces dose-related hypoplasia of the lymphatic tissue and hepatocellular damage in experimental animals. Reports of liver damage previously associated with administration of this product had been variously attributed to the active constituent, the solvent, or to an interaction between the two components. A new amsacrine-containing preparation has recently been registered which is dissolved in a lactic acid solution and which doctors have been advised to use preferentially.


Bemetizide/triamterene: warning of allergic vasculitis

Federal Republic of Germany — The Federal Health Office has decided, on the basis of reported adverse reactions, that the approved information for antihypertensive products containing bemetizide + triamterene should indicate that cases of allergic vasculitis have been associated with the product and that treatment must be discontinued immediately should signs suggestive of such a reaction develop.


Benzodiazepines: warning of dependence liability

United Kingdom — In response to current concern regarding dependence on benzodiazepines, the Committee on Safety of Medicines has recommended that these drugs should be used only in the treatment of anxiety or insomnia that is either severe or disabling or that subjects the individual to extreme stress. Even in these cases, it is emphasized that the lowest effective dose should be used and that treatment should not be continued beyond four weeks. (See also p. 137.)

The Committee has reminded doctors that withdrawal of benzodiazepines can induce anxiety, tremor, confusion, insomnia, perceptual disorders, fits, depression, and gastrointestinal and other somatic symptoms. These effects, which are difficult to distinguish from the symptoms of the original illness, can occur even when dosage has been maintained within the normal therapeutic range and may persist for many weeks or months.


Astemizole: indications and adverse effects

Canada — The Ontario Medical Association's Committee on Drugs and Pharmacotherapy has advised doctors that the maximum therapeutic effect of the long-acting antihistamine, astemizole, may occur as many as three days after its administration. The Committee consequently advises that it should not be used to treat acute conditions such as angioedema. Nor, it suggests, should it be used for symptomatic relief of the common cold since it lacks anticholinergic properties. Because of its prolonged half-life it may also interfere with skin testing for allergy and, when possible, it should be discontinued at least one month prior to testing. The Committee also reminds doctors that, as is the case with many antihistamines, safety during pregnancy has not been established. Astemizole is consequently best avoided during pregnancy, and women of childbearing age should be advised that it can remain detectable in body tissues for as long as seven months.

Bromocriptine: pulmonary changes

Denmark — Since 1981, the National Centre for Adverse Drug Reaction Monitoring has received several reports of lung infiltration, pleural exudate and pleural thickening in patients taking the antiparkinsonism agent, bromocriptine. The Centre has been informed by the major manufacturer that some 90 reports of similar cases have been notified worldwide. About half of these patients had taken at least 40 mg daily and doctors are reminded that the maximum recommended dose is 30 mg per day.


Buspirone: central nervous system and extrapyramidal effects

Federal Republic of Germany — The Federal Health Office has informed doctors that, on the basis of the reports it has received to date, the adverse reaction profile of the anxiolytic agent, buspirone, differs from that of the chemically unrelated benzodiazepines. A comparatively greater proportion of the reports relating to buspirone cite lassitude or somnolence, and a few cases of extrapyramidal symptoms have also been notified. In contrast, relatively few reports of gastrointestinal disturbance and headache have been received.


Calcium channel blocking agents: thyroid hyperplasia

Federal Republic of Germany — In the light of evidence that the calcium channel blocking agent, nitrendipine, has induced dose-dependent hyperplasia of the thyroid gland in baboons, the Federal Health Office has asked doctors to notify any such cases and to ensure that thyroid function is monitored in all patients on long-term treatment with nitrendipine or any other drug of this class. As yet, there is no clinical or histological evidence to indicate that these findings have relevance to man, but particular vigilance is advised when hyperthyroid patients are treated.


Captan: prohibited in cosmetics

Egypt — The Technical Committee for Drug Control has prohibited the use of the antifungal agent, captan, in cosmetic products (1) in the light of evidence that it has carcinogenic potential at high and prolonged dosage in mice, in which it has been associated with an excess of duodenal tumours. This action is consonant with similar measures recently taken within the EEC, where the use of captan will be prohibited as from 1 December 1990 (2). Captan is already banned from use in cosmetics in Australia and Switzerland (3, 4).

References

Cefaclor: restricted use in children

Sweden — Of 129 case reports received by the National Board of Health & Welfare during 1986 and 1987 in which the cefalosporin antibiotic cefaclor was cited, all but three related to children. Most of these events were acute sensitivity-type reactions involving the skin or the musculo-skeletal system, while serum sickness and fever occurred in a smaller number. The Board advises, in the light of this experience, that cefaclor should be used to treat ear, nose and throat infections in children only in cases that fail to respond to penicillin or ampicillin derivatives.

Chemonucleolysis: conditions for application

The Netherlands — A Committee of the National Health Council has advised the Minister of Health that chemonucleolysis, an enzymatic treatment for herniated intravertebral disc, should be practised only by specialized neurosurgeons working in hospitals with adequate technical facilities and that it should never be undertaken in patients with a known or suspected allergic diathesis.


Ciprofloxacin: interaction with theophylline

United Kingdom — Plasma theophylline concentrations may rise as a result of decreased metabolism when the quinolone antibiotic ciprofloxacin is administered concurrently. The Committee on Safety of Medicines has consequently advised doctors that, in these circumstances, the dose of theophylline should be reduced and plasma levels closely monitored in order to avoid toxicity. The Agency has already received 8 reports of clinically-important interactions between ciprofloxacin and theophylline. In most cases the dose of both drugs was well within the recommended range.

Reference: Committee on Safety of Medicines, Current Problems No. 22, 1988

Diethylhexylphthalate (DEHP): call for reports of adverse effects

Federal Republic of Germany — Diethylhexylphthalate (DEHP) is a plasticizer used to increase the flexibility and elasticity of PVC plastics used in many medical appliances such as infusion and ventilation tubes, and transfusion sets. The extent to which it is leached from the plastic matrix is dependent upon environmental variables including pH, temperature, contact with other substances and duration of use.

Animal experiments suggest it has low toxicity. However, its incorporation into artificial ventilation tubes has come under suspicion as a possible cause of impaired pulmonary function in neonates. The Federal Health Office has requested doctors to report all possible adverse effects of DEHP even when causality cannot be securely established. (See also p. 144.)


Estrogen in oral contraceptives

United States of America — In conformity with a recommendation issued by the Food and Drug Administration, US manufacturers have agreed to discontinue the production of high-dose estrogen oral contraceptives.

The Agency's recommendation is based on an advisory committee report which concludes that no advantage is offered by dosage forms containing more than 50 micrograms of estrogen, but that the risk of thromboembolism may be increased.

A six-month phase-out period will allow doctors to switch patients to lower-dose formulations.


Herbal tea (Sou Tsian Te): adverse reactions

Sweden — The National Board of Health & Welfare has alerted doctors to four reports of liver damage, in one case associated with intrahepatic cholestasis, in regular users of the herbal tea Sou Tsian Te, which is marketed as a "natural medicine" and as a slimming product. The Board has requested doctors to report any further cases known to them as a matter of urgency.

