PROPOSED INN LIST 63
INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

WORLD HEALTH ORGANIZATION • GENEVA
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 socioeconomic 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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Clinical pharmacology: twenty years on

Two decades ago, when clinical pharmacology was emerging as an accredited discipline, some of its early exponents were brought together under the aegis of the World Health Organization to discuss its scope and organization (1). At the time it was defined as "the scientific study of drugs in man" — a label broad enough to permit its development as a multidisciplinary activity. In some countries it subsequently became identified as a clinical specialty. In others, it has evolved predominantly as a laboratory-based science. In many, however, it has gained no more than token recognition.

The heartland of the discipline has always been in those countries where drug development is most highly concentrated. Here, it has operated at the interface between the research-based pharmaceutical industry and academic clinical medicine, particularly in relation to the initial phases of the investigation of new compounds in man. It has enhanced standards of clinical investigation of drug responses and it has contributed much to knowledge of the kinetics of drug effects in man and to the mechanisms underlying clinically-significant interactions. Most importantly of all, insofar as it has retained independence from commercial sponsorship, it has influenced the profile of therapeutic research by ensuring that clinical investigation is directed to preparations of greatest therapeutic promise.

At a time when manipulation of synthesized molecules based upon an appreciation of classical receptor theory still offered generous prospects for therapeutic advance, these achievements satisfied all the early expectations of the specialty. Today, the scene is changing. The potential for fundamental therapeutic progress stems increasingly from the products of biotechnology. With the arrival of preparations delivering potent, naturally occurring substances such as erythropoietin and a variety of lymphokines, developmental drug research is establishing flourishing roots in the physiological and immunological sciences as well as in classical pharmacology. The trend will continue as other peptide regulatory factors, previously unobtainable even in the amounts necessary for their precise characterization, become available in quantities of commercial potential. The interface between the developmental laboratory and the clinic will remain. However, to retain command of this ground, clinical pharmacologists will need to apply new knowledge, to develop new skills, and to forge links with a wider range of basic scientists.

This is a challenge that many will doubtless accept with assurance and enthusiasm. But there is a broader charge to be accepted if clinical pharmacology is to be adequately responsive to the needs of the nineties. Therapeutic innovation has immediate implications for therapeutic choice. To whom can the busy practising doctor turn to discuss therapeutic options? Standards of patient care are no longer determined simply by sound application of clinical knowledge and effective therapeutic management. In recent years cost has also become a prime consideration within every health care setting. The time is long past when it could reasonably be claimed that drugs represent a relatively minor charge upon the system. The change may well have been inevitable. The pressures upon the research-based industry are undeniable. Therapeutic targets are becoming more challenging; greater rigour is continuously demanded in the screening and surveillance undertaken to assure the safety of products before and after marketing; more products are now developed for relatively small populations of patients; and the effective patent lives of new products are continuously eroded by ever lengthening development schedules. However, the extent to which these factors justify the prices recently set for key products introduced in the recent past may never become entirely transparent.

Meanwhile, the reality is stark. Drugs are now being developed that few patients will ever be able to afford. It is no longer necessary to refer to conditions in the least developed countries to cite examples of products that cost as much to administer over any given period of time as the median national wage. The potential costs of the drug regimens required to reduce the prevalence of cardiovascular and other diseases in the rapidly expanding elderly populations of developed countries are similarly daunting. The list of illustrative examples can be extended at will, not only with reference to drugs but to every
aspect of patient care. The delivery of medical services is engulfed by an unprecedented cost crisis.

The divide between what is possible and what is practicable has passed the stage at which it might be bridged simply by increased subventions upon patients or public funds. Inevitably, the options are most limited where the need is greatest, but everywhere it is becoming necessary to set priorities and to ensure that they are respected. In varying degree, governments have become engaged directly in cost saving — most notably by promoting generic prescribing, by excluding specific products from reimbursement schemes, by issuing advice to doctors on good prescribing practices and, in some instances, by imposing limits on their drug budgets. The danger is ever present, however, that prescribing regulation may lead to false economies that neither save money in health care provision overall nor maintain standards of patient care and that may well neglect the improved quality of life that drug treatments can offer. In the last analysis, patients and society will be best served where doctors themselves have become attuned, as a matter of course, to considering the cost factor when weighing the relative advantages and shortcomings of different treatment options.

If clinical pharmacology is to develop as a specialty holding relevance to public health, this is surely where the crucial challenge lies. The teaching of therapeutic management too often takes place on disputed ground and, too often, rote still prevails over rationale. Internists, specialist clinicians and information pharmacists each have vital contributions to offer. Few would dispute, however, that it is the clinical pharmacologist who is best placed to instil in doctors under training both the basic principles of rational prescribing and a generally discerning attitude toward the cost of medicines.

To address the challenge, clinical pharmacologists will need to extend their horizons of technical competence to encompass not only the controlled comparative techniques of the laboratory scientist but the more opportunistic and problematic methods of the epidemiologist. Even if they never become involved at first-hand in the design of case-control and cohort studies, they need to develop the judgement to assess the quality of such research and to interpret the findings with confidence and objectivity. Beyond this, they must be prepared — whether or not they are persuaded of the validity of formal approaches to meta-analysis — to render down the products of relevant research to conclusions that provide a basis for rational prescribing practices.

Even then, the charge is not completely satisfied. Prescribing practices need to be shaped to reflect not only the conclusions of published research but of relevant local experience. Doctors will always stalwartly defend their professional freedom to prescribe as their judgement dictates. However, enough has been learned from the introduction of institutional formularies, antibiotics policies and therapeutics committees in recent years to show that peer review of prescribing practices, when undertaken with competence, sensitivity to the need for consultation and feedback of information, can be not only tolerated but welcomed by the profession at large.

There is still much to be accomplished. Within the medical establishment, the challenge lies with clinical pharmacologists to promote the changes of attitude implicit in the rational use of drugs. To the extent that they fail, governments will have no option but to become progressively more interventionist in the controls they impose upon prescribers. Should they succeed, they will at once have secured the future of their specialty, assured its relevance wherever medicine is practised, and provided the health professions as a whole with well-merited respite from administrative challenges to their independence.

Reference

Personal Perspectives

Improving therapeutics through an ADR monitoring centre

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As is the case throughout the developing world, the amount of information generated within India on drug usage and on drug-induced adverse effects is very meagre. At present, no centre operates on a national basis to receive and collate reports of suspected adverse drug effects that are encountered in routine medical practice. Indeed, very few centres exist even at local level to monitor and evaluate such events. One of these operates from the Christian Medical College Hospital, Vellore, a 1500-bed general teaching hospital which for many years has encouraged doctors within the hospital and in the immediate vicinity to notify possible untoward effects of drugs on a voluntary basis. In 1983, this activity was placed on a more formal footing when a centre attached to the unit of clinical pharmacology was set up to monitor and evaluate all suspected adverse drug effects recorded among patients admitted to the hospital that had occurred prior to or subsequent to their date of admission.

Within a span of four years, during which time the centre contributed actively to the Boston Collaborative Drug Surveillance Programme, it was estimated that 8.7% of all inpatients in medical wards developed adverse drug effects during their period in hospital and that a further 3% of these patients were admitted to these wards as a result of iatrogenic conditions. Almost three-quarters of these incidents were moderate to severe in intensity and necessitated a prolongation of inpatient care. Feedback on this experience together with additional information on adverse drug effects and new drugs was issued to collaborating clinicians in periodic newsletters.

The scheme has since been extended beyond the academic milieu to general practitioners and mission hospitals, predominantly in the southern states of India. This has been done in the expectation that, by encouraging spontaneous reporting of adverse drug effects among doctors in general and by feeding back the results to them, a more critical attitude toward therapeutic management could be inculcated and standards of prescribing could be raised. To achieve reasonably representative coverage it was recognized that an economical, flexible and operationally simple system had to be devised and that, for sustained success, effective rapport and assured feedback of information would be crucial.

Support was sought from directors of mission hospitals, alumni of the institute and general practitioners active in its Continuing Medical Education Programme, and each was invited to engage the interest and collaboration of 2 or 3 colleagues. In all, about 1700 doctors and 200 small to medium-sized hospitals received a letter which explained how the delivery of health care might be improved by monitoring the effects of routinely prescribed drugs and, at the same time, each was provided with simple pre-addressed adverse reaction reporting forms, similar to the yellow cards used in the United Kingdom.

Individual practitioners were more readily persuaded to participate in the Scheme than institutions. Of those approached, about 700 individual doctors (40%) and 30 to 40 hospitals (15-20%) have been reporting on a regular basis, notwithstanding the disincentive of having to pay their own postage costs. The only recompense for participants’ allegiance to the scheme is a periodic newsletter which they receive whether or not they correspond regularly. This provides commentaries on drug usage patterns, insofar as these are evident from incoming reports, as well as instructive discussions of typical adverse drug effects. The aim has been to create an educational tool that not only provides occasional alerts regarding unanticipated hazards of therapy but also, in a more general sense, promotes both rational use of drugs and cost-effective use of resources.
For example, out of a total of 446 reports received in a typical year, 35 were attributed to products containing dipyrone\(^1\). Three-quarters of these were classified as severe reactions and death resulted in two instances. Dipyrone-containing preparations are widely prescribed in India when a mild analgesic or antipyretic effect is required, and the newsletter used these data to illustrate the need for prescribers never to select a potentially dangerous drug when a safer alternative may be available.

Similarly, reports submitted to the centre provided a preliminary indication that the new quinolone antibiotics are widely and often inappropriately prescribed in the community, without regard to their cost or the ever-present danger of the emergence of drug-resistant organisms. Surveys on the use of ciprofloxacin and norfloxacin have since been conducted among the participants and they will shortly be informed, on the basis of the data they have supplied, about prevailing prescribing patterns. The results will also subsequently be used to reassert guidelines that need to be respected in the use of these drugs.

The response rate to such surveys among the participants has ranged from 15 to 40 per cent. In most instances this has been sufficient to provide meaningful data in a highly cost-effective way. The programme is run at a small fraction of the cost of an intensive hospital monitoring programme. Moreover, in addition to its obvious educational effect, it provides a means of establishing rapport and interrelationships within the medical community that, in many countries, would otherwise be completely lacking. With time, cumulative computerized storage and retrieval of the incoming data has provided the basis for a drug information service that is of value to the hospital staff and to others seeking information on drug reactions and interactions. Indeed, we have now reached the point where we have acquired the confidence to plan an international workshop on the rational use of antibiotics in the community that is oriented particularly to the work of general practitioners.

The objectives of the centre have broadened considerably since it first became operational. We are now able to claim that we aim, not only to portray prescribing practices and patterns in a systematic way, but to investigate the determinants of these practices and to evaluate the effects of therapy, including adverse reactions and interactions, that occur in hospital and community practice. Once obtained, the information is used in an educational context to influence prescribing attitudes, upgrade therapeutic skills and knowledge, and promote cost-effective prescribing. With some assurance we can say, in the light of the continued evolution of the programme, the enthusiastic feedback we receive from participants and the queries that we handle on therapeutic problems, that we have identified and fulfilled a need that would otherwise remain largely unmet.

\(^{1}\)dipyrone = metamizole sodium (INN).
Reports on Individual Drugs

Misuse of skin bleaching agents

A brisk market for skin lightening creams has existed for many years in many sub-Saharan African countries. Officially, many of the governments have banned them, having regard to the potentially toxic effects of the commonly-used active ingredients — hydroquinone, mercury and corticosteroids. However, it seems that they are still widely but illicitly traded. The adverse effects that result from their use are rarely described in the literature, but they are well known to dermatologists working within the region and they have recently been extensively reviewed (1).

Hydroquinone is the active ingredient of a number of hair dyes and bleaching creams, which are registered for over-the-counter sale in several countries in North America and Europe. In somewhat higher concentrations it is used clinically for localized treatment of chloasma, melasma and freckles (2). At high concentrations hydroquinone is corrosive and its systemic effects are similar to those of phenol. The maximum permissible concentration in products intended for unsupervised topical application in most of the countries where they are available is of the order of 2 per cent, and the product information generally advises that use should not be prolonged for more than 2 months. However, it seems that these guidelines are not always respected since products containing concentrations in excess of 7 per cent have been detected in circulation (3, 4).

Skin bleaching, resulting from depigmentation of melanocytes, occurs within a few weeks of regular daily use and when treatment is discontinued the effect is sustained for several months. However, more prolonged use, particularly of products containing higher concentrations can, paradoxically, induce chloasma-like hyperpigmentation, or acquired localized ochronosis in dark-skinned people (5, 6). This develops particularly in areas of skin exposed to sunlight and the lesions do not fade unless attempts are made to remove them by cryotherapy, abrasion or local injection of corticosteroids.

Aminomercuric chloride and other highly soluble salts of mercury are commonly included, at concentrations of 3 per cent or more, both in medicated "antiseptic" soaps and skin lightening creams. Percutaneous absorption is extensive when they are widely applied in hot, humid climates and particularly when, as some of the promotional literature proposes, they are massaged into the skin. Dermatitis commonly results from prolonged use and, ultimately, accumulation of the absorbed fraction results in systemic poisoning. The signs and symptoms of mercury poisoning are pleomorphic. They develop insidiously, but prolonged accumulation inevitably results in a terminal illness that may simulate and — where diagnostic facilities are limited — readily be mistaken for other diseases, including tetanus, cerebral malaria, or typhoid fever.

Topical corticosteroid preparations are considered, as a class, to have a discernible skin lightening effect, although this probably derives largely from their vasoconstrictor effect (7). Many preparations, some of them containing substances as potent as betamethasone salts and fluocinonide, are now widely used for cosmetic effect in many African countries, despite remaining officially under prescription control (1). The serious adverse consequences of prolonged unsupervised application both locally and systemically are evident, and longstanding doubts about possible teratogenic potential (8) have never been decisively resolved.

Having regard to the apparent extent and the serious consequences of abuse of these products, the African Association of Dermatologists, in 1986, called for skin-lightening products containing hydroquinone or salts of mercury to be banned throughout the continent (9). However, illicit trade in these products has largely undermined attempts at formal regulatory action, and at least one African government has since requested countries identified as major sources of these products to assist by prohibiting their shipment. These actions are clearly not applicable to topical corticosteroid preparations, which must remain available within the legitimate distribution chain. A step in the right direction would be made if the risks associated with excessive and extensive use were fully and prominently described in the labelling.
Community-based ivermectin therapy

When the microfilaricidal agent, ivermectin, first became generally available for the treatment of onchocerciasis some four years ago (1) it attracted particular attention. Although it provided no prospect of a radical cure since it did not kill the adult worms, it was thought to offer the first realistic means of controlling the disease on a mass scale by chemotherapy. Moreover, it was offered free of charge by the manufacturer, Merck, Sharp & Dohme to the governments of all countries in the endemic areas of Africa and South and Central America when it could be shown that arrangements were in place to monitor the response of treated patients. Not only was it important to assess the acceptability of the drug and its suitability for community-based therapy, but cost-effective methods for identifying and treating infected patients needed to be developed, and suitable intervals between successive doses needed to be established in a variety of communities. In addition, crucial decisions still need to be taken on whether larviciding to control the blackfly vector can be suspended where ivermectin is efficiently used.

Initial clinical experience suggested that an annual dose of 150 micrograms per kg would safely and effectively reduce the microfilarial load which is responsible for the pruritus and blindness associated with the disease, and this has now been confirmed in studies conducted in 14 countries. Overall, among some 50 000 patients who received a dose of this order in community-based trials undertaken in Africa and central America, 9 per cent reported adverse effects. The large majority of these were of the Mazzotti type — oedema, pruritus and rash, arthralgia and ocular irritation — resulting from the sudden death of massive numbers of microfilariae, but in only 0.25 per cent of patients were these rated as severe (2). By the end of 1989, a further 67 000 patients had been treated within the internationally-organized Onchocerciasis Control Programme operative in west Africa (3) and, again, no long-term adverse effects of treatment were notified.

