WHO Drug Information

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

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

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Countering the counterfeiters

Many countries still have no significant indigenous pharmaceutical manufacturing industry. They are vitally dependent upon imported drugs, but, as yet, some have not introduced a formal licensing system and still fewer possess an effective governmental quality control laboratory. Wherever controls are deficient, not only are time-expired and degraded products likely to pass unnoticed through the distribution system, but trade in substandard counterfeit products is liable to flourish. Moreover, importing countries are rendered more vulnerable because products that they receive have not always been subjected to the quality assessment and controls that are statutorily applied as a prerequisite to marketing in the country of origin. Indeed, it is often possible for companies engaged solely in exportation to arrange their business in such a way as to escape all statutory controls in the countries from which they operate. In this case no check is made on whether they comply with prevailing standards of good manufacturing practices, or whether they actually manufacture, or even handle at first hand, the products in which they trade.

It is against this background that, over the past few years, trade in bogus medicines has developed into an internationally organized criminal activity. Disquiet is now overtly expressed within some importing countries about the extent to which their standards of health care may be compromised by spurious drugs. Companies of repute have become sensitized to the need to root out trade in counterfeit versions of their own products, and the World Health Organization has been requested, within the context of its Revised Drug Strategy, to study ways of combating the problem from an international standpoint. In fact, much guidance has already been issued to assist countries to develop a capability in quality assurance. WHO's prime responsibility is now to ensure that this advice strikes home in the countries where it is most urgently needed, and to inspire these countries with the confidence and resolution to put into place a framework of regulation that is attuned to their own circumstances.

Two elements are basic to any national strategy in this context: a capacity in chemical analysis that will, at least, deter the worst excesses of criminal enterprise; and a means, dependent upon international collaboration, of establishing the provenance of any imported pharmaceutical product. Much remains for WHO to accomplish in both these respects. Nonetheless, any country aiming to derive the utmost from a modest investment in analytical control or to obtain effective independent assurance regarding the quality of imported pharmaceuticals is well advised to review the recommendations that the Organization has placed on record over the years.

Analytical quality control

Circumstances have changed radically since the first World Health Assembly perceived the International Pharmacopoeia as a means of harmonizing quality specifications of pharmaceutical substances internationally. Indeed, the justification for its continued existence lies in the degree to which it can be made distinctive from the national and regional pharmacopoeias of the major exporting countries, and it is now uncompromisingly oriented to the needs of developing countries. It is devoted to substances contained within WHO's Model List of Essential Drugs and monographs are based, as far as is practicable, upon classical methods of analysis that can be undertaken in a modestly-equipped laboratory. These are complemented by a range of international chemical reference substances that have thus far been generously supplied without charge, as a service to developing countries, by a collaborating centre operating from the Swedish Cooperative of Pharmacies.

In recent years, in an attempt to broaden the scope of analytical control in developing countries, a
volume of basic tests has been compiled that enables the identity of an essential drug substance to be confirmed when no fully-equipped laboratory is available, and a compendium of accelerated stability studies has been issued to indicate which of these substances are most vulnerable to degradation under extreme climatic conditions.

WHO's work is far from complete, however. Efforts are in hand to extend the International Pharmacopoeia to cover widely available dosage forms in addition to pharmaceutical substances. Collaborative schemes are being developed in partnership with pharmaceutical companies and donor organizations to produce more training opportunities for candidates from developing countries in both the administrative and analytical aspects of quality control. Directors of national quality control laboratories in developing countries are being invited by WHO to engage in a series of self-monitoring analytical exercises, and laboratories in highly developed countries are being encouraged to enter into agreements to support their counterparts in less developed countries, on a contract basis, when specific analytical problems arise.

The WHO Certification Scheme

Twelve years have now elapsed since the introduction of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce. Misunderstanding of its objectives continues, on occasion, to generate criticism. Yet, in its essentials, it is unpretentious and straightforward. It seeks to establish an internationally standardized administrative mechanism whereby the competent regulatory authority within an exporting country can certify, at the request of the importing country, whether a specific product is actually sold on its domestic market and whether it has been manufactured in accordance with defined standards of good manufacturing practices. Plans are now in hand to extend its scope to embrace pharmaceutical substances as well as finished dosage forms, and to provide for exchange of the product information approved in the country of origin.

The potential of the Scheme to achieve these objectives is dependent upon the rigour with which it is implemented by participating countries. This demands a clear perception within importing countries of the scope and limitations of the safeguards that it offers and, within exporting countries, a firm commitment to provide the required information explicitly and unambiguously. Effective certification invests a product with an established "pedigree". It should leave no doubt about where it was manufactured or assembled, or on the precise extent to which its quality can be assured. In particular, importing countries should appreciate that, for purposes of certification, general assurances regarding the implementation of good manufacturing practices need to be related to specific products, and that important criteria of quality, including stability and bioavailability, may remain undetermined in products that have not been formally registered in the country of origin.

Registration is a mandatory precondition for the sale of a pharmaceutical product in developed countries; it provides an assurance that the product has been subjected to expert pharmaceutical assessment and that in-process and batch controls are undertaken as required by law. If the prevailing criminal exploitation of export markets is to be exorcized in the short term, importing countries require reassurance, not only that the Certification Scheme is being rigorously and diligently administered, but that exporting countries are seeking to identify and seal any statutory loopholes permitting products destined for export to escape the assurance of quality that they themselves demand.
Points of view

WHO and pharmaceuticals: a prospective view

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Barely twenty years have elapsed since the larger nations within Western Europe started to put their drug control systems into place in the post-thalidomide era. Little more than a decade has passed since the World Health Organization pronounced its "essential drugs" philosophy in a courageous attempt to demonstrate that, whenever resources are inadequate to address fundamental health needs, rationalization of drug procurement and supply become prerequisites to the attainment of economy and efficiency in any health care setting.

Now, with no further stimulation necessary from WHO, all governments are revealing a determination to reduce drug costs, not only through direct price control and selective registration, but also through selective reimbursement of prescription costs, compulsory licensing, or promotion of generic prescribing and dispensing. The dilemma that emerges for governments is to reduce public expenditure on drugs as far as is practicable without eroding the standards of the health services they provide and yet assuring a socially-productive investment in new drug development.

It is, of course, for sovereign governments to elaborate their own national policies and strategies to meet these objectives, but the large majority of WHO's Member States simply do not command the resources of manpower or finance to address these tasks in isolation. They need to look to the Organization to provide a sounding board for projecting policy options as it has done recently within the context of the Nairobi Conference of Experts on the Rational Use of Drugs. They also need to look to the Organization's informational and technical resources to support them in their quest for self-sufficiency. To what extent they can also realistically expect multilateral international initiatives, by themselves, to dispose of the cruel inequalities that derive from 80% of the world's population having access to less than 20% of global resources is more problematic. There is surely both need and scope, having regard to the awesome magnitude of the task at hand, for multilateral programmes and bilateral aid projects to operate in constructive and complementary relationship.

The international organizations, by their very structure and independence are, perhaps, most appropriately equipped to assist countries seeking to acquire a sound technical and administrative basis for drug selection and control. They are ideally constituted to exchange information on a global basis, promulgate internationally-accepted standards and provide advisory services to governments. In many instances, however, it is bilateral aid that is instrumental in providing the capital resources required to establish and upgrade the physical infrastructure required for efficient drug distribution.

A rapid tour d'horizon of what has been accomplished over the past decade or so in the multilateral sector, particularly from the standpoint of WHO, provides many indications that secure foundations have already been laid on which bilateral initiatives can flourish. Over 100 countries now have lists of essential drugs, in most instances stratified to the different levels of the health service. About 40 developing countries, several of them with small populations, have formulated essential drugs policies through legislative action. Others are implementing essential drugs programmes as an inherent element of primary health care. An unrelenting effort is being maintained to ensure that well before the year 2000 every infant born into the world will be vaccinated against the major killing and crippling diseases of childhood. The emphasis that is now accorded to rehydration in the management of infantile diarrhoea is dramatically reducing the
needless and unacceptable mortality that previously resulted simply from fluid and electrolyte deficit. In partnership with pharmaceutical manufacturers, WHO is engaged in the clinical development of new drugs for birth control and for major transmissible diseases endemic in the developing world that have hitherto attracted scant research commitment. The pace of discovery is accelerating perceptibly: a variety of highly effective drugs is now available to treat parasitic worms; several compounds still under development offer new hope to those at risk of onchocerciasis, filariasis and trypanosomiasis; and effective vaccines may ultimately emerge that will provide effective protection against malaria and leprosy.

Amelioration of the overwhelming burden of infective disease is dependent, in the last analysis, on the development of practicable approaches to cure and prevention. In the meantime, however, efforts need to be redoubled both at international and national levels to promote rational drug use within the context of national drug policies and also to foster national self-reliance in drug procurement and control. Perhaps we take for granted some of the elements that are already in place to secure these aims. We have become unquestioningly reliant, for instance, on the system of international nonproprietary names for pharmaceutical substances that assures worldwide communication and understanding in medicine. We accept, also without question, the importance of dialogue between the competent authorities in importing and exporting countries afforded by the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce. We have grown accustomed to our countries’ ready access to the independent information on the safety and quality of marketed products that is disseminated month by month under the aegis of WHO. We may not even have appreciated that this has resulted in accusations of drug dumping being consigned to history. We have possibly not recognized that the new-found confidence with which many small regulatory authorities operate in developing countries derives from direct access to this information, as well as training opportunities largely coordinated through WHO, and from initiatives to bring regulators from developed and developing countries together during the biennial International Conference of Drug Regulatory Authorities.

If, as a result of financial stringency within WHO these activities are allowed to decline so soon after the World Health Assembly endorsed plans for their intensification within the context of the Revised Drug Strategy, the very bedrock of international collaboration may well be destroyed. The fabric of bilateral support is secure only if it is laid on firm foundations. Those foundations are already in place and, if there is an unwavering commitment to build upon them, with a view to helping developing countries help themselves in obtaining the drugs that they really need, I am decidedly optimistic for the future.
Reports on Individual Drugs

Eflornithine in African trypanosomiasis

At least 25,000 new cases of African trypanosomiasis, or sleeping sickness, are estimated to occur each year. Fifty million people are at risk of infection (1) and animal trypanosomiasis remains a critical factor in slowing socioeconomic development in sub-Saharan Africa (2).

The treatment of the disease, which has remained basically unchanged for the past 30 years, is far from satisfactory (3) (see also p. 230). Each of the available drugs causes serious toxic effects. Suramin and pentamidine are effective only in the haemolymphatic stage of the disease, while treatment with melarsoprol, until recently the only substance that offers hope of a cure in the meningoencephalitic stage, is fraught with danger: a substantial proportion of cases are unresponsive (4, 5) and 3-5% of patients die during therapy from reactive arsenical encephalopathy (6). A far safer and more effective form of treatment has now been developed, however, as a result of research on inhibitors of polyamine biosynthesis undertaken within the Merrell Dow Research Institutes.

Polyamines are low molecular weight alkylamines which occur in all growing cells. They are essential for cell division and the formation of macromolecules (7) and it was earlier envisaged that inhibition of their synthesis might provide a new approach to the treatment of cancer (8). In all mammalian and many other eukaryotic cells polyamines are derived exclusively from ornithine, and Merrell Dow's research has stemmed from a series of compounds that irreversibly block the action of ornithine decarboxylase, the first enzyme in the polyamine biosynthetic pathway. The most potent and selective of those initially investigated, eflornithine (alpha-difluoromethylornithine; DFMO) does, indeed, inhibit carcinogenesis in various animal models (7, 9). Clinical investigations into its possible value as an adjunct to established anti-neoplastic drugs are continuing (10), but its potential in this context remains uncertain, since it is far less effective in inhibiting the growth of established tumours (11).

The possibility that eflornithine might have clinical value in the chemotherapy of infectious disease at first seemed unlikely on the basis of studies undertaken on several bacteria and viruses. Polyamines are undoubtedly vital to their replication, but many of these organisms can synthesize these substances from substrates other than ornithine by utilizing independent enzymatic mechanisms as need arises (12, 13). Subsequent studies undertaken on pathogenic protozoa have been decidedly more encouraging. The therapeutic value of eflornithine has already been established in the treatment of *Trypanosoma brucei gambiense* infections (16), promising results have been obtained in *Pneumocystis carinii* pneumonia (14, 15), and leads have been identified to suggest that polyamine inhibitors may ultimately offer an effective approach to the treatment of other protozoal diseases (17) including malaria (18) and coccidiosis. *T. b. gambiense* is apparently vitally dependent upon ornithine as a substrate for polyamine synthesis (19-23) and it is extremely sensitive to the action of eflornithine (23) which has a cytostatic effect on the parasite. In vivo this action is lethal in the presence of an effective immune response (24, 25). Whether *T. b. rhodesiense* is similarly sensitive to eflornithine is uncertain. Some rather scant in vivo data derived from animal models suggest that it may be (9, 20), but, as yet, too few cases of *T. b. rhodesiense* infection have been treated with eflornithine to enable any general conclusions to be drawn.

Eflornithine was first used therapeutically in *T. b. gambiense* infections in the Sudan in 1981 (26) when it was administered orally for 44 days at a dosage of some 250 mg/kg/day to a patient with confirmed meningoencephalitic disease. The patient initially appeared to be clinically and parasitologically cured, but relapse occurred within 10 weeks. Oral dosage was subsequently increased to 400 mg/kg/day for 4-6 weeks and,
more recently, the intravenous route has been used for the first two weeks in the light of dramatic recoveries that have been obtained in comatose patients. The most recently-published summarized information (8, 14) indicates that, in each of 116 surviving patients with late-stage disease, striking clinical recovery occurred and trypanosomes disappeared from body fluids within a few days. These results are the more impressive since nearly all these patients were refractory to treatment with melarsoprol. Although six patients who received oral therapy only are known to have relapsed within the first year of treatment, not one of 61 patients treated parenterally has required a further course of treatment.

However, about one in ten of the patients treated with eflornithine have thus far died during or shortly after therapy. Each had severe encephalitic disease complicated by cachexia or intercurrent infection. In no case has the drug been definitely regarded as contributing to the cause of death, but it is noteworthy that, in many of these patients, examination of samples of cerebrospinal fluid indicated that the infection had been arrested before death occurred. Seizures have also been reported during treatment in about one in ten patients, but this is most reasonably attributed to the disease process rather than to treatment (27, 28).

The unwanted effects that are more definitely drug-induced relate predominantly to the gastrointestinal and haemopoietic systems. Abdominal discomfort, diarrhoea, anorexia and sometimes emesis have occurred in about one half of the treated patients, but these symptoms were usually adequately controlled by reducing or temporarily suspending dosage. Transitory anaemia has been recorded in about one third of patients, but this was only occasionally evident clinically. Reversible thrombocytopenia and leukopenia have been reported less frequently, and alopecia areata has developed in a few instances.

Notwithstanding its dramatic potential to retrieve patients with advanced T. b. gambiense infections from imminent death and its apparent lack of serious toxicity in animal models (29), eflornithine has evident shortcomings as a drug for routine clinical use since it needs to be administered in large quantities, and in part parenterally, for an extended period. The search for more effective analogues that can be more simply and economically administered has already yielded return. A newly synthesized inhibitor, alpha-monofluoromethyldehydro-ornithine methyl ester, is several fold more active against acute trypanosome infections in animal models (30). The hope is that, within a few years, comparably effective short-course, low-dose therapy will be available at a price that will bring it within the ambit of veterinary as well as human medicine.

References


General Information

Original pack dispensing: problems for elderly patients

United Kingdom — Original pack dispensing has proven to be a mixed blessing for many elderly patients according to a recent letter published in the British Medical Journal. Over half of a group of 44 elderly day-hospital patients experienced difficulty in handling the packaging. All the patients — some of whom had parkinsonism, rheumatoid arthritis and hemiparesis — normally took their medicines at home, but 25 were unable to get the tablet out of a blister pack, and 18 still could not manage even after explanation and instruction.