Slimming pills: cautionary information for users

Federal Republic of Germany — The Federal Health Office has renewed an appeal to doctors and pharmacists to refrain from prescribing and formulating products made to special order as weight-reducing agents and to recommend more rational methods of weight reduction.

Such preparations have contained a variety of active ingredients including sympathomimetics, diuretics, spironolactone, tranquilizers, neuroleptics, ergot alkaloids, hypoglycaemic agents, thyroid preparations, pyridoxine (vitamin B6) and various organ or plant extracts. The Agency stresses that these products are inappropriate for weight reduction and that inclusion of ingredients solely to counter the adverse effects of other constituents in such products is never justified. It also emphasizes that organic extracts have not been demonstrated to have any influence on weight reduction and that, this being so, any risk of adverse effects associated with their use is unacceptable.


Terfenadine: adverse reaction reports

Australia — The Adverse Drug Reactions Committee has alerted doctors to an unexpectedly high proportion of adverse reactions involving the skin associated with the antihistamine compound terfenadine. Of the 58 reports the Committee had received by 31 August 1987, 17 referred to skin reactions (rashes 7; pruritus 5; urticaria 5).


Norway — Reports on terfenadine have also been received by the Medicines Control Authority. Of these, four concerned skin reactions and five others were referable to the central nervous system. All were reversible on discontinuation of treatment, but since several were regarded as serious, doctors have been asked to report all suspected reactions to the compound.


Sweden — The National Board of Health and Welfare has similarly focused attention on reported adverse effects to terfenadine. It has concluded that, although its sedative effect may be less than that associated with other antihistamines, it is more often associated with other adverse effects, particularly skin reactions.


Xylane-polyhydrogen sulfate: thrombo-embolism

Federal Republic of Germany — The Federal Health Office has received several reports of cerebral and cardiac thrombo-embolic complications in patients receiving the low-molecular heparinoid xylane-polyhydrogen sulfate, some of which have been fatal. An immune mechanism is probably involved, since some of the patients were found to have thrombocyte-aggregating antibodies. Doctors are advised to be alert to signs of thrombosis and petechial bleeding. Faeces and urine should be examined for blood, and blood counts monitored, especially for thrombocytes. When possible, plasma samples should be tested for thrombocyte-aggregating antibodies.

Leprosy affects more than 10 million people worldwide

Leprosy, a chronic mycobacterial infection which affects some 10 to 12 million people worldwide, occurs mainly in Africa, Asia and South America.

The causative organism, *Mycobacterium leprae*, is a slow-growing intracellular bacillus which produces leprosy by infiltrating the skin, the peripheral nerves, the nasal and other mucosa and the eyes. The disease is transmitted directly from person to person when bacilli are shed from the nose and open skin lesions of patients harbouring large numbers of organisms. *M. leprae* can enter the body through skin abrasions but it is probable that the respiratory tract is the main portal of entry. The leprosy bacilli presumably cross the pulmonary alveoli without causing a primary lesion and reach their sites of nidation by haemogenous spread. The household contacts of leprosy patients are at greatest risk of acquiring the disease. However, most individuals have considerable natural immunity and many infections are suppressed. Indeed, clinical leprosy can be regarded as a consequence of deficient cell-mediated immunity in susceptible individuals.

Paucibacillary leprosy* results when cellular immunity is only partially deficient. Relatively few bacilli are demonstrable. Granulomatous lesions in the dermis, which occasionally heal spontaneously, present as hypopigmented and hypoaesthetic or anaesthetic patches. Peripheral nerve involvement may result in no more than minor localized impairment of sensation but, in severe cases, extensive sensory and motor loss induces trophic changes, muscle wasting and contractures.

Multibacillary leprosy** occurs when cellular immunity is largely deficient. Rugose, nodular skin lesions result from infiltration of the dermis by incompetent macrophages loaded with *M. leprae*. Nerve damage also commonly occurs which, if left untreated, may lead to crippling deformities. This damage is mostly sustained during immunologically-mediated inflammatory exacerbations which are of two types:

- **Type I (reversal reactions)** resulting from a cell-mediated immune process and characterized by acute exacerbation of skin lesions and by focal or more generalized attacks of neuritis, sometimes resulting in permanent nerve damage.
- **Type II (erythema nodosum leprosum)** resulting from an immune-complex reaction and characterized by an antibody-dependent response. Discrete acute inflammatory lesions develop in the skin. Systemic symptoms, when they occur, include fever, lymphadenopathy, acute iridocyclitis and, less frequently, neuritis, polyarthritis and glomerulonephritis.

Visual impairment or blindness is frequent in both types of leprosy. It results either from mycobacterial infiltration and inflammation of structures in the anterior segment of the eye or from trophic changes following damage to the trigeminal and facial nerves resulting in lagophthalmos, deformed eyelids or corneal anaesthesia.

**Control**

Effective control of leprosy is dependent upon:

- efficient case-detection, case-holding and treatment.
- surveillance of contacts.

Those at risk, and particularly close family contacts, should remain under periodic surveillance whenever possible.

Vaccines containing a suspension of killed *M. leprae* are currently being field-tested but none is as yet available for routine use.

* Synonyms include: indeterminate and tuberculoid leprosy (Madrid classification); indeterminate, polar tuberculoid and borderline tuberculoid leprosy (Ridley and Jobling classification).

** Synonyms include: lepromatous and borderline leprosy (Madrid classification); polar lepromatous, borderline lepromatous and mid borderline leprosy (Ridley and Jobling classification).
**Chemotherapy**

Dapsone has served as the mainstay of treatment for many years. Its action is essentially bacteriostatic and long-term continuous daily dosage has always been necessary when administered alone. However, because resistant strains of *M. leprae* are now widespread, monotherapy with dapsone is no longer recommended. It is now used in combination with other anti-leprosy drugs, particularly rifampicin and clofazimine, which are more expensive. Rifampicin is also liable to induce resistance when used alone. Thioamides (ethionamide or prothionamide) can be used instead of clofazimine. However, close medical supervision and monitoring of liver function is then required since they are markedly hepatotoxic. Minocycline and some fluoroquinolones have shown promising bactericidal effects against *M. leprae* in mice but data from formal trials in man are still awaited.

The following relatively short courses of multiple oral chemotherapy are currently recommended by WHO (see *A guide to leprosy control*, 2nd ed., Geneva, WHO, 1988, and *WHO Technical Report Series No. 768, 1988*) on the presumption that they will kill any drug-resistant strains initially present and prevent their subsequent emergence during the period of treatment. It is also anticipated that short-term treatment will improve compliance and that, if a regimen suitable for mass administration can be developed, the intensity of transmission will eventually be reduced.