A detailed account of one of the largest trials to be conducted has now been published (3). This was started in the latter months of 1987 and involved workers on a rubber plantation in the rain forest area of Liberia where over 80 per cent of the adult population have onchocerciasis. Almost 8 000 individuals — some 97 per cent of those eligible — received two doses of ivermectin, one year apart, in the standard regimen of 150 micrograms per kg. Excluded from the study were women who were known to be either pregnant or breast feeding, children under 5 years, and older children aged up to 11 years in whom microfilariae were not demonstrated in skin snips.

The effect of these doses on skin microfilarial counts was measured in a subset of some 8 per cent of the treated individuals. On average, the microfilarial load within this sample was reduced by 86 per cent 6 months after the initial dose and by 78 per cent after one year. None of the treatment-related reactions was serious, and their incidence — estimated,
respectively, at 1.3 and 0.5 per cent following the first and second doses — was particularly low.

Whereas 30 per cent of women of childbearing age were excluded from the initial round of treatment because of a possibility of pregnancy, less than one in five of these was again excluded for the same reason one year later. The authors estimate, by extrapolating this finding, that after three years 99 per cent of women of childbearing age should have received at least one dose and 86 per cent should have received at least two doses. In the longer run, even if pregnancy remains a contraindication to treatment, women of this age group are unlikely to form the only major reservoir for microfilariae in the community.

The trial has also demonstrated the need to establish unequivocally, as a part of the developmental process, whether drugs intended for community-based therapy have teratogenic or embryopathic potential at clinical dosage. Despite every reasonable attempt to exclude potentially pregnant women from the study on the basis of menstrual dates, at least 83 fetuses were exposed to ivermectin within three months of conception. In the event, the results were fully reassuring. In no case were congenital abnormalities detected which, in the view of the investigators, could be attributed to exposure to ivermectin (3). These results, however, provide no grounds for relaxing vigilance at this stage. Full advantage needs to be taken of the unique circumstances in which ivermectin has been launched, not only to provide definitive information on all the potential risks of treatment, but also to set a standard for the investigation and assessment of other drugs used in community-based programmes.

References


Safety of pertussis vaccines

Whole-cell pertussis vaccines have been extensively used for over 40 years. For the past decade, however, controversy has been aroused over their safety. Occasional cases of febrile seizures, new-onset epilepsy and other types of severe permanent neurological damage have been associated with their use (1-3). There is no doubt that, in protecting against pertussis, vaccination has none the less prevented death or retardation in many thousands of children (4). Pressure has consequently arisen for a quantitative reassessment of the safety of vaccination.

Several prospective studies have now been completed. The first results to be published derived from the National Childhood Encephalopathy Study in the United Kingdom (5, 6). These were initially interpreted as indicating that 1 in 140 000 children developed encephalopathy as a result of vaccination and that, of these, some 40 per cent suffered permanent brain damage. Since then, findings obtained in three large controlled studies which involved a total of some 230 000 children in the USA have failed to establish an association between pertussis vaccination and permanent neurological illness (7-9). Moreover, a reworking of the UK data has cast into question whether or not the results truly reflect a positive relationship (10, 11). It has been pointed out, in particular, that the observed excess of cases of brain damage in the seven days following vaccination, as originally reported, is matched by a corresponding decrease in cases presenting over the next three weeks (12, 13). This being so, vaccination appears to do no more than to bring forward in time an event that is already bound to occur.

Recent editorial comment in the Journal of the American Medical Association concludes that "pertussis vaccine encephalopathy" is now a "non-existent problem". This does not imply, it emphasizes, that the currently available whole-cell vaccines are fully satisfactory: their uncontested association with transient febrile seizures, hypotonic hyporesponsive states and uncontrollable crying is amply sufficient to justify the development of a new generation of better tolerated products. None the less, it has been pointed out that a conclusive comparative evaluation would require trials in millions of children simply because the current vaccine is so safe and effective (14). Moreover, in order to establish the degree of protection that a new vaccine
would offer against the major serotypes of the pertussis bacillus, parallel trials would need to be conducted in several countries (15). Hasty reaction to events without heed for secure statistical evaluation has already resulted in too many set-backs in efforts to contain whooping cough. To countenance further uncertainty at this stage would be inadmissible.

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Corticosteroids and spinal-cord injury

United States of America — Fifty years ago, traumatic quadriplegia was rapidly lethal (1). Today, largely as a result of advances in intensive care and rehabilitation, most lives can be saved, although the condition remains devastating (2). Indeed, there has been no clear evidence that any form of pharmacological intervention could reduce the degree of permanent incapacity. Many neurosurgeons have long felt justified, none the less, in prescribing corticosteroids during the acute phase of management (3), primarily on the basis of experiments undertaken on laboratory animals over 20 years ago (4). Information from non-randomized studies provided further encouragement (3) and two multicentre prospective placebo-controlled studies conducted over the past few years have provided persuasive evidence that high dosages of methylprednisolone first administered within 8 hours of the injury result in significant improvement in motor function (5, 6).

When administered as an intravenous bolus of 30 mg per kilogram followed by infusion at 5.4 mg per kilogram for 23 hours, methylprednisolone resulted in significant improvement in motor function and in sensation to pinprick and touch. This benefit was most evident in patients with neurologically incomplete lesions. In fact, no improvement was detected in patients with complete motor loss. The opiate receptor blocking agent, naloxone hydrochloride, which had been of apparent value in animal studies, offered no discernible benefit to patients when administered at high dosage within the same time frame (7).

In objective terms the steroid-induced changes were modest but it has been emphasized (2) that a gain of a few segments of motor or sensory function can
represent the difference between a fully chairbound or a reasonably independent existence. The consensus view from this trial that corticosteroids should now be used routinely at high dosage, and as soon as possible, in the acute management of spinal cord injury.

References


Anticonvulsant-induced malformations: which fetuses are at risk?

All widely available anticonvulsant drugs have been implicated, with varying degrees of certainty, as potential teratogens (1). Aside from the specific association between valproic acid and spina bifida (2), the fetal hydantoin (or phenytoin) syndrome has been most extensively studied (3). Characterized, when fully expressed, by craniofacial abnormalities, mental retardation and limb defects, it is estimated to occur in up to 10 per cent of exposed infants. Lesser changes are considerably more frequent.

There has long been speculation that these changes are due, not to phenytoin itself, but to epoxides — toxic oxidative intermediate metabolites capable of binding covalently to fetal nucleic acids — which are normally eliminated in a reaction catalysed by the enzyme epoxide hydrolase (4). Support for this hypothesis has more recently been provided by tentative evidence that the risk of malformation is compounded when phenytoin is taken together with carbamazepine, another anticonvulsant that generates epoxide metabolites (5, 6).

Epoxide hydrolase activity, it seems, is distributed trimodally rather than normally in the population (7). This suggests that it is regulated by a single gene with two allelic forms. If this is so, strikingly low levels of enzymic activity in the quartile of fetuses homozygous for the recessive allele should be predictive of particular risk from epoxide-generating anticonvulsants. Results fully consonant with this hypothesis have now been obtained in a small prospective study (7). Microsomal epoxide hydrolase activity was measured, using a thin-layer chromatographic assay, in amniocytes obtained from 19 epileptic mothers who were receiving phenytoin monotherapy. All four fetuses with enzyme activity below 30 per cent of the standard were found at birth to have clinical signs of hydantoin syndrome. No such abnormalities were detected in the remaining 15 infants who were identified in utero as having considerably greater enzymic activity.

Should these results be confirmed, a precise and practicable predictive assay will have been established for identifying fetuses at particular risk of congenital malformations induced by anticonvulsant drugs.

References


**Long-term lithium reduces risk of suicide**

**United Kingdom** — It has been estimated from studies conducted in northern Europe that, untreated, about 15 per cent of depressed patients are liable ultimately to commit suicide (1-3). Few studies have as yet been published to indicate whether long-term treatment either with lithium or other antidepressant or neuroleptic drugs significantly reduces this risk, although there is persuasive evidence that it considerably reduces morbidity (4). Results recently reported from a ten-year retrospective review of 104 patients with bipolar or recurrent depressive disorders who attended the same lithium clinic throughout 1977 suggest that mortality is comparably reduced (5).

Almost 95 per cent of these patients, each of whom was seen regularly every six to eight weeks throughout the ten-year period, continued to take a single daily dose of a sustained release preparation of lithium carbonate in an amount sufficient to maintain the plasma concentration between 0.5 and 0.9 mmol per litre. The overall death rate within the group was less than half that anticipated on the basis of published mortality rates for England and Wales as a whole, and no patient died of suicide.

**References**


**Intrauterine devices: longer effective lifespan**

**United Kingdom** — Copper-bearing intrauterine devices, which were first marketed in the 1970s, are currently estimated to be used by about 60 million women. They are more effective than the original inert plastic devices, probably because they release copper at a rate of about 40 micrograms daily into the uterine cavity. The windings of thin wire used in the early models fragmented if they were allowed to remain in place for several years. More recently introduced devices carry thicker gauge wire or solid sleeves of copper. These, according to a statement recently issued by the Medical Advisory Committee of the Family Planning Association and the National Association of Family Planning Doctors, may safely be left in place for at least five years.

Routine changing at greater frequency offers no benefit, it seems (2, 3), whereas less frequent replacement is advantageous, particularly to older women whose families are complete and who want a method that will take them up to the menopause. It reduces not only the cost, inconvenience and pain associated with reinsertion, but also the risks of pelvic inflammatory disease, uterine perforation, expulsion, and other complications associated with the intervention.

**References**


**Long-term use of beta-blockers: the need for sustained compliance**

**United States of America** — Increasingly, beta-adrenoreceptor blocking agents are prescribed pro-
that it is important to take them regularly and that, among a total of 338 patients described in the published literature as suffering withdrawal effects, 8 died suddenly and myocardial infarction supervened in a further 15 (1).

The risk seems to be greatest in patients with a severe degree of cardiac ischaemia (1, 2). Indeed, until recently, it was assumed that patients without symptoms of ischaemia were liable to serious withdrawal effects (3). This view is now challenged by evidence from a large population-based, case-control study of risk factors for first manifestations of coronary heart disease in hypertensive patients (4). Within this study, which involved almost 250 patients with recently-diagnosed coronary heart disease and three times this number of controls, subjects who had recently not refilled their prescriptions on schedule and who were consequently assumed to have suspended treatment temporarily were estimated to be transiently at a fourfold increased risk of coronary heart disease. This association was specific for beta-adrenoreceptor blocking agents and was not evident for diuretics.

It may well be that the capacity of a drug to induce a withdrawal syndrome in these circumstances is also indicative of a capacity to prevent coronary heart disease. Indeed, there is evidence that calcium channel blocking agents and those beta-adrenoreceptor blocking agents with intrinsic sympathomimetic activity are neither effective in the secondary prevention of coronary heart disease nor capable of inducing a withdrawal reaction (5-7). Whatever the mechanism of this effect — which could result most directly from an increase in the number of beta-receptors or from their enhanced sensitivity to circulating catecholamines — it seems that all patients on long-term treatment with beta-adrenoreceptor blocking agents should be advised that it is important to take them regularly and that, should need to withdraw them ever arise, dosage should preferably be tapered off gradually over a period of several weeks (1, 2).

References


**Life after benzodiazepine withdrawal**

**United Kingdom** — The enormity of the scale on which benzodiazepines were used before dependence was first recognized ten years ago as a frequent complication of their long-term use (1, 2) provides one of the most persuasive illustrations of the need for systematic post-marketing evaluation of drug performance. Even now, there is little objective information on the long-range outcome of controlled withdrawal. The recent publication of a five-year follow-up of 41 psychiatric patients who were initially withdrawn from treatment with diazepam between 1980 and 1982 is consequently of particular interest (3).

Most of the patients were originally diagnosed as having generalized anxiety. They were initially treated with daily diazepam, usually in a dose of 10 mg, for an average period of slightly more than three years before a supervised attempt at withdrawal was made using placebo substitution. Five years later, they were interviewed again and their medical records were checked to establish whether they had since received benzodiazepines or other anxiolytic drugs. Disturbingly, in the view of the investigators, and despite widespread publicity about benzodiazepine dependence, three-quarters of the patients had again been supplied with these drugs in the interim. In nearly all cases the prescription had been written by a general practitioner, in some cases only
for insomnia, but more frequently for a recurrence of symptoms of anxiety and stress.

The authors were reassured, none the less, to find that only 14 patients were still taking drugs of this class at the time of interview. Short-term prescription had apparently been successful in many cases and had not induced signs of dependence. They conclude that the continued use of benzodiazepines reflects the absence of satisfactory alternative drugs. Indeed, they accept that "once patients have derived benefit from, or been dependent upon benzodiazepines, other drug and psychological treatments are rarely deemed a satisfactory substitute at times of subsequent stress". This being so, they do not regard previous long-term treatment with these drugs as an absolute contraindication to their further short-term use provided that the risk of dependence is appreciated and that the patient is closely monitored throughout the period of therapy.

It is important, however, that this message should not be misinterpreted to justify any relaxation in the prescribing of benzodiazepines to other patients. Overall, usage of these drugs remains high in the United Kingdom (4). A substantial number of patients still take benzodiazepines for the first time during an admission to hospital, usually simply to satisfy incidental insomnia (5). It seems likely, however, that short-acting preparations — which may be associated with less risk of dependence — are now increasingly preferred for this purpose (4), and that fewer patients than was formerly the case now take home a reserve supply on discharge (5).

Parenteral quinine: an essential drug

United Kingdom — In recent years up to 2000 cases of malaria have been reported annually within the United Kingdom among travellers infected abroad (1) and over the past decade the number of reported cases of *Plasmodium falciparum* infection has increased threefold (2). Seriously-ill patients with falciparum malaria require emergency parenteral treatment with quinine, yet a recent nationwide survey indicated that no injectable formulation was available in the pharmacies of 20 per cent of the acute-care hospitals within the country (3). Some two-fifths of the pharmacies that held stocks had received requests for supplies within the previous two years, and the principal conclusion drawn from the survey is that injectable quinine should be available at all times in the pharmacies of acute-care hospitals. In the face of the relentless advance of chloroquine-resistant falciparum malaria, this advice clearly holds validity everywhere that facilities for intercontinental travel have been developed.

References


Leishmaniasis: prospects of improved treatment

Brazil and India — Visceral leishmaniasis, in which the protozoan parasite replicates throughout the body in the cells of the reticulo-endothelial system remains less amenable to treatment than many other tropical parasitic infections. Pentavalent antimonial drugs, which — after 40 years — remain the mainstay of therapy are toxic compounds and some 15 per cent of cases fail to respond to them (1). In this event, only amphotericin B or pentamidine, which have even greater inherent toxicity, have offered any prospect of cure.

References

Two new approaches to the treatment of the disease, now under investigation, may well ameliorate the situation and will certainly attract further attention. The first reflects the possibility that selective anergy to leishmania antigens, often evident during the acute phase of the disease, may be due to deficiencies in interferon gamma and interleukin-2 (2-4) which are known to promote phagocytosis of protozoa within tissue macrophages (5, 6). If this is so, their administration in pharmacologically-active quantities could well have therapeutic value. Promising responses to a combined parenteral regimen of pentavalent antimony and interferon gamma have already been reported in six of eight patients with visceral leishmaniasis who had been unresponsive to previous courses of pentavalent antimony alone (7).

Doubts have been raised, none the less, as to whether each of the patients had earlier received sufficiently intensive treatment with antimony to identify them as necessarily unresponsive. Moreover, since both the patients who failed to improve subsequently responded satisfactorily to amphotericin B, the latter still holds claim to remain uncontested as the treatment of last resort (8). Despite these uncertainties, and whereas there is no prospect that interferon gamma will become available for the routine management of visceral leishmaniasis in the foreseeable future, these results have focused interest on attempts to stimulate its endogenous production. Indeed, a form of immunotherapy that involves injections of BCG together with heat-killed leishmania organisms is already under investigation in Venezuela (9).