IFPMA Code of Pharmaceutical Marketing Practices

The International Federation of Pharmaceutical Manufacturers’ Associations (IFPMA) has issued its Sixth Status Report on the handling of complaints lodged by organizations or individuals alleging breaches of its Code of Pharmaceutical Marketing Practices. Twenty-six complaints considered during 1986 were upheld by the IFPMA, most of which involved the omission of nonproprietary drug names from advertising copy. A supplementary clause has consequently been added to the code to underscore the need to include approved names in advertisements. A further six breaches arose from the use of the term “safe” in advertisements without qualification. All companies belonging to the Federation are reported to have taken immediate action to assure compliance by either amending or withdrawing the offending advertisements.


A computerized drug information system in France

France — In 1970 the Faculty of Medicine in the university hospitals of Necker-Enfants Malades in Paris and the National Association of Pharmaceutical Industries (S.N.I.P) established a joint computerized information system on drugs available in France. The system, known as B.I.A.M. (Banque d'Informations Automatisée sur les Médicaments), now provides information on about 3000 drug substances contained in some 8000 products. Whereas the full system has long been directly accessible by hospitals and university departments, every doctor and pharmacist throughout the country now has access to its main elements through a telephone terminal (Minitel). Fees for the service are calculated on a time basis.


Compensation for vaccine-related injuries

United States of America — For many years the federal immunization programme has protected millions of children against the effects and complications of the common infectious diseases of childhood. In recent times, however, the programme has operated under a legal cloud that is threatening its stability, forcing the prices of vaccines sharply upwards and inhibiting the development of new products. This has occurred because, even when vaccines are manufactured and used in an exemplary manner, they are liable, very rarely, to cause severe injury to the recipient. The US Congress has reacted to the pressure of litigation and the scale of damages awarded to the injured children by creating a new federal no-fault compensation scheme, but uncertainty remains on how it will be funded and whether it will achieve its goals.
When signing the proposal into law in November 1986, President Reagan expressed serious reservations on the grounds that the scheme would not serve as an exclusive source of compensation for vaccine-related injuries, but rather as alternative to the tort system; that it would entail high administrative costs; and that the law would delegate operational responsibility to the judicial branch.

Before the law can be implemented, Congress still has to determine how the scheme will be funded. This has so far been frustrated by conflicting estimates of its ultimate cost. Figures varying from US$ 153 million to as much as US$ 1.5 billion have been quoted for the five year period 1987-1991. A study commissioned by Lederle Laboratories indicates that a trust fund large enough to offer protection against the worst of these predictions would require, in the first year, a surcharge of US$ 19.71 for each dose of DPT vaccine and US$ 1.28 for each dose of polio vaccine.


**International responses to drug abuse**

A valuable insight into the magnitude of the problem of drug abuse and the measures that are now in place to cope with it is provided in the latest issue of the United Nations Bulletin on Narcotics. Summarized information is provided by the Governments of 105 countries and territories. Emphasis is placed upon the need to develop effective, regionally-based strategies to contain trafficking and an account is provided of ongoing activities within the Council of Europe, the Colombo Plan Bureau, the Association of South-East Asian Nations (ASEAN), the Organization of American States, and the South American Agreement on Narcotic Drugs and Psychotropic Substances. The value of direct intergovernmental collaboration is also underscored with reference to coordinated action within the Caribbean area and between Canada and other countries.


**Regulatory aspects of radiopharmaceuticals**

Whereas nuclear medicine services exist in all European countries, a survey undertaken in 1983 by WHO's Regional Office for Europe revealed that only 6 of a total of 23 countries had introduced specific legal provisions to regulate the manufacture, distribution and use of radiopharmaceuticals. Eight countries applied no controls of any nature and exempted these preparations from prevailing drug licensing requirements.

To follow up these findings the Regional Office convened a workshop in April 1987. In its report, the group recommends that the medicinal use of radiopharmaceuticals should be subject to strict governmental control and it offers detailed proposals on the information which manufacturers should be required to submit for registration purposes. It also highlights the elements of good manufacturing practices peculiar to radiopharmaceuticals and the precautions to be observed when these substances are handled to assure adequate protection of the operators.


**Alcohol and drug-related problems: programmes of assistance for workers**

Alcohol and drug-related problems in the workplace have become an issue of social concern in many countries with the recognition that their consequences impinge not only on the workers themselves, but also on their families, colleagues, employers and society at large. A recent review of the situation published by the International Labour Organisation (ILO), based on experience derived from many industrialized countries, carries the message that much can be done to assuage the problem in the workplace itself through:
• development of policies, guidelines and programmes on alcohol and drugs sponsored by governments and by employers' and workers' organizations;

• creation of centres offering information and assistance that will provide a tangible basis for the implementation of these policies and programmes.

In publishing this review the ILO has also produced a valuable work of reference that includes not only an annotated bibliography of the relevant published literature, but also a catalogue of established assistance programmes and existing audio-visual materials.


Drug delivery system for IV infusions

United Kingdom — A new drug delivery system for intravenous infusion, first introduced in the USA in 1985 and marketed under the proprietary name Add-Vantage™, has been introduced by Abbott Laboratories for its own brands of erythromycin lactobionate and piperacillin sodium.

The system has two components: a glass vial containing sterile drug powder and a PVC bag containing diluent. Before use, caps are removed from the drug vial and from a "vial port" on the diluent bag. Using aseptic technique, the drug vial is then screwed into the vial port. To prepare the mixture, the vial closure is detached and allowed to fall into the bag by manipulating it through the bag wall. The vial contents are then mixed with the diluent, and the bag checked for leaks by squeezing. The manufacturer estimates that the complete preparation can be done in about 20 seconds, which compares with about eight minutes for standard reconstitution. Because the system is so simple, it is claimed that the risk of dilution errors will be minimized.


Acceptable levels of residues of veterinary drugs in foods

At its meeting in June 1987 the Joint FAO/WHO Expert Committee on Food Additives considered the safety of veterinary drugs residues, and particularly of hormones, in foods. Acceptable residue level (ARL) was defined as "the concentration of residue determined from the acceptable daily intake, related to the estimated intakes of relevant foods, and reduced to the lowest concentration that is consistent with good veterinary and animal husbandry practice and practical analytical methods."

The Committee also re-evaluated two xenobiotic hormonally-active growth promoters and three endogenous hormones used as growth promoters. The following recommendations were adopted:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Acceptable Daily Intake (ADI)</th>
<th>Acceptable Level (ARL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol-17β</td>
<td>Not defined*</td>
<td>Not defined*</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Not defined*</td>
<td>Not defined*</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Not defined*</td>
<td>Not defined*</td>
</tr>
<tr>
<td>Trenbolone acetate</td>
<td>0-0.1 μg/kg body weight</td>
<td>1.4 μg/kg (bovine tissue) β-trenbolone; 14 μg/kg (bovine tissue) α-trenbolone</td>
</tr>
<tr>
<td>Zeranol</td>
<td>0-0.5 μg/kg body weight</td>
<td>10 μg/kg (bovine liver) 2 μg/kg (bovine muscle).</td>
</tr>
</tbody>
</table>

* This signifies that dosages used are unlikely to give rise to residues posing a hazard to human health.

100th Orphan drug designated

United States of America — In 1982 the Food and Drug Administration established the Office of Orphan Products Development. Its task is to encourage, through incentives such as exclusive distribution rights and tax credits, research and development directed to drugs and medical devices that are intended for the treatment of uncommon conditions or which, for other reasons, hold little commercial interest.

Diaziquone, the first orphan compound to be designated, provided prospect for the improved management of primary brain malignancies (grade III-IV astrocytomas). The continued importance and success of the programme is exemplified by the recent designation of the 100th orphan compound, 24,25-dihydroxycholecalciferol, which holds promise in the treatment of uraemic osteodystrophy resulting from haemodialysis.


New topical beta-blockers for glaucoma

United Kingdom — Topical β-adrenoreceptor blocking agents effectively lower intraocular pressure in patients with chronic open-angle glaucoma. Since timolol was introduced in 1979 they have been recognized to hold advantage over other eye-drops, such as pilocarpine or adrenaline, because they are better tolerated and need to be administered only twice daily. Several different topical β-blocking preparations are now available for ophthalmic use and their relative merits have recently been reviewed within the Drug and Therapeutics Bulletin. Systemic absorption following instillation of timolol has long been identified as an occasional cause of unwanted systemic effects, particularly bradycardia and bronchospasm. Carteolol may have fewer systemic effects than timolol, although the evidence for this requires confirmation. Betaxolol is selective for β1-adrenergic receptors and may have advantages over timolol in patients with known airways obstruction, although it can also cause respiratory difficulty. Metipranolol costs less than the other preparations and is recommended as worth considering for routine use. It is emphasized that each of these preparations should be used with extreme caution in patients with severe pulmonary or cardiac disease. Moreover, each contains benzalkonium as a preservative which is selectively absorbed into the matrix of soft contact lenses and may subsequently gradually leach out and irritate the cornea.


Harmful antidiarrhoeal drugs

A campaign calling for the removal of over 200 antidiarrhoeal drugs containing antibiotics has been launched by Health Action International (HAI). The campaign is based on a report by A. Chetley alleging that two out of every three antidiarrhoeal drugs in Asia, Africa and Latin America contain an antibiotic. He singles out products containing neomycin, streptomycin, chloramphenicol and the sulfonamides as “the worst of a bad lot” and he claims that some US$150 million a year is wasted on these products — money that could and should be spent on encouraging the use of oral rehydration which is the appropriate treatment for most diarrhoeas. The report will be sent to health ministries, drug regulatory authorities and medical schools around the world.


Qinghaosu: a new antimalarial from traditional medicine

The story of the rediscovery and development of Qinghaosu from the plant Artemisia annua is featured in a recent issue of Far East Health. Much of the credit is accorded to Dr Li Guoqiao of the Guangzhou College of Traditional Chinese Medicine in Canton. His work, during which he intentionally
contracted malaria, has caught the imagination of the Chinese public. The success of his team results from a systematic exploration of the use of Chinese medicinal herbs during which he collected folk remedies, interviewed practitioners of traditional medicine (including his own father) and studied ancient medical literature.

Qinghaosu is not water soluble and initial trials were disappointing until extracts were prepared using the organic solvent diethyl ether. Chinese scientists have since succeeded in isolating the active principle of qinghaosu, a diterpene now accorded the international nonproprietary name of artemisinin, and they have confirmed its efficacy in the treatment of chloroquine-resistant cerebral malaria. Artemisinin is administered by suppository to avoid destruction during the first passage through the liver, but several analogues have now been synthesized which are water soluble and suitable for parenteral administration.

More interesting developments seem destined to stem from Dr Li's discovery since both artemisinin and the active principle of another Chinese plant (Artabotrys uncinatus), which is also claimed to have antimalarial properties, contain peroxide moieties that are rarely found in naturally-occurring substances.


**A review of medicinal plants used in Spain**

Spain — The latest issue of the Information Bulletin produced by the Division of Clinical Pharmacology of the University of Barcelona describes the controls applied to the preparation and sale of medicinal plants in Spain:

- A ministerial order of 1973 authorizes the free sale of 109 preparations, each derived from single plants.

- Preparations of a further 334 species of medicinal plants are subjected to registration requirements which are less stringent than for other drugs.

- All galenical preparations of medicinal plants used in orthodox clinical practice are submitted to the same requirements as other pharmaceutical preparations.

The article emphasizes that claims regarding the value of herbal medicines are rarely based on controlled studies and that many of the widely used preparations are unlikely to have more than placebo value. None the less, it acknowledges that much of interest remains to be discovered and it points to a recent randomized clinical trial that has demonstrated the efficacy of feverfew (*Tanacetum parthenium*) in the prophylaxis of migraine attacks.


**Anthrax: sporadic cases still reported throughout the world**

Anthrax remains a cause of devastating epidemics and epizootics in wild and domestic animals, but its incidence in man has dropped markedly within the past twenty-five years. Probably no more than 500 cases per year occur throughout the whole of Europe. However, in some other regions of the world the prevalence of the disease remains far higher. In 1978-1980 9711 cases of human anthrax were reported in 3 provinces of Zimbabwe alone of which 151 were fatal. Notwithstanding these figures, understanding of the disease and of the anthrax bacillus, have advanced to the point at which control, and even eradication, are feasible objectives. To stimulate a more rigorous attitude toward strategies for controlling the disease, WHO has commissioned a guide to its diagnosis, treatment and prevention that includes practical suggestions on training lay persons to diagnose anthrax in animals.

Revised measles vaccination strategy

United States of America — The Immunization Practices Advisory Committee on measles prevention has recently updated its recommended vaccination policy. It continues to recommend single-dose live measles vaccination at 15 months, although it advises that children of 12 months or more who are moving to areas of endemic or epidemic measles should receive measles-mumps-rubella (MMR) vaccine before arrival. It emphasizes that live measles vaccine is rapidly effective and may protect infants exposed to measles if given within 72 hours of exposure. It also emphasizes the value of revaccination of persons initially vaccinated at 12-14 months of age as an option during epidemics and for medical personnel and international travellers born after 1956 regardless of their vaccination status and assuming that no contraindication exists.


Routine use of beta-blockers following myocardial infarction

Some five years ago the results of two large multicentre studies indicated that the sustained use of α-adrenoceptor blocking agents by patients that had survived a myocardial infarction reduced the death rate by 24-40% over a follow-up period of almost three years (1, 2).

However, most patients die during or immediately after sustaining an infarction. Even without active treatment, 92 out of every 100 patients discharged from hospital may be expected to be alive one year later. Treating all 100 with a β-blocker would only increase survival by 3%, and in an occasional patient it might precipitate atrioventricular block and left ventricular failure, or mask the development of post-infarction angina.

A recent commentary in the *Journal of the Royal Society of Medicine* (3) concludes that, if beta-blockers were routinely used in England and Wales in the first year after myocardial infarction, 61 700 patients would be treated at a cost of about £4 350 000. About 1900 lives might be saved. This would reduce total mortality from myocardial infarction by less than 2%. For a general practitioner this would mean treating about 33 patients and saving a life every 11 years. Persuading survivors of infarction to stop smoking might well be at least equally effective in the long term, at lower cost and with less risk of adverse effects.

References

Tamoxifen in early breast cancer

United Kingdom — Early breast cancer is no longer seen simply as an anatomical problem but as a biological challenge determined by the extent of micrometastases at the time of diagnosis. Cyclical combination chemotherapy has been estimated to offer objective benefit to over 50% of women with advanced breast cancer. However, the systemic toxicity of these regimens renders them inappropriate for women with early lesions who are otherwise entirely well. In these circumstances, endocrine therapy, particularly with the anti-estrogen tamoxifen, possesses the dual advantages of low toxicity and ease of delivery, even though it has been shown to be rather less effective than chemotherapeutic agents in the management of more advanced tumours.

Thus far evidence on the value of tamoxifen as an adjuvant to surgery has been inconclusive, partly as a result of concern regarding possible bias in the early trials. Much of this uncertainty has now been dispelled by a report from the Scottish Cancer Trials
Office on a study involving over 1300 women with early breast cancer, both premenopausal and postmenopausal, who were randomized to receive adjuvant tamoxifen, 20 mg daily for 5 years, either from the time of initial surgery or from the diagnosis of first relapse. These women have now been studied for periods ranging from 2.5-8 years, and the results to date indicate that, overall, continuous post-operative administration of tamoxifen reduces the relapse rate by about 4% in both pre- and post-menopausal women.

References

Drug treatment of manic depressive illness

Australia — Lithium was first discovered to be effective in manic excitement in 1949, but it is now used more frequently in the management of both bipolar and unipolar affective disorders. A recent article in the Australian Prescriber offers the following viewpoint on its current status in the management of these conditions:

• Acute mania: Because antipsychotic drugs are generally more effective, lithium is rarely used alone. However, it remains of value as an adjunct in severely ill patients who require hospitalization, since it accelerates the rate of remissions and averts the need for very high doses of neuroleptics and the consequent risk of tardive dyskinesia. The main disadvantages of lithium, particularly when it is used alone, are its toxicity, the long latency before a response occurs and the need to engage the patient's collaboration since it has to be taken by mouth. Because of the narrow therapeutic index, serum concentrations need to be monitored and initially maintained within the range 1.0 to 1.4 mmol/l 12-14 hours after the night-time dose, although in the post-acute phase this can be reduced to between 0.6 and 1.0 mmol/l.

• Prophylaxis of bipolar disorder: Lithium prophylaxis is warranted only when episodes of mania or depression are both frequent and severe, and are liable to create a need for hospitalization more often than once every 3-5 years. The response to lithium is variable, and relapses can occur during treatment, although their frequency and severity are considerably reduced.

• Prophylaxis of unipolar depression: Because more specific antidepressants are equally effective, there is little justification to use lithium which demands more frequent administration and regular monitoring of blood levels. Lithium should be used only when specific antidepressant treatment has failed or when antidepressants are contraindicated or not tolerated.

• Treatment of depressive episodes: Although lithium is of value in treating episodes of depression as well as for prophylaxis, it is less effective than antidepressant drugs and electroconvulsive therapy. However, used as an adjunct to other treatment it may help to bring about a remission in an unresponsive patient.

Regardless of the context in which lithium is used the dose should always be individually tailored by careful monitoring of blood levels. The total daily requirement may vary from 500 to more than 2000 mg. This should be taken in 2 or even 3 divided doses to avoid peak concentrations that cause nausea, diarrhoea or tremor. Many patients find sustained release preparations easier to tolerate.

Contraindications to treatment include renal failure, cardiac failure or other serious illness and pregnancy, particularly during the first trimester.

A number of recent studies suggest that lithium and carbamazepine may act synergistically and that combined therapy may be effective in the treatment of bipolar conditions resistant to lithium alone. Clonazepam is also claimed to be effective in the manic phase of such illnesses, particularly in relieving hyperactivity and pressure of speech. It is not recommended for prophylactic use and, at present, it is best reserved for the treatment of
severely disturbed patients at dosages of no more than 4-8 mg a day.


Do we need benzodiazepines for treatment of anxiety and insomnia?

**United Kingdom** — A recent article in the *Drug and Therapeutics Bulletin* emphasizes that there are better ways of dealing with anxiety and insomnia than long-term treatment with benzodiazepines. It points out that all benzodiazepines can cause dependence and that withdrawal symptoms are frequent with certain compounds and particularly with lorazepam. Whether benzodiazepines still retain a place in the treatment of these conditions is seriously questioned particularly when factors such as family illness, personal inadequacy, social isolation and housing problems are prominent. Insomnia is often responsive to such simple measures as avoiding coffee, tea, alcohol and exciting TV programmes before going to bed. If short term use of a hypnotic is necessary it may be best used only one night in three. Anxiety can often be treated effectively by short-term drug treatment, or even without resort to drugs, particularly when general practitioners with psychological skills are supported by community psychiatric nurses or social workers. When explanations and reassurance fail other measures, such as relaxation tapes and self-help groups identified with specific social problems, can be of value both in the primary treatment and in facilitating withdrawal from benzodiazepines.


Rubella vaccination policy

**United Kingdom** — Immunization programmes against measles, pertussis and rubella have not been as effective in the UK as in some other European countries. The congenital rubella syndrome continues to occur at an unacceptable level even though it is estimated that, as a result of the current vaccination policy, 97% of pregnant women are now immune. It is now recognized that mass vaccination during infancy is necessary if the disease is to be eliminated. The measles vaccine currently given to young children will consequently be phased out and replaced by a combined measles/mumps/rubella vaccine. Selective rubella vaccination of schoolgirls will be continued, however, until circulation of the virus has ceased.

A recent letter to the *Lancet* emphasizes that selective vaccination should not be dropped prematurely if the risk of emergence of non-immune cohorts of adult women is to be averted in the next century. The Public Health Laboratory Service has consequently set up a surveillance system to monitor changes in immunity to rubella in different age-groups both to detect the emergence of susceptible cohorts and to determine whether they are at risk of infection.


Hepatitis B vaccine from Republic of Korea at US$ 1 per dose?

Frustrated by the prohibitive cost of currently-available hepatitis B vaccines for many developing countries, a team of international experts has formed a task force to promote the manufacture of cheaper products. Alfred Prince of the New York Blood Center, a senior member of the task force, has licensed his purification process for plasma derived vaccine to Cheil Sugar, a subsidiary of Samsung, a conglomerate in the Republic of Korea. Safety tests and clinical trials have been performed according to guidelines of the World Health Organization; trials involving 500 subjects have confirmed the safety, efficacy and immunogenicity of the vaccine which is already sold in the Republic of Korea, India and Indonesia. Dr Jim Maynard, Director of the WHO Collaborating Centre on Hepatitis B at the US Centers for Disease Control
and a member of the task force, has visited the Cheil plant. He confirms that the company relies on newly-developed probes to check batch safety and rejects allegations from competing manufacturers that batches are not adequately tested for safety. Provided that the demand for Cheil's vaccine rises to around five million doses, the company predicts that it will be able to reduce the price from around US$10 to US$1 per dose.


Does vaccination decrease incidence of *H. influenzae* type B infections?

**United States of America** — An *Haemophilus influenzae* type B polysaccharide vaccine was first licensed by the Food and Drug Administration in April 1985. Since then two other companies have marketed similar products. The efficacy of these vaccines was first established in a randomized, controlled clinical trial conducted in Finland involving over 48 000 children aged 18-71 months. The protection rate was estimated to be of the order of 90%. In April 1987 the FDA convened a workshop to discuss the results of ongoing studies in the United States. It was concluded, on the basis of the available data, that the benefits of the vaccine continue to outweigh any potential risk. However, data more recently forthcoming from recent field studies undertaken in the USA are ambivalent on the benefits obtained from vaccination.


**United States of America** — The introduction in April 1985 of the *Haemophilus influenzae* type B (Hib) vaccine is claimed to have significantly decreased the incidence of *H. influenzae* infections among children who attend day-care centres in a metropolitan area of Alabama (1). After administration of 12 800 doses of Hib vaccine to children of 18 months to 5 years of age, a significant decrease of this type of infection was found in 1986. It is estimated that, if these results are representative of the situation nationwide, some 2500 of the 18 000 cases of invasive *H. influenzae* type b infection that occur annually in the United States would be prevented.

This conclusion, however, would be premature since no benefit from the vaccine has yet been demonstrated in case-control studies undertaken in Minneapolis (2). These discordant results underscore the need to establish secure base-line estimates of disease incidence if the effects of an intervention strategy, such as the introduction of a new vaccine, are to be determined with adequate confidence.

References

Accidental drug poisoning in children

**United States of America** — Recently-collated information has been used by the Centers for Disease Control to demonstrate some contemporary trends in cases of accidental poisoning in children. The information, which was obtained from nine poison control centres between February and May 1986, is based upon some 3000 incidents, three-quarters of which involved children aged from 18 to 42 months. Almost half the drugs were intended for the mother or other adult female relative, and one sixth were intended for grandparents. The most frequently ingested products were antimicrobial agents (25%), birth control pills and hormones (15%), analgesics (10%), and cardiovascular drugs (10%) and they were most frequently discovered in the kitchen (50%) or bedroom (24%). Child-resistant containers proved to be far from infallible. Some were simply ineffective. Others, because they were difficult to operate, were either left open or discarded.

The investigators emphasize that this study should be interpreted cautiously since the data may not be fully representative of the population at large. The findings, however, show the extent to which young children are uncritically adventurous in their
tendency to explore the world and to put things in their mouths. They also leave no doubt about the need to educate parents and grand-parents to be vigilant in keeping medicines out of the reach of children, and never to leave them in the kitchen or bedroom. Most importantly, child-resistant containers should always be capped tightly and should never be modified or discarded.


United Kingdom — A similar prospective study, implemented in the course of an investigation into the effectiveness of packaging in preventing childhood poisoning, has been undertaken by the National Poisons Information Service. It is based upon some 2000 cases of suspected accidental poisoning in children aged 0-5 years recorded between July 1982 and February 1984. As in the US study, three-quarters of the children were 2 and 3 year-olds. The products most frequently implicated were drugs (59%), household products (37%) and plants (3%). Among the drugs, analgesics, anxiolytics, cough medicines and oral contraceptives were commonly cited. Less than a quarter of the children had signs or symptoms on presentation and in only two instances were these serious. Treatment other than ipecacuanha and oral fluids was seldom required and less than half the children were admitted to hospital for observation. No deaths occurred and admission to an intensive care unit was required in only seven instances.


Will chloroquine resistance spread throughout the range of Plasmodium falciparum?

The author of a recent review of the current status of chloroquine resistance advises that claims of renewed sensitivity of P. falciparum to chloroquine in areas where its use has been discontinued should be viewed with both scepticism and pragmatism until firmly proven.

Chloroquine resistance, confirmed by clinical and laboratory studies, was first reported in 1960 from South America and South-East Asia. It spread rapidly to cover much of the northern part of South America around the Amazon Basin, and most of the Malaysian peninsula, Thailand and Vietnam. In the 1970s it was notified for the first time from East Africa, and it extended in South-East Asia to many Pacific islands, China, Pakistan, Afghanistan and Iran. Most ominously, cases are now reported from West Africa. It is important that broadly comparable information is obtained from different regions of the world and, since 1985, WHO has developed standard internationally-accepted in vivo and in vitro procedures for assessing the response of malaria parasites to therapeutic doses of antimalarial drugs.

Chloroquine continues to be a cheap, effective and safe antimalarial for treating the indigenous populations of Africa. As yet, there is no firm indication of whether the long-term decline in its use in South-East Asia will result in the resurgence of drug-sensitive populations of P. falciparum. Unfortunately, analogous experience with insecticides has shown that when sensitivity is restored it is usually short-lived once the compound is reintroduced on a wide scale.


Tetracycline prophylaxis for malaria

The need to assess whether selective use of tetracyclines has value in malaria prophylaxis, particularly for non-immune individuals visiting or working temporarily in areas with a high transmission of multidrug-resistant strains of Plasmodium falciparum, is discussed in a recent letter to the Lancet. It is suggested, on the basis of current information, that protection should be obtained if administration is started just before arrival in a malarious area and then maintained daily throughout the period of exposure. Subsequent prophylaxis for several weeks, as recommended for chloroquine, should not be necessary because the
**tetracyclines appear to inhibit completely the development of pre-erythrocytic stages of *P. falciparum.*


## Antibiotic resistance worldwide

**United States of America** — In 1983 the Fogarty Center of the National Institutes of Health sponsored an extensive review of the benefits and problems that derive from widespread use of antibiotics. Individuals from many different countries and disciplines were allocated to six task forces which have recently produced their reports. The conclusions of the group that studied antibiotic resistance are of particular interest:

- The considerable antibiotic exposure to which many bacteria have been subjected over the past half century has resulted in widespread genetically-determined antibiotic resistance. The distribution of this resistance seems to be determined not only by patterns of antibacterial use but also by variations in the genetic potential of the bacteria themselves.

- The prevailing levels of resistance to older antimicrobial agents make them unreliable as drugs of first choice for serious infections. However, these levels seem to have stabilized, possibly because the distribution of genes specifying resistance has in some way equilibrated as a result of sustained exposure. Declining use of some agents, such as streptomycin, has not resulted in a proportionate loss of resistance.

- Some genes specifying resistance to older antimicrobial agents have first appeared in new pathogens relatively recently. On occasion, these incursions have resulted in widespread dissemination of multiresistant pathogens including strains of *Haemophilus influenzae* and *Neisseria gonorrhoeae*. The sporadic emergence of multiresistant strains of *Klebsiella pneumoniae* and *Streptococcus faecalis* strains producing a β-lactamase suggests that other serious problems may lie ahead.

- Resistance to the most recently introduced antibacterial agents including gentamycin, methicillin, and trimethoprim has also been increasing. This is particularly disturbing in the case of trimethoprim because no comparable orally-administered antibiotic is currently inexpensive enough to replace it.
• Isolates of multiresistant shigella, nontyphoidal salmonella, penicillinase-producing *N.* gonorrhea, and isoniazid-resistant *Mycobacterium tuberculosis* appear to be as much as 30 times more prevalent in some regions of developing countries than elsewhere. Moreover, without laboratories to detect resistant strains and without access to more recently introduced antibiotics to treat these infections, the resulting morbidity and mortality is further compounded.


**Hypoglycaemia unawareness in diabetics transferred from animal to human insulin**

United Kingdom — It is becoming evident that the early warning symptoms of hypoglycaemia in insulin-dependent diabetics are less pronounced in patients who have been switched from beef/porcine insulin to biosynthetic human insulin. This phenomenon, known as “hypoglycaemia unawareness” occurs because the warning symptoms of sweating, tachycardia and tremor resulting from sympathoadrenal stimulation are attenuated or suppressed. Patients thus pass directly into a state of neuroglycopenia and have unusually little time to act before lapsing into a state of severe hypoglycaemia. The authors of a recent article in the *Lancet* conclude that the advantages of human insulin are marginal in comparison with the life-threatening hazards associated with hypoglycaemia unawareness. They call into question the marketing strategies of manufacturers that seek to influence physicians to switch all patients from animal to human insulin. The latter, in their view, should be reserved for patients who, as a result of antibody production or for other reasons, do not respond adequately to the animal-derived products.


**Cutaneous reactions to sulfadoxine + pyrimethamine in travellers**

The combination of 25 mg pyrimethamine + 500 mg sulfadoxine (Fansidar®, Roche) occasionally causes severe sulfonamide-induced cutaneous adverse reactions in sensitized individuals using it for malaria prophylaxis. The incidence of such reactions in United States citizens has been estimated as 1 : 5000 to 1 : 8000 with a risk of death of 1 : 11 000 to 1 : 25 000 (1).

Among Swiss travellers the incidence of severe reactions has been estimated to be some 30-fold lower. The possibility has thus been raised that, since practically all the American travellers had concurrently received chloroquine, an unexplained interaction may have potentiated the toxic effect of the sulfonamide.

Twenty-four similar reactions have now been reported among Swedish travellers who used Fansidar alone as prophylaxis. In seven cases the reaction was severe and, in two instances, fatal.

It is estimated that the number of Swedish travellers receiving Fansidar during the period in question is unlikely to have exceeded 70 000. The incidence of severe cutaneous reactions and fatalities is thus estimated respectively as 1 : 10 000 and 1 : 35 000. Since these are of the same order as those generated in the USA, they refute the hypothesis that Fansidar in combination with chloroquine is more hazardous than Fansidar alone.

The authors conclude that Fansidar cannot be unequivocally recommended for short-term prophylaxis, but its continued use might be justified for non-immune subjects living in areas of Africa with a high incidence of chloroquine-resistant *Plasmodium falciparum* and who have already been taking Fansidar for some time.

References
Penicillinase-producing *Neisseria gonorrhoeae*

**United States of America** — The advent of penicillinase-producing *Neisseria gonorrhoea* (PPNG) has greatly increased the cost and complexity of treating gonorrhoeal infections. In the United States the incidence of these infections is being contained to a considerable extent by sustained laboratory surveillance. The success of the strategy is exemplified by a cluster of 40 cases detected in 1986 by a laboratory in Denver. At the outset of the epidemic, the Colorado Department of Health issued an advisory notice requesting other Denver metropolitan laboratories to begin routinely screening all isolates for β-lactamase and recommending that patients with confirmed or suspected PPNG infection be treated with ceftriaxone or spectinomycin. The epidemic declined when a further notice was issued four moths later reiterating the need for effective therapy against PPNG in patients, their sexual partners and any patient who might be unlikely to comply with tetracycline therapy.


Maternal exposure to spermicides does not increase the risk of birth defects

**United States of America** — Whether or not the use of spermicide contraceptives increases the risk of birth defects has recently aroused controversy in the medical press. A large case-control study now published in the *New England Journal of Medicine* is largely reassuring in its conclusions. With the possible exception of a small subgroup of cases (limb reduction defects of unknown cause) no positive associations were demonstrated. Since no differences were detectable when spermicides of different composition were considered separately, the likelihood of a causal relationship was considered to be remote even in this instance. The comparisons were effected by assessing exposure to spermicides in two cohorts of infants. One was composed of infants with one of several commonly-occurring defects (265 with Down's syndrome, 396 with hypospadias, 146 with limb reduction defects, 116 with neoplasms, and 215 with neural tube defects). The other consisted of 3442 control infants with a wide variety of other defects. Possible association of these specific defects with spermicide use was sought in relation to periconceptional exposure, use during the first trimester, and also any use during the lifetime of the mother.


Safety requirements for steroidal contraceptive drugs

Even among highly-evolved drug regulatory authorities important differences of approach exist to the toxicological testing of steroidal contraceptive substances. A WHO Symposium convened in February 1987 concluded that some widely-required studies provide no basis for predicting the consequences of long-term use in women. Particular doubt was expressed about the value of long-term carcinogenicity studies, including 7-year studies in beagle dogs and 10-year studies in non-human primates. It was agreed, having regard to the vagaries of toxicological assessment, that a systematic epidemiological approach to the identification of long-term uncommon effects is of prime importance.

Guidelines for the toxicological and clinical assessment of steroidal contraceptive drugs and for post-registration surveillance, which are based upon the conclusions reached during the Symposium, have been published.

Experimental vaccine against Lassa fever

United Kingdom — The Lister strain of vaccinia virus has been used to construct a recombinant that expresses the nucleocapsid gene of Lassa virus. The bioengineered virus, when inoculated into guinea-pigs, protects them against challenge with Lassa virus which, in control animals, produces viraemia and death. The prospect that protective immunity to Lassa fever can be evoked by an experimental vaccine is particularly encouraging since this infection has been found to be common in the limited areas of West Africa where it has been adequately studied. Although many infections result only in mild or subclinical illness, severe cases are frequent enough to place a substantial burden on the health care services in these areas.


Genetically-engineered vaccines to be developed in India

India and the United States of America have signed an agreement to develop vaccines and diagnostic tests for major communicable diseases. It is estimated that the five-year project will cost US$ 9.6 million, out of which the US government will provide US$ 7.6 million. Particular attention is paid to the rights and welfare of participating subjects who will be protected in accordance with the laws, regulations and ethical precepts of both countries. Within India, all studies will be performed under the aegis of the Indian Council of Medical Research and the Department of Biotechnology of the Indian Ministry of Health. Indian scientists will also work within the US laboratories in which the vaccines will be developed. Among the products to be tested are vaccines against organisms responsible for endemic diarrhoeal diseases including rotavirus, cholera, shigella, E. coli and salmonella, a cellular pertussis vaccine, a recombinant DNA vaccine against hepatitis B and an oral typhoid vaccine.

Equally important, since there are 7 million dog bites a year in India, is a plan for field testing of a vaccinia/rabies glycoprotein recombinant vaccine developed at the Wistar Institute. Originally developed for use in cattle, it will be incorporated in food-bait in an attempt to control rabies in stray dogs.


New developments in biotechnology

United States of America — The proceedings of the Second Annual Conference on Biotechnology, which was sponsored by the American Society for Microbiology and held in San Diego, provide a valuable insight into the variety of ways in which genetic manipulation of microorganisms is already influencing medicine and medical research.

• Drug production:

   The possibility of implanting the genes for bacterially generated antibiotics in other bacteria has created a means of producing purer preparations of some of these substances. C. R. Hutchinson of the University of Wisconsin has cloned the bacterial genes for the anthracycline antitumour agents tetracenomycin C and daunorubicin in species of Streptomyces from which they are readily separated. However, manufacturers will need to assess the recombinant technique carefully because, although cheaper, the production process may pose safety hazards.

   Similarly, as reported by T. H. Ingolia of Eli Lilly, fungal genes for penicillin and cephalosporin can be implanted in Escherichia coli to produce isopenicillin N synthetase, deacetylcephalosporin V synthetase, and deacetoxycephalosporin C synthetase. It is expected that the insertion of multiple copies of the genes will result in increased production.

   Recombinant techniques may also ultimately provide a means of enzyme replacement in patients with certain deficiency diseases. L. J. Hock of Syntro Corp. reported that she and her associates have infected human fibroblasts with cytomegalo-
virus carrying the β-galactosidase gene and shown that these cells produce this enzyme in culture. She is optimistic that attenuated cytomegalovirus may be of value clinically as a vector for a variety of genes for human enzymes.

• Antibody technology:
The creation of human monoclonal antibodies by substituting human for mouse antibody genes in hybridoma clones is now feasible. With the mouse component removed, G. Winter of the British Medical Research Council predicts that many of the adverse effects of monoclonal antibody administration will be eliminated, and that the spectrum of therapeutic applications of these preparations will be broadened.

Monoclonal antibodies can also be used to accelerate biological reactions for which no catalytic enzymes are available. A. Tramontano of Scripps Clinic explained that, although the intermediate products of catalysis are too unstable to observe directly, their structure can often be inferred and approximated by stable analogues.

• Laboratory testing of antitumour agents:
Monitoring the movement of growing cells subjected to an electrical current may have potential in the evaluation of antitumour agents in vitro. C. R. Keese and I. Giaver of the General Electric Research and Development Center exemplified the potential of the process by explaining that, as the cells move across a culture dish with implanted electrodes, electrical resistance increases. In early experiments it was found that signals produced by cancerous fibroblasts differ markedly from those generated by normal fibroblasts.


Pharmaceutical production in Algeria: current trends

Algeria — High priority has been accorded in a recent governmental report to plans to increase national pharmaceutical manufacturing capability. A new antibiotics plant at Medéa is scheduled to produce about 300 metric tons of essential antibiotics each year, including penicillins, tetracyclines and streptomycin. At the same time, total annual production at the three existing formulation plants will be increased progressively from 44 million to 70 million pieces. The broad objectives of national policy are portrayed as aiming:

• to raise technological and economic self-sufficiency in pharmaceuticals;

• to implement an essential drugs strategy that addresses both health policy and the need for industrial development; and

• to develop pharmaceutical production in accordance with an integrated plan.

In the longer term, it is hoped that three important goals can be satisfied:

• the alleviation of much treatable disease through the provision of safe and effective medicinal products;

Biotechnologically-derived TPA patent invalid?

United Kingdom — A recent judgement of the High Court in London seems destined to have an important influence on the future of biotechnological research, and the competitiveness of this sector of the pharmaceutical industry. The Court ruled that Genentech’s patent claim covering the thrombolytic agent tissue plasminogen activator (TPA) is invalid. The case was brought by the British pharmaceutical company, Wellcome Foundation Limited which is among several competing in an intense race to market TPA. This is expected to be the first billion dollar drug emanating from the biotechnology industry. The ruling of the British court has no legal bearing in the United States, where a TPA patent has not yet been issued. Nonetheless, it remains an important test case of the extent to which proprietary rights can be applied to the products of recombinant DNA technology.

• the successful transfer of technologies required for the production of good quality products;
• significant savings of foreign currencies by producing a limited number of products at competitive prices.


**GMP training aids offered for loan**

**Australia** — The medicines inspectorate of the Department of Health has offered to loan to health authorities of developing countries a series of training aids on good manufacturing pharmaceutical practices. Films, slide sets and booklets are available on the understanding that the borrower will pay the transportation costs. A detailed catalogue can be obtained on request from: Inspection Unit, Commonwealth Department of Health, P. O. Box 100, Woden ACT. 2606, Telex AA62149. Telegram “Health” Canberra.

**Indonesia moves to push down drug prices**

**Indonesia** — Dr Suwardjono Surjaningrat, Minister of Health, has placed pharmaceutical firms on notice that, unless they are prepared to implement Good Manufacturing Practices (GMP) to assure the quality of their products, they will be closed down. The warning came during a recent national seminar on guidelines for Good Manufacturing Practice (GMP) organized jointly by the Department of Health and the Pharmacists’ Association of Indonesia. According to Dr Lembong, Chairman of Indonesia’s Pharmaceutical Manufacturers’ Association, the government spends a total of some US$ 50 million per year on drugs, an amount that is equivalent to about one tenth of the private sector market.

The significance of the Minister’s statement derives from the government’s commitment to purchase drugs from foreign manufacturers only when they cannot be made locally. Indonesia’s three government-owned pharmaceutical companies produce low-cost essential drugs to the government’s own requirements as well as generic drugs destined for both the public and private sectors. The 38 foreign joint venture manufacturing facilities in Indonesia service a private market that is some tenfold larger and worth about US$ 250 million annually.

Dr W. Wanandi, a governmental adviser on drugs, claims that free market competition does not always result in the lowest prices to the consumer. To illustrate his point he cites ampicillin which is available under 60 brand names and supplied at a wide variety of prices. To increase efficiency, Dr Wanandi proposes mergers as a possible solution.


**Concern over expanding use and growing cost of laboratory tests**

**United States of America** — A recent article in the *New York Times* predicts that medical tests conducted in hospitals, independent laboratories and doctors’ offices will cost as much as US$ 27 billion this year, or about 6 per cent of the total national health care expenditure of more than US$ 425 billion. This figure now almost matches spending on drugs and medical supplies which amounted to US$ 28.5 billion in 1985. Its size has triggered debate on the need for some of the tests that are used by doctors not only to supplement their clinical judgment, but also as a protection against malpractice lawsuits. Health insurance companies claim that some 20 per cent of the tests undertaken aid neither in the diagnosis nor in the treatment of the illness.

The expansion of testing is, in part, a reflection of advancement in medical technology: automated and computerized machines can perform as many as 24 tests on 150 blood samples each hour. It also represents an important source of income for hospitals and the 40 000 doctors who perform the tests in their own offices.
The American College of Physicians has recently issued guidelines to help physicians decide when to order tests. These, however, have aroused controversy within the profession and Congress has directed the Administration to study whether Federal standards should be imposed to assure proper use of laboratories in physicians' offices.


Future of the world pharmaceuticals market

United Kingdom — Writing in the Pharmaceutical Journal Dr F. Humer of Glaxo expresses optimism that the proportion of gross national product spent on health will tend to increase in future years despite efforts of governments worldwide to contain health costs. Given a choice, he suggests, public opinion would favour greater expenditure on health care. Notwithstanding this favourable prospect for the industry, however, he points to the inherent uncertainty in commercially-based pharmaceutical research. Out of a total of some 28 000 drug products, 52 account for 20 per cent of the total world market of US$ 60 billion. Two products alone — ranitidine (Zantac®, Glaxo) and cimetidine (Tagamet®, Smith, Kline & French) — have sales exceeding US$ 1 billion per year but therapeutic areas such as atherosclerosis, cancer, migraine and hypercholesterolaemia offer similar potential for successful drugs since each submarket tends to be dominated by a few products.

The market for "me too" drugs has become decidedly unfavorable in Dr Humer's opinion. Beta-blockers, for example, still lead in the cardiovascular field, but any new compound of this class launched now could take only a small percentage of the market unless it represents a clear therapeutic advance. Even in the case of truly innovative products, only one in every four will give a worthwhile return, two will give a questionable long-term pay-back, while the fourth will not even allow the recovery of development costs.


Quality control of condoms

United States of America — Between April and July 1987, the Food and Drug Administration impounded 15 shipments of condoms from Korea and four from Malaysia that failed to meet prevailing quality standards. These require that no more than four in one thousand show signs of leakage when they are inflated with 300 mls of water. To ensure that the required standards are met, the FDA has stepped up both its inspection of manufacturers and processors and its testing of all products in the distribution chain. The agency has also urged manufacturers to provide users with more explicit information on how condoms should be used to maximize protection against sexually transmitted diseases, including AIDS.


Tenth anniversary of last smallpox case

Ten years have elapsed since the world's last case of endemic smallpox was recorded in October 1977 in southern Somalia, although a few laboratory-acquired infections were reported as late as 1978. In 1980, on the basis of reports from international commissions of experts, the World Health Assembly confirmed the eradication of the disease and recommended measures for ongoing surveillance. Since then several hundred cases of suspected smallpox have been investigated, but every one has turned out to be a case of "mistaken identity"—usually chickenpox, measles or monkeypox.


Control for anabolic steroids?

United Kingdom — In the light of concern about the misuse of anabolic steroids in sport, the Home Office has asked the Advisory Council on the
Misuse of Drugs to consider whether anabolic steroids should be controlled under the Misuse of Drugs Act, 1971.


Sudden infant death syndrome: unrelated to DPT/IPV immunization

**France** — Between 9 and 28 March 1986, 5 cases of sudden infant death syndrome were reported among children who had received an injection of quadruple vaccine (diphtheria, pertussis, tetanus combined with inactivated poliomyelitis vaccine) within the previous 24 hours.

The cause of this remarkable cluster of cases remains unknown, but a case-control study involving comparison of the records of 153 children certified as dying from sudden infant death syndrome with those of 437 controls failed to reveal a statistical relationship between this syndrome and the vaccine and provided no grounds for modifying the immunization schedule.


National drug policy in India: current trends

**India** — In developing its national drug policies the Government has set itself four major objectives:

- ensuring the availability of essential, life-saving and prophylactic medicines of good quality, at reasonable prices;

- strengthening systems of quality control of medicinal products and promoting their rational use in the country;

- creating an environment conducive to investment in the pharmaceutical industry, encouraging cost-effective production through scaling-up manufacturing capacity, and introducing both new technologies and new drugs;

- strengthening the indigenous capability for production of drugs.

It is recognized that successful implementation of the policy will require much collaboration and coordination between the Ministries of Health and Industry. Important elements of the plan include the creation of a National Drug Authority, the compulsory use of generic names, application of pricing controls to certain important drug substances and effective licensing and regulation of both manufacturers and finished products.

Reference: *Measures for rationalisation, quality control and growth of drugs & pharmaceutical industry in India*. Ministry of Industry, Department of Chemical and Petrochemicals, New Delhi, 1986.

Combined oral contraceptives protect against ovarian neoplasms and functional ovarian cysts

The results of two recently published independently-conducted surveys undertaken respectively in the United Kingdom and the United States of America confirm earlier reports that use of combined steroidal oral contraceptives reduces subsequent risk of ovarian neoplasms and functional ovarian cysts.

The report of a case study involving 17 000 women taking part in the Oxford Family Planning Association Project (1) concludes that epithelial cancer of the ovary is fourfold less common among women who have ever taken oral contraceptives as those who have never done so. However, the data are insufficient to determine whether protection increases with duration of use of oral contraceptives or whether it persists for many years in those who stop taking the pill. There was no firm evidence of any association between use of oral contraceptives and benign teratoma or cystadenoma.
Functional cysts of the ovary occurred much less commonly in women who had taken combined contraceptives in the six months preceding diagnosis than in those who had never taken oral contraceptives or who had not taken them within this period. This protective effect, which did not occur in women taking progestogen-only preparations, was more pronounced for corpus luteum cysts (78% reduction) than for follicular cysts (49% reduction). It is estimated that about 28 operations for functional ovarian cysts are avoided each year among every 100 000 women who take oral contraceptives.

Conversant results have been obtained in a case-control study conducted in the USA that compared 546 women between 20 and 54 years of age with ovarian cancer who were identified from eight population-based cancer registries with over 4000 control subjects. Women who had used oral contraceptives had a risk of epithelial ovarian cancer of 0.6 in comparison with those who had never used them. This protective effect was seen in women who had used oral contraceptives for as little as three to six months, and it remained detectable for 15 years after last use; it was independent of the type of oral contraceptive used and of the histology of the ovarian cancer.

References

"Antiaging" creams: cosmetics or drugs?
United States of America — The Food and Drug Administration has warned cosmetics manufacturers that labelled claims for products containing such phrases as "antiaging", "cellular repair", "age reversal" render them subject to statutory regulatory requirements for drugs including obligatory premarketing approval based upon demonstration of safety and effectiveness for the labelled uses.


Product liability in the USA
United States of America — The implications for the pharmaceutical industry of the "product liability crisis" are reviewed in a recent article by N. Mattison of Ciba-Geigy USA. A sixfold increase in lawsuits filed over the past decade and an even greater increase in the scale of awarded damages has produced a precipitous rise in insurance rates. In 1984 alone damages of more than US$ 1 million were awarded on more than 400 occasions.

Part of the increase may have occurred because product liability in the USA is no longer based on a negligence standard but on strict liability. This does not require the plaintiff to prove that a defective product was knowingly manufactured or sold, only that the product was defective and responsible for the injury.

None the less, proving, in scientific terms, that a drug is unequivocally the sole or major cause of a
specific injury remains difficult and there is a conjecture that attempts will be made to use adverse drug experience reports filed by manufacturers with the Food and Drug Administration as evidence of a causal relationship in court. The number of reports submitted has risen from 15 000 in 1981 to 60 000 in 1986. Some observers believe that firms are over-reporting out of concern that top management will be held criminally liable for failing to report all possible adverse drug experiences but others remain convinced that firms still fail to report all possible adverse drug experiences because of concern about product liability. Initiatives directed at statutory reform are occurring at both federal and state level.

Both Congress and the Administration have proposed a return to a negligence standard. Meanwhile, at state level, efforts have been aimed primarily at underscoring the message that disproportionate awards inevitably drive up both insurance rates and the cost of all marketed drugs.

Reference: Mattison, N. Implications for the pharmaceutical industry of the product liability "crisis" in the USA. Pharmaceutical Medicine, 2:117-126 (1987).

**Egypt: a rapidly expanding pharmaceutical market**

**Egypt** — With annual sales of medicines approaching US$ 700 million, Egypt has become the first pharmaceutical marketplace in Africa and the 14th in the world according to a survey published in Afrique Médecine Santé. The public and the private sector are of almost equal importance.

National drug policy in Egypt aims at developing national production and licensing agreements (with or without joint-ventures) in order to meet local needs and to expand exports within Africa. Both foreign and national public-sector companies feature prominently among the ten leading producers and imports of finished products now represent only about 25% of the total market.


**Self-medication in Brazil**

**Brazil** — An analysis of over 13 000 completed questionnaires issued to households in Rio de Janeiro shows that most families keep medicines at home sometimes in substantial numbers. Elderly patients were the most avid hoarders, but less than half the medicines were prescribed by doctors; friends and non-pharmacist drug sellers were the most popular prescribers. Nearly all of the patients said that they read the package inserts, but 38% did not know that drugs could cause harm. Those that were worried about side-effects usually looked to the pharmacist for help. Only one third went to their doctors.


**Selecting an NSAID**

**United Kingdom** — Faced with a bewildering variety of non-steroidal anti-inflammatory drugs (NSAIDs), prescribers find it virtually impossible to make a choice based on objective criteria of efficacy, safety and cost. The Drug and Therapeutics Bulletin has recently concluded that ibuprofen seems the least hazardous compound and should be the first to be tried, especially in patients with transitory symptoms or with degenerative joint disease who do not respond adequately to paracetamol alone. Treatment should start with the lowest recommended dose and subsequently be carefully titrated against symptomatic relief.

Patients should be warned that they should not expect 24 pain-free hours a day, but if an alternative is needed, this should be substituted and not added. They should be encouraged to report possible adverse effects, and renal function and electrolyte balance should be checked after the first few weeks of regular treatment in patients with cirrhosis, congestive heart failure, renal disease or gout. It should be remembered that the effect of concurrent diuretic or antihypertensive treatment is likely to be reduced by the NSAID.

Although these drugs are highly effective in relieving the symptoms of arthritis, several have been
withdrawn in recent years following reports of serious adverse reactions. In fact, one-quarter of all serious suspected adverse reactions reported to the Committee on Safety of Medicines in 1976-82 implicated an NSAID. Their benefits and risks consequently merit continuous reappraisal, particularly in the elderly, who receive most prescriptions of NSAIDs, and who are likely to be at greater risk.

Among the most widely-reported reactions are damage to the gastrointestinal mucosa and impairment of renal function, both of which are attributed to prostaglandin inhibition. The mechanism of other adverse reactions involving the skin and, rarely, the liver and the bone marrow are less certain, but exacerbations of acute asthma observed in susceptible patients are clearly allergic in nature.


Snake bites in Nepal

Nepal — Over 3000 snake-bites were treated in district hospitals between 1980 and 1985 and 144 of the patients died. Most cases occurred between June and October, during the monsoon, and most of the patients that died received no treatment within 7 hours of being bitten. The Ministry of Health has now entered into arrangements to procure the following types of anti-snake venom from India: cobra (Naja naja), krait (Bungarus caeruleus), Russel's viper (Vipera russelli), and saw-scaled viper (Echis carinatus).


Controversy on generic drugs in the USA

United States of America — The proceedings of a conference on postmarketing surveillance of multisource drugs convened in 1986 by the Center for the Study of Drug Development have recently been published. The participants, which included representatives from academia, health professions and industry, were agreed on the following general analysis of the situation:

• There is indisputable evidence that, in the past, drugs have been marketed which were improperly manufactured and that this has resulted in lack of therapeutic effect or toxicity. These manufacturing errors have been committed by both generic manufacturers and so-called "innovative" manufacturers. Dramatic past examples include multisource digoxin and chloramphenicol.

• With the passage of time, new criteria to assess bioavailability and predict interchangeability have evolved in response to the failure of older criteria and an increase in scientific knowledge.

• At the present time, there is controversy as to whether a bioavailability problem exists with regard to generic drugs approved by the US Food and Drug Administration in the last decade. The FDA, the generic drug industry, and some health professionals assert that there is no problem; the "innovative" pharmaceutical industry and some health professionals assert that there is. The latter, however, have not produced a convincing body of evidence to support their position.

• Anecdotal reports of clinical difficulties seen on changing patients from branded drugs to generic products have almost invariably described loss or diminution of therapeutic effect rather than toxicity. Such instances have generally not been well studied and validated.

• The use of generic drugs is primarily motivated by economic factors, but no one wishes to cut costs at the expense of inadequate treatment. Conversely, there is no desire to increase drug costs needlessly, if cheaper generic versions subjected to sound scientific requirements are available.

Reference: Postmarketing surveillance of multisource drugs, ed. L. Lasagna, Center for the Study of Drug Development, Tufts University, Boston, Massachusetts 02111, USA.
Pharmaceutical Products Approved

Aclarubicin (cytostatic)
Jaclacin®, Lundbeck, Iceland, Sweden.
powder for injection 20 mg/ampoule.
Indications: acute nonlymphoblastic leukaemia, recurrent or unresponsive to other therapy.
Contraindications, precautions, warnings: as for other cytostatic compounds.

Amfenac (nonsteroidal anti-inflammatory agent)
Fenazox®, Meiji Seika Kaisha, Japan.
capsule 50 mg.
Indications: pain in arthritic disease and after surgical or dental procedures.
Contraindications, precautions, warnings: as for other drugs of this class.

Arotinolol (β-adrenoreceptor blocking agent)
Almarl®, Sumitomo, Japan.
tablets 5 and 10 mg.
Indications: mild to moderate essential hypertension, angina pectoris, tachycardia.
Contraindications, precautions, warnings: as for other drugs of this class.

Brovincamine (vasodilator)
Sarbromin®, Sandoz, Japan.
tablet 20 mg.
Indications: symptomatic management of sequelae of cerebral infarction or haemorrhage, arteriosclerosis.
Contraindications: acute phase of cerebral infarction or haemorrhage; pregnancy (teratogenic at high dosage in rabbits); hypersensitivity.
Caution: patients with hepatic insufficiency, hypotension.
Adverse effects: somnolence, tinnitus, vertigo, gastrointestinal distress.

Cioconazole (antimycotic)
Pilzcin®, Shionogi, Japan.
cream, gel 10 mg/g.
Indications: dermatomycoses.
Contraindications: hypersensitivity.
Caution: not to be applied to the cornea, conjunctiva or open skin.
Adverse effects: local irritation.

Cioconazole (antimycotic)
Pilzcin®, Shionogi, Japan.
cream, gel 10 mg/g.
Indications: dermatomycoses.
Contrainindications: hypersensitivity.
Caution: not to be applied to the cornea, conjunctiva or open skin.
Adverse effects: local irritation.

Cloperastine (antihistamine)
Novotusil®, Inpharzam, Luxembourg.
syrup 2 mg/ml.
Indications: symptomatic treatment of cough.

Enoxacin (antibiotic)
Flumark®, Dainippon, Japan.
tablet 100 and 200 mg.
Indications: infection caused by susceptible microorganisms.
Contraindications: hypersensitivity, pregnancy, lactation.
Caution: in patients with severe renal dysfunction or convulsive disorders.

Famotidine (H₂-receptor blocking agent)
Pepcidin®, MSD, Iceland, Sweden.
tablets 20 and 40 mg; powder for injection 40 mg/ampoule.
Indication: gastroduodenal ulcer.

Formoterol (β-adrenoreceptor agonist)
Atock®, Yamanouchi, Japan.
tablets 20 and 40 μg.
Indication: obstructive airway disease.
Contraindications, precautions, warnings: as for other drugs of this class.
Gemeprost (prostaglandin derivative)
Cervagem®, Rhone-Poulenc, Finland.
tablet 1 mg.
*Indication*: termination of pregnancy.

Gestrinone (progesterone antagonist)
Nemestran®, Roussel, Netherlands
capsule 2.5 mg.
*Indications*: severe endometriosis, infertility due to laparoscopically confirmed endometriosis.
*Contraindications*: pregnancy, epilepsy, severe cardiac, hepatic and renal insufficiency.
*Caution*: migraine. Effective contraceptive measures must be instituted throughout treatment.

Mesalazine (anti-inflammatory agent)
Salofalk®, Falk, Netherlands.
suppositories 500 mg;
Asacol®, Cedona, Netherlands.
tablet 400 mg.
Claversal®, S. K. & F., Luxembourg.
*Indications*: ulcerative colitis, Crohn's disease.

Moxisylyte (vasodilator)
Moxyl®, Fujirebio, Japan.
tablet 30 mg.
*Indications*: symptomatic management of sequelae of cerebral infarction or haemorrhage.
*Contraindications*: acute phase of cerebral infarction or haemorrhage; hepatic insufficiency.
*Caution*: hypotension, recent angina pectoris or myocardial infarction. Safety during pregnancy and lactation not established

Nifuroxazide (intestinal disinfectant)
Bacifurane®, Meram, Luxembourg.
capsule 200 mg.
*Indications*: diarrhoea of bacterial origin, secondary infection in inflammatory colonic conditions.
*Adverse effects*: cutaneous or anaphylactic reactions.

Ofloxacin (quinolone antibiotic)
Tarivid®, Hoechst, Luxembourg, Austria, Japan.
coated tablet 100 mg.
*Indications*: infection caused by susceptible microorganisms.

Somatorem (methionyl growth hormone)
Somatonorm®, KabiVitrum, Ireland.
Genotropin®, KabiVitrum, Sweden.
Humatrope®, Lilly, Sweden.
injection 4 IU/ampoule.
*Indication*: short stature due to growth hormone deficiency.
*Caution*: diabetes mellitus.

Thymostimulin (synthetic thymostimulin analogue)
TP-1®, Serono, Luxembourg.
powder for injection 10, 25, 50 mg/ampoule.
*Indications*: primary or secondary immune deficiency with a proven or suspected cellular component.

Tilactase (enzyme preparation)
Millact®, Shionogi, Japan.
granules 0.5 mg/g.
*Indications*: lactose intolerance in infants, and older patients requiring parenteral nutrition or a fluid diet.
*Caution*: patients with a familial history of urticaria, bronchial asthma, hypersensitivity.
*Adverse effects*: rarely, shock and gastrointestinal symptoms.
**Tofisopam** (benzodiazepine tranquillizer)
Grandaxim®, Mochida, Japan.
*Indications:* psychosomatic symptoms such as headache, fatigue, tachycardia, sweating.
*Contraindications, precautions, warnings:* as for other drugs of this class.

**Trilostane** (inhibitor of corticosteroid synthesis)
Desopam®, Mochida, Japan.
*Tablet 60 mg.*
*Indication:* hypersecretion of aldosterone and cortisol.
*Caution:* renal or hepatic disease, adrenocortical insufficiency. Not to be administered during pregnancy.
*Adverse effects:* raised serum transaminases, hypersensitivity.

**Trimebutine** (antispasmodic agent)
Debridat®, Croma-Pharma, Austria.
*Tablet 100 mg.*
*Indication:* irritable colon.
*Contraindications:* hypersensitivity, pregnancy, lactation.

**Vindesine** (cytostatic)
Fildesine®, Shionogi, Japan.
*Powder for injection 1 and 3 mg/ampoule.*
Eldesine®, Lilly Iceland.
*Powder for injection 5 mg/ampoule.*

**Zidovudine** (antiviral)
Retrovir®, Wellcome, France, Luxembourg, Ireland, Norway.
*Capsules 100 and 250 mg.*
*Powder for injection 200 mg/ampoule (Ireland only).*
*Indication:* severe manifestations of HIV infection.
*Contraindications:* hypersensitivity, severe blood dyscrasia, pregnancy, lactation.
*Caution:* combination with paracetamol (increased incidence of neutropenia), probenecid (diminished excretion of zidovudine) and potentially nephrotoxic or myelotoxic compounds must be avoided.
*Adverse effects:* anaemia, neutropenia, leucopenia, nausea, headache, rash, abdominal pain, fever, myalgia, paraesthesiae, vomiting, anorexia.
Reports from Regulatory Agencies

Dipyridamole

Israel — The pharmaceutical branch of the Ministry of Health has amended the approved indications for preparations containing the vasodilator agent dipyridamole as follows:

• prevention of thrombogenic disorders;
• as an adjunct to oral anticoagulants in patients with artificial heart valves;
• for use in association with acetylsalicylic acid (aspirin) in patients with recurrent chronic deep vein thrombosis resistant to oral anticoagulant therapy;
• for patients undergoing coronary artery surgery.

Chronic coronary deficiency was disallowed as an indication having regard to lack of definitive evidence that it is of value in this condition.


Rifampicin

France — The Ministry of Health has additionally approved the use of the antibiotic rifampicin (Rifadin®, Merrel-Dow) for the treatment of brucellosis.


Theophylline (sustained release preparations)

United Kingdom — The Licensing Authority of the Department of Health and Social Security has recently advised doctors that sustained release preparations are unlikely to have identical pharmacokinetic profiles even when they contain the same quantity of the active ingredient. Disparities have been noted particularly in sustained release preparations containing theophylline. Guidelines on the nature of the bioavailability data required in marketing applications have consequently been developed which will also enable companies to generate product specific prescribing information. Companies already marketing such products will be expected to provide information conforming to the requirements of the guidelines at the time that their current product licences are renewed.


Epinephrine

Federal Republic of Germany — Having regard to the associated high incidence of tachycardia, the Federal Health Office has placed manufacturers on notice that it intends to withdraw product licences for preparations, including impregnated materials containing high concentrations of epinephrine (adrenalin), that are used in dental practice to stop bleeding.

Regulatory Matters

Should all ingredients of medicines be disclosed?

United Kingdom — According to the Pharmaceutical Journal the Department of Health has drawn up proposals requiring manufacturers to disclose all the ingredients of medicinal products either on the packaging or in data sheets. Once ministerial approval has been obtained the proposals will be submitted to consultation before regulations are formulated, during which time the pharmaceutical industry and consumer groups will be invited to offer comments.


Applications for product licences in the United Kingdom: revised guidance notes

United Kingdom — The Licensing Authority has recently revised its “Guidance Notes on Applications for Product Licences” which, in addition to a number of amendments and updates to the original text, now includes guidelines issued by the European Economic Community (EEC) on clinical efficacy, fixed-combination products, pharmacokinetics studies in man and investigation of bioavailability.


Advice on drug studies carried out on healthy volunteers

United Kingdom — The Medicines Commission, having completed an inquiry into volunteer studies, has advised the health ministers that the situation does not merit the institution of statutory controls. However, it does call for greater self-control by pharmaceutical companies and universities.

The commission has proposed that a register be compiled of organizations undertaking such studies which specifies the facilities they possess for medical support and resuscitation. The report adds that the procedures for obtaining informed consent from potential subjects should be improved and that a guarantee should be provided that adequate compensation will be payable without the need to prove negligence whenever a volunteer sustains injury.


Health messages on food labels: proposed regulation

United States of America — Consumers are becoming increasingly conscious of the relationship between diet and health and the food industry has responded by issuing health-related messages as a promotional gambit. The Food and Drug Administration now proposes to introduce regulations which will control the use of such information in food labelling and it has proposed criteria that will apply in evaluating the propriety of such labelling. Because of broad public interest the notice in the Federal Register has been widely disseminated with a view to eliciting comments not only from within the United States but also from the competent national authorities in other countries, and particularly those exporting substantial quantities of packaged foods to the United States.

Advisory Notices

Non-ionic radiocontrast media

**Federal Republic of Germany** — The Federal Health Office has informed doctors and professional organizations of its concern that adverse effects to non-ionic radiocontrast agents may be considerably underreported. It emphasizes the necessity for close monitoring of these agents, particularly since their use is rapidly increasing.


French guidelines on Good Clinical Practices

**France** — The Directorate of Pharmacy and Medicines has recently published, in English and French versions, official recommendations on “Good Clinical Practices” which it defines as:

> "the series of measures which must be implemented to ensure the quality and authenticity of the scientific data obtained through trials, combined with a respect for ethics."

These recommendations, which are directed both to sponsors and clinical investigators, are evolutive and they are presented in six sections:

- Definition of terms.
- Responsibilities of the sponsor.
- Responsibilities of the investigator.
- Specific aspects of certain trials (multicentre trial, medical office trial and trial without therapeutic aim).
- Responsibilities of the “ethics committee”.
- Quality control (verifications by the investigator, the sponsor and the authorities).

It is emphasized that Good Clinical Practices are an integral part of the system of quality assurance of drugs, and that they should be applied not only during drug development but also during production and dispensing. The recommendations are primarily intended to reinforce the quality control of clinical trials of drugs in France. They are not designed to evaluate the intrinsic scientific value of the trials.


Non-steroidal anti-inflammatory drugs and asthma

**United Kingdom** — The Committee on Safety of Medicines has received 309 reports of asthma or bronchospasm occurring in association with the ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid (aspirin). Aspirin may provoke or worsen asthma in approximately 5% of asthmatics but this appears to be a general problem with this group of drugs and the Committee is as yet unable to estimate whether one NSAID is more likely to provoke or worsen asthma than another. Although there is little evidence to suggest that there is complete “cross sensitivity” between aspirin and other NSAIDs, it recommends that patients whose asthma is provoked by aspirin should avoid other NSAIDs.

The Committee has been notified of four asthmatics who died in bronchospasm after ingesting an NSAID other than aspirin. Three deaths followed single doses of ibuprofen, and one occurred after a single dose of indometacin. In all cases the asthma became noticeably worse within one hour of taking the drug.

The Committee has reminded doctors that any degree of worsening of asthma may be related to
use of NSAIDs either prescribed or, in case of ibuprofen, purchased over-the-counter.


Beta-blocking agents and fatal bronchospasm

United Kingdom — The Committee on Safety of Medicines has received reports of 347 episodes of bronchospasm in patients under treatment with β-adrenoceptor blocking agents, 25 of which were fatal. Most of these reactions occurred in patients with asthma or a history of obstructive airways disease. In the majority of cases they resulted from use of oral formulations, but 48 cases were associated with the use of eye-drops.

The Committee has advised doctors that beta-blockers, even those with apparent cardio-selectivity, should only be used in patients with asthma or a history of obstructive airways disease when no alternative treatment is available. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.


Bioavailability guidelines

Israel — The Ministry of Health has adopted, in principle, guidelines on bioavailability published by the WHO Regional Office for Europe (1). Relevant information will henceforth be required as a condition of registration for products in the following therapeutic categories:

- cardiovascular agents;
- anti-infective agents;
- sustained release preparations.

Analogous information may also be required, at the Ministry's discretion, on the bioavailability of any other substance that is either already marketed or as a condition of registration and marketing. In all cases, a detailed protocol of the studies must be provided, in conformity with existing regulations.

References:
Essential Drugs

Trypanosomiases

Sleeping sickness: 50 million people at risk in Africa

African trypanosomiasis, or sleeping sickness, is a protozoal infection transmitted by Glossina (tsetse flies). It constitutes a serious health risk to at least 50 million people in sub-Saharan Africa.

Two subspecies of Trypanosoma brucei — T. brucei gambiense and T. brucei rhodesiense — produce distinctive clinical forms of the disease. T. b. rhodesiense is endemic in East Africa where various wild and domestic animals provide important reservoirs of infection. It is largely an occupational hazard of hunters, poachers, honey gatherers and firewood collectors. T. b. gambiense occurs in West and Central Africa where the vectors breed in shaded areas near water. Until recently, man was considered to be the exclusive mammalian host, but wild and domestic animals in West Africa have now been found to be infected with biochemically identical trypanosomes.

Infected flies inoculate metacyclic forms of these trypanosomes from their salivary glands into man. Actively motile forms multiply locally in the subcutaneous tissues, a process often signalled in T. b. rhodesiense infections by a transient indurated wheal or chancre. Inversion of lymphatics and blood vessels occurs a few days later, causing regional or generalized lymphadenopathy and widespread systemic dissemination. Intermittent fevers accompanied by malaise, headaches, joint pains, pruritus, skin rashes and oedema are followed by normochromic or hypochromic anaemia, and a pancarditis resulting in dysrhythmias and heart failure. Other signs of organic involvement are common. In men, endocrine involvement can cause impotence, and in women menstrual disorders, sterility, abortion, premature delivery, stillbirth or perinatal death may occur.

Signs of meningoencephalitis develop within a few weeks in T. b. rhodesiense infections, but only after several months or even years in T. b. gambiense infection. Early symptoms include insomnia, neurological disorders and mental changes. Apathy and somnolence supervene and untreated patients ultimately die from malnutrition, intercurrent infection or deepening coma.

Control

The intensity of transmission can be reduced by:

• sustained detection and treatment of human cases;

• teaching rural communities how to reduce exposure to the tsetse fly by using fly traps and screens; and

• use of insecticides to control the vectors at breeding sites.

Primary health care workers can be trained to recognize early symptoms and signs of the disease. All persons with suspected infection should be referred to specialized treatment centres for confirmation of the diagnosis by microscopic examination of lymph aspirate, blood or cerebrospinal fluid. Rapid serological tests are available for mass screening of communities for T. b. gambiense infections.

Communities can be trained in the use of fly-traps and screens which are effective and non-polluting. In some areas, ground spraying with insecticides such as endosulfan and, more recently, the synthetic pyrethroids has been used to reduce transmission. Aerial spraying has also been employed in areas of intense transmission, but, save in the event of epidemics, it is too costly to be used as a primary means of control.

Treatment

Three drugs are currently used:

• Pentamidine;

• Suramin; and

• Melarsoprol.
The first two drugs are of value only during the early stages of infection. They do not cross the blood-brain barrier and they are therefore ineffective once neurological involvement has occurred. Pentamidine should not be used to treat *T. b. rhodesiense* infections since resistant strains are now widespread.

Melarsoprol, an arsenical compound, was until recently the only substance that could be used to arrest infection of the central nervous system. It has now been established that *eflornithine* (alpha-difluoromethylornithine; DFMO) and, possibly, nifurtimox can also be of value, particularly in advanced *T. b. gambiense* infections, and even in cases refractory to melarsoprol. See also p. 199.

Different treatment schedules for advanced disease involving the central nervous system are used in various regions according to local preference.

### Pentamidine

**Isetionate, powder for injection 200 mg**

A stable and relatively non-toxic diamidine compound with antiprotozoal activity. It is administered parenterally since it is unreliably absorbed from the gastrointestinal tract. It does not enter the cerebrospinal fluid. Detectable amounts remain in the liver and kidney for many months as a result of selective binding. It is excreted unchanged mainly in the bile and, to a much lesser extent, in the urine.

**Uses**

Treatment of *T. b. gambiense* African trypanosomiasis with a view to:

- obtaining a radical cure in the haemolymphatic stage of the disease; and

- clearing the blood and lymph of trypanosomes prior to treatment with melarsoprol.

In areas where pentamidine resistance occurs, suramin may be used as an alternative.

**Dosage and administration**

4 mg/kg (as base) in each of 7-10 intramuscular injections administered either daily or on alternate days.

**Contraindications**

- Known hypersensitivity.

*T. b. rhodesiense* trypanosomiasis, since primary resistance to pentamidine has been observed.

**Precautions**

Pentamidine should generally be used only when examination of the cerebrospinal fluid provides no evidence of involvement of the central nervous system. The criteria generally recognized as indicative of infection are a raised CSF leucocyte count (>5 cells/mm³) and/or total protein content (>37 mg/100 ml) and/or demonstration of trypanosomes in centrifugated deposits of CSF.

All patients should remain supine and under observation for at least thirty minutes after each injection because hypotension and syncope can occur.

When possible, monitoring of blood pressure, full blood count and blood glucose levels should be undertaken daily.

**Use in pregnancy**

Any pregnant woman with *T. b. gambiense* trypanosomiasis should receive pentamidine, even if there is evidence of meningoencephalitic involvement, since melarsoprol should not be used before delivery.

**Adverse effects**

Hypoglycaemia and syncope may occur immediately after the injection. Later, pain, induration and, occasionally, formation of a sterile abscess may occur locally. In the long term, damage to the beta cells of the pancreas may result in hyperglycaemia.
Pancreatitis and cardiac dysrhythmias are other serious adverse effects. Bone marrow suppression has also been reported.

**Storage**

Powder for injection should be stored below 30° C and kept in well-closed containers.

**Suramin sodium**

**powder for injection 1 g vial**

A complex derivative of urea with antiprotozoal activity that is also used in the treatment of onchocerciasis. It enters the extracellular space but does not cross the blood-brain barrier. Because it forms stable complexes with protein, suramin is not absorbed from the gastrointestinal tract and must be administered by intravenous injection. It dissociates slowly from plasma proteins and is detectable unchanged in the urine for up to three months after the last dose.

**Use**

Treatment of *T. b. gambiense* and *T. b. rhodesiense* African trypanosomiasis with a view to:

- obtaining a radical cure in the haemolymphatic stage of the disease; or
- clearing the blood and lymph of trypanosomes prior to treatment with melarsoprol.

**Dosage**

All doses should be administered by slow intravenous injection of a 10% aqueous solution.

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>11</th>
<th>17</th>
<th>23</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemolymphatic stage mg/kg</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Prior to melarsoprol mg/kg</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Contraindications and precautions**

Suramin should always be given under medical supervision, preferably in specialized treatment centres. The general condition of the patient should be improved as far as possible before treatment is started and a satisfactory food and fluid intake maintained throughout the period of therapy. A patient who experiences an anaphylactic reaction following the first injection should *never* receive suramin again. It should not be administered to patients with severe renal disease.

Urine should be examined weekly. Moderate proteinuria is usual, but heavy proteinuria with the passage of casts calls for immediate discontinuation of treatment.

**Use in pregnancy**

Suramin must be given to pregnant women with *T. b. rhodesiense* trypanosomiasis even if there is evidence of meningoencephalopathic involvement, since melarsoprol should not be used before delivery.

**Adverse effects**

Common adverse effects are pyrexia, pains in the joints and in the soles of the feet, skin rashes and desquamation. The more severe adverse effects of suramin that result from treating patients with onchocerciasis are not seen in trypanosomiasis.

Nausea, vomiting and abdominal pain are also common.

**Storage**

Powder for injection should be kept in well-closed containers protected from light.
Melarsoprol
injection 3.6% solution in propylene glycol

An organic arsenical compound that is used in cases of African trypanosomiasis with CNS involvement. It is administered intravenously because it is unreliably absorbed from the gastrointestinal tract and is too irritant for intramuscular administration. However, it enters the central nervous system in sufficiently high quantities to kill the trypanosomes. It is largely metabolized to nontoxic pentavalent compounds and is excreted in the urine and faeces within a few days.

Uses

Treatment of confirmed cases of *T. b. gambiense* or *T. b. rhodesiense* African trypanosomiasis with meningoencephalitic involvement. Relapse occurs in less than 5% of cases.

Because drug-induced fatalities occasionally occur, melarsoprol should be used only in hospitals and specialized treatment centres.

Dosage and administration

Melarsoprol should always be administered by slow intravenous injection through a fine needle. The solution is intensely irritant. Particular care must be taken to avoid extravasation during injection.

Several treatment regimens are currently used in the absence of clear evidence that one is better than another (see tables). They each comprise 3-4 series of daily injections with intervening rest periods of 7-10 days.

Patients should subsequently be seen every 6 months for at least 2 years. An increase in the leucocyte and protein content of CSF or the reappearance of trypanosomes are indicative of relapse. In this event, a second complete course of treatment may be administered. However, this is rarely successful and, if it is available, DFMO offers a more effective alternative.

A Herxheimer reaction resulting from massive destruction of parasites is particularly dangerous during treatment with melarsoprol. For this reason two preliminary injections of suramin or pentamidine are often administered to induce the reaction beforehand.

*Treatment schedule for* *T. b. rhodesiense* *trypanosomiasis as used particularly in Kenya and Zambia*

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug (IV)</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>suramin</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>suramin</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>suramin</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>melarsoprol</td>
<td>0.36</td>
</tr>
<tr>
<td>8</td>
<td>melarsoprol</td>
<td>0.72</td>
</tr>
<tr>
<td>9</td>
<td>melarsoprol</td>
<td>1.1</td>
</tr>
<tr>
<td>16</td>
<td>melarsoprol</td>
<td>1.4</td>
</tr>
<tr>
<td>17</td>
<td>melarsoprol</td>
<td>1.8</td>
</tr>
<tr>
<td>18</td>
<td>melarsoprol</td>
<td>1.8</td>
</tr>
<tr>
<td>25</td>
<td>melarsoprol</td>
<td>2.2</td>
</tr>
<tr>
<td>26</td>
<td>melarsoprol</td>
<td>2.9</td>
</tr>
<tr>
<td>27</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
<tr>
<td>34</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
<tr>
<td>35</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
<tr>
<td>36</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*Treatment schedule for* *T. b. rhodesiense* *trypanosomiasis as used particularly in Tanzania and Uganda*

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug (IV)</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>suramin</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>melarsoprol</td>
<td>1.8</td>
</tr>
<tr>
<td>6</td>
<td>melarsoprol</td>
<td>2.2</td>
</tr>
<tr>
<td>7</td>
<td>melarsoprol</td>
<td>2.56</td>
</tr>
<tr>
<td>14</td>
<td>melarsoprol</td>
<td>2.56</td>
</tr>
<tr>
<td>15</td>
<td>melarsoprol</td>
<td>2.9</td>
</tr>
<tr>
<td>16</td>
<td>melarsoprol</td>
<td>3.26</td>
</tr>
<tr>
<td>23</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
<tr>
<td>24</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
<tr>
<td>25</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
</tbody>
</table>
Treatment schedule for T. b. gambiense trypanosomiasis as used in the Ivory Coast

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug (IV)*</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pentamidine IM</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>pentamidine IM</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>melarsoprol</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>melarsoprol</td>
<td>2.4</td>
</tr>
<tr>
<td>6</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
<tr>
<td>17</td>
<td>melarsoprol</td>
<td>1.2</td>
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<tr>
<td>18</td>
<td>melarsoprol</td>
<td>2.4</td>
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<tr>
<td>19</td>
<td>melarsoprol</td>
<td>3.6</td>
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<tr>
<td>20</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
<tr>
<td>30</td>
<td>melarsoprol</td>
<td>1.2</td>
</tr>
<tr>
<td>31</td>
<td>melarsoprol</td>
<td>2.4</td>
</tr>
<tr>
<td>32</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
<tr>
<td>33</td>
<td>melarsoprol</td>
<td>3.6</td>
</tr>
</tbody>
</table>

* Except where otherwise indicated.

**Contraindications and precautions**

Patients should be hospitalized and remain under close supervision throughout treatment. Most clinicians suspend treatment during episodes of reactive encephalopathy.

Intercurrent infections, such as pneumonia and malaria, should be treated before melarsoprol is administered. Wherever possible, malnutrition should be corrected with a protein rich diet. Systemic prednisolone at a dose of 1 mg/kg/day has been used to reduce the risk of fatal reactions during treatment but its value is disputed.

Severe haemolytic reactions have occurred in patients with G6PD deficiency.

**Use in pregnancy**

Treatment should be deferred until immediately after delivery since safety during pregnancy cannot be assured. Pregnant women with meningoencephalitic involvement should receive pentamidine (T. b. gambiense) or suramin (T. b. rhodesiense).

**Adverse effects**

Although up to 95% of patients can be cured without serious complications, 1-5% of patients die during treatment.

Reactive encephalopathy characterized by headache, tremor, slurring of speech, convulsions and ultimately coma is the most serious complication. It appears 3-10 days after the first dose of melarsoprol. Hypertonic infusions or mannitol are used to reduce cerebral oedema. Sedatives and anticonvulsants are of value in controlling convulsions.

Hypersensitivity reactions are uncommon, but when they do occur (usually during a second or subsequent period of treatment) corticosteroid therapy and desensitization with a series of increasing doses can be effective. Agranulocytosis is a particularly dangerous but rare reaction. Dose-related renal and hepatic dysfunction can occur during the later phases of treatment.

Less serious adverse effects include hyperthermia, urticarial rashes, headache, diarrhoea and vomiting.

**Storage**

Melarsoprol should be kept protected from light.

**Chagas' disease affects 16-18 million people in Central and South America**

American trypanosomiasis, which is caused by the protozoan parasite *Trypanosoma cruzi*, affects some 16-18 million people and a wide variety of domestic and wild animals in the rural areas of tropical and subtropical countries in Central and South America.

It is transmitted by several species of triatomine bugs, by blood transfusion, organ transplantation, congenital infection or, occasionally, by accidental
contact with the blood of infected individuals or animals. Metacyclic forms of the parasite, excreted by the vector as it bites, enter the wound to produce a raised, reddish skin nodule (or chagoma). If this occurs near the eye it produces a unilateral inflammatory conjunctivitis (Romana's sign).

After penetration, the metacyclic forms mature and multiply in local tissue macrophages where they pass through several distinct morphological stages and induce a specific immune response and, later, an inflammatory reaction. After a period of some 5 days, the host cell ruptures and a further generation of trypomastigotes is released into the circulation. In the early stages of the disease nests of parasites are readily detectable in the myocardium and the smooth muscle of the gut.

Although the parasite is initially readily detectable in the blood, the acute febrile phase of the disease frequently passes unrecognized. Occasionally, however, the infection follows a fulminating course terminating in a fatal myocarditis and meningoencephalitis. In about half of the surviving cases, and after a latent interval ranging from 10 to more than 20 years, chronic myopathic degeneration results in dysrhythmias, cardiac enlargement and, less frequently, oesophageal and colonic dilatation. At this stage, only symptomatic treatment is of benefit.

**Control**

Spraying with insecticides and upgrading standards of accommodation offer the most direct means of reducing transmission. Covering the outer walls of houses with a malathion-containing paint is claimed to repulse the vector and, more recently, spraying with the pyrethroid, deltamethrin, supplemented by fumigation with lindane has been used.

Health education aimed to teach communities how to avoid contact with the vector and control of blood transfusion are also important.

Various serological tests have been developed to detect *T. cruzi* antibodies in donated blood. At least two different tests should be performed on each sample. Normally, if either test is positive or borderline the sample should be rejected. However, samples suspected of being infected can be sterilized by the addition of gentian violet.

Research aimed to identify and select suitable antigens for the development of a safe and effective vaccine is ongoing.

**Treatment**

At present the only therapeutic agents of value are:

- Benznidazole, and
- Nifurtimox.

Both suppress parasitaemia and are efficacious during the early stages of infection. Studies are in progress to determine whether they have any influence on the later manifestations of the disease. Symptomatic treatment may be necessary in advanced cases. Heart failure initially responds to digoxin and diuretics. Antidysrhythmic drugs may be required, sometimes in emergency, but β-blocking agents are contraindicated. Complete heart atrioventricular block and sick sinus syndrome respond to a pacemaker. Megaoesophagus and megacolon may require surgical treatment.

**Benznidazole**

**scored tablets 100 mg**

Benznidazole is a trypanocidal nitroimidazole derivative which is rapidly absorbed from the alimentary tract. Peak plasma concentrations are reached after two to four hours and then decay with a half-life of approximately 12 hours. It is partly metabolized in the body and all metabolites are rapidly eliminated in the urine and stools.

**Uses**

Treatment of acute American trypanosomiasis (Chagas' disease). Cure rates of 80% - 90% have been recorded.
Dosage and administration

ADULTS: 5-7 mg/kg orally in two divided doses for 60 days.

CHILDREN (up to 12 years): 10 mg/kg orally in two divided doses for 60 days.

Contraindications and precautions

Patients with hepatic, renal or haematological insufficiency should receive the drug only under close medical supervision. The blood count, especially leucocytes, should be monitored throughout treatment and patients should be advised to abstain from alcohol.

Use in pregnancy

Safety in pregnancy has not been established and treatment should be deferred until after the first trimester. It should then be instituted to avoid the risk of congenital transmission.

Adverse effects

Rashes may appear during the first two weeks of treatment. They are usually mild but when they are severe and accompanied by fever and purpura treatment should be definitively discontinued. Nausea may also occur during the initial phase of therapy. Paraesthesiae or symptoms of peripheral polyneuritis are dose-related effects; if they occur it is advisable to discontinue treatment.

More serious adverse effects include leucopenia and rarely agranulocytosis.

Storage

Tablets should be kept in well-closed containers, protected from light.

Nifurtimox

tablet 30 mg, 120 mg, 250 mg.

A synthetic trypanocidal nitrofuran compound which is efficiently absorbed from the gastrointestinal tract. It is rapidly and extensively metabolized and little is excreted in the urine. Intracellular forms are more susceptible than extracellular forms under experimental conditions.

Uses

Treatment of acute American trypanosomiasis (Chagas' disease). The response is variable. Cure rates of 80-90% have been recorded but in some areas of Central Brazil higher failure rates have occurred.

Dosage and administration

ADULTS: 8-10 mg/kg orally in three divided daily doses for 90 days.

CHILDREN: 15-20 mg/kg orally in four divided daily doses for 90 days.

Precautions

Gastrointestinal irritation may be reduced if an aluminium hydroxide preparation is taken simultaneously. Alcohol should be avoided since it may increase the incidence and severity of adverse effects.

Nifurtimox should be administered to patients with a history of convulsions, psychiatric disease or alcoholism only under close medical supervision.

Daily dosage schedules should be reduced if weight loss, neurological disturbances or other manifestations of intolerance occur.

Use in pregnancy

Safety in pregnancy has not been established and treatment should be deferred until after the first trimester. It should then be instituted to avoid the risk of congenital transmission.
Adverse effects

Adverse effects are frequent, dose-related and reversible. They include anorexia, vomiting, gastric pain, insomnia, headache, vertigo, excitability, myalgia and arthralgia. Seizure may be controlled symptomatically with anticonvulsants.

A peripheral polyneuritis can occur which may necessitate discontinuation of treatment.

Storage

Tablets should be kept in well-closed containers, protected from light.

A new price control order issued in India on 166 essential drugs

India — The new Drugs (Prices Control) Order issued in August 1987, and which comes into force with immediate effect, aims at a system of price control which would ensure a reasonable return to the producers of essential drugs and yet ensure that there is no undue increase in prices.

The order bears upon two categories of essential drugs:

*Category I* — Twenty-seven bulk drugs and their formulations used in governmental programmes for leprosy, tuberculosis, trachoma, malaria, filariasis and oral rehydration salts, and for which a maximum mark-up of 100 per cent is permitted.

*Category II* — Another 139 bulk drugs and their formulations required for the National Health Programme for which a maximum mark-up of 75 per cent is permitted.

However, every company will need to make a specific application for any proposed revision of its prices even when the increases fall within the permitted limits.

The order also contains new measures to protect indigenous manufacturers through tariff mechanisms and taxation.

**Coming in the next issue!**

**Essential Drugs: Fifth Model List**

The next issue of *WHO Drug Information* (Vol. 2, No. 1) will feature WHO's Fifth Model List of Essential Drugs, with some twenty additions and a number of significant deletions. The list was drawn up by the WHO Expert Committee on the Use of Essential Drugs at its meeting from 30 November to 4 December 1987.

The report of the Expert Committee is of importance to everyone concerned with the rationalization of drug use and procurement, or with optimal management of resources within the health sector. It provides a stimulus for considering the advantages that can stem from structuring drug requirements at institutional, regional or national level, wherever priorities need to be addressed.

The full report will be published in the WHO Technical Report Series.

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**Basic Tests for Pharmaceutical Substances**

It is often important to check that gross degradation has not occurred in consignments of drug substances during transit or storage, particularly in tropical countries, and to verify the identity of such consignments whenever labelling has been damaged or fraudulent substitution is suspected.

WHO has produced a compendium of basic tests for these purposes which cover most substances within its Model List of Essential Drugs. These tests are not, in any circumstances, intended to replace the requirements of pharmacopoeial monographs. The latter give an assurance of quality whereas basic tests merely confirm identity and exclude gross degradation. Their importance is in the fact that they can be performed outside a fully equipped laboratory using a limited range of widely available reagents whenever they need to be undertaken, whether at the dockside or at any other point within the distribution chain.

The compendium, titled *Basic Tests for Pharmaceutical Substances*, was published by WHO in 1986. As the *American Journal of Pharmaceutical Education* has noted, the tests, despite their simplicity, "can serve a valuable purpose when only elementary supplies and materials are available".

1986, vi + 204 pages; ISBN 92 4 154204 7; Sw.fr. 34.-/US$17.00

Address orders to: World Health Organization, Distribution and Sales, 1211 Geneva 27, Switzerland, or to any of the sales agents listed on inside back cover.
Recent Publications

New Pharmacopoeias

Czechoslovakia — The fourth edition of the Czechoslovak Pharmacopoeia which is now available (in Czechoslovak) became official in January 1988. Almost half of the 1048 monographs (601 substances and 483 dosage forms) are either newly introduced or extensively revised. Domestically produced drugs are cited by brand names and names of manufacturers. A set of 46 reagents frequently used in hospitals for diagnostic in vitro laboratory tests has also been incorporated. Official recognition is accorded to the main principles of WHO’s Good Manufacturing Practices which now acquire the force of law.

Switzerland — The 7th edition of the Swiss Pharmacopoeia (Pharmacopoeia Helvetica), which is now available in French, German and Italian versions, is distinctive in that, for the first time, monographs of the European Pharmacopoeia are incorporated. Apart from general monographs, the volume contains 382 monographs for substances, 137 for pharmaceutical aids, 113 for crude drugs, 57 for vaccines and sera, 24 for general galenical preparations and 150 for dosage forms.

References

French drug compendium 1987

France — The latest edition of the Dictionnaire Vidal contains 570 new monographs which have been approved by a special commission of the Ministry of Health and it has been expanded to include information on drug interactions. Although products are listed by brand name, they are cross-indexed with a list of international nonproprietary names of active substances.


EEC directives and recommendations on pharmaceuticals in a single volume

Italy — A compendium containing the full English, French and Italian versions of all EEC directives and guidelines relating to pharmaceuticals is now available. The texts and indices have been arranged to facilitate consultation and to enhance the value of the volume as a work of reference.

Abnormal laboratory results

Australia — The need for defining biochemical profiles, performing screening tests and selecting pertinent tests from the ever-growing range of routine biochemical investigations has complicated rather than simplified medical management. A booklet recently published by the Commonwealth Department of Health attempts to answer some of the more fundamental questions that arise when a doctor is faced with interpreting the results of biochemical investigations: When should an abnormal result be considered undebatably abnormal? When should it be acted upon? How vigorously should it be pursued? When should it be ignored? It is emphasized that the statistical chance of a false positive result is increased when a number of unrelated tests are carried out on the same patient. The booklet also includes a series of concise explanations of the investigations that are most widely used in a routine clinical context.


Commonwealth Pharmaceutical Association Newsletter

The Newsletter of the Commonwealth Pharmaceutical Association provides a channel of information on the activities of its Council as well as news from member countries. The August 1987 issue is of particular interest because it includes details of new training opportunities for pharmacists and of a compendium of legislation in Commonwealth countries called for by the Fourth Commonwealth Pharmaceutical Conference held in Nairobi in March 1987. Workshops are planned on management of drug supplies and this was the main theme of the Sixth General Assembly of the West African Pharmaceutical Federation held in May 1987 in the Gambia. Opportunity was also taken to welcome the introduction of essential drug lists and national drug formularies in countries of the region. The need for relevant drug information at all levels of health care was emphasized as well as a need to update and enforce existing drug laws and regulations.

Reference: Newsletter of the Commonwealth Pharmaceutical Association, No. 8, August 1987. 1 Lambeth High Street, London SE1 7JN.

Advanced Drug Delivery Reviews: a new journal

This new international journal is concerned with current and prospective aspects of research on the design and development of advanced drug delivery systems and their applications in experimental and clinical therapeutics. The scope and pace of discovery in cell and molecular biology has already provided unprecedented opportunities for the design of novel classes of therapeutic agents. However, their application in clinical therapy will be dependent upon the development of effective and practicable delivery systems.

Articles contained in the journal leave no doubt that considerable progress has already been made in this connection. Pulsed-release devices constructed from biodegradable polymer implants offer considerable promise in the delivery of contraceptive steroids, long-term antibiotic therapy and booster doses of vaccines. By using polymer drug delivery systems the drug release can be engineered so that precisely determined pulses of drug are delivered at preselected times that may be hours or even weeks apart.

Single dose delivery systems of this nature assure compliance and could, by reducing the costs of conventional modes of drug administration, hold particular advantage in developing countries.

Existing technologies, using copolymers of lactic and glycolic acid, can confidently be anticipated to offer reliable delivery systems. Their value will depend on how well they are accepted and whether their manufacture can be scaled up to the point at which their use would become cost-effective.

International Nonproprietary Names for Pharmaceutical Substances

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

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

Recommended International Nonproprietary Names (Rec. INN): List 27

<table>
<thead>
<tr>
<th>Recommended International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description and Molecular Formulae</th>
</tr>
</thead>
<tbody>
<tr>
<td>acidum piridronicum piridronic acid</td>
<td>[2-(2-pyridyl)ethylidene]diphosphonic acid C₁₇H₁₁NO₆P₂</td>
</tr>
<tr>
<td>acitretinum acitretin</td>
<td>((all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid) C₂₁H₂₆O₃</td>
</tr>
<tr>
<td>adibendanum adibendan</td>
<td>5,7-dihydro-7,7-dimethyl-2-(4-pyridyl)pyrrolo[2,3-f]benzimidazol-6(3H)-one C₁₆H₁₄N₄O</td>
</tr>
<tr>
<td>albendazolum oxidum albendazole oxide</td>
<td>methyl 5-(propylsulfinyl)-2-benzimidazolcarbamate C₁₁H₁₂N₂O₄S</td>
</tr>
<tr>
<td>aloxistatinum aloxatin</td>
<td>ethyl ((+)-(2S,3S)-2,3-epoxy-N-[((S)-1-(isopentylcarbamoyl)-3-methylbutyl)succinamate) C₁₇H₂₀N₂O₅</td>
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<tr>
<td>ampiroxicamum ampiroxicam</td>
<td>((+)-4-(1-hydroxyethoxy)-2-methyl-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide ethyl carbonate (ester), 1,1-dioxide) C₂₉H₂₇N₂O₇S</td>
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2 Other lists of recommended international nonproprietary names can be found in Cumulative List No. 6, 1982.
<table>
<thead>
<tr>
<th>Chemical Name or Description and Molecular Formulae</th>
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<tbody>
<tr>
<td>anaritidum anaritide</td>
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| \(-\text{arginyl}-\text{seryl}-\text{seryl}-\text{cysteinyl}-\text{phenylalanylglycylglycy}l-\text{arginyl}-\text{methionyl}-\text{aspartyl}-\text{arginyl}-\text{isoleucylglycy}l-\text{alanyl}-\text{glutaminyl}-\text{asparaginyl}-\text{phenylalanylglycy}l-\text{tyrosine cyclic (4\text{--}20)}\text{-disulfide}
| \(C_{112}H_{175}N_{39}O_{35}S_3\)                     |
| arbekacinum arbekacin                             |
| \(O-3\text{-amino-3-deoxy-\(\alpha\text{-D-glucopyranosyl-}(1\text{\rightarrow}4)\text{-O-[2,6-diamino-2,3,4,6-tetra-deoxy-\(\alpha\text{-D-erythro-hexopyranosyl-}(1\text{\rightarrow}6)\text{-N'[2S-4-amino-2-hydroxybutyl]-2-deoxy-\(\alpha\text{-streptamine}}
| \(C_{22}H_{44}N_{6}O_{10}\)                         |
| arnololum arnolol                                |
| \((\pm)-3\text{-amino-1-[p-(2-methoxyethyl)phenoxy]-3-methyl-2-butanol}
| \(C_{13}H_{18}NO_3\)                              |
| artemisininum artemisinin                         |
| \(1\text{-[[[5-(p-bromophenyl)-2-oxazolyl]methylene]amino]hydantoin}
| \(C_{15}H_{21}BrN_4O_3\)                          |
| azumolenum azumolene                             |
| \(1\text{-[[(5-(p-bromophenyl)-2-oxazolyl]methylene]amino]hydantoin}
| \(C_{17}H_{20}N_5O_3\)                            |
| baquiloprimum baquiloprim                        |
| \(5\text{-[(2,4-diamino-5-pyrimidinyl)methyl]-6-(dimethylamino)-7-methylquinoline}
| \(C_{17}H_{22}N_6\)                               |
| bazinaprinum bazinaprine                         |
| \(3\text{-[(2-morpholinoethy lamino]-6-phenyl-4-pyridazinecarbonitrile}
| \(C_{17}H_{19}N_5O\)                             |
| bemarimonum bemarimone                          |
| \(5,6\text{-dimethoxy-4-methyl-2(1H)-quinazolinone}
| \(C_{18}H_{17}N_3O_3\)                           |
| benexatum benexate                               |
| \(benzyl salicylate, trans-4-(guanidinomethyl)cyclohexanecarboxylate}
| \(C_{20}H_{22}N_2O_3\)                           |
| beperidii iodium beperidium iodiide              |
| \(cis-1\text{-ethyl-4-hydroxy-1-methylpiperidinium iodide \((\pm)-\alpha-(hexahydro-1H-azepin-1-yl)-1,2-benzisoxazole-3-acetate, mixture with trans-1\text{-ethyl-4-hydroxy-1-methylpiperidinium iodide \((\pm)-\alpha-(hexahydro-1H-azepin-1-yl)-1,2-benzisoxazole-3-acetate \(1\text{:}1\)}
| \(C_{22}H_{31}IN_3O_3\)                          |
| bermoprofenum bermoprofen                        |
| \((\pm)-10,11\text{-dihydro-\(\alpha,8\text{-dimethyl-11-oxodibenz}[b,f]oxepin-2\text{-acetic acid}}
| \(C_{13}H_{18}O_4\)                              |
| bifemelanum bifemelane                           |
| \(N\text{-methyl-4-[(\alpha-phenyl-\(\alpha\text{-tolyl})oxy]butyramine}
| \(C_{18}H_{28}NO\)                               |
| bifeprofenum bifeprofen                          |
| \((\pm)-2\text{'-chboro-\(\alpha\text{-methyl-4-biphenylacetic acid, ester with 1-glycoloyl-4-methylpiperazine}}
| \(C_{22}H_{27}CIN_2O_3\)                         |
| bistentidinum bistentidine                       |
| \(N\text{-isopropyl-\(\alpha\text{-[p-(2-methylimidazol-4-yl)]phenyl}formamidine}
| \(C_{19}H_{25}N_4\)                              |
| brefonalolum brefonalol                          |
| \((\pm)-6,6\text{-[1,1-dimethyl-3-phenylpropyl]amino]-1\text{-hydroxyethyl-3,4-dihydro-carbostyril}}
<p>| (C_{22}H_{25}N_2O_2)                           |</p>
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<thead>
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<th>Recommended International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description and Molecular Formulae</th>
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</thead>
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<tr>
<td>budotitanum</td>
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<td>budotitane</td>
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<td>1-[[[(6R,7R)-7-[2-amino-5-thiazolyl]glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl][methyl]pyridinium hydroxide, inner salt, 7a-(E)-[O-(2-oxo-3-pyridinyl)oxime]</td>
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<td>cefempidone</td>
<td>C₁₉H₁₉N₀₂S₂</td>
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<td>cefmepidium chloride</td>
<td>7a-(Z)-[O-(1-carboxy-1-methylethyl)oxime] S-oxide</td>
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<td>cefpodoximum</td>
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<td>(±)-[2-chloro-4-(4,5-dihydro-3,5-dioxo-as-triazin-2(3H)-yl)phenyl]-[p-chlorophenyl]acetonitrile</td>
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</tr>
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</tr>
<tr>
<td>datelliptium chloride</td>
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<td>dembrexinum</td>
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<tr>
<td>dembrexine</td>
<td>C₁₇H₁₉Br₂N₂O</td>
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<td>detirelixum</td>
<td>N-acetyl-3-(2-naphthyl)-α-α-alanyl-p-chloro-α-phenylalanyl-α-tryptophyl-α-tyrosyl-α-lysyl-α-leucyl-α-arginyl-α-prolyl-α-alaninamide</td>
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<td>detirelix</td>
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<td>dexamethasoni acefuras</td>
<td>9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate 17-(2-fluorate)</td>
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<td>diclazuril</td>
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<td>disuprazolum</td>
<td>2-[(4-ethylthio)-3-methyl-2-pyridyl]methyl)sulfinyl</td>
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<td>disuprazole</td>
<td>C₁₄H₁₃N₂OS₂</td>
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<td>ditiocarb natricum</td>
<td>sodium diethyldithiocarbamate</td>
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<td>ditiocarb sodium</td>
<td>C₃H₁₃NNaS₂</td>
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<td>Recommended International Nonproprietary Name (Latin, English)</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
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<tr>
<td>4-amino-2-butoxy-5-chloro-N-[1-(1,3-dioxolan-2-ylmethyl)-4-piperidyl]benzamide</td>
<td>dobupridum dobupride</td>
</tr>
<tr>
<td>5-[(1,2-dihydro-2-oxo-4-pyridyl)methyl]-2-[[5-[[dimethylamino]methyl]furanyl]thio]ethyl]amino]-4(1H)-pyrimidinone</td>
<td>donetidinum donetidine</td>
</tr>
<tr>
<td>Acetone (±)-6-[3-[3,4-dimethoxyphenethyl]amino]-2-hydroxypropoxy]-3-pyridazinyl]hydrazone</td>
<td>dramedilolum dramedilol</td>
</tr>
<tr>
<td>(-)-threeo-3-(3,4-dihydroxyphenyl)-l-serine</td>
<td>droxidopa droxidopa</td>
</tr>
<tr>
<td>2-[bis(2-hydroxyethyl)amino]-4'-chloro-2'-(o-chlorobenzoyl)-N-methylacetanilide</td>
<td>duloozafonum duloozafone</td>
</tr>
<tr>
<td>l-methionyl-l-glutamyl-l-histidyl-l-phenylalanine-o-lysyl-N-(8-amino-octyl)-l-phenylalaninamide S,S-dioxide</td>
<td>eibiratidum eibiratide</td>
</tr>
<tr>
<td>(±)-4'-[3-[3,4-dimethoxyphenethyl]amino]-2-hydroxypropoxy]-3'-[5-isoxazoly]butyranilide</td>
<td>ecastololum ecastolol</td>
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<td>10-(2-aminoethyl)estr-5-ene-3,17-dione, cyclic bis(ethylene acetal)</td>
<td>edifolonum edifolone</td>
</tr>
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<td>1-(1,4-benzodioxan-5-yl)piperazine</td>
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<td>6,7-dimethoxy-4-[[4-(o-methoxyphenyl)-1-piperazinyl]methyl]-1-veratrylisoquinoline</td>
<td>elziverinum elziverine</td>
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<td>1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid</td>
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<td>(±)-2-[cyclohexylcarbonyl]-2,3,6,7,8,12b-hexahydropyrazino[2,1-a][2]benzazepin-4(1H)-one</td>
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<td>4-[2-((2E,3aS,4S,5R,6aS)-hexahydro-5-hydroxy-4-[(3S,4S)-3-hydroxy-4-methyl-1,6-nonadiynyl]-2(1H)-pentalenyldene)ethoxy]butyric acid</td>
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| exametazimum | (±)-(3RS, 3'SRS)-3,3'-(2,2-dimethyltrimethylene)diiminodioxygen 
dioxime |
<p>| exametazine | C₁₃H₂₈N₄O₂ |
| fazarabinum | 4-amino-1-β-β-arabinofuranosyl-s-triazin-2(1H)-one |
| fazarabine | C₉H₁₂N₄O₃ |
| fleroxacinum | 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolincarboxylic acid |
| fleroxacin | C₁₇H₁₈F₃N₃O₃ |
| flosequinanum | 7-fluoro-1-methyl-3-(methylsulfinyl)-4(1H)-quinolone |
| flosequinan | C₁₁H₁₀FNO₂S |
| fosinoprilum | (4S)-4-cyclohexyl-1-[[((RS)-1-hydroxy-2-methylpropoxy)(4-phenylbutyl)- phosphiny]l]-proline propionate (ester) |
| fosinopril | C₉₀H₄₆NO₇P |
| fotemustinum | (±)-diethyl [1-3-[2-chloroethyl]-3-nitrosoureido]ethyl]phosphonate |
| fotemustine | C₉₃H₁₅ClN₄O₃P |
| ganciclovirum | 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine |
| ganciclovir | C₹₂H₁₄N₄O₄ |
| gosereulinum | 1-(5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-1-seryl-L-tyrosyl-O-tet-butyl-o-seryl-L-leucyl-L-arginyL-L-prolyl)semicarbazide |
| goserelin | C₉₉H₆₄N₁₆O₁₄ |
| guaisteinum | thioacetic acid, S-ester with (±)-3-(mercaptoacetyl)-2-[(o- methoxyphenoxy)methyl]thiazolidine |
| guaisteine | C₁₃H₁₉NO₃S₂ |
| ibacitabinum | 2'-deoxy-5-iodocytidine |
| ibacitabine | C₉H₁₂I₅N₄O₄ |
| ilmofosinum | choline hydroxide, (±)-3-(hexadecylthio)-2-(methoxymethyl)propyl hydrogen phosphate, inner salt |
| ilmofosine | C₉₈H₆₅NO₃PS |</p>
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| ritiometanum | (methylidynetriethio)triacetic acid  
| ritiometan | C₇H₁₀O₆S₃ |
| rocastinum | (±)-2-[2-(dimethylamino)ethyl]-3,4-dihydro-4-methylpyrido[3,2-f]-1,4-oxazepine-5(2H)-thione  
| rocastine | C₁₉H₂₄N₈O₂S |
| ronactololum | (±)-4'-[2-hydroxy-3-(isopropylamino)propoxy]-p-anisanilide  
| ronactolol | C₂₀H₂₆N₂O₄S |
| rufloxacinum | 9-fluoro-2,3-dihydro-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzothiazine-6-carboxylic acid  
| rufloxacin | C₁₇H₁₈FN₃O₃S |
| sabeluzolum | (±)-4-(2-benzothiazolylmethylamino)-α-[p-fluorophenoxy)methyl]-1-piperidineethanol  
| sabeluzole | C₂₀H₂₆N₂O₄S |
| saterinonum | (±)-1,2-dihydro-5-[p-[2-hydroxy-3-[4-(o-methoxyphenyl)-1-piperazinyl]-propoxy][phenyl]-6-methyl-2-oxonicotinonitrile  
| saterinone | C₂₇H₃₀N₄O₄ |
| savoxepinum | 3-(cyclopentylmethyl)-2,3,4,5-tetrahydro-1H-dibenzo[2,3:6,7]oxepino[4,5-d]-azepine-7-carbonitrile  
| savoxepin | C₂₀H₂₄N₄O |
| sedecamycin | C₂₇H₃₅NO₈ |
| seganserinum | 3-[2-[4-[bis(p-fluorophenyl)methylene]piperidino]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one  
| seganserin | C₂₉H₂₇F₂N₃O₂ |
| seglitidum | cyclo(N-methyl-L-alanyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-phenylalanyl)  
| seglitide | C₄₄H₅₆N₈O₇ |
| sequifenadinum | α,α-di-o-tolyl-3-quinuclidinemethanol  
| sequifenadine | C₁₈H₂₂NO |
| sermorelinum | growth hormone-releasing factor (human)-(1-29)-peptide amide  
| sermorelin | C₁₉₄H₂₄₆N₄₄O₄₂S |
| sertaconazolium | (±)-1-[2,4-dichloro-β-[(7-chlorobenzo[b]thien-3-yl)methoxy]phenethyl]-imidazoline  
| sertaconazole | C₂₉H₂₀Cl₂N₄O₄S |
| setiptilinum | 2,3,4,9-tetrahydro-2-methyl-1H-dibenzo[3,4;6,7]cyclohepta[1,2-c]pyridine  
| setiptiline | C₁₉H₂₃N |
| sevitropii mesilas | (±)-3α-[6,11-dihydrodibenzo[b,e]thiepin-11-yl]oxy]-6β,7β-epoxy-8-methyl-1α,5α-tropanium methanesulfonate  
| sevitropium mesilate | C₂₉H₂₉NO₅S₂ |
| siagosidum | N-[(N-acetylneuraminosylgangliotetrasyl)ceramide, intramolecular ester  
<p>| siagoside | C₇₃H₁₂₂N₄₀O₃₀ |</p>
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WHO Chronicle, Supplement to Vol. 35, N. 5, 1984

International Nonproprietary Names (Rec. INN): List 21

p. 4 defibrotidum defibrotide

*the description should be replaced by:
Polydeoxyribonucleotides from bovine lung or other mammalian organs with molecular weight between 15,000 and 30,000

p. 8 omoconazolum omoconazole

*in the chemical name replace "(E)" by "(Z)"

WHO Chronicle, Supplement to Vol. 38, N. 6, 1984

International Nonproprietary Names (Rec. INN): List 24

p. 1 ademetioninum ademetionine

*the amendment in List 24 rec. is superseded and the chemical name should be replaced by:
(±)-5′-[(R*)-[(R*)-3-amino-3-carboxypropyl]methylsulfonio]-5′-deoxy-adenosine hydroxide, inner salt

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