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<thead>
<tr>
<th>Paucibacillary Leprosy</th>
<th>Multibacillary Leprosy</th>
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<tr>
<td><strong>Minimum duration of treatment</strong></td>
<td><strong>Minimum duration of treatment</strong></td>
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<td>6 months</td>
<td>2 years</td>
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<td><em>Dapsone</em></td>
<td><em>Dapsone</em></td>
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<td>100 mg/day</td>
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<tr>
<td><em>Rifampicin</em></td>
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<td>600 mg monthly supervised</td>
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<tr>
<td><em>Clofazimine</em></td>
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<tr>
<td>50 mg daily + 300 mg monthly, supervised</td>
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*Doses for adults of 50 - 70 kg.

Multiple chemotherapy must be sustained for at least six months in paucibacillary leprosy and for at least two years in multibacillary disease or, when monitoring is feasible, until skin smears are negative. Subsequently, patients with paucibacillary disease should remain under supervision for at least a further 2 years and those with multibacillary leprosy for a further 5 years.

**Management of exacerbations**

Chemotherapy should never be suspended during an exacerbation and acute neuritis must be treated as a medical emergency. Type I reactions frequently respond to corticosteroids administered immediately in high dosage (40 - 60 mg prednisolone daily) for several days and subsequently tapered off over a period of several weeks or months in accordance with the clinical response. Surgery may be needed to relieve focal compression of peripheral nerves. The pain and inflammation associated with type II reactions (erythema nodosum leprosum) may be largely suppressed by analgesics and anti-inflammatory agents. When the response to full doses of corticosteroids or clofazimine is inadequate, thalidomide, which is a potent anti-inflammatory agent, can offer valuable relief. However its use in women of child-bearing age is justifiable only when pregnancy can be excluded with confidence. The initial adult dosage of 100 - 400 mg each evening, which may cause drowsiness, should be tapered off gradually.

**Care of trophic lesions**

Secondary bacterial infection of trophic ulcers may lead to osteomyelitis necessitating antibiotic therapy and surgical care.

**Ocular lesions**

The eyes should be examined regularly even in patients with no ocular symptoms. Closure of the eyelids can often be improved in mild degrees of lagophthalmos simply by application of a good quality dermal tape, but in severe cases tarsorrhaphy is necessary. In the absence of corneal ulcers, iridocyclitis should be treated until the attack subsides with topical corticosteroids applied six times daily and with daily instillations of atropine or another long-acting mydriatic until the attack subsides. Corticosteroids should then be reduced.
decrementally over a period of one week, and twice daily applications continued for at least one further week before final withdrawal. Mydriatics should similarly be administered two or three times weekly for a further period of two to four weeks.

Corneal abrasions need to be treated as early as possible with an antibiotic eye ointment (tetracycline 1%). This is particularly important in patients with lagophthalmos and when corneal sensitivity is impaired. Several applications daily may be needed for a prolonged period. The patient should be referred urgently to an ophthalmologist if a corneal ulcer develops.

**CLOFAZIMINE**
capsule 50 mg, 100 mg

A substance which has both anti-leprosy and anti-inflammatory activity. It is weakly bactericidal against *M. leprae* and antimicrobial activity can be demonstrated in man only after continuous exposure for about 50 days. When taken orally it is well absorbed and intermittent dosage is effective because it accumulates in fatty tissues and the cells of the reticuloendothelial system. It is very slowly eliminated in the faeces with an approximate half-life of 70 days. As yet, resistance to clofazimine is rare.

**Uses**

Treatment of multibacillary leprosy in combination with other anti-leprosy drugs.

Treatment of type II reactions: clofazimine may be used as an alternative or, in addition to, corticosteroids or thalidomide.

**Dosage and administration**

Clofazimine should be taken with food or milk.

*Multibacillary leprosy* (in combination with dapsone and rifampicin).

**Adults:** 0.8 - 1.6 mg/kg/day (adult dose usually 50 mg daily) supplemented by one monthly supervised dose of 300 mg.

**Children:** 1 mg/kg/day (if body weight is less than 25 kg two daily doses may be combined and given on alternate days).

**Erythema nodosum leprosum**

**Adults and children:** 200 - 300 mg daily for no longer than three months.

**Contraindications and precautions**

The high doses used in erythema nodosum leprosum should not be given for longer than three months. Patients with pre-existing gastrointestinal disease should be kept under medical supervision. If symptoms become severe, it may be necessary to reduce the dosage or to prolong the interval between doses.

**Use in pregnancy**

Since leprosy is exacerbated during pregnancy, it is important that treatment should be continued. Infants exposed in utero may be more deeply pigmented than normal at birth.

**Adverse effects**

Reversible skin discoloration may occur during treatment to an extent that some lighter-skinned patients find unacceptable. Discoloration of the hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine also occur.

Dose-related gastrointestinal symptoms include pain, nausea, vomiting and diarrhoea.

Clofazimine tends to accumulate in the phagocytic monocytes of the small intestine. Prolonged treatment with doses higher than those currently recommended for the treatment of multibacillary disease has resulted in mucosal and submucosal oedema severe enough to produce symptoms of subacute small bowel obstruction. Because of this rare but serious adverse effect it is recommended that the high dosages used in the treatment of erythema nodosum leprosum should be given only under medical supervision and for no longer than 3 months.

**Storage**

Clofazimine capsules should be kept in well-closed containers.
DAPSONE
tablet 50 mg, 100 mg

Dapsone, a sulfone, remains of prime importance in the treatment of leprosy. It is both bacteriostatic and weakly bactericidal against M. leprae, the minimum inhibitory concentration for fully sensitive organisms being approximately 0.003 micrograms/ml. However, resistant strains can develop de novo during prolonged treatment with dapsone alone, and their incidence is increasing in previously untreated patients. In some areas the prevalence of primary resistance is currently estimated to be as high as 40 per cent.

Following its absorption from the gastrointestinal tract dapsone is distributed widely in body tissues and it is subsequently retained selectively in skin, muscle, liver and kidneys. It is partially acetylated or conjugated in the liver and ultimately excreted in the urine as metabolites. A dose of 100 mg produces a peak serum concentration of approximately 2 micrograms/ml which declines with a half-life ranging from 1 to 2 days.

Uses

Treatment of paucibacillary and multibacillary leprosy in combination with other anti-leprosy drugs.

Dosage

**Paucibacillary leprosy** (in combination with rifampicin).

*Adults and children:* 1 - 2 mg/kg daily (adult dose usually 100 mg daily) for 6 months.

**Multibacillary leprosy** (in combination with rifampicin and clofazimine).

*Adults and children:* 1 - 2 mg/kg daily (adult dose usually 100 mg daily) for at least 2 years.

Contraindications

Dapsone should not be given to patients hypersensitive to sulfones, and any preexisting severe anaemia should be treated first.

Precautions

Dapsone can induce haemolysis of varying degree, particularly in patients with G6PD deficiency. Dose-dependent methaemoglobinaemia may supervene during the second week of treatment. The clinical response to treatment and the blood count must be closely monitored in susceptible patients during the first weeks of treatment. Dapsone therapy should not be discontinued if exacerbations occur.

Use in pregnancy

Since leprosy is exacerbated during pregnancy, it is important that treatment should be continued.