The second initiative, in contrast, raises the possibility that a less toxic alternative to amphotericin B and pentamidine may immediately be to hand. It is reported from India that each of 10 patients with visceral leishmaniasis resistant to a pentavalent antimony salt, subsequently responded excellently to the soluble gold salt, sodium aurothiomalate (10). In each case, a total of 250 mg was administered intramuscularly in doses of 20 mg on alternate days. All patients, it is claimed, were apparently cured without evident toxicity, and all have remained in good health for at least one year after discharge from hospital. The authors offer no suggestion as to how the effect is mediated. They undertook the study on the intuitive assumption that, because gold is selectively deposited in tissue macrophages, it might have therapeutic potential in a disease that primarily affects this population of cells. In a broader context, confirmation of these findings could presage advances in the management of other infections that are contained largely by the immunological competence of the macrophage system.

References
Calcium blockers and diuretics: an additive antihypertensive effect

Calcium channel blocking agents are increasingly used in the management of mild to moderate hypertension, largely as a result of the high incidence of dose-related metabolic and symptomatic adverse effects reported with the longer-established thiazide diuretics and beta-adrenoreceptor blocking agents. However, combination therapy remains necessary in many instances since no single antihypertensive agent induces an adequate blood pressure response in all patients. Calcium channel blocking agents and diuretics can reasonably be expected to exert an additive antihypertensive effect since they have independent and markedly different pharmacological actions. The former act primarily as vasodilators (1, 2), while the latter reduce blood volume as a result of persistent natriuresis (3).

However, attempts to demonstrate such synergism within relatively small studies have not provided consistent results (4, 5). Indeed, some studies have shown that salt restriction reduces the efficacy of calcium antagonists (6, 7) and this has raised the possibility that thiazide diuretics could even antagonise the antihypertensive effects of calcium channel blocking agents. Persuasive evidence that the two types of agent have an additive effect on blood pressure throughout their full response curves has recently been obtained in a factorial analysis of antihypertensive responses to various doses of diltiazem and hydrochlorothiazide administered concurrently for six weeks to patients with uncomplicated mild to moderate hypertension (8).

A questioning attitude needs to be maintained, none the less, as to whether these results can be extrapolated to conditions of routine therapeutic practice. Normally, a second drug is prescribed in antihypertensive therapy only when the response to the first is deemed inadequate. In this case, dose-order effects may well be important. As the authors themselves point out, other studies have failed to demonstrate a further statistically significant fall in blood pressure when, as is often the case, a diuretic is added after a full response has been obtained to a calcium channel blocking agent (9-11). The discrepancies between these various findings are important and point to the need for further, longer-term studies.

References


Thiazides in hypertension: a case of chronic overdosage?

Thiazide diuretics first became established in the treatment of essential hypertension almost 30 years ago (1). More recently, their value has been disputed
with the acceptance that their long-term use has been associated with more adverse effects than was earlier recognized (2, 3). Among the unwanted biochemical responses is a change in lipoprotein metabolism resulting in a rise in cholesterol and apolipoprotein B concentrations (4-6); an impairment of glucose tolerance (6, 7); and a tendency to hypokalaemia (6, 8).

These reactions are dose-related and it has recently been claimed that they can be largely avoided, without compromising the hypotensive response, merely by decreasing dosage (9). Initially, recommended antihypertensive doses of thiazides were determined on the basis of short-term dose-response relationships (1,10). Evidence is now presented that, when the response is assessed after three months of treatment, the full hypotensive effect can be realised at much lower dosage. Within a sample of 257 adult Danish patients with pretreatment mean diastolic blood pressures of 100-120 mm Hg, the therapeutic response to 1.25 mg bendrofluazide daily was not discernibly different at the end of this period from that induced by the generally recommended dosage of 10 mg daily (9). In contrast, the higher dosage was associated with adverse changes in plasma potassium, urate, glucose, total cholesterol and apolipoprotein B concentrations, while only plasma urate concentrations were disturbed at the lower dosage.

References


Isomerism as a determinant of pharmaceutical activity

Evidence that it is the spacial configuration of a molecule as much as its chemical composition that determines its biological activity is not only the basis of pharmacological receptor theory, it is one of the fundamental axioms of the natural sciences. It is this awareness that underlies current scientific interest not only in stereoisomerism but also in polymorphism and the macromolecular arrangement of peptides. Many therapeutically active compounds, and nearly all those of natural origin, are chiral structures containing at least one asymmetric atom — usually a carbon atom — which permits the existence of two optically active, mirror image, enantiomers. Commonly, these have strikingly different therapeutic potencies and occasionally — as in the case of quinine and quinidine — quite different pharmacological properties (1). Interactions between drugs and cellular components, enzymatically-catalysed reactions and active transport systems are thus frequently stereoselective in their behaviour (2-4). Moreover, it is claimed that in some instances, exemplified by thalidomide and benoxaprofen, one enantiomer in a racemic mixture contributes largely to the therapeutic action while the other is responsible for the adverse effects (5).

Clinically important confusion between different isomers has arisen even with relatively simple substances. It has been claimed, for instance, that some preparations of a decongestant product labelled as phenylpropanolamine, or dl-norpseudoephedrine, actually contain another isomer, cathine, or d-norpseudoephedrine, which is considerably more vasoactive (7). It is more difficult to establish the precise stereochemical composition of drugs with more complex chiral structures, including antibiotics such as penicillins and tetracyclines, dopa derivatives, steroids, opiates and — most challenging of all — peptide molecules in which most, if not all the amino acid residues contain an asymmetric carbon atom (8). Not surprisingly, stereochemical problems have frustrated attempts to develop a synthetic polio vaccine. Also, as might be expected, problems have arisen over defining an international standard for low molecular weight heparins, which are currently prepared in five different ways by fractionating naturally occurring heparin. Differences in configuration as well as chemical structure could well account for the wide variations in biological activity that exist between these preparations (9).

Clearly, as far as is possible, any chiral substance that is being screened for biological activity, or that is under development as a drug substance, should be specified in a way that establishes its isometric composition. Concern for this principle has recently resulted in proposals that the stereochemical configuration of every chiral compound should be reflected in its nonproprietary name (10). However, this essential element of knowledge for the research worker is rarely, if ever, relevant to the practising doctor. The vital consideration for the clinician is not a knowledge of stereochemistry and its problems, but an assurance that a medicine labelled with a given active ingredient should be clinically interchangeable with any other preparation labelled in the same way. The responsibility to provide this assurance is shared between official pharmacopoeial commissions, national drug regulatory authorities and national and international drug nomenclature commissions. If different stereoisomers of a substance are registered as medicinal products, they must be presumed to differ in biological activity and they must be identified by different nonproprietary names.
The principles at issue are already reflected in regulatory guidelines issued in Japan, the USA and the member states of the European Community (11). They have also recently been discussed by the Swiss Intercantonal Office for Drug Control (12) which has suggested to pharmaceutical companies — without regulatory intent at present — that a specific section be accorded to a discussion of stereochemical problems in product marketing applications, not only for new drug entities, but also for generic versions of products that contain a chiral substance as an active ingredient. The purpose is to:

- identify centres of asymmetry in the chiral compound;
- establish the relative quantities of different isomers present in the finished product;
- ensure that all developmental clinical studies were undertaken with a preparation of comparable composition;
- provide data on the pharmacodynamics, metabolism and pharmacokinetics of each of the active components of mixtures of isomers and, for pure isomers, to establish tolerances for stereochemical impurities based upon their relative efficacy and toxicity and their potential for accumulation; and
- discuss the clinical implications of these data.

If such a system were to be introduced it would hold particular implications, in the view of the Intercantonal Office, in two circumstances. Firstly, in the case of an application for the approval of a pure isomer of a substance already registered as the racemate, since the pure isomer may differ importantly from the mixture in its pharmacological activities, its potential to interact with other substances, and the way in which it is handled and metabolized within the body. Secondly, in the case of generic versions of chiral preparations, since it is important for any divergencies from the original preparation in the relative proportions of isomers present to be identified and discussed having regard to the clinical implications. Even differences in the release characteristics, it is suggested, may hold clinical implications insofar that the change can sometimes alter the relative bioavailability of the different isomers. When possible, therefore, data on bioavailability should be presented for each of the included isomers separately.

As yet, financial as well as technical considerations preclude the possibility, even within the most affluent countries, of imposing a requirement that each chiral substance in a finished pharmaceutical product should exist as a single pure enantiomer. Such a proposal could not apply, of course, to enantiomers that are unstable either in vivo or within the anticipated shelf-life of the product, nor in the few cases in which two enantiomers exert a beneficial counteractive pharmacological interaction (13). Even if the proposal were practicable, its cost-benefit implications would need to be carefully analysed. It is inevitable, however, that regulatory authorities will become more vigilant in their requirements. The point at issue is that every pharmaceutical manufacturer must command the expertise to ensure that products are not only efficacious, safe and of satisfactory quality, but that they are acceptably interchangeable with other identically labelled preparations currently marketed. Generic competition cannot reasonably be fostered on any other basis.

References


**Orphan drugs: have the aims been met?**

**United States of America** — The appearance of acquired immunodeficiency syndrome (AIDS) has provided an irrefutable demonstration that infectious disease is a moving target that can strike unpredictably with devastating consequence. Less spectacularly, but just as persuasively, the need for constant vigilance is illustrated by the unrelenting emergence of acquired resistance to antimicrobials among pathogenic bacteria and parasites. Analogous problems are now arising in the use of anticancer drugs (1). Sustained effort is required simply to hold the ground already gained and there are many objectives as yet still unsecured.

Given the consequential need for continued pharmaceutical development, how can the innovative effort be directed preferentially — even selectively — to priority needs? Over the past 50 years an unfeathered, but rigorously controlled, research-based pharmaceutical industry has transformed the practice of medicine within virtually every specialty. In doing so, it has enhanced the quality of life for countless patients, and particularly those afflicted with chronic or terminal disease. But, as the readily-realizable objectives are met, the options for further research become more difficult to select. The one immutable consideration in a market economy is that, in the interest of corporate survival, a tangible prospect must always exist for a reasonable return on investment.

In an attempt to reconcile financial incentive with therapeutic need the Orphan Drug Act was introduced in the United States of America in 1983. A drug under development qualifies for orphan status if the population of patients within the United States for whom it is intended numbers 200,000 or less. The designation enables the sponsor to apply for subsidies to support the clinical phases of development, for tax credits and — in the event that the resulting product is ultimately registered — for seven-year marketing exclusivity. These facilities have resulted in the development of many effective drugs that, otherwise, would simply not have materialized. However, they have not necessarily assured their availability at a price that is affordable to the patients who need them. The cost of a year’s supply of zidovudine, for instance, which remains the only anti-retroviral drug approved in the United States for the treatment of AIDS, is in the order of $4000 to $5000 per patient. This is not an isolated case. Other recently-marketed drugs, including aerosolized pentamidine, epoetin alfa, alteplase (TPA) and human growth hormone, bear comparable price tags.

In 1988, the United States Congress reacted by appropriating $30 million to pay for the zidovudine required for indigent patients with AIDS. Additional subventions have subsequently been required. This is but one event that has inspired calls to reform the Orphan Drug Act, possibly by shortening the period of exclusivity when the target population for a drug is estimated to rise above the 200,000 threshold, by permitting market sharing between two or more drugs developed virtually simultaneously and, in the case of anti-AIDS drugs, by imposing price restraints. It has also prompted a request to the Office of Technology Assessment to institute an independent study of the costs of new drug development.

These proposals are resisted by bodies representing research-based pharmaceutical manufacturers on the grounds that such amendments would slow the pace of orphan drug development and that retroactive provisions would unfairly penalize companies currently developing such products. Meanwhile, the pricing controversy remains unresolved. Critics contend that, by helping to shorten the normal timetable of development and by yielding important tax credits, orphan drug status should reduce the costs of bringing a drug to the market and that these savings should be passed on to the consumer. In the admittedly special case of zidovudine, however, the manufacturer claims that the unparalleled concentration of effort required to complete the development process in the shortest practicable time, far from producing economies, committed the company to considerable extraordinary expenditure and
disrupted the development of other products. A detailed independent commentary on the complex issues involved has recently been published from the Center for the Study of Drug Development, Tufts University, Boston (2). This accepts, as a basic tenet of policy, that access to drugs for all who need them should remain an axiomatic objective of national policy. The challenge can be met, it is suggested, only through comprehensive collaborative programmes involving the private sector and government which encourage, rather than discourage, socially-responsive pharmaceutical research and development. First, however, the need exists to "start treating drugs as the remarkable medical advances that they are" and to create a general awareness of the massive contribution that they now offer to contemporary standards of patient care.

References


Drug information for patients: how does it help?

Until a few years ago, the feeling was widely entrenched among doctors that patients would become alarmed or upset if they were provided with information about the adverse effects of their medicines (1). This, it was considered, could well cause a breach of trust sometimes resulting in rejection of medical advice and even in a degradation of the relationship between patient and doctor. This concern has now been dispelled. Many studies have shown that, far from destroying patients' confidence in prescribed medicines, thoughtfully presented information about possible adverse effects can actually increase the degree to which they are accepted (2). There is also now greater appreciation that patients become forgetful with age and that, without written confirmation of the doctor's instructions, misunderstandings over treatment regimens frequently arise (3).

A recent survey undertaken in the United Kingdom has confirmed that, regardless of class, age or educational attainment, patients overwhelmingly favour the provision of practical written information about prescribed medicines (4). This study and many others leave no doubt that access to such information enhances patients' insight into the properties of the medicines they take and the purposes for which they are prescribed. The extent to which it affects therapeutic outcome is less certain (5). It must be presumed to reduce the incidence of avoidable adverse effects and interactions, but there is no assurance that it will promote compliance with instructions in other respects. This is likely to be more dependent upon the quality of the relationship between the patient and the doctor, and the doctor's understanding of the patient's beliefs, concerns and expectations. This being so, well prepared written information is a supplement but never a substitute for good communication between patient and doctor (5).

References


Prescription costs: doctors need more information

United Kingdom — In 1992 the national health service will be changed in a way that places greater budgetary responsibility on the end-providers of medical care. Among the most radical of these changes is a requirement for family doctors to keep their annual prescribing costs below a specified ceiling. Doctors who exceed this limit will be subject to peer review and, in some cases, to sanctions. With the implications of these changes in view, a sample of doctors in Scotland has been questioned to assess their knowledge of the cost of the drugs
they prescribe (1). Their standard of awareness is apparently no higher than that of a similar group of doctors interviewed in neighbouring England several years ago (2, 3). Only one-third of estimates were correct to within 25 per cent of the actual cost. Moreover, real differences were systematically underestimated since cheap drugs tended to be overpriced and expensive drugs underpriced. In many cases doctors were unaware of the relative costs of competing products or of price differentials between proprietary products and equivalent generics.

In a future paper the authors will establish whether doctors with a better perception of costs actually prescribe more efficiently. If, as might reasonably be expected, this is confirmed, the need to provide doctors with more extensive pricing information will be clearly evident. Three-quarters of those who participated in the survey agreed that costs should be taken into account when prescriptions are written. The information that they require can be most readily provided in computerized format. As yet, little more than one-third of general practitioners in Scotland have access to a computer. Plans to introduce a system providing information on the clinical properties of drugs as well as the relative costs of products with comparable therapeutic effects seems likely to induce many more doctors to invest in computer support. If the potential savings in prescribing costs are realized these should rapidly offset the costs of introducing and maintaining the system.