Adverse effects

Dapsone is generally well-tolerated at recommended dosages, but symptoms of gastrointestinal irritation occasionally occur. Other, less common reactions include headache, nervousness and insomnia.

Blurred vision, paraesthesiae, reversible peripheral neuropathy, drug fever, skin rashes and psychoses have also been reported. Hepatitis, Herxheimer reactions and agranulocytosis may rarely occur.

Storage

Dapsone tablets should be kept in well-closed containers protected from light.

RIFAMPICIN

**capsule or tablet** 150 mg, 300 mg

**syrup** 100 mg/5 ml

Rifampicin is a semisynthetic derivative of rifamycin B, a complex macrocyclic antibiotic with a broad spectrum of antimicrobial activity. It inhibits ribonucleic acid synthesis which accounts for its particularly rapid and potent bactericidal action against mycobacteria.

Rifampicin is lipid soluble and following oral administration it is efficiently absorbed and distributed.
throughout cellular tissues and body fluids. If the meninges are inflamed significant amounts enter the cerebrospinal fluid. A single dose of 600 mg produces a peak serum concentration of about 10 micrograms/ml in 2 - 4 hours which subsequently declines with a half-life of 2 - 3 hours. Much of the absorbed drug is eliminated in the bile, some is first deacetylated in the liver, and the parent drug, but not the deacetylated metabolite, is recycled in the enterohepatic circulation. Eventually up to 60 per cent is excreted in the faeces.

Since acquired resistance readily occurs, rifampicin must always be administered in combination with other effective antimycobacterial agents, both in the treatment of leprosy and tuberculosis.

Uses

Treatment of paucibacillary and multibacillary leprosy in combination with other antileprosy drugs.

Dosage and administration

Rifampicin should preferably be administered at least 30 minutes before meals since absorption is reduced when it is taken with food.

Multibacillary leprosy (in combination with dapsone and clofazimine).

Adults: 600 mg once a month for at least 2 years.
Children: 10 mg/kg once a month for at least 2 years.

Paucibacillary leprosy (in combination with dapsone).

Adults: 600 mg once a month for 6 months.
Children: 10 mg/kg once a month for 6 months.

Contraindications

Hypersensitivity to rifamycins. Hepatic insufficiency.

Precautions

Careful monitoring of liver function is required in the elderly and in patients who are alcoholic or who have hepatic disease.

If treatment with rifampicin is resumed after a prolonged interval, it can lead, in some patients, to serious immunologically-determined adverse effects (renal impairment, haemolysis or thrombocytopenia). In this event the drug should be immediately and definitively withdrawn.

Patients should be warned that treatment may produce a reddish discoloration of urine and tears and that contact lenses may be irreversibly stained.

Use in pregnancy

Since leprosy is exacerbated during pregnancy it is important that treatment should be continued.

Rifampicin may cause post-natal haemorrhage in both the mother and infant which may require treatment with vitamin K. However, its potential benefit outweighs the vascular risk.

Adverse effects

Most patients experience no adverse effects when rifampicin is taken at recommended dosages; gastrointestinal intolerance occasionally demands withdrawal of treatment.

Serum bilirubin and transaminases often rise at the outset of treatment. Disturbances in hepatic function are usually transient and subclinical, but in susceptible patients rifampicin can cause potentially fatal hepatitis.

Other adverse effects (rashes, fever, influenza-like syndromes and thrombocytopenia) are more likely to occur when rifampicin is administered on a weekly basis. Temporary oliguria, dyspnoea and haemolytic anaemia have also occasionally been reported in these circumstances, but they have never been associated with the monthly dosage schedules advocated in leprosy.

Drug interactions

Rifampicin is a potent inducer of liver enzymes when it is administered daily. The dosage of other drugs metabolized in the liver may need to be increased when they are taken concomitantly. These include steroid contraceptives, corticosteroids, anticoagulants, oral hypoglycaemic agents, dapsone and...
digitalis glycosides. However, this effect is less pro-
nounced when rifampicin is administered monthly.

Because enzyme induction reduces the reliability of
steroid contraceptives, patients should be strongly
advised to use a non-hormonal method of birth
control throughout the duration of treatment.

The biliary excretion of radiocontrast media and
sulfobromophthalein sodium may be reduced.

Microbiological techniques for assay of folic acid and
cyanocobalamin (vitamin B12) may be disturbed.

Overdosage

Gastric lavage may be of value if performed within a
few hours of ingestion.

Very large doses may have a depressant effect on
the central nervous system. There is no specific
antidote and treatment is supportive.

Storage

Rifampicin capsules should be kept in tightly closed
containers, protected from light at a temperature not
more than 25°C.

ETHIONAMIDE/ PROTIONAMIDE

Tablet 125 mg, 250 mg.

The thioamides, ethionamide and proctionamide are
derivatives of thioisonicotinic acid, both are weakly
bactericidal to M. leprae. Their biological properties
and therapeutic potency are very similar. They are
readily absorbed from the gastrointestinal tract and
widely distributed throughout body tissues. The
plasma half-life of both compounds is approximately
2 to 4 hours and they are excreted in the urine
largely as metabolites.

Uses

To prevent emergence of drug resistance during
combination anti-leprosy chemotherapy in patients
intolerant of clofazimine.

Dosage

Multibacillary leprosy (in combination with
dapsone and rifampicin).

Adults and children: 5.0 to 7.5 mg/kg daily.

Contraindications

Hypersensitivity.

Hepatic dysfunction. Because of their hepatotoxicity
thioamides should only be used when clofazimine is
contraindicated or not available.

Precautions

Liver function should be monitored throughout
treatment.

Use in pregnancy

Treatment with thioamides is contraindicated during
pregnancy.

Adverse effects

Liver dysfunction and toxic hepatitis, particularly
when given in combination with rifampicin.

Gastrointestinal disturbances are common. Other
reported adverse effects include acne, allergic
reactions, alopecia, convulsions, dermatitis,
diplopia, dizziness, headache, hypotension,
peripheral neuropathy, rheumatic pains.

Storage

Ethionamide and proctionamide tablets should be
kept in tightly-closed containers protected from light.
Newly Registered Products

**alminoprofen**

nonsteroidal anti-inflammatory agent
Minalfen®: Fujirebio, Japan
tablets 100, 200 mg
*Indications:* symptomatic treatment of arthritic disease.

**antilymphocyte-T immunoglobulin**

rabbit anti-T-lymphocyte immunoglobulin
Thymoglobulin®: Merieux, Belgium
ATG-Fresenius®, Fresenius, Belgium
solution for intravenous infusion, 2%
*Indications:* prophylaxis and therapy of impending rejection of organ and tissue transplants, particularly renal transplants.
*Contraindications:* hypersensitivity to rabbit protein, bacterial or viral infection, mycosis, massive thrombopenia.
*Precautions:* daily monitoring of blood count. Hypersensitivity to rabbit globulins should be tested before treatment.