References


Drug supplies in disasters

Union of Soviet Socialist Republics — After every major natural disaster doubts arise about the effectiveness of the relief operations. It is inevitable that, out of urgent commitment to contribute something of value in the immediate aftermath of tragedy, misjudgements will be made about what is needed. Improvement in the international response to these situations is clearly needed and this can derive only from hard experience. Much of value has already been learned in this way and existing guidelines (1-4) now need to be re-examined in the light of a report on the flow of drug supplies to the stricken areas of Armenia following the earthquake of December 1988 in which as many as 60 000 people may have died (5). Prepared jointly by the health authorities of the Soviet Socialist Republic of Armenia, Médecins sans Frontières (Brussels) and the European Association for Health and Development, it should be mandatory reading for everyone involved in emergency relief operations.

Over two days passed before international aid was mobilized. During this time Armenian medical teams had to rely exclusively on locally-available drugs. Stocks of vital items were rapidly depleted, with the consequence that injectable analgesics, first-line antibiotics, anaesthetic agents, intravenous fluids, syringes and needles, and equipment for handling and transporting the injured were lacking in many places.

Subsequently, unprecedented quantities of goods arrived at Yerevan airport. Up to 150 landings a day were registered. Most drugs arrived unaccompanied and boxes were simply dropped on the airstrip. Transport, storage and handling capacity was rapidly overwhelmed. Despite advice — which was immediately transmitted to the international community — that the stricken area was inhabited by only 700 000 people, at least 5 000 tons of drugs and medical supplies were ultimately received. Fifty people worked for six months merely to gain a clear picture of what had been sent.

Only one-third of the drugs received were sorted and relevant to immediate needs. In many instances, however, these were not easily identifiable since they were labelled only with brand names. To add to the confusion many of the remaining drugs were inappropriate and, overall, more than a quarter were either already past or within one year of their expiry date. Inevitably, many valuable intravenous fluids and injectable agents were lost as a result of exposure to freezing temperatures.

In their conclusions, the authors of the report enumerate a series of factors critical to the efficient delivery of emergency relief. In particular they point to the need to:

- discourage the collection of unsorted medicines and to avoid the supply of unsold surpluses;
• ensure that medicines are identified in a widely-used language, by their international nonproprietary name and also by their expiry date;

• arrange for international donations to be accompanied by someone who will care for the shipment up to the place of storage or use;

• provide transportable warehouses and handling equipment to reinforce local facilities;

• package drugs intended for use during the immediate emergency period in small boxes that can be transported by car and lifted by no more than two people.

Much time and energy, it is pointed out, can be wasted on the ground in an attempt to arrange the provisional storage of medicines systematically. Instead, a drug management centre should be created to register the arrival and destination of all sorted medicines and to inform users of their existence and location. For each warehouse, a plan should be prepared indicating where specific drugs are located and identification stickers in the local language should be placed on each box. The drug management centre should prepare notices explaining the use of valuable products that are unfamiliar locally. Much clearly depends upon the availability of trained teams, including pharmacists, that are constantly maintained in a state of disaster relief preparedness.

References


Regulatory Matters

Adenosine deaminase: replacement therapy

United States of America — A preparation of the enzyme, adenosine deaminase, coated with the polymer polyethylene glycol has been approved by the Food and Drug Administration for the treatment of the rare genetic disorder, severe combined immunodeficiency syndrome. Hitherto, the afflicted children who lack this enzyme have usually died from infection before they are two years old unless bone marrow from a closely matched donor could be transplanted.

The product, which is the first "orphan drug" to have been developed on trials directly supported by the FDA, needs to be administered weekly throughout the patient's life. It has markedly reduced the incidence of infections among the few children who have already been treated for six months or more and, as yet, no significant adverse effects have been reported.


Analgesic combinations: toward a more rational market

Malaysia — The Drug Control Authority has announced that analgesic combinations will no longer be registered unless a rational basis for the formulation is provided. Among the types of product already rejected are those containing two or more active components having the same mode of action and products containing either caffeine or vitamins as supplementary ingredients. Caffeine is disfavoured because its stimulant effect may in part determine the extent to which these products are abused. Vitamins are disallowed because supplements are required only for the treatment and prevention of specific deficiency states and because no circumstances have been defined in which small quantities taken sporadically are known to be beneficial.

An immediate ban has been imposed on the importation and manufacture of these products and existing stocks must be withdrawn from the market by the end of 1990.

Source: Communication to the World Health Organization, 28 February 1990.

BCG instillation in bladder cancer

United States of America — The Food and Drug administration has approved a live BCG preparation intended for vesicular instillation in the treatment of stage 1 bladder carcinoma, or carcinoma-in-situ. Instillations are repeated weekly for 6 weeks and then monthly for 6 to 12 months. An inflammatory response is elicited which eliminates many of the neoplastic cells. In controlled multicentre studies sponsored by the National Cancer Institute a significant remission was obtained in almost three-quarters of the cases, and the median time for recurrence was about 4 years. Adverse effects reported thus far are largely a consequence of the local inflammatory effect. In a few cases, however, two of which were fatal, generalized dissemination of the BCG organism has occurred. Doctors are advised of the need for close observation of patients throughout the period of therapy and for prompt institution of antituberculosis therapy should need arise.


Combination products: guidelines for registration applications

Switzerland — The Intercantonal Office for Control of Medicines has issued revised guidelines on the principles that it applies to the registration of combination products. Not only must each of the active ingredients be justified in terms of their contribution to the therapeutic effect and the selected dosages be suited to the intended use of the product, but the proposed combination must also hold advantage over separate administration of the individual components.

In addition to the necessary pharmaceutical
specification, applications for registration of combination products containing one or more novel ingredients should contain data on the pharmacological and toxicological profile of these ingredients as well as of the proposed combination. When each of the ingredients is already registered, only clinical evidence of the efficacy of the combination is normally required.

Applications will generally be rejected for products deemed to be irrational on the following grounds:

• one of the ingredients has a narrow therapeutic index and its dosage consequently needs to be carefully titrated to individual requirements.

• the active ingredients have markedly different serum half-lives and durations of action.

• two or more ingredients are drawn from the same pharmacoechemical class of compounds with the result that their effects are no more than additive yet the potential for adverse effects is liable to be increased.


Cytomegalovirus immune globulin

United States of America — The Food and Drug Administration has approved a new immune globulin derived from human plasma for protecting renal transplant patients from infection with cytomegalovirus. This virus, which is widespread and normally harmless, is a frequent cause of severe disseminated infection when it is carried via a donated kidney to an immune-suppressed recipient with no protective antibodies. It is anticipated that the product will benefit a large number of patients who require renal transplants since well-matched organs are generally difficult to find and kidneys are commonly infected with the virus.

A controlled trial and an open study have both shown that the immune globulin, when administered immediately before and for some time after transplantation, can dramatically reduce the incidence of severe cytomegalovirus infection. A few patients have complained of transient chills, flushing, muscle cramps, back pain, nausea, vomiting and wheezing, but no serious adverse effects have yet been identified and the only labelled contraindication is hypersensitivity to immunoglobulin A.


Disintegration specifications for tablet formulations

Canada — The Ministry of Health has issued regulations requiring that all tablet forms of pharmaceutical products that are intended to be swallowed whole comply with the following disintegration times:

• uncoated tablets: not more than 45 minutes.

• plain coated tablets: not more than 60 minutes.

• enteric coated tablets: not more than 60 minutes when exposed continuously to simulated gastric fluid.

The regulation does not apply to extended release formulations, or to those products which have been demonstrated by other means to be adequately bioavailable.

Source: Food and Drug Regulations C.01.015 as amended 21 September 1989.

Epoetin alfa approved for zidovudine-induced anaemia

United States of America — The Blood Products Advisory Committee of the Food and Drug Administration has recommended that the approved indications for epoetin alfa (erythropoietin) be extended to include treatment of severe zidovudine-induced anaemia in patients with AIDS. It was previously approved in June 1989 for the treatment of anaemia associated with chronic renal failure.


Fenoterol: safety in severe asthma questioned again

Australia — In recommending that the beta-adrenoreceptor agonist, fenoterol, be indicated exclusively for the treatment of mild to moderate asthma, the Australian Drug Evaluation Committee has followed the precedent established in New
Zealand where recently generated data were interpreted as indicating that the risk of death is increased when fenoterol is used during a severe exacerbation of asthma [see *WHO Drug Information*, 4: 24 (1990)].

**Source:** Communication to the World Health Organization from the Therapeutic Goods Administration, Department of Community Services and Health, 27 March 1990.

**Ibuprofen: exacerbation of renal disease**

**United States of America** — The Food and Drug Administration has asked manufacturers or companies marketing nonprescription forms of the nonsteroidal anti-inflammatory drug, ibuprofen, to highlight the currently required cautionary labelling (1). Patients are urged to consult a doctor should they develop any unusual or unexpected symptoms while using the product and to take it only on medical advice should they be under care for any serious condition. Concern has arisen because ibuprofen taken in prescription dosages of 800 mg three times daily for less than two weeks can transiently exacerbate renal dysfunction in patients with pre-existing mild kidney disease (2).

**References**


**Liquid paraffin: further restrictions**

**United Kingdom** — In several countries, sale of laxative preparations containing liquid paraffin have been restricted in recent years. Initially, concerns arose because cases of lipoid pneumonitis resulting in permanent granulomatous fibrosis were reported among small children and patients with debilitating neurological conditions who had accidentally inhaled the product. More recently, habitual use has been shown to induce similar changes in the intestinal wall and, more diffusely, in the reticuloendothelial system.

The Committee on Safety of Medicines has consequently decided that additional restrictive measures now need to be applied to the sale of these products. It has recommended that these should include:

- limitation of the pack size to 160 ml (one week's supply at the maximum recommended dose);
- restriction of the indications exclusively to symptomatic relief of constipation;
- contraindication of usage in children under 3 years of age;
- provision of warnings regarding the dangers of prolonged use coupled with explicit labelled instructions advising patients that repeated use is not recommended; and
- advice that a doctor must be consulted if laxatives are needed every day, or if the user has persistent abdominal pain or a condition which makes swallowing difficult.

**Methylene blue: an antidote reappraised**

**Federal Republic of Germany** — Methylene blue (methylthioninium chloride) is still sometimes used as an antidote in carbon monoxide poisoning. In the view of the Federal Health Office it is now unsuitable for this purpose, having regard to the availability of other treatments, since it exacerbates pre-existing haemolysis.

It has also been proposed as an antidote in cases of cyanide poisoning. In normal circumstances, it favours the conversion of haemoglobin into methaemoglobin which binds strongly to cyanide. However, the reaction attains equilibrium when only 8 per cent of the available haemoglobin is converted and this is too little to assure adequate capture of cyanide. The Federal Health Office has consequently advised that p-dimethylaminophenol, which converts up to 50 per cent of the available haemoglobin to methaemoglobin within a few minutes, should now be preferred for this purpose.
Paradoxically, methylene blue remains of value in the treatment of the severe methaemoglobinaemia induced by aniline and other poisons. In these circumstances, it drives the haemoglobin/methaemoglobin reaction in the converse sense toward the 8 per cent equilibrium point.


Phenolic throat sprays and oedema of the larynx

United Kingdom — The Committee on Safety of Medicines has recently received 4 reports of epiglottal or laryngeal oedema resulting from the use of a throat spray containing 1.4 per cent phenol. One of the patients died and 2 others required emergency hospital treatment.

The product, which is available over-the-counter, is indicated for the symptomatic relief of sore throat, mucosal trauma following dental surgery, and halitosis resulting from oral infections. Since sales estimates suggest that as many as 2 million bottles are sold annually, such reactions are extremely uncommon. The Committee has requested doctors to notify it of any such cases that come to their notice. Meanwhile, the labelled contraindications to the use of the product have been extended to include all children under 6 years of age; patients who have difficulty in breathing or swallowing; and those with severe sore throat that has lasted for more than 2 days or that is accompanied by high fever, nausea or vomiting.


Triazolam and amnesia

United States of America — On the advice of its Psychopharmacological Drugs Advisory Committee the Food and Drug Administration has decided that the approved product information for sedative products containing the benzodiazepine substance, triazolam, should be amended to place greater emphasis on their propensity to cause amnesia. The Committee noted that, although reporting rates for certain other adverse psychological and behavioural effects including anxiety, insomnia and hallucinato-

tions are higher than those associated with other benzodiazepines, it is not clear whether this reflects a real augmentation in the incidence of these types of reactions.


Trimethoprim-sulfamethoxazole: risks in the elderly

Australia — The Drug Reaction Committee has recommended that product information for all formulations of trimethoprim-sulfamethoxazole should contain a warning of the increased risk of adverse effects of treatment in elderly patients and discourage their use in this age group. Age-adjusted numbers of serious reactions have shown that this trend is particularly evident for blood disorders and adverse renal and hepatic reactions in patients over 60 years of age. Blood dyscrasias, in particular, appear to be some twelvefold more frequent among patients over 80 on the basis of this evidence than in young adult populations.


L-tryptophan and eosinophilia-myalgia syndrome: an update

United States of America — The Food and Drug Administration has announced that ongoing epidemiological investigations indicate that almost all the 1500 cases of eosinophilia-myalgia syndrome notified in the USA over the past year have occurred in patients who had consumed products containing L-tryptophan manufactured by a single Japanese company (1). This suggests that a toxic impurity may be implicated. However, this hypothesis provides no explanation for the few cases attributed to the products of other manufacturers, or for the small number of cases described in the literature before the current epidemic became apparent (2-4). Because of these uncertainties, and because the manufacturer of the suspect material was a supplier to several other companies, the FDA has decided that its recall of all L-tryptophan supplements remains warranted and that the warnings regarding their use issued in November 1989 should remain in effect.
In addition to the cases notified in the USA, 60 have been reported in the Federal Republic of Germany and isolated cases have also been described in France, Switzerland and the United Kingdom (5, 6). In most instances the typical features of the disease — fatigue, generalized muscular pain and weakness associated with perivascular inflammatory infiltrations, oedematous and urticarial skin lesions, mouth ulcers, eosinophilia and extracellular deposition of eosinophil-derived protein (7, 8) — have resolved rapidly following withdrawal of L-tryptophan supplements. However, it has been estimated that in as many as one-third of the cases the disease enters a chronic phase in which scleroderma-like skin changes, myocarditis, pulmonary infiltration, pleural exudates and potentially fatal ascending polyneuropathy (9) have been described. Parallels have been drawn between this condition and the toxic oil syndrome which became epidemic in Spain in 1981 (2, 6, 10). In all, 21 deaths have been reported thus far. High doses of corticosteroids have been administered to some of the more seriously ill patients but, although this results in a rapid reduction in the number of circulating eosinophils, the value of such treatment remains uncertain (5-8).

References


Xamoterol: yet more restrictions

United Kingdom — The Committee on Safety of Medicines has advised that xamoterol, a newly-introduced partial agonist at beta, receptors, should be prescribed exclusively for the management of chronic mild heart failure (1). Treatment should be started, in the Committee's view, only in a hospital setting after the severity of the condition has been established through a full clinical assessment, including an exercise test. It is recommended that the starting dosage should be 200 mg daily, and that this may be increased to a maximum of 200 mg twice daily after one week provided that no adverse effects are detected. Should any deterioration of cardiac function occur, treatment must be withdrawn immediately. These recommendations are already reflected in the revised product labelling which includes a detailed statement of contraindications that relate to moderate or severe heart failure, asthma, or renal impairment sufficient to cause accumulation of the drug.

In low concentrations xamoterol stimulates beta, receptors, whereas in high concentrations it blocks both beta, and beta, receptors. It shares this pattern of activity with some of the early beta-adrenoceptor blocking agents, such as oxprenolol and pindolol (2, 3) and it has been suggested that much misunderstanding might have been avoided if this had been made clear when the drug was launched (4). When sympathetic tone is low it increases the rate and force of contraction but, as heart failure worsens, it attenuates the high resting sympathetic drive required to maintain cardiac output (5, 6).

A recent commentary in the Drug and Therapeutics Bulletin (4) concludes that xamoterol holds no advantage over more conventional therapies for mild heart failure, such as diuretics, digoxin and nitrates, and that it is a difficult drug to use safely. Not only is a thorough evaluation of the patient necessary before treatment is started, but regular monitoring is
subsequently needed to ensure that, as the underlying disease progresses, the treatment regimen will be changed before continued reliance on xamoterol becomes hazardous. These concerns will have been intensified by subsequent publication of a trial in which mortality within 100 days of enrolment was over 9 per cent among 352 patients randomly allocated to xamoterol yet only 3.7 per cent among the 164 patients who received placebo (7). It would be unreasonable to place undue emphasis on these results at this stage since the trial was not designed to assess mortality. Detailed information on the causes of death are not available, and the cumulative results of other trials are claimed to indicate that treatment is associated with reduced mortality (8). None the less, the outcome creates a mandatory requirement for further searching evaluations of the drug with a view to defining circumstances, if such exist, in which it holds tangible advantage over alternative treatments.

References

Advisory Notices

Aluminium content of parenteral drug products

The Food and Drug Administration is soliciting comments on proposed limits for the aluminium content of parenteral drug products intended either for repeated use or for infusion in large volumes over a short period of time (1). Three specific groups of patients are considered to be at particular risk of toxicity from these products:

- Patients with renal failure treated by haemodialysis and chronic ambulatory peritoneal dialysis who are at risk of developing aluminium-related osteodystrophy and encephalopathy (2, 3). The risk has been substantially decreased by reducing the aluminium content of the dialysis water and restricting the use of aluminium compounds used as phosphate binders (4).

- Patients requiring long-term parenteral nutrition (5). However, the relationship between the associated bone diseases and aluminium deposition remains controversial (6).

- Premature infants receiving fluids parenterally who are susceptible to aluminium loading because of their reduced renal capacity, their relatively high fluid requirements, and their greater need for calcium and phosphate. Parenteral solutions containing the latter substances are particularly likely to be contaminated with aluminium.

With a view to limiting the total daily parenteral aluminium intake for adults to less than 100 micrograms, the FDA may impose an upper limit of 25 micrograms per litre for large volume parenterals, although it recognizes that greater latitude may need to be accorded to some types of dialysis fluids and some antibiotic solutions. It has also noted that the maximum safe intake of parenteral aluminium in neonates and patients with renal impairment has yet to be established and it is calling for relevant data.

Small volume parenterals, the agency considers, will be best controlled by a mandatory declaration of the total aluminium content on the immediate label. It is proposed to apply this requirement to solutions intended for use in — or commonly used in — the preparation of total parenteral nutrition solutions and to all regularly-used additives including vitamins, minerals and trace elements, which commonly constitute the major source of aluminium in the administered preparation. A need to standardize the units of measurement of aluminium content is recognized in order to avoid confusion and errors, and the agency is requesting comments on how these should be selected.

References


Antibiotic prophylaxis of infective endocarditis

United Kingdom — The endocarditis working party of the British Society for Antimicrobial Chemotherapy has recently reviewed and amended its guidelines for the antibiotic prophylaxis of infective endocarditis (1-3).
Previously, the group had recommended that adults who are at risk for endocarditis, are allergic to penicillins, or are not to have a general anaesthetic, should be given 1.5 g erythromycin stearate orally, under supervision 1 to 2 hours before a dental procedure followed by 0.5 g 6 hours later. Since it has been found that the 1.5 g dose sometimes induces nausea, the group has decided to follow advice issued in Switzerland in 1984 which proposes the use of clindamycin in a single dose of 600 mg 1 hour before the procedure (4). A review of all available adverse reaction reports in the United Kingdom and the United States of America has not revealed a single instance of serious sequelae following such a dose. None the less, the group has requested information from dentists and doctors on any unwanted effects that they may encounter.

Two other substantive amendments are made. Firstly, dentists are advised to apply an antiseptic such as 0.2 per cent chlorhexidine to the gingival margins of susceptible patients before treatment to reduce the severity of any resulting bacteraemia. Secondly, the group reiterates the importance of long-term prophylaxis for patients with a damaged or deficient endocardium as a consequence of acquired or congenital disease. In doing so, however, it acknowledges recent evidence that, in the relatively common condition of mitral leaflet prolapse, patients are at increased risk of infective endocarditis only when there is an associated systolic murmur (5).

References

**Beta blockers: is there true cardioselectivity?**

**United Kingdom** — The Committee on Safety of Medicines has advised doctors that episodes of bronchospasm appear to be reported as frequently in association with cardioselective beta-adrenoreceptor blocking agents as with the nonselective congener. In all, the Committee has received 747 such reports, 34 of which were fatal. Of these, 66 cases, including three of the fatalities, occurred following the use of eyedrop formulations.

Whereas it is probable that patients most at risk of bronchospasm were among those who received the cardioselective agents, the use of these drugs in this population of patients is clearly attended by appreciable hazard. The Committee consequently recommends that no beta adrenoreceptor blocking agent should be prescribed for patients with reversible obstructive airways disease unless there are compelling reasons to use them. This warning applies to all products containing these substances, either as single components or in combination, and to eyedrops as well as orally-administered dosage forms.


**Biperiden: dependence liability**

**Japan** — The Pharmaceutical Affairs Bureau has recently received two reports of suspected dependence upon the antiparkinsonism drug, biperiden. Both patients described a feeling of elevated mood when taking the drug and similar cases have been reported in other countries.

This apparent hazard is now cited in the product information and doctors have been advised to use the drug with discretion and to monitor treated patients closely.


**Bronchodilator drugs and hypokalaemia**

**United Kingdom** — Drugs used in the treatment of asthma including the xanthine derivatives, theo-
Phylline and aminophylline, as well as salbutamol and other selective beta₂ adrenoreceptor agonists have long been recognized to induce hypokalaemia. Over the years, the Committee on Safety of Medicines has received 26 such reports, 9 of which relate to patients who were receiving both types of drugs. The latter tended to be relatively severe and included 2 patients who developed cardio-respiratory arrest.

The Committee has consequently advised doctors that, whenever possible, plasma potassium concentrations should be monitored when patients with severe asthma are treated with beta₂ adrenoreceptor agonists and that hypokalaemia may be potentiated in these circumstances by hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics.


Carbamazepine: stability problems

United States of America — The Food and Drug Administration has announced that findings to be published shortly show that tablets of the anticonvulsant compound, carbamazepine, readily lose as much as one-third of their activity when they are stored in a humid environment. At the same time the tablets become harder in consistency, and dissolution is impaired. This, it is suggested, may account for complaints that "breakthrough" seizures have occurred as a result of apparent variation in potency between different preparations. Manufacturers have been asked to ensure that these products are distributed in moisture-resistant packaging and doctors have been asked to advise patients to ensure that their tablets are stored in a cool, dry place.


Citiolone: hypersensitivity reactions

Spain — The National Committee on Drug Monitoring has reported that it has received 30 notifications of adverse events associated with the use of preparations containing the mucolytic agent, citiolone, either alone or in combination with antibiotics and other substances. The most severe of these were 6 hypersensitivity reactions, including bronchospasm, periorbital oedema and angio-oedema. Of these, 4 patients required admission to hospital for emergency treatment.

The Committee points to the important possibility that, since mucolytics are often taken concurrently with antibiotics, hypersensitivity to citiolone can readily be incorrectly ascribed to antibiotic allergy.


Flucloxacillin and hepatitis

Australia — Over the past decade the Drug Reactions Advisory Committee has received an average of two to three reports each year of hepatitis in patients receiving flucloxacillin. During the first eight months of 1989, however, a cluster of 9 reports was received. Clinically, the illness usually presented with deep jaundice, pruritus, dark urine, pale stools, elevated alkaline phosphatase and aminotransferase concentrations. Serum bilirubin concentrations were in some cases extremely high — over thirtyfold greater than the upper limits of the normal range.

In all, 17 cases of this distinctive pattern of mixed cholestatic/hepatocellular jaundice have been notified. The reactions usually became apparent a few weeks after the patient's first exposure to flucloxacillin and in some cases the course of the treatment had been terminated up to three weeks earlier. Thus far, 9 of the patients are regarded as completely recovered, but in others hepatic function has not returned to normal over periods ranging up to 8 months.

Doctors have been alerted to the apparent association of this condition with flucloxacillin, and they have been asked to report any cases they may encounter to the Committee.

References

**HIV-2 screening test**

**United States of America** — The Blood Products Advisory Committee of the Food and Drug Administration has advised that blood donations collected within the USA need not be routinely screened for HIV-2, a rare cause of the AIDS syndrome, because there is no evidence that this virus currently represents a risk to blood supplies in the USA. An enzyme-linked immunosorbent assay for detecting antibodies to the virus has recently been approved by the FDA.


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**Isotretinoin: yet more rigorous labelling proposed**

**United States of America** — The Dermatologic Drugs Advisory Committee to the Food and Drug Administration has received information to indicate that the package of measures devised by the manufacturer to warn women of the danger of becoming pregnant during and following treatment with isotretinoin (Accutane®: Hoffmann-La Roche) is largely effective. Whereas the use of this product, which is indicated for severe cystic acne, resulted in a disturbing number of serious birth defects in 1986 and 1987, only one such case had been notified in the first five months of 1990.

The measures include selling the product in blister packs that feature warnings and pictures of typical malformations; requiring signed and informed parental consent to treatment; stating on the label that the drug should be prescribed only after pregnancy has been positively excluded by biochemical testing; reimbursing the patient for a gynaecological consultation; providing clinicians with additional educational material, and undertaking to study the effects of these requirements by epidemiological means.

Notwithstanding the apparent success of these measures, the Committee has recommended that the following supplementary precautions be instituted:

- more emphasis be placed on the need for informed consent and the form for signature be provided in several languages;
- professional counselling on avoidance of pregnancy be made available to patients in need of advice;
- a system be devised by the manufacturer to ensure that patients return all surplus supplies of the product so that residues cannot subsequently be taken without the necessary supervision.

The FDA has yet to announce the actions that it proposes to take in the light of this advice.


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**Imipenem and cilastatin: CNS disturbances**

**Japan** — More than two-thirds of 30 adverse reaction reports submitted to the Pharmaceutical Affairs Bureau that refer to a product containing the antibiotics imipenem and cilastatin in combination cite it as a possible cause of convulsions. Several of the remaining reports also allude to central nervous disturbances, including tremor, delirium and hallucinations. The apparent risk seems to be greatest among patients with pre-existing central nervous lesions or with renal impairment. The Agency has requested doctors to report any such events that come to their notice and it has advised them that when need arises to prescribe the product for patients at particular risk, it should be administered in reduced dosage.

**Source:** Ministry of Health and Welfare. *Information on Adverse Reactions to Drugs*, No.99 (1989).

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**Loperamide: voluntary withdrawal of infant formulations**

As was reported in the previous issue of WHO Drug Information, 18 infants with paralytic ileus attributed to the use of a paediatric drop preparation of the antimotility agent, loperamide, were admitted within a span of two months to the same medical service in a hospital in Pakistan. Six of the children subsequently died.
The leading international supplier of this preparation, Johnson and Johnson, has since informed WHO that having regard to the dangers inherent in improper use and overdosing, this formulation (Imodium Drops®), was voluntarily withdrawn from Pakistan in March 1990. The company has since decided not only to withdraw this preparation worldwide but also to remove all syrup formulations from countries where WHO has a programme for control of diarrhoeal diseases. This action has been taken on the grounds that, although the syrup is only one-tenth as potent as the drops, the risk of overdosing cannot be excluded in countries where illiteracy and lack of medical supervision could result in misuse in infants. The company will continue to market tablets and capsules of loperamide, as well as the syrup formulation, in other countries.

Source: Letter from Messrs Johnson and Johnson, New Jersey, USA, dated 21 June 1990.

Metoclopramide: the need always to weigh hazards and benefits

Australia and Federal Republic of Germany — It has long been recognized that the antidopaminergic antiemetic agent, metoclopramide, is occasionally associated both with extrapyramidal reactions and with the malignant neuroleptic syndrome. Because such cases continue to be reported, sometimes in patients with self-limiting gastrointestinal disorders that do not merit antiemetic therapy, two national regulatory authorities have recently reissued cautionary advice to doctors.

An advisory committee to the Australian authorities, in expressing concern about the numbers of patients that still develop extrapyramidal signs, emphasized that the reaction is dose dependent and that the daily intake of metoclopramide should never exceed 0.5 mg/kg, particularly in children and young adults. In almost two-thirds of the 128 cases reviewed by the committee the daily dosage had been either the maximum recommended or in excess.

The Federal Health Office of the Federal Republic of Germany has further reminded doctors that extrapyramidal disturbances are sometimes the premonitory signs of malignant neuroleptic syndrome. This is a potentially fatal condition in which the prodromal neurological disturbance is accompanied by a severe constitutional disturbance characterized by pyrexia, rapid breathing, tachycardia, salivation, sweating and impairment of consciousness. Hyperpyrexia, rigors, and disturbances of autonomic function supervene in the terminal phases of the most severe cases.

Both authorities emphasize that metoclopramide should never be prescribed unless a clear indication for its use has been established, and that patients should be kept under close supervision in order that treatment can be withdrawn, if necessary, at the earliest opportunity.

Sources


Pirprofen: withdrawal following hepatotoxic reactions

Ciba-Geigy has announced that it has withdrawn from sale worldwide all formulations of the non-steroidal anti-inflammatory agent, pirprofen, having regard to reported adverse reactions including gastrointestinal lesions and cases of fulminant hepatitis, some of which have been fatal. The dosage recommendations were previously amended in 1989 in an attempt to reduce the incidence of these reactions which were considered to be associated with high doses and prolonged use of the drug. Since this time, the labelled indications have been limited to short-term treatment of acute pain attributable to rheumatic conditions. The company considers that, having regard to its limited indications, the product can no longer compete effectively with other marketed anti-inflammatory products.

Source: Communication from Ciba-Geigy dated 13 March 1990.
Essential Drugs

ATYPICAL MYCOBACTERIA

Nontuberculous mycobacteria are ubiquitous in the environment. They exist in food, soil, water, on the surface of many plants, and in buildings, particularly within water pipes. For many years they were thought to be implicated in human disease only as saprophytic contaminants in tuberculous lesions. Now, several species are recognized to be facultative parasites capable of causing chronic granulomatous diseases that can be pathologically indistinguishable from tuberculosis.

These infections are not readily identified because the causative bacteria can be distinguished from M. tuberculosis only in specialized reference laboratories. However, they have latterly attracted attention for two reasons. Firstly, wherever tuberculosis has declined within the population at large they now account for a greater proportion of cases of granulomatous disease. Secondly, like tuberculosis, they have emerged as common secondary infections among patients with acquired immunodeficiency syndrome (AIDS).

Most localized infections result from inoculation of organisms into the skin. Pulmonary infection usually occurs only in patients with predisposing disease, while disseminated infection is confined almost exclusively to patients with impaired immune responses. Thus far, there is no evidence of case-to-case transmission.

Clinically, four types of disease are described.

Localized cutaneous lesions

Inoculation of organisms into superficial abrasions and into puncture wounds can result in the formation of localized nodular or ulcerative lesions. The organisms most commonly implicated are M. marinum, which colonizes swimming pools and fish aquaria, and M. ulcerans which is largely restricted to Australia and some tropical regions and causes deep necrotic lesions known as Buruli ulcers. M. haemophilum has more recently been associated with similar lesions in immunosuppressed patients. Abscesses resulting from contaminated injections have most frequently been attributed to two rapidly growing species, M. chelonae and M. fortuitum. More such cases are to be anticipated among drug addicts who are immunosuppressed as a result of AIDS but, as yet, most have occurred either among diabetics or as a result of injecting contaminated drugs and vaccines.