**bopindolol**

long-acting beta-adrenoreceptor blocking agent
Sandonorm®, Sandoz, Luxembourg
tablet 1 mg
*Indications:* hypertension.
*Contraindications:* digitalis-resistant cardiac insufficiency, cor pulmonale, severe bradycardia, second or third degree AV-block, bronchial asthma.

**cilostazol**

platelet-aggregation inhibiting agent
Pletaal®, Otsuka, Japan
tablets 50, 100 mg
*Indications:* ischaemia due to occlusive arterial disease.
*Contraindications:* haemorrhage, women of childbearing potential, lactation.
*Caution:* close monitoring is required of patients with a bleeding diathesis, severe renal or hepatic dysfunction, and those receiving anticoagulants or antiplatelet agents.

**cyamemazine**

neuroleptic
Tercian®, Theraplix, France
tablet 20, 100 mg, capsule 25 mg, injection fluid 20 mg/ml, solution for oral use 4%
*Indications:* anxiety, aggressivity.
*Contraindications:* narrow-angle glaucoma, urinary retention.
*Caution:* alcohol should be avoided during treatment.
*Adverse effects:* sedation, tardive dyskinesia, torticollis, oculogyric crisis, trismus, extrapyramidal symptoms, endocrinological disturbances.

**denopamine**

cardiac stimulant
Kalgu®: Tanabe Seiyaku, Japan
tablets 5, 10 mg; granules 50 mg/g
*Indications:* chronic heart failure.
*Contraindications:* not to be used during pregnancy or lactation, or in women of childbearing age.
*Precautions:* regular monitoring required throughout treatment.

**flumequine**

quinolone antibiotic
Apurone®, Riker, Luxembourg
tablet 400 mg
*Indications:* infections of the lower urinary tract due to susceptible microorganisms.
*Contraindications:* quinolone hypersensitivity, G6PD deficiency.
*Caution:* avoid exposure to direct sunlight.
*Adverse effects:* antagonism with nitrofuran antibiotics and tetracyclines and synergism with polymyxin and aminoside antibiotics has been demonstrated in vitro.
**Gallopamil**

Calcium channel blocking agent

*Procorum®*: Ebewe, Austria
- Tablet 400 mg

**Indications**: Coronary disease; Prinzmetal angina, angina pectoris after cardiac infarction, hypertension, prophylaxis of angina pectoris.

**Contraindications**: Hypersensitivity, sinus bradycardia, severe hypotension, SA and AV-block, WPW-syndrome, cardiac insufficiency.

**Caution**: Safety during pregnancy and lactation not established.

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**Halopredone**

Corticosteroid

*Haloart®*: Taiho Pharmaceuticals, Japan
- Injection fluid 12.5, 25 mg/ml

**Indications**: Chronic rheumatoid arthritis.

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**Indeloxazine**

Neuroleptic

*Elen®*: Yamanouchi, Japan
- Tablet 20 mg

**Indications**: To allay autonomic hyperactivity following cerebral infarction, cerebral haemorrhage or atherosclerosis.

**Contraindications**: In women of childbearing potential.

**Warning**: Ophthalmological monitoring is necessary during long-term treatment.

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**Isepadam**

Broad spectrum antibiotic

*Isepadam®*: Essex, Japan
- Injection fluid 200 mg/ampoule

**Indications**: Infections due to susceptible microorganisms.

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**Ivermectin**

Anthelminthic with microfilaricidal activity

*Mectizan®*: MSD, France
- Tablet 6 mg

**Indications**: Onchocerciasis (river blindness).

**Contraindications**: Pregnancy, lactation.

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**Ispamulin**

Broad spectrum antibiotic

*Ispamulin®*: Essex, Japan
- Injection fluid 20 mg/ampoule

**Indications**: Cerebral vasospasm and ischaemia following surgical management of subarachnoid haemorrhage.

**Warning**: Supraventricular extrasystoles require reduction of dose or, if persistent, withdrawal of treatment.

**Adverse effects**: Elevation of transaminase levels, gastrointestinal symptoms, supraventricular extrasystoles and bleeding tendency.

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**Ivermectin**

Cerebral vasodilator

*Cataclot®*: Ono Pharmaceutical, Japan
- Injection fluid 20 mg/ampoule

**Indications**: Cerebral vasospasm and ischaemia following surgical management of subarachnoid haemorrhage.

**Warning**: Supraventricular extrasystoles require reduction of dose or, if persistent, withdrawal of treatment.

**Adverse effects**: Elevation of transaminase levels, gastrointestinal symptoms, supraventricular extrasystoles and bleeding tendency.
**promestriene**

synthetic estrogen

Colpotrophine®: Schering, Italy
capsule 10 mg

*Indications:* vulvo-vaginal atrophy, retarded vaginal post-partum cicatrization, gynaecological surgery.

*Contraindications:* pregnancy, vaginal bleeding of unknown origin, endometriosis, severe impairment of hepatic function, estrogen-dependent carcinoma, myoma, mastopathy, thromboembolism, hypersensitivity.

**roxithromycin**

macrolide antibiotic

Rulid®: Roussel, France
tablet 150 mg

*Indications:* infections due to susceptible microorganisms, particularly of the oral cavity, bronchopulmonary and urogenital tracts, skin; prophylaxis of meningitis.

**teicoplanin**

antibiotic

Targocid®: Merrell Dow, France
powder for injection 200 mg/ampoule

*Indications:* infections in adults due to sensitive Gram-positive microorganisms unresponsive to meticillin and in patients allergic to beta-lactam antibiotics.

*Contraindications:* children, pregnancy.

*Caution:* Haematological, hepatic and renal function should be monitored during long-term treatment. Cross-hypersensitivity with vancomycin may occur.

**tibolone**

progestogen with weak estrogenic and androgenic properties

Livial®: Organon, Netherlands
tablet 2.5 mg

*Indications:* symptomatic treatment of post-menopausal disorders.

*Contraindications:* pregnancy, hormone-dependent tumours, history of thromboembolic disease, vaginal bleeding of unknown origin, severe liver disease.

*Warnings:* patients with impaired renal function, epilepsy, migraine, hypercholesterolaemia or disturbed carbohydrate metabolism must be closely monitored. Signs of thromboembolism and abnormal hepatic function necessitate discontinuation of therapy. The response to anticoagulants may be potentiated.

*Adverse effects:* change in body weight, headache, vertigo, seborrhoeic dermatosis, vaginal bleeding, change in hepatic function, increased facial hair growth, pretibial oedema.

**tick-borne encephalitis (TBE) virus vaccine**

inactivated vaccine

FSME-IMMUN®: Immuno, Luxembourg
suspension for injection,
≥0.35 micrograms/ampoule

*Indications:* protection against tick-borne encephalitis.

*Contraindications:* acute febrile illness, allergy to bovine proteins, somatic diseases of the central nervous system, severe nephritis.

*Precautions:* patients with immunological deficiency should receive a supplementary injection 4 to 6 weeks after the second dose. Non-vaccinated persons additionally need TBE human immunoglobulin for immediate protection.