Pulmonary disease

The lung is the most frequent site of opportunistic mycobacterial infection and lesions are clinically and radiologically indistinguishable from pulmonary tuberculosis. Predisposing conditions include chronic bronchitis, occupational dust diseases, residual tuberculous lesions, cystic fibrosis, carcinoma, AIDS and other conditions resulting in immunosuppression. Most recorded cases have been attributed to M. avium-intracellulare, M. kansasii and, to a lesser extent, M. xenopi but in some regions M. scrofulaceum, M. chelonae, M. szulgai and M. malmoense are also of significance.

Lymphadenitis

The lesions are usually unilateral and self-limiting and most cases occur in children under five. However, lymphadenitis is also sometimes a prominent feature of disseminated disease in adults. Most reported cases have been attributed to the closely-related species M. avium-intracellulare and M. scrofulaceum (known as the MAIS complex). Any of the organisms implicated in pulmonary disease can also cause lymphadenitis and the other forms of non-pulmonary disease which are more commonly associated with M. tuberculosis.

Disseminated disease

Single or multiple foci of granulomatous disease can occur in virtually any system or organ and, when cellular immunity is depressed, dissemination of the infection can occur as rapidly as in miliary tuberculosis. The majority of such cases have been attributed to M. avium-intracellulare and to M. chelonae.

Management

Diagnosis is dependent upon the clinical characteristics of the disease and identification of the causative organism, when this is possible. Whereas all mycobacterial infections are presumed to give rise
to a positive tuberculin test, conversion usually results from previous infection with *M. tuberculosis* and is thus of little practical help in the diagnosis of nontuberculous infections.

It is not known to what extent the BCG group of vaccines protect against infection by any of the nontuberculous mycobacteria and as yet, no specific vaccines have been developed. The management of established infection is determined by the anatomical focus of the disease, the identity of the organism, the age of the patient, and the competence of the immune system.

**General principles**

Deep and widely disseminated infections can only be treated by chemotherapy. However, even when treatment is prolonged, the response is uncertain, and surgical resection — now rarely employed in tuberculosis — remains of value in localized nontuberculous pulmonary disease. Surgical excision is also frequently used to hasten resolution of localized lymphadenopathy and of solitary skin lesions, even though these lesions are likely to be self-limiting.

The isolation of nontuberculous mycobacteria from biopsy of a chronic granulomatous lesion generally provides evidence of a causal association. However, the identification of these ubiquitous facultative parasites in sputum or urine requires guarded interpretation. Only when tuberculosis has been rigorously excluded and positive cultures consistently obtained over a period of several weeks should the patient be committed to the prolonged, costly and sometimes hazardous courses of chemotherapy required. Whenever possible, the identity of the causative organism and its sensitivity to candidate antibiotics should be established within a specialized reference laboratory. None the less, in *vivo* sensitivity tests can be misleading and treatment may need to be determined empirically on the basis of published case reports and retrospective surveys.

**Selection of chemotherapeutic agents**

Most experience has been gained in the treatment of localized pulmonary disease caused by the more prevalent, relatively slow-growing mycobacteria *M. kansasii*, *M. xenopi*, *M. malmoense* and *M. avium-intracellulare* in immunocompetent hosts. Ultimately, they are usually responsive to standard antituberculosis chemotherapy — even though *M. avium-intracellulare* can be relatively resistant *in vitro*. However, it is often necessary to administer a combination of rifampicin, ethambutol and isoniazid for at least 18 to 24 months.

Several other antibiotics that are not normally used to treat tuberculosis have been claimed to be of value. These include erythromycin in infections due to *M. kansasii*, *M. scrofulaceum* and *M. avium-intracellulare*, and the combination of sulfamethoxazole and trimethoprim in infections attributed to *M. avium-intracellulare*, *M. chelonae*, *M. marinum* and *M. xenopi*. Reports also exist of *M. chelonae* and *M. xenopi* infections responding to a combination of amikacin and doxycycline, and of *M. marinum* infections responding to minocycline. However, the evidence supporting the use of these drugs is largely anecdotal, and firm recommendations cannot be made.

Clofazimine, which is concentrated in epithelial tissues, the bone marrow and the reticulo-endothelial system, is claimed to be of particular value in the suppression of disseminated disease due to *M. avium-intracellulare*. It has also been advocated in combination with rifamycin in the management of opportunist infections in patients with AIDS, but insufficient information is currently available to determine whether this regimen has significant effect on morbidity and survival time.

**RIFAMPICIN**

*capsule or tablet 150 mg, 300 mg*

A semisynthetic derivative of rifamycin, a complex macrocyclic antibiotic which inhibits nucleic acid synthesis in a broad range of microbial pathogens. Rifampicin is lipid soluble. Following oral administration, it is rapidly absorbed and distributed throughout the cellular tissues and all body fluids, including 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 decays with a half-life of 2–3 hours. It is extensively recycled in the enterohepatic circulation, and metabolites formed by deacetylation in the liver are eventually excreted in the faeces.

**Uses**

In combination with ethambutol and isoniazid in the treatment of infections due to *M. kansasii*, *M. mal-
moense, M. xenopi and M. avium-intracellulare in immunocompetent hosts.

**Dosage and administration**

Rifampicin should preferably be taken at least 30 minutes before meals, since food impairs its absorption.

**Adults and children**

10 mg/kg (maximum 600 mg) daily or 2 or 3 times weekly for 24 months. There is some evidence to suggest that *M. kansasii* infections require treatment for only 12 months.

**Contraindications**

- Hypersensitivity to rifamycin and its derivatives.
- Hepatic dysfunction.

**Precautions**

Serious immunological reactions resulting in renal impairment, haemolysis or thrombocytopenia are on record in patients who resume taking rifampicin after a prolonged lapse of treatment. In this rare situation it should be immediately and definitively withdrawn. Patients should be warned that treatment may produce reddish discoloration of urine, tears, saliva and sputum.

**Use in pregnancy and lactation**

Treatment should not be interrupted or postponed should pregnancy intervene. Vitamin K should be administered routinely at birth because of a risk of postnatal haemorrhage in the neonate.

**Adverse effects**

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe, in which case treatment should be discontinued. Other adverse effects (skin rashes, fever, influenza-like syndrome and thrombocytopenia) are more likely to occur during intermittent (once or twice-weekly) administration, and temporary oliguria, dyspnoea and haemolytic anaemia have also been reported. These reactions subside when daily dosage is instituted.

Moderate rises in serum bilirubin and transaminases, which are common at the outset of treatment, are often transient and without clinical significance. However, dose-related hepatitis can occur which is potentially fatal. It is consequently important not to exceed the maximum recommended dose of 10 mg/kg.

**Drug interactions**

Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver. These include corticosteroids, steroidal contraceptives, oral hypoglycaemic agents, oral anticoagulants, dapsone, phenytoin and digitalis glycosides. Women of child-bearing age should consequently be advised to use a non-hormonal method of birth control throughout treatment and for at least 1 month subsequently.

Biliary excretion of radiocontrast media and sulfobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B₁₂ (cyanocobalamin) disturbed.

**Overdosage**

Gastric lavage may be of value if undertaken within a few hours of ingestion. Very large doses may depress central nervous function. There is no specific antidote and treatment is supportive.

**Storage**

Capsules and tablets should be kept in tightly closed containers, protected from light.

**ETHAMBUTOL**

*tablets 100 mg, 400 mg (hydrochloride)*

Ethambutol, a synthetic congener of ethylene diamine, is bactericidal against some atypical mycobacteria. It is readily absorbed from the gastrointestinal tract. Peak plasma concentrations, which are attained in 2–4 hours, decay with a half-life of 3–4 hours. It is excreted in the urine both unchanged and as inactive hepatic metabolites.

**Uses**

In combination with rifampicin and isoniazid in the treatment of infections due to *M. kansasii*, *M. malmoense*, *M. xenopi* and *M. avium-intracellulare* in immunocompetent hosts.

**Dosage**

**Adults and children**

25 mg/kg daily for no more than 2 months followed by 15 mg/kg daily or 30 mg/kg 3 times a week for 24 months. There is some evidence to suggest that
**M. kansasii** infections require treatment for only 12 months.

Dosage must always be carefully calculated on a weight basis in order to avoid toxicity.

**Contraindications**
- Known hypersensitivity.
- Pre-existing optic neuritis from any cause.
- Children too young to report symptomatic visual disturbances.
- Patients with a creatinine clearance of less than 50 ml/minute.

**Precautions**
Patients should be advised to discontinue treatment immediately and to report to a doctor should their sight or perception of colour deteriorate. Patients who are too young or otherwise unable to comprehend this warning should not receive ethambutol. Whenever possible, renal function should be assessed prior to treatment.

**Use in pregnancy**
Treatment should not be interrupted or postponed should pregnancy occur.

**Adverse effects**
Dose-dependent optic neuritis can readily result in impairment of visual acuity and colour vision. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly. Signs of peripheral neuritis occasionally develop in the legs.

**Overdosage**
Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. Subsequently, dialysis may be of value. There is no specific antidote and treatment is supportive.

**Storage**
Tablets should be stored in well-closed containers.

**ISONIAZID**
*tablet 100 mg, 300 mg*
*injection 25 mg/ml in 2-ml ampoule*

Isoniazid, the hydrazide of isonicotinic acid, is bactericidal against some atypical mycobacteria. It is rapidly absorbed and diffuses readily into all fluids and tissues. The plasma half-life, which is genetically determined, varies from less than 1 hour in fast acetylators to more than 3 hours in slow acetylators. It is largely excreted into the urine within 24 hours, mostly as inactive metabolites.

**Uses**
In combination with rifampicin and isoniazid in the treatment of infections due to **M. kansasii**, **M. malmoense**, **M. xenopi** and **M. avium-intracellulare** in immunocompetent hosts.

**Dosage and administration**
Isoniazid is normally taken orally. However, it may be administered to critically ill patients intramuscularly.

**Adults and children**
5 mg/kg daily or 15 mg/kg 2 or 3 times weekly for 24 months. There is some evidence to suggest that **M. kansasii** infections require treatment for only 12 months.

**Contraindications**
- Known hypersensitivity.
- Active hepatic disease.

**Precautions**
Serum concentrations of hepatic transaminases should be monitored whenever possible.

Patients at risk of peripheral neuropathy as a result of malnutrition, chronic alcohol dependence or diabetes should additionally receive pyridoxine, 10 mg daily. Where the standard of health in the community is low this should be offered routinely.

Epilepsy should be effectively controlled since isoniazid may provoke attacks.

**Use in pregnancy**
Treatment should not be interrupted or postponed if pregnancy occurs.

**Adverse effects**
Isoniazid is generally well-tolerated at recommended doses.

Systemic or cutaneous hypersensitivity reactions occasionally occur during the first weeks of treatment.

Peripheral neuropathy can be averted if vulnerable
patients routinely receive supplements of pyridoxine. Other less common forms of neurological disturbance, including optic neuritis, toxic psychosis and generalized convulsions, which can develop in susceptible individuals particularly in the later stages of treatment, occasionally necessitate the withdrawal of isoniazid.

Hepatitis is an uncommon but potentially serious condition that can usually be averted by prompt withdrawal of treatment. More often, however, a sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is not of serious significance. If it regresses rapidly when dosage is suspended, it is unlikely to recur when treatment is re instituted.

Drug Interactions
Isoniazid tends to raise plasma concentrations of phenytoin and carbamazepine by inhibiting their metabolism in the liver.

Absorption is impaired by aluminium hydroxide.

Overdosage
Nausea, vomiting, dizziness, blurred vision and slurring of speech occur within 30 minutes to 3 hours of overdosage. Massive poisoning results in coma preceded by respiratory depression and stupor. Severe intractable seizures may occur. Emesis and gastric lavage can be of value if instituted within a few hours of ingestion. Subsequently, haemodialysis may be of use. Administration of pyridoxine may prevent peripheral neuritis.

Storage
Tablets should be kept in well-closed containers, protected from light. Solution for injection should be stored in ampoules protected from light.
Recent Publications

Regulating change

The United States Food and Drug Administration has recently celebrated the fiftieth anniversary of the Federal Food, Drug and Cosmetic Act of 1938 which effectively launched it into the modern era. The occasion was used as an opportunity to look at the challenges of the future rather than the achievements of the past. Representatives drawn from industry, academia, the legal community and consumer organizations were invited to participate in a series of round-table discussions covering various key aspects of the FDA’s mandate, and the edited proceedings of these meetings have now been published.

The basic issue that predictably permeates the book is the need to accommodate society’s desire for the progress that is promised by technological change yet, at the same time, to assure its protection from the inevitable hazards of innovation. This was undoubtedly as true 50 years ago as it is today. What is new is that demand for protection has to be satisfied, particularly in the USA, in the face of growing consumer pressure for earlier and freer access to regulated products.

Society is also impatient for new drugs that will give hope to the many patients for whom effective therapies still remain elusive. For the Food and Drug Administration, commitment to this expectation represents far more than an obligation to accord priority to innovative marketing applications. Through the Orphan Drug Act, in particular, the Agency has acquired influence actively to promote the development of needed drugs that would otherwise never emerge because of lack of commercial incentive. The results have been impressive and it is heartening that the FDA Commissioner, in his foreword to this book, is bold enough to set as his first objective for the immediate future “to find, test, and approve drugs for the desperately ill.” In no other country could the regulatory authority claim to exert a direct and positive influence on the drug development process.

He is equally positive in his view that collaboration with academia and industry must be active and supportive if full advantage is to be gained in the short term from the advent of biotechnology, and he sees closer cooperation between practicing doctors, pharmaceutical companies and regulators as the key to more effective surveillance of drugs subsequent to their registration. At a time of diminishing resources, he underscores the need “to focus on real, not imagined, threats to public health”.

He appreciates, however, that a collaborative relationship between the industry and regulators — no matter how strong may be its justification in terms of social benefit — can only be countenanced by society with equanimity when the regulatory authority has both the resolve and the resources to take vigorous and even-handed enforcement action whenever occasion demands. At all costs, he recognizes, public trust must be preserved. Its erosion would inevitably and profoundly set back the evolutionary process of therapeutic innovation which still, for so many, holds out the prospect for improved quality of life.

International Nonproprietary Names for Pharmaceutical Substances

In accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, notice is hereby given that the following names are under consideration by the World Health Organization as Proposed International Nonproprietary Names.

Comments on, or formal objections to, the proposed names may be forwarded by any person to the Pharmaceuticals unit of the World Health Organization within four months of the date of their publication in WHO Drug Information, e.g., for List 63 Prop. INN not later than 31 January 1991.

Proposed International Nonproprietary Names (Prop. INN): List 63

The inclusion of a name in the lists of proposed international nonproprietary names does not imply any recommendation for the use of the substance in medicine or pharmacy.

Action and Use
The statements in italics indicating the action and use are based largely on information supplied by the manufacturer. The information is meant to provide an indication of the potential use of new substances at the time they are accorded proposed INNs. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature these descriptors will be neither revised nor included in the Cumulative Lists of INN.

Comprehensive information on the INN programme can be found in: WHO Technical Report Series, No. 581, 1975 (Nonproprietary Names for Pharmaceutical Substances, twentieth report of the WHO Expert Committee). ISBN 92 4 120561 4 (price: Sw. fr. 6.--), an account of this publication will be found in Annex 2 of the present List. All names from Lists 1-58 of Proposed International Nonproprietary Names, together with a molecular formula index, will be found in: International Nonproprietary Names (INN) for Pharmaceutical Substances. Cumulative List No. 7, 1988, World Health Organization, Geneva (ISBN 92 4 0560149) (price: Sw. fr. 65.--). This publication consists, in the main, of a computer printout which groups together all the proposed and recommended international nonproprietary names (INN)—in Latin, English, French, Russian, and Spanish—published up to March 1988. The printout also indicates in which of the 58 individual lists of proposed names and 27 lists of recommended names each INN was originally published, and gives references to national nonproprietary names, pharmacopoeia monographs, and other sources. In addition, the list contains molecular formulae and Chemical Abstracts Service registry numbers. For easy reference, national nonproprietary names that differ from INN, molecular formulae, and Chemical Abstracts Service registry numbers are indexed in a series of annexes. A final annex describes the procedure for selecting recommended INN and outlines the general principles to be followed in devising these names. All the textual material published in this volume appears in both English and French.