**urapidil**

peripheral vasodilator, alpha-1-adrenoreceptor blocking agent

Ebrantil®: Byk Gulden, Italy
injection fluid 5 mg/ml

*Indications:* hypertensive crisis.

*Contraindications:* pregnancy, lactation.

*Adverse effects:* transient vertigo, nausea, headache.

**zinc sulfate**

zinc salt for replacement therapy

Solvazinc®: Thames Laboratories, Ireland
effervescent tablet 200 mg

*Indications:* acrodermatitis enteropathica due to zinc deficiency, severe malabsorption syndrome or in patients requiring prolonged parenteral nutrition.

*Contraindications:* active peptic ulcer, renal insufficiency.

*Caution:* tetracyclines, chelating agents and calcium should not be administered concurrently. Only to be used under specialist supervision.
Recent Publications

A monthly newsletter on AIDS

United Kingdom — The diversity of the problems associated with AIDS, both medical and social, has led the Royal Society of Medicine to launch a monthly AIDS Letter which provides authoritative, up-to-date information and commentary on all aspects of the subject, ranging from progress in relevant research to implications for life insurance cover.


Responsibility for drug-induced injury

The scope of this new monograph is aptly summarized in the opening paragraph of its introductory chapter: "this is a book about justice and therefore about rights and duties. Every day, throughout the world, people are being injured by medicines. Sometimes that is inevitable; often it could have been prevented. Once it has happened it is important to find out what went wrong, and what the legal and social consequences of the injury are. It can be at least as important to determine how one can prevent the same injury being unnecessarily inflicted again. It is that process of enquiry — judicial, disciplinary or social — which this book is intended to serve".

In presenting the relevant issues and problems the book is encyclopaedic in its coverage. It is less impressive in discussing the solutions. This is not through lack of research or scholarship. The reality is that very few countries have instituted or even contemplated a system of compensation for drug-induced injury that either supplants or complements the traditional slow, costly and uncertain process of litigation between parties. Many have yet to organize effective adverse drug reaction monitoring programmes. Any prospect of setting up compensatory schemes in countries that have yet to develop other forms of health insurance is far distant. The emphasis must consequently be placed on prevention rather than cure. More countries must be persuaded that monitoring and assessing the performance of widely-used medicines is not only cost-effective, but fundamental to improved patient care, and vital to WHO’s broader objective of the rational use of drugs.


Guidelines for the control of Shigella dysenteriae 1

In the early decades of this century the classical shiga bacillus, S. dysenteriae 1, was a virulent pathogen responsible for widespread epidemics characterized by high case fatality and extreme debilitation. In the 1930s, for reasons that remain undetermined, such epidemics became rare and the disease virtually disappeared from industrialized countries. In the late 1960s, however, it suddenly reappeared in epidemic form, first in Central America and Mexico where it has again become a major public health problem and, more recently, in Asia and Africa.

These guidelines, issued by the Diarrhoeal Diseases Control Programme of WHO, include an up-to-date review of the epidemiology and clinical features of the disease and propose strategies for the prevention and control of epidemics.


Information on veterinary products

The increasing use of drugs in animal husbandry, not only to combat disease in farm animals but to increase the yields of food obtained from them, has important public health implications. The need to
ensure that food for human consumption is free from potentially hazardous drug residues has become a major focus of attention within drug regulatory authorities. Not only do commercially-available products need to be formally registered, their legitimate use needs to be clearly defined and monitored and, in particular, safe withdrawal periods need to be defined if drugs are not to be administered to meat-producing animals unacceptably close to the time of slaughter.

International harmonization of requirements is imperative if a reasonably open international market in meat, milk and eggs is to be maintained, and national regulatory officials consequently need to view their responsibilities within a broader, international context. This resulted, in 1982, in the foundation of the International Technical Conference on the Registration of Veterinary Medicines as an informal forum for promoting common approaches to shared problems. The initiative has now become more securely established through the publication of a six-monthly information letter (in English, French and Spanish) which is issued under the auspices of the International Office of Epizootics in Paris.


Why report adverse drug reactions?

As yet, relatively few countries have instituted national systems for the spontaneous reporting of suspected adverse drug reactions by doctors and other health professionals. Moreover, even where such systems have been in place for some years, many serious reactions remain unreported. In an effort to stimulate more effective reporting, the Committee on Safety of Medicines in the United Kingdom has produced a 10-minute video entitled "Help make medicines safer". Its aim is to explain why an effective voluntary reporting scheme represents a worthwhile investment in preventive medicine.

It is directed to all members of the medical profession and, within the United Kingdom, copies have been sent to all pre- and post-registration schools of Medicine and Pharmacy. Limited numbers are available to other national regulatory authorities and teaching institutions.

International Nonproprietary Names for Pharmaceutical Substances

In accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, notice is hereby given that the following are selected as recommended international nonproprietary names.

Recommended International Nonproprietary Names (Rec. INN): List 28

<table>
<thead>
<tr>
<th>Recommended International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description and Molecular Formulae</th>
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<tbody>
<tr>
<td>alaninum alanine</td>
<td>$\alpha$-alanine, $\alpha$-alanine, methyl ester</td>
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<td>alonacicum alonacic</td>
<td>$N-[(2RS,4R)-2$-methyl-4-thiazolidinyl]carbonyl]-$\beta$-alanine, methyl ester</td>
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<td>ansoxetinum ansoxetine</td>
<td>$\pm$-$6-[[\alpha-[2-(dimethylamino)ethyl]benzyl]oxy]flavone $C_{26}H_{25}NO_{3}$</td>
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<td>atipamezolum atipamezole</td>
<td>4-${2-ethyl-2-indanyl}imidazole $C_{14}H_{16}N_{2}$</td>
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<td>azithromycinum azithromycin</td>
<td>${2-R,3-S,4-R,5-R,8-R,10-R,11-R,12-S,13-S,14-R}$-$13-{[2-6-dideoxy-3-C-methyl-3-O-methyl-a-a--ribo-hexopyranosyl]oxy}$-$2-ethyl-3-4-10-trihibydroxy-3-5-6-8-10-12-14-heptamethyl-11-{[3-4-6-trideoxy-3-dimethylamino]-$\beta$-xylo-hexopyranosyl}$-$oxy}$-$1-oxa-6-azacyclopentadecan-15-one $C_{38}H_{72}N_{2}O_{12}$</td>
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<td>bamaluzolum bamaluzole</td>
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<td>benafentrinum benafentrine</td>
<td>$cis-4-{(1,2,3,4,4a,10b-hexahydro-8,9-dimethoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl}acetalanilide $C_{22}H_{27}N_{2}O_{3}$</td>
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<td>(3S)-3-[(1S)-1-carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-benazepine-1-acetic acid C_{22}H_{24}N_{2}O_{5}</td>
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<td>(3S)-3-[(1S)-1-carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-benazepine-1-acetic acid, 3-ethyl ester C_{26}H_{26}N_{2}O_{5}</td>
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<td>benidipinium benidipine</td>
<td>(±)-(R')-3-[(R')-1-benzyl-3-piperidyl] methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate C_{28}H_{31}N_{3}O_{6}</td>
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<td>l-cysteine C_{3}H_{7}NO_{2}S</td>
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<td>denipridum denipride</td>
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<td>deprodonum deprodone</td>
<td>11β,17-dihydroxypregna-1,4-diene-3,20-dione C_{21}H_{28}O_{4}</td>
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<td>nicotinic acid, tetraester with N,N'-[dithiobis(ethyleneiminocarbonyl-ethylen)]bis[(R)-2,4-dihydroxy-3,3-dimethylbutyramide] C_{46}H_{46}N_{4}O_{12}S_{2}</td>
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<td>insulinum arginum</td>
<td>insulin argine</td>
</tr>
<tr>
<td>irsogladinum</td>
<td>irsoglaine</td>
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<tr>
<td>isamoltanum</td>
<td>isamoltan</td>
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<td>isoleucinum</td>
<td>isoleucine</td>
</tr>
<tr>
<td>leucinum</td>
<td>leucine</td>
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<tr>
<td>levdropropizinum</td>
<td>levdropropizine</td>
</tr>
<tr>
<td>levomoprololum</td>
<td>levomprolol</td>
</tr>
<tr>
<td>libenzapril</td>
<td>libenzapril</td>
</tr>
<tr>
<td>linsidominum</td>
<td>linsidomine</td>
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<tr>
<td>Chemical Name or Description and Molecular Formulae</td>
<td>Nonproprietary Name (Latin, English)</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>lomefloxacinum lomefloxacin</td>
<td>(±)-1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid C_{17}H_{19}F_{2}N_{3}O_{3}</td>
</tr>
<tr>
<td>lysinum lysine</td>
<td>L-lysine C_{6}H_{14}N_{2}O_{2}</td>
</tr>
<tr>
<td>mivacurii chloridum mivacurium chloride</td>
<td>(R)-1,2,3,4-tetrahydro-2-(3-hydroxypropyl)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium chloride, (E)-4-octenedioate (2:1) C_{56}H_{80}Cl_{2}N_{2}O_{14}</td>
</tr>
<tr>
<td>montirelinum montirelin</td>
<td>N-[(3R,6R)-6-methyl-5-oxo-3-thiomorpholinyl]carbonyl]-\alpha\text{-}histidyl\text{-}L-prolinamide C_{17}H_{24}N_{6}O_{4}S</td>
</tr>
<tr>
<td>moveltiprilum moveltipril</td>
<td>(–)-1-[2-(3R)-3-mercapto-2-methylpropionyl]-L-proline, ester with N-(cyclohexylcarbonyl)thioo-\alpha\text{-}alanine C_{19}H_{32}N_{2}O_{3}S</td>
</tr>
<tr>
<td>naxaprostenum naxaprostene</td>
<td>\alpha\text{-}[(2E,3aS,4R,5R,6aS)-4-[(1E,3S)-3-cyclohexyl-3-hydroxypropenyl]hexahydro-5-hydroxy-2[1\text{H}]-pentalenylidene]-m-toluic acid C_{25}H_{34}O_{5}</td>
</tr>
<tr>
<td>neraminolum neraminol</td>
<td>(±)-1-(1H-indazol-4-yloxy)-3-[[2-(2,6-xylidino)ethyl]amino]-2-propanol C_{20}H_{35}N_{4}O_{2}</td>
</tr>
<tr>
<td>norfloxacinum succinimum norfloxacin succinil</td>
<td>7-[4-(3-carboxypropionyl)-1-piperazinyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid C_{20}H_{22}FN_{3}O_{6}</td>
</tr>
<tr>
<td>onapristonum onapristone</td>
<td>11\beta\text{-}[(p-dimethylamino)phenyl]-17\alpha\text{-}hydroxy-17-(3-hydroxypropyl)-13\alpha\text{-}estra-4,9-dien-3-one C_{26}H_{39}NO_{3}</td>
</tr>
<tr>
<td>ornithinum ornithine</td>
<td>L-ornithine C_{5}H_{12}N_{2}O_{2}</td>
</tr>
<tr>
<td>orotirelinum orotirelin</td>
<td>N-[(1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinyl)carbonyl]-\alpha\text{-}histidyl\text{-}L-prolinamide C_{16}H_{18}N_{5}O_{5}</td>
</tr>
<tr>
<td>palatrinum palatrigine</td>
<td>5-amino-6-(2,3-dichlorophenyl)-2,3-dihydro-3-imino-2-isopropyl-as-triazine C_{12}H_{13}Cl_{2}N_{6}</td>
</tr>
<tr>
<td>panomifenum panomifene</td>
<td>(E)-2-[[2-(p-[3,3,3-trifluoro-1,2-diphenylpropenyl]phenoxy)ethyl]amino]ethanol C_{25}H_{24}F_{3}NO_{2}</td>
</tr>
<tr>
<td>pemedolacum pemedolac</td>
<td>(±)-4-benzyl-1-ethyl-1,3,4,9-tetrahydroprano[3,4-b]indole-1-acetic acid C_{22}H_{22}NO_{3}</td>
</tr>
<tr>
<td>perbufyllinum perbufyline</td>
<td>7-[4-4-(p-flurobenzoyl)piperidino]butyl]theophylline C_{25}H_{28}FN_{3}O_{5}</td>
</tr>
<tr>
<td>phenylalaninum phenylalanine</td>
<td>L-phenylalanine C_{6}H_{11}NO_{2}</td>
</tr>
<tr>
<td>Nonproprietary Name (Latin, English)</td>
<td>Recommended International Chemical Name or Description and Molecular Formulae</td>
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<td>-------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
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<tr>
<td>pirazmonamum</td>
<td>2-[[[(2-amino-4-thiazolyl)][1-[[[3-1,4-dihydro-5-hydroxy-4-oxopicolinamido]-2-oxo-1-imidazolidinyl][sulfonyl][carbamoyl]-2-oxo-3-azetidinyl][carbamoyl]-methylenecoaminooxy]-2-methylpropionic acid</td>
</tr>
<tr>
<td>pirazmonam</td>
<td>C_{22}H_{24}N_{12}O_{13}S_{2}</td>
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<tr>
<td>ponairestatum</td>
<td>3-(4-bromo-2-fluorobenzyl)-3,4-dihydro-4-oxo-1-phthalazineacetic acid</td>
</tr>
<tr>
<td>ponarrestat</td>
<td>C_{17}H_{12}BrFNO_{3}</td>
</tr>
<tr>
<td>pramipexolum</td>
<td>(S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole</td>
</tr>
<tr>
<td>pramipexole</td>
<td>C_{10}H_{17}N_{3}</td>
</tr>
<tr>
<td>prolinum</td>
<td>\textit{l}-proline</td>
</tr>
<tr>
<td>proline</td>
<td>C_{5}H_{9}NO_{2}</td>
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<tr>
<td>quinaprilum</td>
<td>(S)-2-[(S)-N-[(S)-1-carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-3isoquinolinecarboxylic acid, 1-ethyl ester</td>
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<tr>
<td>quinapril</td>
<td>C_{25}H_{30}N_{2}O_{5}</td>
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<tr>
<td>rilozaronum</td>
<td>1-bromo-2-phenyl-3-indoliziny-3-chloro-4-[3-(dibutylamino)propoxy]phenyl ketone</td>
</tr>
<tr>
<td>rilozarone</td>
<td>C_{32}H_{36}BrCINO_{2}</td>
</tr>
<tr>
<td>romilidinum</td>
<td>2-(2-bromo-6-fluoroanilino)-2-imidazoline</td>
</tr>
<tr>
<td>romidine</td>
<td>C_{6}H_{4}BrFN_{3}</td>
</tr>
<tr>
<td>salmisteinum</td>
<td>\textit{N}-acetyl\textit{l}-cysteine salicylate (ester), acetate (ester)</td>
</tr>
<tr>
<td>salmisteine</td>
<td>C_{14}H_{15}NO_{4}S</td>
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<tr>
<td>saruplasum</td>
<td>prourokinase (enzyme activating) (human clone pUK 4/pUK 18 protein moiety reduced)</td>
</tr>
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<td>saruplase</td>
<td>C_{2031}H_{3145}N_{585}O_{601}S_{31}</td>
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<tr>
<td>selprazinum</td>
<td>6-[3-[4-(\textit{o}-ethoxyphenyl)-1-piperazinyl]propoxy]-3,4-dihydrocarbostyril</td>
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<td>selprazine</td>
<td>C_{22}H_{35}N_{5}O_{3}</td>
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<tr>
<td>sematilidum</td>
<td>\textit{N}-[2-(diethylamino)ethyl]-\textit{p}-methanesulfonamidobenzamide</td>
</tr>
<tr>
<td>sematilde</td>
<td>C_{11}H_{22}N_{5}O_{3}S</td>
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<tr>
<td>serinum</td>
<td>\textit{l}-serine</td>
</tr>
<tr>
<td>serine</td>
<td>C_{3}H_{7}NO_{3}</td>
</tr>
<tr>
<td>setastinum</td>
<td>1-[[p-chloro-\textit{a}-methyl-\textit{a}-phenyl(benzyl)oxy]ethyl]hexahydro-1H-azepine</td>
</tr>
<tr>
<td>setastine</td>
<td>C_{20}H_{26}CINO</td>
</tr>
<tr>
<td>sevopramidum</td>
<td>(\pm\textit{-}\textit{a}-benzamido-\textit{p}-[3-diethylamino]propoxy]-\textit{N},\textit{N}-dipropylhydro-</td>
</tr>
<tr>
<td>sevopramide</td>
<td>cinnamamid</td>
</tr>
<tr>
<td>simvastatin</td>
<td>2,2-dimethylbutyric acid, 8-ester with (4\textit{R},6\textit{R})-6-[2-[(1\textit{S},2\textit{S},6\textit{R},8\textit{S},8\textit{a}R)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,5-dimethyl-1-naphthylethyl]tetrahydro-4-hydroxy-2H-pyran-2-one</td>
</tr>
<tr>
<td>simvastatin</td>
<td>C_{20}H_{26}O_{5}</td>
</tr>
<tr>
<td>somidobovum</td>
<td>1-[\textit{N}^{2}\textit{N}-[\textit{N}-[\textit{N}^{-1}\textit{N}-methionyl-\textit{l}-phenylalanyl]-\textit{l}-prolyl]-\textit{l}-leucyl]-\textit{l}-aspartyl]-\textit{l}-aspartyl]-\textit{l}-aspartyl]-\textit{l}-lysine]growth hormone (ox)</td>
</tr>
<tr>
<td>somidobove</td>
<td>C_{1020}H_{1593}N_{771}O_{302}S_{9}</td>
</tr>
<tr>
<td>Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description and Molecular Formulae</td>
</tr>
<tr>
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<tr>
<td>sornidipinum</td>
<td>(+)-1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-3,5-pyridinedicarboxylic acid, methyl ester, 5-ester with 1,4: 3,6-dianhydro-α-D-glucitol</td>
</tr>
<tr>
<td>sornidipine</td>
<td></td>
</tr>
<tr>
<td>sudismasum</td>
<td>N-acetylsuperoxide dismutase (human clone pS 61-10 copper-zinc subunit protein moiety reduced)</td>
</tr>
<tr>
<td>sudismase</td>
<td></td>
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<tr>
<td>taprostenum</td>
<td>α-[(2Z,3aR,4R,5R,6aS)-4-[(1E,3S)-3-cyclohexyl-3-hydroxypropyl]hexahydro-5-hydroxy-2H-cyclopenta[b]furan-2-ylidene]-m-toluic acid</td>
</tr>
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<td>taprostene</td>
<td></td>
</tr>
<tr>
<td>taurinum</td>
<td>taurine</td>
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<tr>
<td>taurine</td>
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</tr>
<tr>
<td>tepoxalinum</td>
<td>5-(p-chlorophenyl)-1-(p-methoxyphenyl)-N-methylpyrazole-3-propionohydroxamic acid</td>
</tr>
<tr>
<td>tepoxalin</td>
<td></td>
</tr>
<tr>
<td>texacromilum</td>
<td>(±)-5-[2-hydroxy-3-(methylthio)propoxy]-4-oxo-4H-1-benzopyran-2-carboxylic acid</td>
</tr>
<tr>
<td>texacromil</td>
<td></td>
</tr>
<tr>
<td>threoninum</td>
<td>L-threonine</td>
</tr>
<tr>
<td>threonine</td>
<td></td>
</tr>
<tr>
<td>tibenelastum</td>
<td>5,6-dietoxybenzo[b]thiophene-2-carboxylic acid</td>
</tr>
<tr>
<td>tibenelast</td>
<td></td>
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<tr>
<td>traboxopinum</td>
<td>(±)-2-chloro-12-[3-(dimethylamino)-2-methylpropyl]-12H-dibenzo[d,g][1,3,6]-dioxazocine</td>
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<tr>
<td>traboxopine</td>
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<td>tryptophanum</td>
<td>L-tryptophan</td>
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<td>tyrosinum</td>
<td>L-tyrosine</td>
</tr>
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<td>tyrosine</td>
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<tr>
<td>ufiprazolium</td>
<td>5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]thio]benzimidazole</td>
</tr>
<tr>
<td>ufiprazole</td>
<td></td>
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<tr>
<td>valinum</td>
<td>L-valine</td>
</tr>
<tr>
<td>valine</td>
<td></td>
</tr>
<tr>
<td>zabiciprilum</td>
<td>(3S)-2-[(2S)-N-[(1S)-1-carboxy-3-phenylpropyl]alanyl]-2-azabicyclo[2.2.2]-octane-3-carboxylic acid, 1-ethyl ester</td>
</tr>
<tr>
<td>zabicipril</td>
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</tbody>
</table>
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