These publications may be obtained, direct or through booksellers, from the sales agents listed on the back cover of WHO Drug Information. Orders from countries where sales agents have not yet been appointed may be addressed to: World Health Organization, Distribution and Sales Service. 1211 Geneva 27, Switzerland.


Other lists of proposed and recommended international nonproprietary names can be found in Cumulative List No. 7, 1988.
<table>
<thead>
<tr>
<th>Name</th>
<th>Chemical Name or Description</th>
<th>Molecular and Graphic Formulae</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>acidum penteticum</td>
<td>$N,N$-bis[2-[bis(carboxymethyl)amino]ethyl]glycine</td>
<td>$C_{14}H_{23}N_3O_{10}$ 67-43-6</td>
<td>diagnostic aid</td>
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<tr>
<td>pentetic acid</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>adaprololum</td>
<td>$2\text{-(1-adamantyl)ethyl (±)}\text{-}[p\text{-}[2\text{-hydroxy-3-}(\text{isopropylamino)}\text{-propoxy}]\text{phenyl}]\text{acetate}$</td>
<td>$C_{26}H_{39}NO_4$ 101479-70-3</td>
<td>$\beta$-adrenoreceptor antagonist</td>
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<tr>
<td>adaprolol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adosopinum</td>
<td>$N\text{-(5,6-dihydro-5-methyl-6,11-dioxo-10-morphanthridinyl)}\text{acetamide}$</td>
<td>$C_{17}H_{14}N_2O_3$ 88124-26-9</td>
<td>urinary incontinence agent</td>
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<td>adosopine</td>
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<td></td>
<td></td>
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<tr>
<td>afalaninum</td>
<td>$N\text{-acetyl-3-phenyl-DL-alanine or }N\text{-acetyl-DL-phenylalanine}$</td>
<td>$C_{11}H_{13}NO_3$ 2901-75-9</td>
<td>antidepressant</td>
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<tr>
<td>afalanine</td>
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<tr>
<td>aldesleukininum</td>
<td>$125\text{-serine-2-133-interleukin 2 (human reduced)}$</td>
<td>$C_{690}H_{1115}N_{177}O_{203}S_6$ 110942-02-4</td>
<td>immunomodulator</td>
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<tr>
<td>aldesleukin</td>
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<td></td>
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<tr>
<td>asobamastum</td>
<td>$2\text{-ethoxyethyl [4-}[3\text{-methyl-5-isoxazolyl]}\text{-2-thiazolyl}]\text{oxamate}$</td>
<td>$C_{13}H_{15}N_2O_3S$ 104777-03-9</td>
<td>antiallergic, antiasthmatic</td>
</tr>
<tr>
<td>asobamast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
<td>Action and use</td>
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<tr>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>berlafenonum</td>
<td>(±)-1-(2-biphenyloxy)-3-(tert-butylamino)-2-propanol</td>
<td>C&lt;sub&gt;19&lt;/sub&gt;H&lt;sub&gt;25&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt; 18965-97-4</td>
<td>antidysrhythmic</td>
</tr>
<tr>
<td>berlafenone</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td></td>
<td></td>
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<tr>
<td>bidisomidum</td>
<td>(±)-α-(o-chlorophenyl)-α-[2-(N-isopropylacetamido)ethyl]-1-piperidinebutyramide</td>
<td>C&lt;sub&gt;23&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;ClN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; 116078-65-0</td>
<td>antidysrhythmic</td>
</tr>
<tr>
<td>bidisomide</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>butixocortum</td>
<td>11β,17-dihydroxy-21-mercaptopregn-4-ene-3,20-dione 17-butyrate</td>
<td>C&lt;sub&gt;23&lt;/sub&gt;H&lt;sub&gt;36&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;S 120815-74-9</td>
<td>anti-inflammatory, glucocorticosteroid</td>
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<tr>
<td>butixocort</td>
<td><img src="image3" alt="Chemical Structure" /></td>
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<td></td>
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<tr>
<td>caidiamidum</td>
<td>hydrogen [N,N-bis[2-[(carboxymethyl) [(methylcarbamoyl)methyl]-amino]ethyl]glycinato(3-)]calciate(1-)</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;27&lt;/sub&gt;CaN&lt;sub&gt;5&lt;/sub&gt;O&lt;sub&gt;8&lt;/sub&gt; 128326-81-8</td>
<td>diagnostic aid</td>
</tr>
<tr>
<td>caidamide</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td></td>
<td></td>
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<tr>
<td>cefetecolum</td>
<td>(6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7&lt;sup&gt;α&lt;/sup&gt;-(Z)-[O-[(S)-α-carboxy-3,4-dihydroxybenzyl]oxime]</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;6&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt; 117211-03-7</td>
<td>antibiotic</td>
</tr>
<tr>
<td>cefetecol</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td></td>
<td></td>
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<tr>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Proposed International</td>
<td>Nonproprietary Name (Latin, English)</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>-------------------------</td>
<td>-------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>cilobradinum (cilobradine)</td>
<td>(±)-3-[1-(3,4-dimethoxyphenethyl)-3-piperidyl][methyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one</td>
<td>C₂₈H₃₈N₂O₅</td>
<td>109859-50-9</td>
</tr>
<tr>
<td>crilvastatinum (crilvastatin)</td>
<td>5-oxo-L-proline, (±)-cis-3,3,5-trimethylcyclohexyl ester</td>
<td>C₁₄H₂₃NO₃</td>
<td>120551-59-9</td>
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<tr>
<td>dacopatantum (dacopatant)</td>
<td>(3R)-3-(3-pyridyl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxamide</td>
<td>C₁₂H₁₁N₃OS</td>
<td>125372-33-0</td>
</tr>
<tr>
<td>docetaxolum (docetaxol)</td>
<td>(2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate</td>
<td>C₄₃H₅₃NO₁₄</td>
<td>114977-28-5</td>
</tr>
</tbody>
</table>
**Proposed International Chemical Name or Description, Molecular and Graphic Formulae**

**Nonproprietary Name (Latin, English)**

**Chemical Abstracts Service (CAS) registry number**

**Action and use**

**doramectinum**


C$_{50}$H$_{74}$O$_{14}$ 117704-25-3  antiparasitic

**drospirenonum**

(6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13,14,15,16-hexadecahydro-10,13-dimethylspiro-[17'H-dicyclopropa[6,7:15,16]cyclopenta[a]phenanthrene-17,2'(5'H)-furan]-3,5'(2'H)-dione

C$_{24}$H$_{30}$O$_3$ 67392-87-4  progestogen

**flosulidum**

$\text{N-[6-(2,4-difluorophenoxy)-1-oxo-5-indanyl]methanesulfonamide}$

C$_{16}$H$_{15}$F$_2$NO$_4$S 80937-31-1  nonsteroidal anti-inflammatory

**fomepizolum**

4-methylpyrazole

C$_4$H$_6$N$_2$ 7554-65-6  antidote
Proposed International Chemical Name or Description, Molecular and Graphic Formulae

Nonproprietary Name (Latin, English) Chemical Abstracts Service (CAS) registry number

<table>
<thead>
<tr>
<th>Proposed Name</th>
<th>Molecular and Graphic Formulae</th>
</tr>
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<tbody>
<tr>
<td>gadodiamide</td>
<td>$C_{16}H_{28}GdN_{5}O_{9} \times H_2O$ 122795-43-1 paramagnetic contrast medium</td>
</tr>
<tr>
<td>giracodazolum</td>
<td>($\alpha$S)-2-amino-$\alpha$-[1S]-amino-1-chloroethyl]imidazole-4-methanol</td>
</tr>
<tr>
<td>giracodazole</td>
<td>$C_6H_{11}ClN_4O$ 110883-46-0 antineoplastic</td>
</tr>
<tr>
<td>ibutilidum</td>
<td>($\pm$)-4'-[4-(ethylheptylamino)-1-hydroxybutyl]methanesulfonanilide</td>
</tr>
<tr>
<td>ibutilide</td>
<td>$C_{20}H_{36}N_2O_3S$ 122647-31-8 antidysrhythmic</td>
</tr>
<tr>
<td>isalsteinum</td>
<td>($\pm$)-N-[2-[2-[2-methyl-4-oxo-1,3-benzodioxan-2-yl]thio]propionyl]glycine</td>
</tr>
<tr>
<td>isalsteine</td>
<td>$C_{14}H_{15}NO_6S$ 116818-99-6 mucolytic</td>
</tr>
<tr>
<td>ledazerolum</td>
<td>2-hydroxy-3-(imidazol-4-ylmethyl)benzyl alcohol</td>
</tr>
<tr>
<td>ledazerol</td>
<td>$C_{11}H_{12}N_2O_2$ 116795-97-2 antianginal</td>
</tr>
<tr>
<td>levosulpiridum</td>
<td>($\pm$)-N-[[[S]-1-ethyl-2-pyrrolidinyl]methyl]-5-sulfamoyl-6-anisamide</td>
</tr>
<tr>
<td>levosulpiride</td>
<td>$C_{13}H_{23}N_3O_4S$ 23672-07-3 antiemetic</td>
</tr>
<tr>
<td>Nonproprietary Name (Latin, English)</td>
<td>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</td>
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<tr>
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<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>lisadimatum</td>
<td>(±)-glycerol 1-(p-aminobenzoate)</td>
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<tr>
<td>lisadimate</td>
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<tr>
<td>lometrexolum</td>
<td>N-[p-2-[(R)-2-amino-3,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl]ethyl]benzoyl]-L-glutamic acid</td>
</tr>
<tr>
<td>lometrexol</td>
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<tr>
<td>masoprocolum</td>
<td>meso-4,4'-(2,3-dimethyltetramethylene)dipyrocatechol</td>
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<tr>
<td>masoprocol</td>
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<tr>
<td>midesteinum</td>
<td>2-thiophenecarbothioic acid, S-ester with (±)-2-mercapto-N-(tetrahydro-2-oxo-3-thienyl)propionamide</td>
</tr>
<tr>
<td>midesteine</td>
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</tr>
<tr>
<td>miripirii chloridum</td>
<td>1-tetradecyl-4-picolinium chloride</td>
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<tr>
<td>miripirium chloride</td>
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</table>
**mivazerolum**
mivazerol

Proposed International Chemical Name or Description, Molecular and Graphic Formulae

<table>
<thead>
<tr>
<th>Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description</th>
<th>Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>mivazerolum</td>
<td>α-imidazol-4-yl-2,3-cresotamide</td>
<td>C_{11}H_{11}N_{3}O_{2} 125472-02-8</td>
<td>antianginal</td>
<td></td>
</tr>
</tbody>
</table>

| modecainidum                        | (±)-2'-[2-(1-methyl-2-piperidyl)ethyl]vanillinamide | C_{22}H_{28}N_{2}O_{3} 81329-71-7 | antidysrhythmic |

| naroparcilum                       | p-[p-[(5-thio-β-o-xylopyranosyl)thio]benzoyl]benzonitriile | C_{19}H_{17}NO_{4}S_{2} 120819-70-7 | antithrombotic |

| nemazolinum                        | 2-(4-amino-3,5-dichlorobenzyl)-2-imidazoline | C_{10}H_{11}Cl_{2}N_{3} | nasal vasoconstrictor |

| neticonazolum                      | (E)-1-[2-(methylthio)-1-[o-(pentyloxy)phenyl]vinyl]imidazole | C_{17}H_{22}N_{2}O_{8} 11178-99-9 | antifungal |

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<table>
<thead>
<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulæ</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
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<td>Proposed International Chemical Name or Description, Molecular and Graphic Formulæ</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
<td>Action and use</td>
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<tr>
<td><strong>nicoracetamum</strong></td>
<td>1-(6-methoxynicotinoyl)-2-pyrrolidinone</td>
<td>128326-80-7</td>
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<tr>
<td><strong>ormaplatinum</strong></td>
<td>(+)-trans-tetrachloro(1,2-cyclohexanediamine)platinum</td>
<td>62816-98-2</td>
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<td><strong>otenzepadum</strong></td>
<td>(±)-11-[(2-[(diethylamino)methyl]piperidino)acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazipin-6-one</td>
<td>100158-38-1</td>
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<td><strong>pegademasum</strong></td>
<td>adenosine deaminase, reaction product with succinic anhydride, esters with polyethylene glycol monomethyl ether</td>
<td>enzyme</td>
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<tr>
<td><strong>pidotimodum</strong></td>
<td>(R)-3-[(S)-5-oxopropyl]-4-thiazolidinecarboxylic acid</td>
<td>121808-62-6</td>
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<td><strong>pirodavirum</strong></td>
<td>ethyl p-[2-[(6-methyl-3-pyridazinyl)-4-piperidyl]ethoxy]benzoate</td>
<td>124436-59-5</td>
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Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)

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<th>Action and use</th>
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<tbody>
<tr>
<td>prisotinolum (±)-6-{2-(isopropylamino)propyl}-3-pyridinol C_{11}H_{18}N_{2}O</td>
<td>nootropic agent</td>
</tr>
<tr>
<td>propagermanium polymer obtained from 3-(trihydroxygermyl)propionic acid (C_{3}H_{5}GeO_{3.5})_{n}</td>
<td>immunomodulator</td>
</tr>
<tr>
<td>remacemidum (±)-2-amino-N-(1-methyl-1,2-diphenylethyl)acetamide C_{19}H_{20}N_{2}O</td>
<td>antiepileptic</td>
</tr>
<tr>
<td>repagermanium poly-trans-{[2-carboxyethyl]germasquioxane} (C_{18}H_{30}GeO_{21})_{n}</td>
<td>immunomodulator</td>
</tr>
<tr>
<td>rispenzepinum (±)-6,11-dihydro-11-(1-methylnipecotoyl)-5H-pyrido[2,3-b][1,5]benzodiazepin-5-one C_{19}H_{20}N_{2}O</td>
<td>antispasmodic</td>
</tr>
<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
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<tr>
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<td>----------------------------------------------------------</td>
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<tr>
<td>roxadimatum roxadimate</td>
<td>ethyl (±)-p-[bis(2-hydroxypropyl)amino]benzoate</td>
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<tr>
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<td><img src="image1" alt="Chemical Structure" /></td>
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<tr>
<td>sarpogrelatum sarpogrelate</td>
<td>(±)-2-(dimethylamino)-1-[o-(m-methoxyphenethyl)phenoxy]methyl]ethyl hydrogen succinate</td>
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<td><img src="image2" alt="Chemical Structure" /></td>
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<tr>
<td>serazapinum serazapine</td>
<td>methyl (±)-3,4,16b-tetrahydro-2-methyl-2H,10H-indolo[2,1-c]pyrazino-[1,2-a][1,4]benzodiazepine-16-carboxylate</td>
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<td><img src="image3" alt="Chemical Structure" /></td>
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<tr>
<td>siltenzepinum siltenzepine</td>
<td>5-[N,N-bis(2-hydroxyethyl)glycyl]-8-chloro-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one</td>
</tr>
<tr>
<td></td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>somagrebovum somagrebove</td>
<td>1-[N²-(M-1-methionyl-L-α-aspartyl)-L-glutamine]growth hormone (ox reduced)</td>
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<td></td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>
Proposed International Chemical Name or Description, Molecular and Graphic Formulae

Nonproprietary Name (Latin, English)  
Chemical Abstracts Service (CAS) registry number  
Action and use

somavubovum  
somavubove  
127-L-leucine growth hormone (ox)  
C_{976}H_{1533}N_{265}O_{286}S_{8} 126752-39-4 growth hormone (vet.)

sparfloxacinum  
sparfloxacin  
5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-
dihydro-4-oxo-3-quinolinecarboxylic acid  
C_{19}H_{22}F_{2}N_{4}O_{3} 110871-86-8 antibacterial

spiriprostilum  
spiriprostil  
(±)-(5 R\(^*\),6 S\(^*\),7 R\(^*\))-7-hexyl-2,4-dioxo-1,3-diazaspiro[4,4]nonane-6-heptanoic acid  
C_{20}H_{34}N_{2}O_{4} 122946-42-3 antiulcer

sucrosofatum  
sucrosofate  
sucrose octakis(hydrogen sulfate)  
C_{12}H_{22}O_{35}S_{8} 57680-56-5 antiulcer

sulazurilum  
sulazuril  
2-[3,5-dichloro-4-[p-(methylsulfonyl)phenoxy]phenyl]dihydro-1-methyl-
as-triazine-3,5(2H,4H)-dione  
C_{17}H_{15}Cl_{2}N_{3}O_{5} 108258-89-5 coccidiostatic

suleparoidum natricum  
suleparoid sodium  
heparitin sulfate, sodium salt  
(C_{14}H_{18}NO_{7}S_{3}Na_{3})_{n} 57459-72-0 fibrinolytic
<table>
<thead>
<tr>
<th>Proposed International Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>sulfendonum</td>
<td>1-((p-chlorophenyl)-3-(5-indanylsulfonyl)urea</td>
<td>antineoplastic</td>
</tr>
<tr>
<td>sulfenur</td>
<td>C₁₆H₁₅ClN₂O₃S 110311-27-8</td>
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<td></td>
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<tr>
<td>sulukastum</td>
<td>3-[[1(R,2E,4Z)-1-[(αS)-α-hydroxy-m-1H-tetrazol-5-ylbenzyl]-2,4-tetradecadienyl]thio]propionic acid</td>
<td>antiasthmatic</td>
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<tr>
<td>sulukast</td>
<td>C₂₅H₃₆N₄O₃S 98116-53-1</td>
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<td></td>
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<tr>
<td>taurosteinum</td>
<td>N-2-thenoyltaurine</td>
<td>mucolytic</td>
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<tr>
<td>taurosteine</td>
<td>C₇H₉NO₄S₂ 124066-33-7</td>
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<tr>
<td>tebufelonum</td>
<td>3’,5’-di-tert-butyl-4’-hydroxy-5-hexynophenone</td>
<td>nonsteroidal anti-inflammatory</td>
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<tr>
<td>tebufelone</td>
<td>C₂₀H₂₈O₂ 112018-00-5</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>technetium(⁹⁹mTc) siboroximum</td>
<td>[bis[(2,3-butanedione dioximato)(1-)-O][2,3-butanedione dioximato] (2-)]isobutyborato[2-]-N,N’,N,’,N’,’’,N’’’]-chloro[⁹⁹mTc]technetium(III)</td>
<td>diagnostic agent</td>
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<tr>
<td>technetium(⁹⁹mTc) siboroxime</td>
<td>C₁₈H₂₆BICN₂O₆ 106417-28-1</td>
<td></td>
</tr>
<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Action and use</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>telmesteinum</td>
<td>(-)-3-ethyl hydrogen $(R)$-3,4-thiazolidinedicarboxylate</td>
<td>mucolytic</td>
</tr>
<tr>
<td>teimesteine</td>
<td>$\text{C}<em>7\text{H}</em>{11}\text{NO}_4\text{S}$ 122946-43-4</td>
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<tr>
<td></td>
<td><img src="image" alt="Molecular Structure" /></td>
<td></td>
</tr>
<tr>
<td>tenosalum</td>
<td>2-thiophenecarboxylic acid, ester with salicylic acid</td>
<td>nonsteroidal anti-inflammatory, analgesic</td>
</tr>
<tr>
<td>tenosal</td>
<td>$\text{C}<em>{12}\text{H}</em>{8}\text{O}_4\text{S}$ 95232-68-1</td>
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<td></td>
<td><img src="image" alt="Molecular Structure" /></td>
<td></td>
</tr>
<tr>
<td>tenosiprolum</td>
<td>$(R)$-4-hydroxy-$L$-proline 2-thiophenecarboxylate (ester)</td>
<td>nonsteroidal anti-inflammatory</td>
</tr>
<tr>
<td>tenosiprol</td>
<td>$\text{C}<em>{10}\text{H}</em>{11}\text{NO}_4\text{S}$</td>
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<tr>
<td></td>
<td><img src="image" alt="Molecular Structure" /></td>
<td></td>
</tr>
<tr>
<td>terbequinil</td>
<td>1,4-dihydro-1-(methoxymethyl)-4-oxo-N-propyl-3-quinolinecarboxamide</td>
<td>partial benzodiazepine receptor inverse agonist</td>
</tr>
<tr>
<td>terbequinil</td>
<td>$\text{C}<em>{15}\text{H}</em>{18}\text{N}_2\text{O}_3$ 113079-82-6</td>
<td></td>
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<tr>
<td></td>
<td><img src="image" alt="Molecular Structure" /></td>
<td></td>
</tr>
<tr>
<td>tiagabinum</td>
<td>$(-)(R)$-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid</td>
<td>antiepileptic</td>
</tr>
<tr>
<td>tiagabine</td>
<td>$\text{C}<em>{20}\text{H}</em>{22}\text{NO}_2\text{S}_2$ 115103-54-3</td>
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</tr>
<tr>
<td></td>
<td><img src="image" alt="Molecular Structure" /></td>
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</tr>
</tbody>
</table>
tirilazadum
tirilazad
21-[4-(2,6-dimethylpyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione
C_{38}H_{52}N_{6}O_{2} 110101-66-1 lipid peroxidation inhibitor

utibaprilum
utibapril
\( (S)-2-\text{tert-buty}l-4-\{(S)-N-\{(S)-1-carboxy-3-phenylpropyl\}alanyl\}-\Delta^2-1,3,4-thiadiazoline-5-carboxylic\ acid, 4-ethyl ester\nC_{22}H_{31}N_{3}O_{5}S 109683-61-6 angiotensin converting enzyme inhibitor

vanoxerinum
vanoxerine
1-[2-[bis(p-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine
C_{28}H_{32}F_{2}N_{2}O 67469-69-6 antidepressant, antiparkinsonian

zeniplatinum
zeniplatin
\( cis-[2,2\text{-bis(aminomethyl)-1,3-propanediol}]\{1,1\text{-cyclobutane-dicarboxylato}\}\)platinum
C_{11}H_{20}N_{2}O_{6}Pt 111490-36-9 antineoplastic
<table>
<thead>
<tr>
<th>Proposed International Name or Description, Molecular and Graphic Formulae</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>zilascorbum (2H)</td>
<td>antineoplastic</td>
</tr>
<tr>
<td>zilascorb (2H)</td>
<td></td>
</tr>
<tr>
<td>5,6-O-[[RS]-benzylidene-α-L]-L-ascorbic acid</td>
<td></td>
</tr>
<tr>
<td>C_{13}H_{11}DO_6</td>
<td>122431-96-3</td>
</tr>
<tr>
<td>zileutonum</td>
<td></td>
</tr>
<tr>
<td>zileuton</td>
<td>leukotriene synthesis inhibitor</td>
</tr>
<tr>
<td>(±)-1-(1-benzo[b]thien-2-ylethyl)-1-hydroxyurea</td>
<td></td>
</tr>
<tr>
<td>C_{11}H_{12}N_{2}O_{2}S</td>
<td>111406-87-2</td>
</tr>
<tr>
<td>zofenopriлатum</td>
<td></td>
</tr>
<tr>
<td>zofenopriлат</td>
<td></td>
</tr>
<tr>
<td>(4S)-1-[(S)-3-mercapto-2-methylpropionyl]-4-(phenylthio)-L-proline</td>
<td>angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>C_{15}H_{19}NO_{3}S_{2}</td>
<td>75176-37-3</td>
</tr>
</tbody>
</table>
Names for Radicals and Groups

Some substances for which a proposed international non-proprietary name has been established may be used in the form of salts or esters. The radicals or groups involved may be of complex composition and it is then inconvenient to refer to them in systematic chemical nomenclature. Consequently, shorter nonproprietary names for some radicals and groups have been devised or selected, and they are suggested for use with the proposed international non-proprietary names.

docosilum
docosil
docosyl
$C_{22}H_{45}$

xinafoas
xinafoate
1-hydroxy-2-naphthoate
$C_{11}H_{7}O_{3}$
AMENDMENTS
TO PREVIOUS LISTS

WHO Drug Information Vol. 1, No. 3, 1987

Proposed International Nonproprietary Names (Prop. INN): List 58

p. 188  saruplasum
saruplase

replace the definition and the molecular formula by the following:
prourokinase (enzyme-activating) (human clone pUK4/pUK18)
C_{292}H_{312}N_{58}O_{50}S_{37}


Proposed International Nonproprietary Names (Prop. INN): List 59

p. 9  muroderminum
murodermin

replace the molecular formula and the CAS registry number by the following:
C_{257}H_{375}N_{73}O_{83}S_{7}  54017-73-1


Proposed International Nonproprietary Names (Prop. INN): List 61

p. 9  delete
émonapridum
émonapride

insert
némonapridum
némonapride

p. 14  moxidectinum
moxidectin

replace the graphic formula by the following:

p. 18  tenidapum
tenidap

replace the chemical name, the CAS registry number and the graphic formula by the following:
(Z)-5-chloro-3-(α-hydroxy-2-thenylidene)-2-oxo-1-indolinecarboxamide
120210-48-2
Proposed International Nonproprietary Names (Prop. INN): List 62

p. 3  brifentanilum  
      replace the chemical name by the following:  
      (±)-cis-N-[1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-3-methyl-4-piperidyl]-2’-fluoro-2-methoxyacetanilide

p. 4  ciclesonidum  
      add the following CAS number:  
      126544-47-6

p. 5  delete
      dapropterinum
      sapropterinum

p. 18 etomoxirum  
      replace the chemical name, the CAS registry number and the graphic formula by the following:
      ethyl (±)-(R)-2-[6-(p-chlorophenoxy)hexyl]glycidate
      124083-20-1

\[
\text{\includegraphics[width=0.3\textwidth]{etomoxir.png}}
\]
The following procedure shall be followed by the World Health Organization in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with the World Health Assembly resolution WHA3.11:

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefor.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the "General principles for guidance in devising International Nonproprietary Names", appended to this procedure. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

A. Such notice shall be given by publication in the Chronicle of the World Health Organization and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

   (i) Notice may also be sent to specific persons known to be concerned with a name under consideration.

B. Such notice shall:

   (i) set forth the name under consideration;
   (ii) identify the person who submitted a proposal for naming the substance, if so requested by such person;
   (iii) identify the substance for which a name is being considered;
   (iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;
   (v) state the authority under which the World Health Organization is acting and refer to these rules of procedure.

C. In forwarding the notice, the Director-General of the World Health Organization shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the Chronicle of the World Health Organization.

5. A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in the Chronicle of the World Health Organization.

   A. Such objection shall:

      (i) identify the person objecting;
      (ii) state his interest in the name;
      (iii) set forth the reasons for his objection to the name proposed.

6. Where there is a formal objection under article 5, the World Health Organization may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by the World Health Organization of a substitut name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:

   A. request that it be recognized as the nonproprietary name for the substance; and

   B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or trade-name.

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

   These primary principles are to be implemented by using the following secondary principles

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. "oxacillin" and "oxacillin sodium", "ibufenac" and "ibufenac sodium".

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ
only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, "i" should be used instead of "phi", "l" instead of "th", "e" instead of "ae" or "oe", and "o" instead of "y"; the use of the letters "h" and "k" should be avoided.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.¹ Where a stem is shown without any hyphens it may be used anywhere in the name.

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-ac</td>
</tr>
<tr>
<td>-actidum</td>
<td>-actide</td>
</tr>
<tr>
<td>-adolum</td>
<td>-adol</td>
</tr>
<tr>
<td>-adol-</td>
<td>-adol-</td>
</tr>
<tr>
<td>-astum</td>
<td>-ast</td>
</tr>
<tr>
<td>-astinum</td>
<td>-astine</td>
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<td>-azepam</td>
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<tr>
<td>-bactamum</td>
<td>-bactam</td>
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<tr>
<td>bol</td>
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<td>cef-</td>
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<td>-conazole</td>
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<td>cort</td>
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<td>-dipine</td>
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<tr>
<td>-metacinum</td>
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<td>-olol-</td>
<td>-olol-</td>
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<td>-oxacinum</td>
<td>-oxacin</td>
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<tr>
<td>-pridum</td>
<td>-pride</td>
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<td>-pril(at)um</td>
<td>-pril(at)</td>
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<td>prost</td>
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<td>-verinum</td>
<td>-verine</td>
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<td>vin-</td>
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</table>

1 A more extensive listing of stems is contained in the working document Pharm S/Nom 15 which is regularly updated and can be requested from Pharmaceuticals, WHO, Geneva.
In its twentieth report\(^1\) the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant recent change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic "stem" indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed. Also reported is the intention to change the practice with regard to the nomenclature of individual members of polymeric series.

Other sections of the report concern instructions to be followed by bodies making application for international nonproprietary names, the availability of computer-printed cumulative lists of international names, information supplied by WHO Member States concerning their official use of national or international names for pharmaceutical products, and proposals relative to the withdrawal of international nonproprietary names allocated to substances that are no longer in use.

The official texts relating to the procedures for selecting, and general guidance for devising, international nonproprietary names are reproduced in two annexes to the report. Other annexes give examples of international nonproprietary names that incorporate selected stems, the most frequently used initial groups of letters in international nonproprietary names, a historical review of the programme of selecting international nonproprietary names, some useful literature references, and a model of the form to be used in all applications for international nonproprietary names.

## SELECTED WHO PUBLICATIONS OF RELATED INTEREST

*Price* *(Sw. fr.)*

<table>
<thead>
<tr>
<th>Title</th>
<th>Year</th>
<th>Pages</th>
<th>Price</th>
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<tbody>
<tr>
<td><strong>The use of essential drugs</strong></td>
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<tr>
<td>Third report of the WHO Expert Committee</td>
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<tr>
<td><strong>Guidelines for developing national drug policies</strong></td>
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<tr>
<td>1988 (iv + 52 pages)</td>
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<td>11.-</td>
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<tr>
<td><strong>The International Pharmacopoeia, third edition</strong></td>
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<tr>
<td>Volume 1: general methods of analysis. 1979 (223 pages)</td>
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<td>24.-</td>
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<tr>
<td>Volume 2: quality specifications. 1981 (342 pages)</td>
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<td>36.-</td>
</tr>
<tr>
<td>Volume 3: quality specifications. 1988 (407 pages)</td>
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<td>64.-</td>
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<tr>
<td><strong>International Nonproprietary Names (INN) for pharmaceutical substances, cumulative list no. 7</strong></td>
<td>1988</td>
<td>xviii + 617 pages</td>
<td>65.-</td>
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<tr>
<td><strong>Basic tests for pharmaceutical substances</strong></td>
<td>1986</td>
<td>vi + 204 pages</td>
<td>34.-</td>
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<tr>
<td><strong>International travel and health: vaccination requirements and health advice, 1990</strong></td>
<td>1990</td>
<td>89 pages</td>
<td>14.-</td>
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<tr>
<td><strong>Vector control in primary health care</strong></td>
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<tr>
<td>Report of a WHO Scientific Group</td>
<td>1987</td>
<td>61 pages</td>
<td>9.-</td>
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*Prices in parentheses apply in developing countries.*

Further information on these and other World Health Organization publications can be obtained from Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland.