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

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

WHO Drug Information is published 4 times a year in English and French.

Annual subscription: Sw. fr. 50.—
Airmail rate: Sw. fr. 60.—
Price per copy: Sw. fr. 15.—
WHO Drug Information

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General Policy Topics

Drug control in small countries

The recent evolution of drug control in highly-developed countries was set on course by the thalidomide catastrophe of the early 1960s which imposed an onerous commitment on regulatory authorities to prevent the admission of unacceptably hazardous new drugs to the market. Primacy is still widely accorded in these countries to the assessment of newly-developed drugs and to complex technical considerations regarding their potential safety in man on the basis of experimental data generated largely in animal models. With the passage of time, the information obtained from these models, although of value, has been acknowledged as fallible and a need has been perceived for routine systematic post-marketing surveillance of newly-registered products and for the development of epidemiologically-based approaches to the monitoring process. Orientations have changed, but the technical basis of new drug assessment remains a complex, multidisciplinary process.

This image provides a commonly-projected but singularly incomplete picture of the broader process of drug control, and its sophistication has created a disincentive for many small developing countries to become engaged in the complementary administrative aspects of the regulatory process. New drug assessment holds scant relevance to countries that, because of their lack of market potential, need actively to commission medical supplies from foreign manufacturers. For them, the challenge is to set into place a system of product licensing that provides a sound basis for rationalizing their procurement policies and for assuring the quality and safety of the products they select.

The importance of establishing guiding principles for national drug regulatory authorities in small countries was emphasized in 1985 during the Nairobi Conference on the Rational Use of Drugs, and a consultation recently convened by WHO, in which representatives from six such countries participated, has provided important insights both into the problems at issue and into the existing infrastructure of drug control in the developing world. Although these countries varied strikingly in population, location, geographic characteristics, demography and affluence, striking similarities were evident in the staffing structures of their regulatory authorities. On average, three full-time pharmacists with a similar number of supporting staff were engaged in drug registration and, in most cases, these were supported by a small advisory committee of independent doctors and pharmacists convened on either a regular or ad hoc basis. In one case this group also served as the National Formulary Committee. In no instance were more than two pharmacists employed full-time within the drug inspectorate where reliance was often placed on auxiliary personnel and part-time support, sometimes offered on a voluntary basis. One authority possessed laboratory facilities for full pharmacopoeial analyses; others had none and, of these, only one had ready access to a regional quality control laboratory. None had developed a structured system for post-marketing surveillance of registered drugs.

It is to this reality that guiding principles must be addressed if they are to hold practical significance. It would be a mistake, however, to view the challenge in a negative light. Developing countries are inevitably severely restricted — as are many more affluent nations — in their capacity to engage in a systematic approach to quality control involving either inspection or pharmacopoeial analysis. They are bound to remain largely reliant, in matters of quality assurance, on rigorous implementation of the WHO Certification Scheme, although they might consider, with advantage, the wider application of simple chemical identification tests outside the laboratory to detect fraudulent products and gross degradation of supplies in the distribution chain. However, limitations in resources and manpower are less critical to the creation of a sound administrative structure. A number of small regulatory authorities have already undertaken a full inventory of the medicinal products circulating in their domestic markets and of the responsible importers, wholesalers and manufacturers. In so doing, they have taken the first essential step in the creation of the licensing system that must be in place to provide an effective basis for regulatory action.
Their immediate requirements are twofold. Firstly, they need to organize this information in a computerized data-base that will provide for its systematic and selective retrieval. Secondly, they need to assure their access to the existing international communications network developed for drug regulators under the aegis of WHO.

Given little more than strong motivation and resolution of purpose, these needs can surely be met. Much information on national drug regulatory decisions is now disseminated month by month by WHO to all ministries of health, and the biennial International Conferences of Drug Regulatory Authorities have done much to dispel feelings of isolation among regulators from smaller countries.

Equally significantly, recent developments in microcircuitry and commercialized computer software packages have created the possibility of organizing and operating a basic, yet effective, national drug licensing system from a standard desktop computer. Over the years, inconsistencies in the format of product-specific information required by different regulatory authorities have proved irritating and burdensome to regulators and regulated alike. Much advantage and cost-saving will accrue both to regulatory authorities and pharmaceutical companies if early initiatives are taken to promote international harmonization in the design and content of the many data-bases that will inevitably materialize in the near future to support the licensing process.

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The Rational Use of Drugs

As a unique record of the views and interests of all parties concerned in the world drug situation, this book serves as a key source of guidance in the development and planning of actions necessary to ensure that drugs are used more rationally throughout the world.

1987 • 329 pages • ISBN 92 4 156104 1 • Sw.fr. 52.- / US $31.20

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

The essential drug concept

By Professor A.W. El Borolossy
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Medicinal drugs are vital to the delivery of effective health care, but they are not required in every clinical situation nor can every pharmaceutical product currently in commerce be regarded as essential, or even relevant, to good clinical practice. The correct choice of a drug for an individual patient can raise complex clinical and pharmacological considerations. Similarly, the matching of drug supplies to local health needs, particularly where resources for procurement are stringently limited, needs to be based upon a variety of clinical and socioeconomic considerations. These include the pattern of prevalent diseases, the degree of development of the community, the capacity of available pharmaceutical manufacturing facilities, and the availability and distribution of health services and particularly of health workers with the necessary skills in clinical diagnosis. These factors are interdependent: socioeconomic standards determine the patterns of health care delivery which, in turn, determine the elements of a national drugs policy.

In developed countries with an advanced pharmaceutical industry and a sound health-care infrastructure the availability of effective drugs of adequate quality is largely taken for granted. This contrasts vividly with the situation in developing countries where many factors compromise access to drugs, including shortage of foreign exchange, the ever-rising cost of health services, lack of an effective distribution system, and lack of technical manpower. Nonetheless, it would be a fallacy to assume that developing countries are all at the same level of economic achievement; some possess a pharmaceutical industry which satisfies up to 80 per cent of local needs while others depend wholly on the importation of finished products. In every case, however, they have to ensure that the most effective use is made of available resources in the public sector through rigorous rationalization of services.

It is now over 10 years since the World Health Assembly first delineated the benefits to be gained from rationalizing drug availability in developing countries in the light of health priorities, therapeutic value, safety and cost. Experience over the past decade leaves no doubt that implementation of a rigorous "essential drugs" policy is of crucial importance in optimizing the deployment of available financial resources. Much of this experience has been gained with the operational assistance of WHO. Its multipartite support to Member States requesting such assistance has been of value in many contexts. These extend from advising on the drafting of national drug policy as an element within a broader health strategy, to assisting in the procurement of essential drugs at advantageous prices within the context of the Action Programme on Essential Drugs, and to assuring effective use of the Certification Scheme on the quality of pharmaceutical products moving in international commerce.

It is for sovereign governments to determine the statutory and administrative framework of drug supply and control, but WHO has a responsibility to define the options. It has made a persuasive case for the adoption of national lists of essential drugs wherever basic needs compete for available resources; it has stressed the importance of ensuring that local pharmaceutical production and formulation plants operate in consonance with national policy; it has promoted effective quality control both in principle and through the development of technical norms and training programmes and it has pointed to the need for effective use of the Certification Scheme as an aid to drug procurement. Not least, it has called for more effective dissemination of objective information about available drugs for prescribers and patients, and it has started to compile comprehensive Model Prescribing Information for adaptation by governments seeking to develop national formularies and drug licensing systems.

Central to many of these varied activities is WHO's Model List of Essential Drugs, a compilation of 279 substances classified by their international nonproprietary names and organized into standard pharmacological and therapeutic groups.
First issued in 1977, in accordance with the recommendations of an Expert Committee, the list seeks to identify those drugs — or types of drugs — in appropriate dosage forms which “should be available at all times in adequate amounts”. Nonetheless, emphasis is placed upon the impossibility of constructing a model list of global relevance and upon the need for national administrations to identify their own priorities and to make their own selection. Although the list is thus purely illustrative, importance has been accorded to its updating at biennial intervals in order that it should continue to serve as a stimulus to all countries to create and maintain cost-effective drug policies in the public sector, and to provide a renewed challenge and incentive to pharmaceutical companies to remain vigilant to global health needs. That an important commitment to socially-productive research exists within the pharmaceutical industry is evident from the 21 drugs newly included in the Model List when it was last revised in December 1987. (See p. 31).

In the final analysis, it is the use that countries make of the list that determines its value. Unless it is critically studied at governmental level to determine its relevance to local needs, unless relevant listings of drugs of varying length and complexity are established nationally by competent multi-disciplinary committees for use at the primary, secondary and tertiary levels of health care, and unless these lists are complemented by prescribing information adapted to the knowledge and training of the various cadres of prescriber and issued in a national formulary, much will have been lost. Alone, these efforts are not enough. The active collaboration of health authorities and teaching institutions needs to be engaged. Effective management of drug supplies must be assured; procedures and facilities must be set in place to ensure that quality is never compromised by other considerations in drug procurement; storage and distribution facilities must be upgraded where necessary and, whenever possible, provision for research on drug usage should be encouraged to obtain the vital confirmation that priority needs are being satisfied.

It is gratifying that WHO is pledged to sustain its patronage of the Model List and to continue to develop its collateral programmes concerned with quality assurance and dissemination of regulatory and prescribing information. It can take pride that the stimulus of its message, at global, regional and national level, has persuaded as many as 100 of its Member States to set in place, in one form or another, an administrative commitment to the concept of essential drugs.
When oral contraceptives first became widely available in the early 1960s the possibility that their extended use might carry a risk of cancer was a distant hypothetical concept. Estrogens and progestogens, including those of synthetic origin, were regarded as essentially physiological, non-toxic substances. This complacency was short-lived. Within a decade it had become apparent that estrogens administered alone to older women have an undoubted carcinogenic potential. Over 15,000 cases of endometrial cancer diagnosed among post-menopausal women in the USA in the five years from 1971 to 1975 were attributed, on the basis of epidemiological evidence, to estrogen replacement therapy (1). Sequential contraceptives, which provided estrogen alone during the proliferative phase of the menstrual cycle, were hurriedly withdrawn from use in 1975 by the United States Food and Drug Administration as soon as case reports and cancer registry data suggested they might also invoke this risk (2-4). Shortly afterwards, diethylstilbestrol, a synthetic estrogenic substance once widely used in high-risk pregnancies because it was claimed to reduce the risk of spontaneous abortion, was similarly withdrawn in the USA when it was discovered that a high proportion of women exposed in utero had developed vaginal adenosis during adolescence and early adulthood (5, 6).

More recently, a small but significant increase in the incidence of breast cancer has been reported among the treated mothers (7, 8). This trend only became apparent 20 years or more after exposure and, as yet, no such risk has been associated with post-menopausal use of estrogens (9).

Such findings leave no doubt about the need to remain alert to possible long-term effects of combined steroidal contraceptive preparations. There is now much evidence, however, that concomitant administration of progestogens negates the potential carcinogenic effect of estrogens on the female reproductive system. No less than five retrospective studies undertaken in the USA suggest that combined oral contraceptives reduce the risk of endometrial cancer (10-14). In each case, the incidence of this cancer was halved among oral contraceptive users, at least during the period of exposure. Moreover, three case-control studies reported from the USA (15-17), and an interim analysis of an ongoing prospective study in the United Kingdom (18), suggest that prolonged use has an even greater and more persistent protective effect against ovarian cancer.

As yet, less certainty exists regarding the influence of oral contraception on cancers of the cervix and the breast. Studies in both industrialized and developing countries on invasive and non-invasive cancerous lesions of the cervix have, in several instances, demonstrated a positive association with long-term use (19-23). Most investigators agree that this association is unlikely to be causal, and they point to confounding bias arising from differences in sexual behaviour, the incidence of sexually transmitted disease, and even enhanced detection rates of carcinoma in situ among users of oral contraceptives.

An even more intensive effort has been directed to the influence of these preparations on breast cancer which, overall, remains the most highly prevalent cancerous lesion among women in industrialized countries. At least ten substantial case-control studies have been undertaken since 1980 (24-33). In several of these, no evidence of an association has been found (30-33), but in others a moderately increased risk was reported among women who started to use the pill at an early age before their first pregnancy (24-29). Interpretation of the association is complicated because postponement of child-bearing is known, of itself, to raise the risk of breast cancer (34). Moreover, because the nature and amounts of the estrogens and progestogens contained in marketed combined contraceptive preparations have changed over the years, the relevance of the results to current contraceptive use is uncertain.

It is important to recognize that no substantiated risk of cancer has been attributed to the use of oral contraceptives within a family setting for birth spacing following a pregnancy. Concern is directed only to their prolonged use early in reproductive life. This relates not only to the possible association with breast cancer, but to the increased risk of cervical
cancer resulting from multiple sexual partners. With the advent of AIDS oral contraceptive use seems destined to decrease in this population of women. A recent statement by the Committee on Safety of Medicines in the United Kingdom (35) reflects a widely-held view that there is no call to recommend any change in contraceptive practice in the light of the epidemiological findings, except to emphasize the need to prescribe a product with the lowest content of estrogen and progestogen that is suited to each woman's needs.

Despite difficulties inherent in the interpretation of the data, it is vital to continue to monitor cancer incidence in the first generation of women to use steroidal contraceptives. There is now no doubt that these substances exert an important influence on the development of the endocrine-sensitive neoplasms of the reproductive system. However, the estimated reduction in ovarian and endometrial cancer seems destined to outweigh any adverse effect on the breast (36). This conclusion is tentative and needs to be verified in the light of further investigation. Ultimately, the aim must be to advise women with reasonable confidence on how contraceptive use can best be planned to minimize the known risks.

References


Auranofin licensed in the UK

United Kingdom — Until 1982 gold salts could only be administered to patients with rheumatoid arthritis by intramuscular injection. In that year a lipid-soluble, orally-active gold preparation, auranofin (Ridaura®: SK&F), was introduced which has now been registered in most countries with highly-evolved drug regulatory authorities.

About 20 to 30 per cent of the administered gold is absorbed and, like gold injections, auranofin tablets are intended as a "second line" drug for patients with active, progressive rheumatoid arthritis in whom the response to nonsteroidal anti-inflammatory drugs is inadequate. Although the manufacturer claims that auranofin efficacy is comparable to that of injectable gold, some rheumatologists consider that it is somewhat less active. All are agreed that close monitoring of therapy is required, particularly for serious haematological adverse reactions.


Efficacy of Salmonella typhi (Vi) capsular polysaccharide vaccine in Nepal

A preliminary report has recently been published of the performance of the Vi capsular polysaccharide S. typhi vaccine in a double-blind community trial undertaken in some 7000 residents of five Nepalese villages. The vaccine, manufactured by the Institute Merieux, was administered intramuscularly in single-dose syringes containing 25 µg in 0.5 ml. Controls received pneumococcus capsular polysaccharide vaccine. Seventeen months after vaccination, the codes were broken for 71 patients who had developed either culture-positive or clinically-suspected typhoid. The attack rate of typhoid was 16.2 per 1000 among the controls and 4.1 per 1000
among those immunized ($P < 0.00001$). The efficacy of Vi vaccine was estimated as 72 per cent in the culture-positive cases and 80 per cent in the clinically-suspected cases. Surveillance is being maintained to determine the duration of effective immunity.

Although the efficacy of the vaccine was lower than had been hoped, it holds several advantages over the cellular attenuated strain Ty-21 vaccine. One dose gave the same level of protection as two oral doses of the cellular vaccine. Adverse reactions were rare and similar to those elicited by other capsular polysaccharide vaccines. Vi vaccine may be reliably standardized using physicochemical methods and is stable at ambient temperatures, which greatly simplifies its use in the field.


### Efficacy of thrombolysis with streptokinase after myocardial infarction

**United States of America** — A double-blind trial on the use of streptokinase in acute myocardial infarction recently reported from the United States indicates that this form of treatment is effective in improving left ventricular function and in reducing early mortality. A total of 219 patients presenting consecutively with a first myocardial infarction within four hours of the onset of chest pain were randomly assigned to treatment with intravenous streptokinase (1.5 million units given over 30 minutes). Mortality within the first 30 days was reduced from 12.9 per cent to 2.5 per cent. On average, the left ventricular ejection fraction was six per cent higher and the end-systolic volume smaller. These benefits occurred in both anterior and inferior infarctions whether or not intravenous propranolol was given concomitantly. Adverse effects were uncommon and reinfarction was infrequent, despite a conservative approach to the need for angioplasty or surgery.


### Ciclosporin

**United Kingdom** — A group of doctors in a London teaching hospital have reported the case of a woman with polycystic renal disease who developed insulin-dependent diabetes twenty-five days after first receiving ciclosporin to prevent rejection of a renal allograft. The patient had no family history of diabetes; preoperative plasma glucose concentrations had been within normal limits on six separate occasions; and at no time were islet-cell antibodies detectable.

The authors note that post-transplantation diabetes has occurred in other renal allograft recipients in whom ciclosporin was not apparently implicated. Nonetheless, having regard to the apparent correlation between the intensity of the metabolic disturbances and the dose of ciclosporin in this case, they suggest that the effect may be due to a recently postulated toxic effect of the drug on pancreatic beta-cells.


**United States of America** — Ciclosporin is frequently used to prolong graft survival, particularly in renal transplantation. Its use in children concurrently treated with prednisone has been associated in the USA with changes in facial appearance, including thickening of the nose and ears, puffiness of the cheeks, prominent orbital ridges and prognathism. Since such changes have not been seen in patients treated with azathioprine and prednisone, ciclosporin is clearly implicated in their etiology. The authors draw attention to the consequences that such striking and detrimental changes might have on compliance with therapy.


### Glibenclamide

**Norway** — The case is reported of a mildly diabetic patient who was given glibenclamide after having previously been treated with zuclopenthixol. He subsequently became jaundiced and increasingly fatigued, and was found to have developed haemolytic anaemia. After withdrawal of gliben-
clamid, recovery was rapid and complete. The authors suggest that an immune haemolytic response was triggered by non-specific binding of serum proteins, including IgG and complement, to a damaged or altered erythrocyte surface. However, sulfonylureas have seldom been implicated in haemolytic reactions and this is the first report of a possible association with glibenclamide. This patient was found to have selective IgA deficiency which, for unknown reasons, is often associated with immunological disorders and which, on this occasion, may have caused the drug-induced haemolytic anaemia.


Human insulin

**Switzerland** — Human insulin is often claimed to be equivalent in its effect to animal insulin and less likely to induce adverse effects. Transfer from porcine or bovine to human preparations was not anticipated to give rise to difficulty. However, reports that three patients experienced serious hypoglycaemia after changing from animal to human insulin have inspired a follow-up study involving 176 patients who switched from animal to human insulin. Over one third reported changes in symptoms. Most strikingly, the prodrome of hypoglycaemia — the classical warning signs of sweating and tremor — was much shorter than usual and sympatho-adrenal symptoms were not prominent. The patients were therefore much less aware of imminent hypoglycaemia. The authors conclude that human insulin is of benefit to patients with insulin allergy and the very rare condition of insulin resistance, but that the classical products of animal origin may hold advantage in other patients.


**Federal Republic of Germany** — The Federal Health Office has received 12 reports of hypoglycaemia in diabetic patients who have switched from animal insulin to human insulin. The hypoglycaemia was atypical in that it was not heralded by the warning symptoms of restlessness, tremor, perspiration and hunger and the patients lost consciousness without warning.

The Federal Health Office and the Insulin Committee of the German Diabetes Society are seeking further information to establish if the absence of warning symptoms is specific to human insulin. Meanwhile, doctors are advised to exercise particular caution when transferring patients from animal to human insulin.


Loperamide

**United Kingdom** — A case is reported in the *British Medical Journal* of a 15-month-old girl who developed acute diarrhoea after accidental scalding involving 35 per cent of the body area. The diarrhoea, which was diagnosed as a stress-response to injury, was treated on the ninth day with a single 1 mg oral dose of loperamide. Within 50 minutes she was collapsed, pale and unresponsive to pain. Pulse rate was 120/min and the respiratory rate 14/min. She was resuscitated with oxygen by Ambu bag and intravenous naloxone 0.3 mg. Within two minutes consciousness had improved and the respiratory rate had risen to 30/min, although she remained drowsy throughout the following day.

Loperamide is known to produce respiratory depression and coma after overdosage and prolonged therapeutic use. No other case of opioid toxicity after a single therapeutic dose is known to the authors. Serious toxicity is a rare occurrence but, particularly since loperamide is available over-the-counter in the United Kingdom, doctors are advised to be alert to the possibility of accidental overdosage.


Nitrate tolerance reversed by acetylcysteine?

Acetylcysteine has been available for many years in an oral formulation as a mucolytic agent. More recently, its action as a donor of sulfhydryl groups has resulted in its use in the treatment and prevention of paracetamol poisoning. Its efficacy in this situation has now led to speculation that it may be of value for the treatment of nitrate tolerance. This is
based on the suggestion that nitrates produce their therapeutic vasodilator effect by reacting with sulphydryl-containing molecules on receptors in vascular smooth muscle and that tolerance may occur when the sulphydryl groups become flooded. Some preliminary trials with an intravenous formulation have recently been reported to have produced positive results. This is regarded as particularly encouraging, having regard to the increasing trend towards use of sustained long-term nitrate therapy in the management of stable angina and the frequency with which nitrate tolerance develops in these patients, particularly those in whom constant blood concentrations are maintained by using transdermal nitrate patches as a sustained-release delivery system.


Nonsteroidal anti-inflammatory drugs

United States of America — In a large-scale study undertaken in the USA that provided information on 584 million person days at risk, no evidence was generated to relate use of non-salicylate nonsteroidal anti-inflammatory drugs with gastro-duodenal perforation. Only 54 patients with perforated ulcers had presented a prescription for an NSAID within 90 days of admission. This provides a crude estimate of 0.26 per million person-days at risk. The crude admission rate among non-users was 0.09 per million person-days at risk. Adjusted for age and sex, the rate ratio for NSAID-users compared with non-users was 1.6 (95 per cent confidence interval 0.68-3.7). The case-control analysis yielded a similar result. The authors comment that, although few analogous data are available on long-term use, there is no suggestion that long-term users of NSAIDs are at greater risk than non-users. (see also, however, p. 46).


Oral rehydration salts

Global production of oral rehydration salts for use in acute diarrhoeal diseases has increased rapidly in the last few years. According to WHO’s estimates, the total stood at some 270 million litre equivalents in 1986. The substitution of sodium bicarbonate by trisodium citrate dihydrate in the recommended WHO formula, as revised in 1984, has considerably improved the stability of the preparation. A number of manufacturers are additionally adding flavouring and colouring materials. This is a practice that is not recommended by WHO, since assurances need to be provided that these additives affect neither the safety nor the stability of the formulation.


Phenytoin

United Kingdom — Five male patients are reported to have developed gynaecomastia after being treated with phenytoin for several years. The condition resolved in two cases when phenytoin was replaced by other anticonvulsants. The data are consistent, it is suggested, with the hypothesis that phenytoin both decreases free testosterone concentrations by stimulating the production of sex-hormone-binding globulin and also promotes the conversion of testosterone to 17-beta estradiol.


Retinoids — Oral therapy

Retinoids are naturally-occurring compounds with vitamin A activity. A number of compounds with analogous activity have recently been synthesized and two, isotretinoin and etretinate, have already been registered in many countries for use in specific disorders of keratinization. Their general advantage is that they are less likely than vitamin A to induce signs of hypervitaminosis at therapeutic dosage. However, extended administration can result in bone lesions and raised serum lipid concentrations. Most importantly, particularly since these products are commonly prescribed for younger women of child-bearing age, it is of paramount importance to exclude pregnancy before treatment is started, and that the patient understands and accepts the need to maintain effective
body. Use of these products has already resulted in several cases of serious congenital deformity. The search for further analogues with more potent antipsoriatic and anti-inflammatory effects and with substantially shorter elimination half-lives is ongoing. At least three compounds (acitretin and two ar tinoid analogues) are already under clinical trial. As yet, however, isotretinoin and etretinate remain the only two synthetic retinoids in widespread routine use. Isotretinoin is used primarily in the treatment of severe acne, and also in severe Gram-negative folliculitis and rosacea unresponsive to other therapy. Etretinate, in contrast, is used in severe forms of psoriasis, generalized lichen planus, Darier’s disease and severe congenital ichthyosis. Both drugs are used in dosages ranging from 0.2 to 1.0 mg/kg/day for several months, following which a potential teratogenic risk persists for one month in the case of isotretinoin and for up to 12 months in the case of etretinate.


Warfarin: interaction with imidazoles

United Kingdom — The antimycotic substances ketoconazole and miconazole are known to potentiate the anticoagulant effect of warfarin, probably by inhibiting its metabolism in the liver. A case report has recently been published of marked loss of anticoagulant control in a patient who received miconazole as an oral gel whilst under treatment with warfarin. The authors conclude that, even with this dosage form, sufficient buccal absorption may occur to exert a systemic effect and they recommend that patients receiving these drugs in combination be carefully monitored.

General Information

Schools of pharmacy in Central America

A report recently issued jointly by the Pan American Health Organization and the International Health Council provides a series of recommendations on the curricula to be followed in schools of pharmacy in Central America and Panama which, if adopted, will have a fundamental influence on the organization of the profession. A four-tier career structure is envisaged based upon a training programme that provides for:

- **In-post education of pharmacy clerks or supportive personnel.**
- **A one-year structured course for pharmacy technicians to equip them for performing a range of non-judgemental tasks in the delivery of pharmaceutical services.**
- **A five-year programme that would assure a university degree-level education for the majority of pharmacists practising throughout the region.**
- **A six-year programme with areas of specialization for the clinical and executive pharmacists who will implement the reorganization.**

Reference: Evaluation and recommendations on the curricula of the schools of pharmacy in Central America and Panama. International Health Council, 1425 N W Tenth Avenue, Miami, Florida 33136, USA.

Rubella immunization strategy

United States of America — The intensity with which a rubella vaccination strategy needs to be pursued and maintained if it is to have an appreciable impact on the incidence of congenital rubella syndrome has become evident from experience gained within the United States since rubella vaccine was first licensed there in 1969. Initially, immunization was directed exclusively to young school-aged children and pre-school children over one year old who were considered to be the primary source of rubella transmission. By 1977, a marked decline in the incidence of the disease had been reported in children and the characteristic 6 to 9-year rubella epidemic cycle had been interrupted. Nonetheless, serological surveys of various post-pubertal populations carried out during the 1970s and early 1980s demonstrated that the rates of rubella susceptibility in adolescents and young adults had remained unchanged at 10 to 20 per cent.

In the light of these findings, vaccination was extended, as from 1977, to all susceptible post-pubertal females. It is now evident that, between 1979 and 1985, the reported incidence rates of congenital rubella syndrome and of rubella among young women over 15 years of age declined by approximately 96 per cent. In 1986, only 551 cases of rubella and 12 cases of congenital deformation were attributed to the disease nationwide. Incidence rates of rubella in children have also continued to decline and, as this highly immune group enters the childbearing years, the incidence of congenital rubella syndrome can be expected to decrease further. As yet, however, rates of susceptibility to rubella among adults have not declined appreciably. Elimination of rubella and congenital rubella remains a feasible goal, but it can only be attained through a highly-intensive and long-sustained programme of vaccination.


Combined vaccination against measles, mumps and rubella in Sweden

A two-dose combined vaccination regimen, involving inoculation at 18 months and 12 years, has been advocated in Sweden since 1982 to protect against measles, mumps and rubella. The initial aim of vaccinating 90 per cent of the target population has now been reached nationally, although not in
each municipality. It will not be possible for many years to know whether the programme will reach its aim of providing long term protection — and, if possible, lifelong immunity — but rates of seroconversion are already encouraging.

- Measles: rates of seroconversion have increased from 82 to 96 per cent (almost 100 per cent with neutralization antibody testing) and the two-dose schedule has averted an accumulation of large numbers of non-immune adolescents, as has occurred in the United States of America and Canada, where vaccination was offered initially only to pre-school children.

- Mumps: seroconversion is thus far estimated to be between 80 and 92 per cent. Nonetheless, an unexpectedly mild outbreak of the disease in 1983 suggests that the vaccination programme is already exerting an impact, particularly since most of the infected children were aged 5 to 9 years and had not yet been immunized.

- Rubella: seroconversion is already almost 100 per cent. Although 12-year-old girls have been vaccinated against the disease since 1974, morbidity was not demonstrably influenced until the beginning of 1980. Sex and age analysis of serologically-verified cases during the 1985 outbreak indicated, however, that the vaccination of schoolgirls had been epidemiologically effective virtually from the beginning of the campaign.


Rubella vaccination during pregnancy

United States of America — From the time that rubella vaccination was first extended to women of childbearing age, it has been regarded as important in the USA to monitor the outcome of pregnancy in women who conceive within three months of receiving the vaccine. The Centers for Disease Control have now prospectively monitored over 1000 such pregnancies and, thus far, no congenital abnormalities consonant with the rubella syndrome have been identified within this cohort. Two infants had mild degrees of hypospadias, but no serological evidence of rubella virus infection. Eight other infants born to mothers known to be immune at the time of vaccination had evident and varied defects, none of which was compatible with congenital rubella syndrome, and serological testing, when done, provided no confirmation of rubella virus infection.

Surveillance undertaken in other countries, notably the Federal Republic of Germany and the United Kingdom, has provided similar reassurance. Nonetheless, because no amount of data collection can absolutely exclude the possibility of a theoretical risk to the fetus, the US Immunization Practices Advisory Committee continues to regard pregnancy as an absolute contraindication to rubella vaccination.


New screening strategy for identifying potential anticancer drugs

United States of America — The National Cancer Institute is introducing a new tissue culture screening system in the hope that it may provide a more rapid and effective indication of antineoplastic activity in the several thousands of compounds and substances it reviews each year. At present, initial screening is undertaken solely in mice with a specific form of leukaemia. This test has yielded some notable successes, mainly in identifying substances active against leukaemias and lymphomas. It has failed, in contrast, to identify compounds effective against the common, slower growing, solid tumour cancers of the lung, colon and breast. Each compound will now be tested against more than 100 cultured lines of human tumour cells which, collectively, will include several strains of each major type of cancer. Chemicals that show initial promise against particular cancers in culture will then be further studied in immuno-suppressed mice in which the same tumour strains have been implanted in order to gain information about the compound's systemic toxicity and whether it is metabolized in a way that changes effectiveness. The initial objective is to pass between 10 000 and 20 000 compounds a year through the new system as well as some of the compounds previously screened in mice.
Both synthetic and naturally-occurring substances will be examined, including extracts from sea-floor organisms such as corals, sponges and anemones and plant tissues and extracts from tropical species selected, in part, on the basis of advice from traditional healers. Many important anticancer compounds have already been obtained from plants, and there is every reason to believe that others remain undiscovered.


Fourth International Conference on Pharmacoepidemiology

The Fourth International Conference on Pharmacoepidemiology is scheduled to be held in Minneapolis, Minnesota, United States of America, from 9 to 11 September 1988.

Information can be obtained from Stanley A. Edlavitch, Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, Minnesota 55455, United States of America.

New developments in hormonal contraception

United Kingdom — Hormonal contraception retains its pre-eminence as a means of birth control within the family setting, and developmental research remains ongoing in an attempt to identify compounds with a more specific action and to produce dosage forms of currently-used compounds that result in lessened systemic exposure. These developments have been succinctly reviewed in a recent issue of Health Trends published by the Department of Health and Social Security.

- Levonorgestrel-releasing intrauterine devices. Earlier use of intrauterine contraceptive devices as vehicles to carry hormones direct to the uterus met with limited success because they were relatively bulky and short-lasting in their action. A new slow-release device which liberates approximately 10 µg of levonorgestrel daily can be left in utero for five years and, in a Population Council trial, the pregnancy rate was estimated to be in the order of one per 100 woman-years.

- The contraceptive vaginal ring. In this device the hormones are contained in a hollow silastic ring, similar in texture to the ring pessary. This is inserted by the user high in the vagina around the cervix (as in the management of prolapse) where it releases norgestrel at a rate of approximately 20 µg/day over its effective life-span of 90 days.

- Subdermal implants. Various slow-release carriers of progestogen have been developed which are inserted under the skin of the upper arm or the forearm. The necessary 5 mm incision needs to be made under local anaesthesia using a strict sterile technique. The most widely used of these devices, (Norplant®: Leiros, Finland), consists of a silicon rubber (silastic) membrane in the form of a capsule containing 36 mg of levonorgestrel. The pregnancy rate and the delay in the return of fertility after discontinuation are comparable to those associated with combined oral contraceptives.

- New progestogens. Among these new compounds, which are claimed to be more "selective" and more potent in their action, are gestodene which is now being tested in a monophasic and a triphasic combined pill, and norgestimate which has a marked antiovulatory effect and is already available in combination with ethinylestradiol.

- Anti-progesterone. Mifepristone (RU 486) is a derivative of norethisterone which competitively inhibits progesterone and which may be used either to disrupt ovulation or to prevent implantation. When administered in the luteal phase from day 5 to 26 before a period is missed it induces menstruation regardless of whether conception has occurred. Complete abortion is produced in 90 per cent of cases. Later in pregnancy, the expulsion rate is lower, but it can be raised by concomitant use of a prostaglandin.

- LHRH analogues. The secretion of luteinizing hormone releasing hormone can either be enhanced or inhibited by peptide analogues. These substances offer a safe and effective alternative to steroid contraception and they also have potential as post-coital agents. However, they are costly and induce menstrual irregularity in long-term users. Various compounds designed for administration by nasal spray, subcutaneous infusion, or injection are under development and slow-release polymer biodegradable implants are also being tested.
• **The male pill.** Various combinations of long-acting androgens and progestogens have been used to suppress sperm production. The most promising is a monthly injection of 200 mg *depo-medroxyprogesterone* acetate and 250 mg *testosterone enantate*. Gossypol, a constituent of cotton seed oil has been discovered in China to inhibit sperm motility within days of its first administration by altering cell membrane permeability. Prolonged use completely arrests sperm production — sometimes permanently. *Inhibin*, in contrast, is an endogenous peptide which selectively suppresses both spermatogenesis and ovulation by inhibiting the secretion of follicle-stimulating hormone, an action which provides tangible prospect for a "unisex" pill.


### Animal models for testing drugs against dracunculiasis

The WHO Collaborating Centre within the Centers for Disease Control, Atlanta, USA, has developed animal models in rhesus monkeys, raccoons and ferrets for screening compounds for activity against *Dracunculus medinensis*. Tests involving *albendazole*, *ivermectin*, and *mefronate* are already in progress.


### Changing needles but not syringes: an unsafe practice

The WHO Expanded Programme on Immunization has issued a warning that successive injections of vaccines or other substances should never be administered from the same syringe since changing needles alone does not eliminate the risk of cross infection. It is essential that a sterile needle and a sterile syringe be used for injections given to each individual. It is claimed that disposable and inexpensive sterilizable plastic syringes are now available at a cost that every health centre can afford. A strong plea is made to health adminis-
promote better understanding of medicines by patients. The focus for this year’s activities is the proper use of medicines by the elderly. A public service announcement has been prepared for television and a brochure has been published under the title “Medicine: Before you take it, talk about it”. Copies of the brochure can be obtained from NCPIE, P.O. Box 32328, Washington DC 20007. The cost is US$10 for 50 copies.

United Kingdom — In October 1987 the Association of the British Pharmaceutical Industry (ABPI) issued a report on “Information to patients on Medicines” which has been accepted in principle by the General Medical Services Committee of the Department of Health and Social Security and the Pharmaceutical Society of Great Britain. The basic thrust of the message is that little improvement can be expected in the provision of information to patients until original pack dispensing is fully implemented. Only then will manufacturers be provided with an effective means of educating patients in the use of drugs through the medium of package inserts.

Reference: Information to patients on Medicines. ABPI, 12 Whitehall, London SW1A 2DY. (1987)

Predictive value of animal studies in toxicology

Switzerland — Professor G. Zbinden, Director of the Institute of Toxicology, in Zurich, who has long been a trenchant critic of the unvalidated use of animal models as indicators of potential toxicity of chemical substances in man, has recently summarized his position in a lecture delivered at the Centre for Medicines Research in the United Kingdom. His reservations address two basic postulates of toxicological practice:

- administration of high (toxic) doses improves the predictability of animal experiments; and
- comparison of the dose causing toxicity in animals and that expected to be used in man permits risk assessment for exposed humans.

Professor Zbinden argues that these postulates are based on doubtful assumptions of interdependence between two very different kinds of events: the induction of lesions in laboratory animals by toxic doses of chemicals under highly standardized conditions, and sporadically-occurring adverse reactions in a heterogeneous human population exposed to much lower doses. Nonetheless, current guidelines for safety testing issued by national regulatory authorities leave no doubt that industrial and contract laboratories are still encouraged to operate to standard protocols determined by these assumptions.

Professor Zbinden hastens to concede that many chemicals studied over the past decade cause identical or at least comparable toxic effects in animals and man, but he amply substantiates his concerns with illustrations involving several substances of therapeutic importance. He thus questions the very touchstone of experimental toxicology and acknowledges that no ready solutions are at hand. In his view, the rethinking that is required can stem only from changes in attitudes and working practices. Toxicology cannot be pursued effectively as an isolated discipline; it has immediate relevance to clinical practice and must consequently become closely integrated with scientific medicine.


Industry’s view on restricted drug lists

United States of America — There is now general acceptance that, wherever resources are inadequate to address even the most pressing public health issues, rationalization of drug purchasing in the public sector and implementation of an essential drugs programme are of critical significance to a national drugs policy. However, a polarization of opinion exists in more affluent countries on the extent to which the state should intervene to restrict the range of drugs that is admitted to the market or that is reimbursable from public funds.

Drug manufacturers operating in free market economies are bound to take the view that any product that meets prevailing governmental requirements relating to quality, efficacy and safety should be made available and a recent report published by the United States Pharmaceutical
Manufacturers Association entitled “Restricted Drug Lists: Bad Medicine, Bad Economics” gives substance to this viewpoint. In essence, it argues against the application of a “needs test” in the product licensing procedure on the grounds that:

• it could threaten innovation in pharmaceutical research and health professionals’ ability to provide quality care;

• it would add yet another hurdle to the drug approval process by requiring proof that a new drug is therapeutically superior or less expensive than existing medicines; and

• it could have adverse consequences for health because factors such as the incidence of bacterial resistance and allergic reactions vary from place to place and from patient to patient.


Comments on the essential drug concept: an industry viewpoint

An editorial in a recent issue of Health Horizons, published by the International Federation of Pharmaceutical Manufacturers Associations, reviews progress in the implementation of WHO’s Revised Drug Strategy, and comments supportively on the essential drug concept when it is directed to rationalization of drug procurement and use in countries with very limited resources. It takes issue, however, with attempts to use the concept to define and confine the totality of drug requirements in rich as well as poor countries. It argues that presentation of the essential drug approach as a restrictive device, rather than a basic core of vital medicines, can only alienate key partners in the provision of health care, including the professions, the innovative drug industry and much public opinion. The support of these interests is vital, it contends, if the economically-deprived countries for whom the concept is intended are to derive full benefit from its implementation.


Several hundred thousand children go blind each year due to vitamin A deficiency

Serious vitamin A deficiency in children is recognized as an urgent public health problem in at least 34 developing countries. The condition is most commonly portrayed as a cause of xerophthalmia, a leading form of blindness. However, it also often results in mental retardation, defective bone formation and susceptibility to infections, including measles which remains a leading cause of death among children in these countries. The World Health Organization, the Food and Agriculture Organization of the United Nations and other international agencies have recently re-emphasized that practicable and effective therapeutic strategies can be applied wherever the deficiency is endemic. Three options are recommended:

• adjustment, whenever possible, of the normal diet to assure adequate intake of vitamin A;

• administration of single large oral doses of vitamin A in capsules or oily solution every six months to vulnerable groups;

• addition of vitamin A to widely distributed foodstuffs in quantities sufficient to satisfy minimum daily requirements.


Aztreonam: an alternative to aminoglycosides

United Kingdom — A recent article published in the Drug and Therapeutics Bulletin reviews the properties of aztreonam, the first monobactam (monocyclic bacterially produced ß-lactam) marketed in the United Kingdom. It differs from cefalosporins, other ß-lactams and aminoglycosides in that its antibacterial spectrum is restricted to the Gram-negative aerobes. It has no activity against staphylococci or streptococci.

The review concludes that aztreonam should never be used alone when the causative pathogen remains unidentified, except possibly as an
alternative to cefalosporins in severe pyelonephritis. In other circumstances its value is limited to infections known to be due to multiple-resistant Gram-negative bacteria, or suspected to be due to β-lactamase-producing gonococci. It provides a useful, if expensive, alternative to aminoglycosides in patients allergic to β-lactams and to cefalosporins in patients with renal failure. However, there is no evidence that its use will reduce selection for cefalosporin-resistant bacteria.

In combination, aztreonam offers a less toxic alternative to an aminoglycoside for empirical treatment of mixed infections acquired in hospital, but several well-established cefalosporins can also be used in this way, provided an adequate spectrum is assured by other drugs.


Guidelines for the manufacture of bulk drugs

The Secretariat of the EFTA Convention for the Mutual Recognition of Inspections has issued guidelines for the manufacture of active (or bulk) drug substances. Their purpose is to offer practical advice on what is required from companies to assure their compliance with basic standards of good manufacturing practices. In so doing, they provide a valuable insight into the expectations and methods of assessment of the official governmental inspectors.


Antidotes: preparation of international guidelines

In collaboration with WHO’s International Programme on Chemical Safety (IPCS) and the Commission of the European Communities (CEC), the World Federation of Clinical Toxicology and Poison Control Centres is preparing guidelines for the use of antidotes to widely-available industrial chemicals and drug substances. An antidote is defined as "a therapeutic substance used to counteract the toxic actions of a specified xenobiotic". It is, however, recognized that other agents excluded from this definition may be used to prevent the absorption of poisons, to enhance their elimination, or to treat their effects symptomatically.

Preliminary meetings have already been held to review the use and availability of these substances and to study problems of their supply, particularly in developing countries. This information has now been used, together with a survey undertaken by Dr B. Rumack of the Rocky Mountain Poison and Drug Center, to compile a list of those substances that are currently in widespread clinical use. The need for their further evaluation is now under consideration and plans are in hand for creating an international mechanism for exchanging case reports and for compiling a handbook on symptomatic treatment of poisonings.


More attention to over-the-counter drugs

United Kingdom — When formal product-licensing requirements were first introduced in the United Kingdom in the early 1970s, more than 39,000 marketed products were notified by manufacturers and accorded licences of right. Since then, 22,000 have subsequently been withdrawn either voluntarily by manufacturers or on the advice of the Committee for the Review of Medicines. Many of these were non-prescription items for which evidence of efficacy did not meet contemporary requirements of controlled comparison. Now, however, there is a recrudescence of interest in over-the-counter preparations both within the pharmaceutical industry and within governments because these products are seen as offering a means of relieving over-stretched medical services from caring for minor and intercurrent illness.

In discussing the implications of this trend in a recent editorial in the British Medical Journal, Dr G.N. Volans chastises doctors for their lack of knowledge about non-prescription medicines, even within the ambit of their own specialty. Safe use of over-the-counter drugs, he contends, requires more complete education not only of the public but of the
profession. It also demands rigorous assessment of these products by regulatory authorities and intensified monitoring of their safety in use. Because the safety profile of a drug cannot be assumed to remain unchanged when it is released from prescription control, he argues that there is a strong case for pharmacists to be actively involved in the monitoring strategy.


Increase in licence fees in the United Kingdom

United Kingdom — Because of the skilled manpower required, new product assessment is a particularly costly aspect of drug control. It is estimated that, in the United Kingdom, salaries account for about 75 per cent of the overall costs of the drug licensing authority. In the past, the industry has contributed about two-thirds of these costs directly in licensing fees. It has recently agreed to increase this subvention in the expectation that the added revenue will result in speedier approval of new products. A decision has consequently been taken to raise certain licensing fees and extra staff are being recruited and trained by the licensing authority which is also exploring ways of using new technology, such as a bar code file location system, to improve the service.

Reference: MAIL (Medicines Act Information Letter) No. 51, November 1987

Recombinant organisms: no special environmental risks

United States of America — A report by the National Academy of Sciences has emphasized that the environmental risks posed by a particular organism are dependent upon its properties, not the methods by which it was made. "There is adequate knowledge of the relevant scientific principles, as well as sufficient experience with recombinant DNA techniques, to guide the safe and prudent use of such organisms outside research laboratories", says the panel in its report which concludes that recombinant DNA microbes pose precisely the same hazards as those presented by organisms modified by other genetic methods.

Regulatory Matters

Acetylsalicylic acid

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

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

Acipimox

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


Alkylpoly(oxyethylene) sulfates

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

Alkylpoly(oxyethylene) sulfates are used as detergents largely but not exclusively in externally-applied products. When ethylene oxide is used in their synthesis, they may contain several hundred parts per million of dioxan. This compound, administered to rats at a concentration of 1 per cent in drinking water, has induced hepatic and renal necroses within five months in a high proportion of the animals. Occasional animals have also developed hepatomas and carcinomas of the nasal cavity.


Amantadine

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


Antihistamines

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

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


Anti-inflammatory proteolytic enzymes

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


Bupivacaine-containing anaesthetics

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


Butalbital (combination product)

Luxembourg — Following discussion with the Bureau for Drug Registration, the manufacturer of an analgesic combination preparation containing butalbital + propyphenazone + caffeine (Optalidon®: Sandoz) has agreed to reformulate the product to exclude the barbiturate component.


Calcitonin

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


Ceftriaxone

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

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

Cell therapy

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

The reported adverse effects comprise allergic manifestations, shock, and delayed reactions involving the central nervous and respiratory systems. Moreover, the possibility of contamination of these preparations with human viral pathogens including Visna-Maedi virus and scrapie virus.
cannot be excluded, even when they are derived from healthy animals.

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


Cyproterone acetate

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


Cimetidine

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


Clometacin

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


Cyclophosphamide

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


Dihydroergotamine mesilate + heparin sodium + lidocaine hydrochloride

**United States of America** — The Food and Drug Administration has approved an extension of the indications for dihydroergotamine mesylate +
heparin sodium + lidocaine hydrochloride (Embolex®: Sandoz), injection fluid 0.5 mg + 5,000 IU + 7.46 mg per 0.7 ml, for the prevention of post-operative deep venous thrombosis and pulmonary embolism in total hip replacement surgery.

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

**Flunitrazepam**

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

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

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

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

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

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

**Fluvoxamine**

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


**Glyceryl trinitrate**

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


**Herbal products**

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

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

A separate system of registration is proposed for herbs and botanical preparations and a review procedure is under consideration that will require marketed products to meet specifications contained in a “standardized drug monograph”. The format of
these monographs has yet to be settled but they will include reference to ingredients listed quantitatively and identified by the part of the plant as required; labelled and advertised claims; cautionary or warning statements; quality assurance with respect to both good manufacturing practice and identification of ingredients. Combination products will be accepted only if they are justified on sound therapeutic principles.

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

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


**Ibuprofen**

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

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

The Committee thus proposes that ibuprofen 200 mg be available to adults from pharmacies without prescription on the understanding that the pharmacist will personally advise customers on its use at the time of sale.

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

Required warnings on retail containers include the following:

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

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

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

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

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


**Interferon alfa-2a**

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

Interleukin-2

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

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

Ipratropium bromide

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


Metoclopramide

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


Mucopolysaccharide polysulfuric acid esters

Federal Republic of Germany — The Federal Health Office is planning to withdraw from the market two injectable preparations containing mucopolysaccharide polysulfuric acid esters (Arteparon®, Arteparon Forte®: Luitpold-Werk) that are indicated for the treatment of arthroses. It is claimed that their efficacy has never been adequately demonstrated and that both products have been associated with a variety of adverse effects including exacerbation of damage to the treated joint, allergic phenomena and anaphylactic shock.


Nabilone

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


Oral contraceptives: revised patient package insert

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

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

The package insert is required to contain the following information:

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

**Oral contraceptives**

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


**Phenylpropanolamine**

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


**Piroxicam**

**Iceland** — The Committee on Pharmaceuticals has additionally approved the use of piroxicam (Felden®: Pfizer) for the treatment of dysmenorrhoea. Two new pharmaceutical forms have also
been approved: suppositories in strengths of 10 and 20 mg, and dispersible tablets 20 mg.

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

Rifampicin

France — The Ministry of Health has additionally approved the use of rifampicin (Rifadin®: Merrell-Dow) in combination with doxycycline for the treatment of brucellosis. The recommended dosage schedule is:
- 3 x 300 mg rifampicin in the morning before breakfast.
- 2 x 100 mg doxycycline with the evening meal.


Saccharin

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

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


Syringes and needles for parenteral injection: restricted use

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


Ticlopidine

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

Triazolam

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

References

Trimethoprim/sulfonamide combinations

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

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

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

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


Vincamine in herbal medicines

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


Vitamins

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

• monocomponent products containing retinol (vitamin A), cyanocobalamin (vitamin B12), ergocalciferol (vitamin D), or vitamin E;

• injectable forms of monocomponent products containing thiamine (vitamin B1) or pyridoxine (vitamin B6).

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


VETERINARY DRUGS

Detomidine

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

Lasalocid sodium

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


Luprostiol

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


Monensin

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


Tiamulin

**Sweden** — The National Board of Health and Welfare has approved tiamulin (Tiamutin® vet.: Lövens) injection fluid 200 mg/ml for treatment of dysentery in pigs. A solution containing 125 mg/ml for addition to the drinking water is also available. Its use is contraindicated in pregnant sows. Withdrawal period before slaughter: 14 days.


Dispensing of veterinary products in pharmacies

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

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


Generic substances used in animal feeds

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

Applicants must provide data on the quality of each product, its acceptability and stability in animal feeds and information on its safety and efficacy under the proposed conditions of use. Since standard withdrawal periods must appear on the product labelling, no residue data are needed.
Licensed products may be supplied for incorporation in animal feeds for the treatment of animal diseases only on veterinary prescription. The licence will carry no recommendation for use against specific conditions or in particular species, nor will they give any information as to the dosage.


Withdrawal periods for medicated animal feeds

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

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


Oil-based veterinary vaccines

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

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

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

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

Reference: Committee on Safety of Medicines, Current
Essential Drugs

WHO Drug Information Vol. 2, No. 1, 1988

Section 1. Anaesthetics

1.1 GENERAL ANAESTHETICS AND OXYGEN
ether, anaesthetic (2) inhalation
diazepam (1b, 2) injection, 5 mg/ml in 2-ml ampoule
halothane (2) inhalation
ketamine (2) injection, 50 mg (as hydrochloride)/ml in 10-ml vial
nitrous oxide (2) inhalation
oxygen inhalation (medicinal gas)
thiopental (2) powder for injection, 500 mg, 1.0 g (sodium salt) in ampoule

1.2 LOCAL ANAESTHETICS
*bupivacaine (2, 9) injection, 0.25%, 0.5% (hydrochloride) in vial
*lidocaine injection, 1%, 2% (hydrochloride) in vial
+ epinephrine 1:200 000 in vial
+ epinephrine 1:200 000 in vial
+ epinephrine 1:200 000 in vial
+ epinephrine 1:200 000 in vial
+ epinephrine 1:200 000 in vial
+ epinephrine 1:200 000 in vial
+ epinephrine 1:200 000 in vial

1.3 PREOPERATIVE MEDICATION
atropine injection, 1 mg (sulfate) in 1 ml ampoule
chloral hydrate syrup, 200 mg/5 ml
*diazepam (1b) injection, 5 mg/ml in 2 ml ampoule
*morphine (1a) injection, 10 mg (sulfate or hydrochloride) in 1 ml ampoule
*promethazine elixir or syrup, 5 mg (hydrochloride)/5 ml

Section 2. Analgesics, antipyretics, nonsteroidal anti-inflammatory drugs and drugs used to treat gout

2.1 NON-OPIOIDS
acetylsalicylic acid tablet, 100 - 500 mg
allopurinol (4) suppository, 50 - 150 mg
*ibuprofen tablet, 100 mg
*indometacin tablet, 200 mg
paracetamol capsule or tablet, 25 mg
tablet, 100 - 500 mg
suppository, 100 mg
syrup, 125 mg/ 5 ml

Explanatory Notes

When the strength of the drug is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

* Example of a therapeutic group. Various drugs can serve as alternatives.

Numbers in parentheses following the drug names indicate:
(1a) Drugs subject to international control under the Single Convention on Narcotic Drugs (1961);
(1b) Drugs subject to international control under the Convention on Psychotropic Substances (1971);
(2) Specific expertise, diagnostic precision, or special equipment required for proper use;
(3) Greater potency or efficacy;
(4) In renal insufficiency, contraindicated or dosage adjustments necessary;
(5) To improve compliance;
(6) Special pharmacokinetic properties for purpose;
(7) Adverse effects limit benefit/risk ratio;
(8) Limited indications or narrow spectrum of activity;
(9) For epidural anaesthesia.

Letters in parentheses following the drug names indicate the reasons for the inclusion of complementary drugs:
(A) When drugs in the main list cannot be made available;
(B) When drugs in the main list are known to be ineffective or inappropriate for a given individual;
(C) For use in rare disorders or in exceptional circumstances.
(D) For use only where appropriate facilities for drug surveillance are available.
2.1 NON-OPIOIDS (cont.)

**Complementary Drugs**

- colchicine (C) (7) tablet, 500 µg
- *probenecid (C) tablet, 500 mg

2.2 OPIOID ANALGESICS

- *codeine (1a) tablet, 30 mg (phosphate) injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule oral solution, 10 mg/5-ml tablet, 10 mg (sulfate)

**Complementary Drug**

- *pethidine (A) (1a, 4) injection, 50 mg (hydrochloride) in 1-ml ampoule tablet, 50 mg, 100 mg (hydrochloride)

Section 3. Antiallergics and drugs used in anaphylaxis

- *chlorphenamine tablet, 4 mg (hydrogen maleate) injection, 10 mg (hydrogen maleate) in 1-ml ampoule
- *dexamethasone tablet, 500 µg, 4 mg injection, 4 mg (as sodium phosphate) in 1-ml ampoule
- epinephrine injection, 1 mg (as hydrochloride) in 1-ml ampoule
- hydrocortisone powder for injection, 100 mg (as sodium succinate) in vial
- *prednisolone tablet, 5 mg

Section 4. Antidotes and other substances used in poisonings

4.1 GENERAL

- *charcoal, activated powder
- ipecacuanha syrup, containing 0.14% ipecacuanha alkaloids calculated as emetine

4.2 SPECIFIC

- atropine injection, 1 mg (sulfate) in 1-ml ampoule
- deferoxamine powder for injection, 500 mg (mesilate) in vial
- dimercaprol (2) injection in oil, 50 mg/ml in 2-ml ampoule
- *DL-methionine tablet, 250 mg

methylthioninium chloride injection, 10 mg/ml (methylene blue) in 10-ml ampoule
naloxone injection, 400 µg (hydrochloride) in 1-ml ampoule
penicillamine (2) capsule or tablet, 250 mg sodium calcium edetate (2) injection, 200 mg/ml in 5-ml ampoule
sodium nitrite injection, 30 mg/ml in 10-ml ampoule
sodium thiosulfate injection, 250 mg/ml in 50-ml ampoule

Section 5. Antiepileptics

carbamazepine scored tablet, 100 mg, 200 mg
*diazepam (1b) injection, 5 mg/ml in 2-ml ampoule
ethosuximide capsule or tablet, 250 mg syrup, 250 mg/5 ml
phenobarbital (1b) tablet, 15 - 100 mg elixir, 15 mg/5 ml
phenytoin capsule or tablet, 25 mg, 100 mg (sodium salt) injection, 50 mg (sodium salt)/ml in 5-ml vial
valproic acid (7) enteric coated tablet, 200 mg, 500 mg (sodium salt)

Section 6. Antiinfective drugs

6.1 ANTHELMINTHICS

6.1.1 INTESTINAL ANTHELMINTHICS

- *mebendazole chewable tablet, 100 mg niclosamide chewable tablet, 500 mg piperazine tablet, 500 mg hydrate (as adipate or citrate) elixir or syrup (as citrate) equivalent to 500 mg hydrate/5 ml praziquantel tablet, 150 mg, 600 mg pyrantel chewable tablet, 250 mg (as embonate) oral suspension, 50 mg (as embonate)/ml tiabendazole chewable tablet, 500 mg lotion, 500 mg/5 ml

**Complementary Drug**

levamisole (B) tablet, 50 mg, 150 mg

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* Example of a therapeutic group. Various drugs can serve as alternatives.
1 This solution may be used rectally if sterile preparations are not available.
# Essential drugs

## 6.1.2 ANTIFILARIALS
- **diethylcarbamazine**
  - tablet, 50 mg (dihydrogen citrate)
- **suramin sodium**
  - powder for injection, 1 g in vial

**Complementary Drug**
- **ivermectin (D)**
  - scored tablet, 6 mg

## 6.1.3 ANTISCHISTOSOMALS
- **mefloquine**
  - tablet, 100 mg
- **oxamniquine**
  - capsule, 250 mg
  - syrup, 250 mg/5 ml
  - tablet, 600 mg
- **praziquantel**

## 6.2 ANTIBACTERIALS
### 6.2.1 PENICILLINS
- **ampicillin (4)**
  - capsule or tablet, 250 mg, 500 mg (anhydrous)
  - powder for oral suspension, 125 mg (anhydrous)/5-ml
  - powder for injection, 500 mg (as sodium salt) in vial
- **benzathine benzylpenicillin (5)**
  - powder for injection, 1.44 g benzylpenicillin (=2.4 million IU) in 5-ml vial
- **benzylpenicillin**
  - powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU)
  - powder for injection, 500 mg (as sodium salt in vial)
- **cloxacillin**
  - capsule, 500 mg (as sodium salt)
  - powder for oral solution, 125 mg (as sodium salt)/5 ml
  - powder for injection, 500 mg (as sodium salt) in vial
- **phenoxymethylpenicillin**
  - tablet, 250 mg (as potassium salt)
  - powder for oral suspension, 250 mg (as potassium salt)/5 ml
- **piperacillin**
  - powder for injection, 1 g, 2 g, (as sodium salt) in vial
- **procaine benzylpenicillin**
  - powder for injection, 1 g (= 1 million IU), 3 g (= 3 million IU)

### 6.2.2 OTHER ANTIBACTERIAL DRUGS
- **chloramphenicol (7)**
  - capsule, 250 mg
  - oral suspension, 150 mg/5 ml (as palmitate salt)
  - powder for injection, 1 g (as sodium succinate) in vial

**Complementary Drugs**
- **erythromycin**
  - capsule or tablet, 250 mg (as stearate or ethyl succinate)
  - powder for oral suspension, 125 mg (as stearate or ethyl succinate)/5 ml
  - powder for injection 500 mg (as lactobionate) in vial
- **gentamicin (4)**
  - injection, 10 mg, 40 mg (as sulfate)/ml in 2-ml vial
- **metronidazole**
  - tablet, 200 - 500 mg injection, 500 mg in 100-ml vial
  - suppository, 500 mg, 1 g oral suspension, 200 mg (as benzoate)/5 ml
- **spectinomycin (8)**
  - powder for injection, 2 g (as hydrochloride) in vial
- **sulfadimidine (4)**
  - tablet, 500 mg oral suspension, 500 mg/5 ml injection, 1 g (sodium salt) in 3-ml ampoule
- **sulfamethoxazole + trimethoprim (4)**
  - tablet, 100 mg + 20 mg, 400 mg + 80 mg oral suspension, 200 mg + 40 mg/5 ml
- **tetracycline**
  - capsule or tablet, 250 mg (hydrochloride)

### 6.2.3 ANTILEPROSY DRUGS
- **clofazimine**
  - capsule, 50 mg, 100 mg
dapsone
capule, 50 mg, 100 mg
- **rifampicin**
  - capsule or tablet, 150 mg, 300 mg
  - powder for injection, 150 mg, 300 mg
  - tablet, 150 mg, 300 mg

### 6.2.4 ANTITUBERCULOSIS DRUGS
- **ethambutol (4)**
  - tablet, 100 - 500 mg (hydrochloride)
- **isoniazid**
  - tablet, 100 - 300 mg
- **pyrazinamide**
  - tablet, 500 mg
- **rifampicin**
  - capsule or tablet, 150 mg, 300 mg
- **streptomycin (4)**
  - powder for injection, 1 g (as sulfate) in vial
- **thioacetazone + isoniazid**
  - tablet, 50 mg + 100 mg, 150 mg + 300 mg

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1. Example of a therapeutic group. Various drugs can serve as alternatives.
2. Two strengths are required for individual dosage adjustment.
6.3 ANTIFUNGAL DRUGS
amphotericin B (4) powder for injection, 50 mg in vial
griseofulvin capsule or tablet, 125 mg, 250 mg
eketoconazole (2, 7) tablet, 200 mg
oral suspension, 100 mg/5 ml
nystatin tablet, 500 000 IU
Complementary Drug
flucytosine (B) (4, 8) capsule, 250 mg
infusion, 2.5 g in 250 ml
sulfadoxine + pyrimethamine (B) tablet, 500 mg + 25 mg
tetracycline (B) capsule or tablet, 250 mg
(hydrochloride)
b) PROPHYLAXIS
chloroquine tablet, 150 mg
(as phosphate or sulfate)
syrup, 50 mg (as phosphate or sulfates)/5 ml
proguanil tablet, 100 mg (hydrochloride)

6.4 ANTIPROTOZOAAL DRUGS
6.4.1 ANTIAMOEBIC DRUGS
*diloxanide tablet, 500 mg (furoate)
*metronidazole tablet, 200 - 500 mg
injection, 500 mg in 100-ml vial
oral suspension, 200 mg (as benzoate)/5 ml
Complementary Drugs
chloroquine (B) tablet, 150 mg
(as phosphate or sulfate)
dehydroemetine (B) (7) injection, 60 mg
(hydrochloride) in 1-ml ampoule

6.4.2 ANTILEISHMANIASIS DRUGS
meglumine antimoniate injection, 30% equivalent to approx 8.5% antimony in 5-ml ampoule
pentamidine (5) powder for injection, 200 mg (as isethionate) in vial
*sodium stibogluconate injection, 33%, equivalent to 10% antimony, in 30-ml vial

6.4.3 ANTIMALARIAL DRUGS
a) CURATIVE TREATMENT
*chloroquine tablet, 150 mg
(as phosphate or sulfate)
syrup, 50 mg (as phosphate or sulfate)/5 ml
primaquine tablet, 7.5 mg, 15 mg (as diphosphate)
quinine tablet, 300 mg (bisulfate or sulfate)
injection, 300 mg (dihydrochloride)/ml in 2-ml ampoule
Complementary Drugs
mefloquine (B) tablet, 250 mg (as hydrochloride)

Section 7. Antimigraine drugs
acetylsalicylic acid tablet, 300 - 500 mg
ergotamine (7) tablet, 2 mg (tartrate)
paracetamol tablet, 300 - 500 mg

Section 8. Antineoplastic and immunosuppressive drugs
8.1 IMMUNOSUPPRESSIVE DRUGS
*azathioprine (2) tablet, 50 mg
powder for injection, 100 mg (as sodium salt) in vial

8.2 CYTOTOXIC DRUGS
bleomycin (2) powder for injection, 15 mg (as sulfate) in vial
cisplatin (2) powder for injection, 10 mg, 50 mg in vial
cyclophosphamide (2) tablet, 25 mg
powder for injection, 500 mg in vial

* Example of a therapeutic group. Various drugs can serve as alternatives.
8.2 CYTOTOXIC DRUGS (cont.)
cytarabine (2) powder for injection, 100 mg in vial
dactinomycin (2) powder for injection, 500 µg in vial
*doxorubicin (2) powder for injection, 10 mg, 50 mg (hydrochloride) in vial
etoposide (2) capsule, 100 mg injection, 20 mg/ml in 5-ml ampoule
fluorouracil (2) injection, 50 mg/ml in 5-ml ampoule
mercaptopurine (2) tablet, 50 mg injection, 2.5 mg (as sodium salt) in vial
procarbazine capsule, 50 mg (as hydrochloride)
vincristine (2) powder for injection, 10 mg (sulfate) in vial
vinblastine (2) powder for injection, 1 mg, 5 mg (sulfate) in vial

Complementary Drug
calcium folinate (C) (2)3 tablet, 15 mg injection, 3 mg/ml in 10-ml ampoule

8.3 HORMONES AND ANTIHORMONES
*dexamethasone tablet, 500 µg, 4 mg injection, 4 mg (as sodium phosphate) in 1-ml ampoule
*ethinylestradiol tablet, 50 µg
*prednisolone tablet, 5 mg injection, 20 mg, 25 mg (as sodium phosphate or sodium succinate) in vial
tamoxifen tablet, 10 mg, 20 mg (as citrate)

Section 9. Antiparkinsonism drugs
*biperiden tablet, 2 mg (hydrochloride)

levodopa + *carbidopa (5, 6)
tablet, 100 mg + 10 mg, 250 mg + 25 mg

Section 10. Blood, Drugs affecting the

10.1 ANTIANAEMIA DRUGS
ferrous salt tablet, equivalent to 60 mg iron oral solution, equivalent to 25 mg iron (as sulfate) in 1 ml
ferrous salt + folic acid 4 tablet, 60 mg + 250 µg
folic acid (2) tablet, 1 mg injection, 1 mg (as sodium salt) in 1-ml ampoule
*hydroxocobalamin (2) injection, 1 mg in 1-ml ampoule

Complementary Drug
*iron dextran (B) (5) injection, equivalent to 50 mg iron/ml in 2-ml ampoule

10.2 ANTICOAGULANTS AND ANTAGONISTS
heparin sodium injection, 1000 IU/ml, 5000 IU/ml, 20 000 IU/ml in 1-ml ampoule
phytomenadione injection, 10 mg/ml in 5-ml ampoule
protamine sulfate injection, 10 mg/ml in 5-ml ampoule
*warfarin (2, 6) tablet, 1, 2 and 5 mg (sodium salt)

Section 11. Blood products and blood substitutes

11.1 PLASMA SUBSTITUTE
*dextran 70 injectable solution, 6%

11.2 PLASMA FRACTIONS FOR SPECIFIC USE 5 albumin, human (2, 8) injectable solution, 25%

Complementary Drugs
factor VIII concentrate (C) (2, 8) (dried)
factor IX complex (coagulation factors II, VII, IX, X) concentrate (C) (2, 8) (dried)

* Example of a therapeutic group. Various drugs can serve as alternatives.
3 Drug for "rescue therapy" with methotrexate.
4 Nutritional supplement for use during pregnancy.
5 All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Human Blood and Blood Products as found in the twenty-seventh Report of the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 628, 1978, Annex 1).
Section 12. Cardiovascular drugs

12.1 ANTIANGINAL DRUGS

glycerol trinitrate tablet, (sublingual) 500 µg
*isosorbide dinitrate tablet, (sublingual) 5 mg
*propranolol tablet, 10 mg, 40 mg (hydrochloride) injection, 1 mg (hydrochloride) in 1-mlampoule
*nifedipine capsule or tablet, 10 mg

12.2 ANTIDYSRHYTHMIC DRUGS

lidocaine injection, 20 mg (hydrochloride)/ml in 5-ml ampoule
*propranolol tablet, 10 mg, 40 mg (hydrochloride) injection, 1 mg (hydrochloride) in 1-mlampoule
verapamil (8) tablet, 40 mg, 80 mg (hydrochloride) injection, 2.5 mg (hydrochloride)/ml in 2-mlampoule

Complementary Drugs
*procainamide (B) tablet, 250 mg, 500 mg (hydrochloride) injection, 100 mg (hydrochloride)/ml in 10-mlampoule
*quinidine (A) tablet, 200 mg (sulfate)

12.3 ANTIHYPERTENSIVE DRUGS

*hydralazine tablet, 25 mg, 50 mg (hydrochloride) powder for injection, 20 mg (hydrochloride) in ampoule
*hydrochlorothiazide tablet, 25 mg, 50 mg
*nifedipine capsule or tablet, 10 mg
*propranolol tablet, 40 mg, 80 mg (hydrochloride)

Complementary Drugs
methyldopa (B) (7) tablet, 250 mg
*reserpine (A) tablet, 100 µg, 250 µg injection, 1 mg in 1 ml-ampoule
*sodium nitroprusside powder for preparing (C) (2, 8) infusion, 50 mg in ampoule

12.4 CARDIAC GLYCOSIDES

digoxin (4) tablet, 62.5 µg, 250 µg oral solution, 50 µg/ml injection, 250 µg/ml in 2-mlampoule

Complementary Drug
digitoxin (B) (6) tablet, 50 µg, 100 µg oral solution, 1 mg/ml injection, 200 µg in 1-mlampoule

12.5 DRUGS USED IN VASCULAR SHOCK
dopamine injection, 40 mg hydrochloride/ml in 5-ml vial

Section 13. Dermatological drugs

13.1 ANTIFUNGAL DRUGS

benzoic acid + salicylic acid ointment or cream, 6% + 3%
miconazole ointment or cream, 2% (nitrate)
ystatin ointment or cream, 100 000 IU/g

13.2 ANTIINFECTIVE DRUGS

methylrosanilinium chloride aqueous solution, 1% (gentian violet) tincture, 1%
*neomycin + *bacitracin ointment, 5 mg neomycin sulfate + 500 IU bacitracin zinc/g
silver sulfadiazine cream 1%, in 500-g container

13.3 ANTIINFLAMMATORY AND ANTIPRURITIC DRUGS

*betamethasone (3) ointment or cream, 0.1% (as valerate)
calamine lotion
*hydrocortisone ointment or cream, 1% (acetate)

13.4 ASTRINGENT DRUGS

aluminium diacetate solution, 13% for dilution

13.5 KERATOPLASTIC AND KERATOLYTIC AGENTS

coal tar solution, topical 20%
dithranol ointment, 0.1 - 2%
*podophyllum resin (7) solution, 10 - 25%
salicylic acid solution, topical 5%

13.6 SCABICIDES AND PEDICULICIDES

benzyl benzoate lotion, 25%
lindane (7) cream, lotion or powder, 1%

* Example of a therapeutic group. Various drugs can serve as alternatives.
Section 14. Diagnostic agents

14.1 OPHTHALMIC DRUGS
- fluorescein eye drops, 1% (sodium salt)
- *tropicamide eye drops, 0.5%

14.2 RADIOCONTRAST MEDIA
- *amidotrizoate injection, 140 - 420 mg iodine/ml (as sodium or meglumine salts) in 20-ml ampoule
- barium sulfate powder suspended in water
- *iopanoic acid tablet, 500 mg
- *propyliodone water suspension

Complementary Drugs
- *iohexol (C) injection, 140-350 mg iodine/ml in 5, 10 or 20-ml ampoule
- *iotroxate (C) solution, 5 - 8 g iodine (as meglumine) in 100-250 ml

Section 15. Disinfectants and antiseptics
- *chlorhexidine solution, 5% (digluconate) for dilution
- *iodine solution, 2.5%

Section 16. Diuretics
- *amiloride (4, 7, 8) tablet, 5 mg (hydrochloride)
- *furosemide tablet, 40 mg
- *hydrochlorothiazide tablet, 25, 50 mg

Complementary Drugs
- mannitol (C) injectable solution, 10%, 20%
- spironolactone (C) tablet, 25 mg

Section 17. Gastrointestinal drugs

17.1 ANTACIDS AND OTHER ANTIULCER DRUGS
- aluminium hydroxide tablet, 500 mg
- oral suspension, 320 mg/5-ml

* Example of a therapeutic group. Various drugs can serve as alternatives.

7 This suspension is for administration only into the bronchial tree.

8 Trisodium citrate dihydrate may be replaced by sodium bicarbonate (sodium hydrogen carbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.
Section 18. Hormones, other endocrine drugs and contraceptives

18.1 ADRENAL HORMONES AND SYNTHETIC SUBSTITUTES
- dexamethasone tablet, 500 µg, 4 mg injection, 4 mg (as sodium phosphate) in 1-ml ampoule
- hydrocortisone powder for injection, 100 mg (as sodium succinate) in vial
- prednisolone tablet, 1 mg, 5 mg

Complementary Drug
- fludrocortisone (C) tablet, 100 µg (acetate)

18.2 ANDROGENS

Complementary Drug
- testosterone (C) (2) injection, 200 mg (enantate) in 1-ml ampoule

18.3 CONTRACEPTIVES

18.3.1 HORMONAL CONTRACEPTIVES
- ethinylestradiol + levonorgestrel tablet, 30 µg + 150 µg, 50 µg + 250 µg
- ethinylestradiol + norethisterone tablet, 50 µg + 1.0 mg

Complementary Drugs
- depot medroxyprogesterone acetate (B) (7, 8) injection, 150 mg/ml in 1-ml, 3-ml vials
- norethisterone (B) tablet, 350 µg
- norethisterone enantate (B) (7, 8) injection, 200 mg in vial

18.3.2 INTRAUTERINE DEVICES
- copper containing device

18.3.3 BARRIER METHODS
- condoms with or without spermicide (nonoxinol)
- diaphragms with spermicide (nonoxinol)

18.4 ESTROGENS
- ethinylestradiol tablet, 50 µg

18.5 INSULINS AND OTHER ANTIDIABETIC AGENTS
- insulin injection (soluble) injection, 40 IU/ml in 10-ml vial, 80 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial
- intermediate acting insulin injection, 40 IU/ml in 10-ml vial, 80 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial (as compound insulin zinc suspension or isophane insulin)
- tolbutamide tablet, 500 mg

18.6 OVULATION INDUCERS

Complementary Drug
- clomifene (C) (2, 8) tablet, 50 mg (citrate)

18.7 PROGESTOGENS
- norethisterone tablet, 5 mg

18.8 THYROID HORMONES AND ANTITHYROID DRUGS
- levothyroxine tablet, 50 µg, 100 µg (sodium salt)
- potassium iodide tablet, 60 mg
- propylthiouracil tablet, 50 mg

Section 19. Immunologicals

19.1 DIAGNOSTIC AGENTS
- tuberculin, purified protein derivative (PPD) injection

19.2 SERA AND IMMUNOGLOBULINS
- anti-D immunoglobulin (human) injection, 250 µg/ml
- antirabies hyperimmune serum injection, 1000 IU in 5-ml ampoule
- antivenom serum injection
- antiscorpion serum injection
- diphtheria antitoxin injection, 10 000 IU, 20 000 IU in vial

Immunoglobulin, human normal (2) injection

* Example of a therapeutic group. Various drugs can serve as alternatives.

9 All plasma fractions should comply with the WHO requirements for the collection, processing and quality control of human blood and blood products (WHO Technical Report Series, No. 626, 1978, Annex 1).
19.2 SERA AND IMMUNOGLOBULINS (cont.)
tetanus antitoxin injection, 50 000 IU in vial
tetanus antitoxin (human) injection, 500 IU in vial

19.3 VACCINES10

19.3.1 FOR UNIVERSAL IMMUNIZATION
BCG vaccine (dried) injection
diphtheria-pertussis-tetanus vaccine injection
diphtheria-tetanus vaccine injection
measles vaccine injection
poliomyelitis vaccine (inactivated) injection
poliomyelitis vaccine (live attenuated) oral solution
tetanus vaccine injection

19.3.2 FOR SPECIFIC GROUPS OF INDIVIDUALS
hepatitis B vaccine injection
influenza vaccine injection
meningococcal vaccine injection
rabies vaccine injection
rubella vaccine injection
typhoid vaccine injection
yellow fever vaccine injection

Section 20. Muscle relaxants (peripherally acting) and cholinesterase inhibitors

*gallamine (2) injection, 40 mg (triethiodide)/ml in 2-ml ampoule

*neostigmine tablet, 15 mg (bromide)
suxamethonium (2) injection, 500 µg (metilsulfate) in 1-ml ampoule
powder for injection (chloride)

Complementary Drug
pyridostigmine (B) (2, 8) tablet, 60 mg (bromide)
injection, 1 mg (bromide) in 1-ml ampoule

Section 21. Ophthalmological preparations

21.1 ANTIINFECTIVE AGENTS
*idoxuridine solution (eye drops), 0.1% eye ointment, 0.2%
silver nitrate solution (eye drops), 1%
sulfacetamide eye ointment, 10% (sodium salt)
solution (eye drops), 10% (sodium salt)
tetracycline eye ointment, 1% (hydrochloride)

21.2 ANTI-INFLAMMATORY AGENTS
*hydrocortisone (2, 7) eye ointment, 1% (acetate)

21.3 LOCAL ANAESTHETICS
*tetracaine solution (eye drops), 0.5% (hydrochloride)

21.4 MIOTICS AND ANTIGLAUCOMA DRUGS
acetazolamide tablet, 250 mg
*pilocarpine solution (eye drops), 2%, 4% (hydrochloride or nitrate)

* Example of a therapeutic group. Various drugs can serve as alternatives.
Section 25. Respiratory tract, drugs acting on the

25.1 ANTIASTHMATIC DRUGS
*aminophylline (2) tablet, 100 mg, 200 mg injection, 25 mg/ml in 10-ml ampoule
epinephrine injection, 1 mg (as hydrochloride) in 1-ml ampoule
*salbutamol tablet, 2 mg, 4 mg (as sulfate) inhalation (aerosol), 100 µg (sulfate) per dose syrup, 2 mg (as sulfate)/5 ml injection, 50 µg (as sulfate)/ml in 5-ml ampoule

Complementary Drugs
beclometasone (B) inhalation (aerosol), 50 µg (dipropionate) per dose
*cromoglicic acid (B) inhalation (cartridge), 20 mg (sodium salt) per dose
ephedrine (A) tablet, 30 mg (hydrochloride) elixir, 15 mg (hydrochloride)/5 ml injection, 50 mg (sulfate) in 1-ml ampoule

25.2 ANTITUSSIVES
*codeine (1a) tablet, 10 mg (phosphate)

Section 26. Solutions correcting water, electrolyte and acid-base disturbances

26.1 ORAL
oral rehydration salts see 17.7.1 potassium chloride oral solution

26.2 PARENTERAL
*compound solution of sodium lactate injectable solution

* Example of a therapeutic group. Various drugs can serve as alternatives.
26.3 MISCELLANEOUS

water for injection in 2-ml, 5-ml, 10-ml ampoule

Section 27. Vitamins and minerals

*ergocalciferol capsule or tablet, 1.25 mg (50 000 IU)
oral solution, 250 µg/ml (10 000 IU/ml)

*nicotinamide tablet, 50 mg

pyridoxine tablet, 25 mg (hydrochloride)

*retinol sugar-coated tablet, 10 000 IU (as palmitate) (5.5 mg)
capsule, 200 000 IU (as palmitate) (110 mg)

*retinol (cont.) oral oily solution, 100 000 IU/ml (as palmitate) in multiple-dose dispenser
water miscible injection, 100 000 IU (as palmitate) (55 mg) in 2-ml ampoule

riboflavin tablet, 5 mg

sodium fluoride (8) tablet, 500 µg

thiamine tablet, 50 mg (hydrochloride)

Complementary Drugs

ascorbic acid (C) tablet, 50 mg

calcium gluconate (C), (2, 8) injection, 100 mg/ml in 10-ml ampoule

* Example of a therapeutic group. Various drugs can serve as alternatives.

WHO Expert Committee on the Use of Essential Drugs

The full report of this Expert Committee, which met in Geneva in 1987, will appear shortly in the WHO Technical Report Series.

Members

Professor A. W. El Borolossy, Senior Advisor, Alquds Open University, Amman, Jordan (Chairman).

Professor Y. F. Krylov, Director, State Research Institute for Standardization and Control of Drugs, Moscow, USSR.

Professor Li Jia Tai, Director, Institute of Clinical Pharmacology, Beijing, China.

Professor M. D. Rawlins, University of Newcastle upon Tyne, United Kingdom.

Professor R. J. Royer, Centre de Pharmacovigilance, Nancy, France.

Professor L. A. Salako, University of Ibadan, Nigeria (Rapporteur).

Professor S. Shapiro, Boston University School of Medicine, United States of America.

Dr Kin Shein, Burma Pharmaceutical Industry, Rangoon, Burma.

Professor U. K. Sheth, Houston, United States of America (formerly Director of Pharmacology, Seth G. S. Medical College, Bombay, India).

Professor A. C. Zanini, Istituto de Ciencias Biomedicas USP, Sao Paulo, Brazil (Vice-Chairman).

Other organizations represented by observers:


United Nations Industrial Development Organization (UNIDO).

International Pharmaceutical Federation.

International Federation of Pharmaceutical Manufacturers Associations.

International Union of Pharmacology.

World Federation of Proprietary Medicines Manufacturers.

In revising the Model List of Essential Drugs the Committee made the following changes:

Deletions: amodiaquine, calcium carbonate, chloralhydrate, ethionamide, glibenclamide, imipramine, isoprenaline, levodopa, magnesium sulfate, prothionamide.

Additions: benznidazole, chloral hydrate, contraceptives (condoms, diaphragms, spermicides, IUDS), dithranol, hepatitis B vaccine, idoxuridine, ivermectin, ketoconazole, levamisole, mefloquine, meglumine antimoniate, methionine, nifedipine, piperacillin, promguanil, rubella vaccine, silver sulfadiazine, sodium citrate, tolbutamide, trimethoprim, tropicamide.
Advisory Notices

Beta-adrenoreceptor blocking agents

United Kingdom — The Committee on Safety of Medicines has received a total of 347 reports of bronchospasm, including 25 deaths, in patients treated with beta-adrenoreceptor blocking agents. These reactions have mostly occurred in predisposed patients with a history of obstructive airways disease or asthma. Both oral (299 cases) and ocular (48 cases) preparations were involved, and both cardioselective and non-selective compounds have been implicated.

Doctors are advised not to use preparations containing these compounds in patients at risk when alternative treatment is available.


Sweden — The Adverse Drug Reactions Advisory Committee of the National Board of Health and Welfare has reminded doctors that beta-adrenoceptor blocking agents share with several other drugs a propensity to induce nasal congestion. The frequency seems to be low: in 10 years the Committee has received only 15 reports. Nasal congestion can, nonetheless, be a problem for individual patients and it is therefore considered to be important for doctors to be aware of this effect.


Bromocriptine

United Kingdom — Four patients with Parkinson’s disease complained of impotence during treatment with the dopamine agonist bromocriptine (Parlodel®: Sandoz). In each case, the condition was reversible on withdrawal of the drug.

This effect has not been reported previously and is unexpected in dopaminergic drugs. It is suggested that patients treated with bromocriptine should be specifically monitored to gather more precise information, particularly on the incidence of the condition.


Brotizolam

Federal Republic of Germany — Within the past two years the Federal Health Office has received reports of adverse effects involving the central nervous system in patients receiving the benzodiazepine-related hypnotic brotizolam (Lendormin®: Boehringer Ingelheim). They include headache, sleep disturbances, nightmares, depression and visual disturbances. These effects have not been associated with benzodiazepines and doctors are requested to report suspected reactions that they encounter with this newly introduced drug.


Buprenorphine

Sweden — The Adverse Drug Reactions Committee of the National Board of Health and Welfare has received three reports of post-operative respiratory depression in patients receiving buprenorphine. The reaction did not become evident until about 2.5 hours after administration, and it persisted for some nine hours. The Committee urges doctors, in particular anaesthesiologists, to remain alert to this hazard which has occurred, in each case, at normal therapeutic dosage.


Camphor

Spain — The Health Council of Andalusia has drawn attention to the potential toxicity of topical preparations containing camphor and their propensity to cause severe adverse effects.
including gastrointestinal symptoms, abdominal cramps, excitability, behavioural changes and liver dysfunction, when accidentally ingested or inhaled. Warnings regarding the use of camphor in children are required in several countries as a result of reports of accidental poisoning. It is emphasized that, save for its rubefacient effect, camphor is little more than a placebo.


**Cefacolor**

**Federal Republic of Germany** — The Federal Health Office has informed doctors of the apparent propensity of the cefalosporin antibiotic cefacolor (Panoral®: Lilly) to induce reversible serum sickness — characterized by erythema, oedema, itching, fever, arthritic pain and rigidity — more frequently than other substances of this class. To establish whether cefacolor differs specifically from its congeners in this respect, doctors are requested to report all adverse effects they may encounter.


**Ciprofloxacin**

**Federal Republic of Germany** — The new fluoroquinolone broad spectrum antibiotic ciprofloxacin (Ciprobay®: Bayer) has been approved for the treatment of uncomplicated urinary tract infections (tablet 100 mg) and complicated and uncomplicated infections of the respiratory tract, internal ear, sinus, eye, skin and soft tissues, bone and joints, sex organs and peritoneal cavity (tablet, 250, 500 and 750 mg) due to susceptible microorganisms. Intravenous treatment is recommended in sepsis, life-threatening infectious disease and prophylaxis of infection in immuno-compromised patients.

At present no specific reports have been received of adverse effects associated with ciprofloxacin but, having regard to the properties of other members of this group of antibiotics, the following may be expected:

- effects on the central nervous system;
- hypersensitivity;
- skin reactions;
- blood dyscrasias;
- kidney damage;
- hyperglycaemia, muscle pain, tendovaginitis;
- disturbed taste and vision.

The Federal Health Office urges doctors to restrict prescription of ciprofloxacin exclusively to the approved indications and to be on the alert for adverse effects, including those listed above.


**Chlorofluorocarbon propellants**

**Federal Republic of Germany** — Manufacturers within the Federal Republic of Germany have announced that, as from 1999, they will voluntarily discontinue using chlorofluorocarbon propellants (Freons) in aerosol preparations. The decision is documented in a letter from the Association of Chemical Industries to the Minister of the Environment. Chlorofluorocarbons have been implicated in the progressive destruction of the ozone layer in the upper atmosphere which screens out excessive ultraviolet radiation.


**Chorionic gonadotrophin: risk of adverse effects**

**Federal Republic of Germany** — Human chorionic gonadotrophin (HCG) is registered in the Federal Republic of Germany for the treatment of cryptorchidism, secondary male hypogonadism and certain types of amenorrhoea. However, it is being used increasingly in slimming institutes to promote rapid weight loss.

The Federal Health Office of the Federal Republic of Germany warns against this use and cites the risk of adverse effects including headache, irritability, restlessness, depression, lassitude, oedema, gynaecomastia, ovarian cysts and pain at the injection site.

Clomethiazole

**United Kingdom** — The Committee on Safety of Medicines has drawn the attention of doctors to the potential of clomethiazole to induce fatal respiratory depression when it is used to treat the symptoms of acute alcohol withdrawal. The Committee considers it essential that:

- patients refrain from drinking alcohol when under treatment; and that clomethiazole should never be prescribed either for an alcoholic who continues to drink alcohol or as a treatment for alcoholism.

- patients should be treated in hospital or, in exceptional circumstances, as outpatients within specialist units, in order that the daily dosage of clomethiazole can be monitored closely.


Corticosteroids in the eye

**United States of America** — Two cases reported in the *New England Journal of Medicine* provide a salutary reminder that corticosteroids should be instilled in the eye only when the diagnosis is certain and the indication is compelling. Used inappropriately, corticosteroids may invoke cataracts, glaucoma and enhance infection. Both patients, in whom herpetic infections were misdiagnosed until after treatment was instituted, developed severe keratitis, in one case necessitating corneal transplantation.


Etodolac

**United Kingdom** — The Committee on Safety of Medicines has reminded doctors that the non-steroidal anti-inflammatory agent, etodolac (Lodine®, Ramodar®: Ayerst), is licensed only for the treatment of rheumatoid arthritis. It emphasizes that the efficacy of the compound has not been demonstrated, either as an analgesic or in the treatment of osteoarthritis.

Fenfluramine

**Sweden** — The Adverse Drug Reaction Committee of the National Board of Health and Welfare has advised doctors to be alert for psychotropic changes in patients receiving the sympathomimetic agent fenfluramine (Ponderal®: Servier). This compound is registered in Sweden for the treatment of severe obesity not responding to dietary measures and about 1.2 million “defined daily doses” were sold during the biennium 1985-1986. During this time the drug was the subject of 22 adverse reactions notified to the Committee. Thirteen of the reports were of psychological symptoms including psychosis (4 cases) and depression (5 cases). Lassitude was reported on 5 occasions and diarrhoea twice.


Hepatitis-B (re)vaccination: guidelines for selection of patients

**The Netherlands** — The National Health Council has recently revised its guidelines on hepatitis-B vaccination. Revaccination will now be offered routinely to individuals in high-risk groups who have not developed anti-hB antibodies.

Persons who are both HBs and HBe antigen-positive will be regarded as adequately protected against further infection and will not be vaccinated. However, persons with a positive test for HBs only will be offered vaccination and parents of babies born to HBsAg and/or HBeAg-positive mothers will be encouraged to have them immunized immediately after birth.


Human dura mater graft: transmission of pathogenic viruses

**United States of America** — The Food and Drug Administration has recently received a report of Creutzfeldt-Jakob disease in a 28-year-old woman who died 22 months after receiving a graft of lyophilized irradiated human cadaveric dura mater (1). A causal relationship has not been unequivocally proved, but current procedures used to sterilize human dura mater do not guarantee complete inactivation of the causal organism, and even the most rigorous donor screening cannot exclude asymptomatic carriers.

Methods of preparation used for commercially-available products give a reasonable degree of assurance that they are free of the risk of transmitting human immunodeficiency virus. The FDA urges physicians to use only human tissue products that have been handled in strict accordance with guidelines established by the American Association of Tissue Banks, and records should be maintained so that any subsequent infections can be linked with specific batches of these products.

**United Kingdom** — In the light of the above risk, the Licensing Authority is investigating, together with manufacturers, possible ways of improving the processing of dura mater selected for grafting (2). Existing products remain available for essential repairs but surgeons are urged to consider the use of autografts or synthetic materials whenever possible.

References

Mesalazine

**Federal Republic of Germany** — The Federal Health Office has received a report of elevated serum lipase in a patient treated with mesalazine (5-aminosalicylic acid) for non-specific colitis. This is regarded as strong presumptive evidence of acute pancreatitis, although the patient had no clinical symptoms of the condition. Clinicians are alerted to the possibility that sulfasalazine may have a similar effect, since this is metabolized in the gut to mesalazine and sulfapyridine (see sulfasalazine below).


Misoprostol

**Federal Republic of Germany** — The Federal Health Office has reminded doctors that treatment
of gastrointestinal ulceration with the prostaglandin derivative misoprostol (Cytotec®: Searle) can induce smooth muscle contractions sufficiently intense to cause severe abdominal pain and diarrhoea. Uterine bleeding may also occur and, although abortion has occurred only on rare occasions when treatment has been instituted, pregnancy should be regarded as an absolute contraindication.


**Nonsteroidal anti-inflammatory drugs**

**Belgium** — During a four-year period commencing in November 1982, the Centre for Drug Monitoring received 286 reports of adverse effects related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) excluding salicylates and pyrazolone derivatives. Lesions of the digestive tract were most prevalent (111 cases, 39 per cent) particularly in elderly patients. The median age of 38 patients with gastro-duodenal ulceration (12 of which were perforated) was 70 years. The Centre reminds doctors that nonsteroidal anti-inflammatory agents should be prescribed for elderly patients with great prudence. (See also, however, page 10).


**United Kingdom** — The Committee on Safety of Medicines has received 309 reports of bronchospasm and asthma associated with the use of nonsteroidal antiinflammatory agents. Three patients died following ingestion of a single dose of ibuprofen, and one after a single dose of indometacin. It is not possible to estimate from available evidence whether one NSAID is more likely than another to produce or worsen asthma. Acetylsalicylic acid may provoke or worsen asthma in approximately 5 per cent of asthmatics and, while there is little evidence to suggest that there is a complete "cross sensitivity" between acetylsalicylic acid and other NSAIDs, patients whose asthma is provoked by acetylsalicylic acid should be advised to avoid all NSAIDs. The Committee reminds doctors that otherwise unexplained worsening of asthma may result from use of NSAIDs which may have either been prescribed or purchased over-the-counter.


**Oral contraceptives**

**United States of America** — The Centers for Disease Control together with the National Institute of Child Health and Human Development have reported the results of a study on the possible relationship between oral contraceptive use and the risk of endometrial cancer. A total of 433 women aged between 20 and 54 years with histologically-confirmed epithelial cancer were compared with a control group of 3191 women selected at random from populations from the the same areas. Women who had used combination oral contraceptives for at least 12 months had an age-adjusted risk of developing endometrial cancer of 0.6 relative to those women who had never used them (95 per cent confidence interval, 0.3 to 0.9) and this protective effect persisted for at least 15 years after last use. Examination of the eight most frequently used formulations revealed little difference in the age-adjusted risks, which ranged from 0.2 to 0.7 for women who had ever used a formulation compared with women who had never used them. Continuous use for 12 months or longer conferred protection against all three major histological subtypes of endometrial cancer. (See also page 5).


**Paraformaldehyde**

**United Kingdom** — The Committee on Dental and Surgical Materials has received three reports of allergic angio-oedema following periapical extrusion of root canal sealants containing paraformaldehyde. Dentists are reminded that the greatest care should be exercised to ensure that root canal sealing substances are not extruded beyond the apex.


**Prescription of pharmaceuticals for serious chronic diseases**

**Norway** — The Board of Health and Social Affairs has issued guidelines to doctors on the prescription of pharmaceuticals for serious chronic diseases. When initiating therapy, they are urged to prescribe
the cheapest available product unless there are overwhelming medical reasons not to do so. If treatment with another product has already been started, they are asked to consider whether the patient can be switched to a cheaper product without detriment.


**Progestogens**

**United States of America** — The Center for Drugs and Biologics of the Food and Drug Administration has reviewed epidemiological studies on the use of progestogens during pregnancy with particular regard to the occurrence of urogenital malformations in exposed offspring. Two types of malformation were studied: hypospadias in exposed males and masculinization of exposed females.

In all, nine published epidemiological studies of hypospadias and progestin exposure have been published. In general, the case-control studies have demonstrated a low but consistent risk (approximately twofold). This has not been confirmed in prospective studies but these have lacked sufficient statistical power to exclude the existence of a low risk.

No published epidemiological studies of masculinization of exposed females seem to have been undertaken; however, case reports of such occurrences are numerous and are clearly biologically plausible.


**Propofol**

**United Kingdom** — The Committee on Safety of Medicines has received within the past 12 months nine reports of convulsions and non-voluntary movements in patients anaesthetized with propofol (Diprivan®: ICI). The Committee has asked anaesthetists to report all such reactions and to provide as many clinical details as possible.


**Slimming products**

**Belgium** — The Centre for Drug Monitoring has issued a statement deprecating as irresponsible the prescription of potent therapeutic agents such as thyroid extracts and cathartics as slimming aids. It cites as an example the case of a woman who developed clinically apparent hyperthyroidism and hypokalaemia after being treated for a year with a mixture of thyroid powder, tiratricol (triiodo-thyrono-acetic acid), cardiac glycosides, amfepramone, furosemide, irritant laxatives and pituitary, hypothalamus and adrenal extracts. The Centre emphasizes that, in some cases, patients have been reluctant to inform other doctors whom they consult that they are receiving such treatment.


**Sulfamethoxazole + trimethoprim (co-trimoxazole)**

**Singapore** — On the basis of a review of the literature on the adverse effects associated with sulfamethoxazole/trimethoprim combinations, the National University of Singapore has advised doctors that three categories of patients are at particular risk:

- patients with blood dyscrasias, in whom the preparation is contraindicated having regard to its myelotoxic potential;
- pregnant women, since teratogenic changes have been demonstrated in animal models;
- elderly patients, in whom the incidence of adverse effects is increased.


**Sulfasalazine**

**United States of America** — Sulfasalazine has long been prescribed to treat ulcerative colitis but it is now claimed that the salicylate moiety may occasionally cause paradoxical exacerbation of the condition. The hypothesis is based on experience
with two patients whose colitis was apparently worsened both by sulfasalazine and, subsequently, by olsalazine sodium. Each exposure was accompanied by an increase in abdominal pain and bloody diarrhoea, which subsided within 36 hours of withdrawal of the treatment. It is emphasized that doctors should be aware of this adverse effect since salicylates are used increasingly in enemas and oral preparations for treatment of ulcerative colitis.


Theophylline (sustained-release preparations)

United Kingdom — The Council of the Pharmaceutical Society of Great Britain has issued a warning regarding inequivalence of sustained-release oral theophylline preparations. Pharmacists are advised to contact the general practitioner who has prescribed a sustained-release oral theophylline preparation without specifying a brand in order to establish which brand should be dispensed.

It is regarded as essential that a patient stabilized on a particular brand in hospital should receive the same preparation on discharge. Hospital pharmacists should thus ensure that the discharge procedures include a notification of the appropriate brand for the discharged patient’s general practitioner.

The Licensing Authority has not granted any product licences for generic, oral sustained-release theophylline preparations because those available have a variety of different release mechanisms and dissolution rates, and are thus unlikely to have identical pharmacokinetic profiles even if the same total quantity of theophylline is contained in each preparation.


Trazodone

Belgium — The Centre for Drug Monitoring has drawn the attention of doctors to the case of a patient who developed hypotension and syncope with vertigo when treated with the antidepressant trazodone (Trazolan®: Roussel) and which recurred on rechallenge. It also requests doctors to report cases of priapism associated with use of the drug, since this effect has also been reported to other national drug monitoring centres. Typically, it has appeared after two to three weeks’ treatment and, in some instances, active medicinal treatment and even surgery have been required. It is suggested that male patients should be informed of this risk and advised to stop treatment immediately, should symptoms occur.

Pharmaceutical Products Approved

alfentanil
Narcotic analgesic
Rapifen®: Janssen, Austria
injection fluid 0.5 mg/ml
*Indication:* anaesthesia in short-lasting surgical procedures, and as an adjuvant analgesic in procedures of longer duration.

amrinone
Coronary vasodilator
Inocor®: Winthrop, Sweden
injection fluid 5 mg/ml
*Indication:* acute cardiac insufficiency when the response to treatment with glycosides, diuretics and vasodilators is insufficient.

amiodarone
Antidysrhythmic
Cordaronex®: Sanofi, Sweden
tablet 200 mg
injection fluid 50 mg/ml
*Indication:* tachydysrhythmia in Wolff-Parkinson-White syndrome and other paroxysmal tachydysrhythmias.
*Contraindications:* sinus bradycardia, AV-block.
Injectable form only: circulatory collapse, arterial hypotension.

befunolol
β-adrenoreceptor blocking agent
Glaucconex®: Dr Thilo, Austria
eye drops 5 mg/ml
*Indication:* glaucoma.
*Contraindications, precautions and warnings as usual for drugs of this class.

bepridil
Calcium influx blocking agent
Cordium®: Organon, Ireland
tablet 100, 200, 300 mg
*Indication:* prophylaxis of stable angina pectoris.
*Contraindications:* hypersensitivity, second degree or complete heart block, cardiogenic shock, severe hypotension, concurrent treatment with β-adrenoreceptor blocking agents, uncompensated heart failure, severe bradycardia, sick sinus syndrome, hypo- or hyperkalaemia, severe renal or hepatic insufficiency.
*Caution:* To be used only under specialist supervision. Not to be used during pregnancy or lactation.

bifonazole
Antimycotic
Mycosporin®: Bayer, Austria
solution 0.01 mg/ml
*Indication:* topical treatment of dermal mycoses.

cadexomer iodine
Topical antiseptic
Iodosorb®: SKF, Austria
powder 100% (iodine 1%)
*Indication:* wound dressing, in particular ulcer cruris and decubitus.
*Contraindications:* iodine hypersensitivity, hyperthyroidism, pregnancy, lactation and young children.

calcitonin, synthetic salmon
Synthetic salmon calcitonin
Miacalcic®: Sandoz, Ireland
*Indications:* Paget's disease of bone, hypercalcaemia, pain associated with metastatic bone cancer, post-menopausal osteoporosis.
*Contraindication:* lactation.
*Caution:* Specialist supervision with appropriate monitoring of clinical biochemical and radiological response is required. Not to be used in women of childbearing age unless considered essential since animal studies suggest a causal relationship between calcitonin and retardation of fetal growth and inhibition of lactation.

carboplatin
Cytostatic
Paraplatin®: Bristol, Luxembourg, Ireland
powder for intravenous injection 50, 150, 450 mg/ampoule
*Indication:* advanced ovarian carcinoma of epithelial origin, small-cell lung carcinoma, epithelial carcinoma of head and neck.
**Pharmaceutical Products Approved**

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**Adverse effects:** subclinical hearing loss has occasionally been reported. 
*Contraindications, precautions, warnings* as usual for drugs of this class.

**carpipramine**
Tricyclic antidepressant
Defekton®: Yoshitomi Pharmaceutical Industry, Japan
 coated tablet 25, 50 mg
*Indications:* chronic schizophrenia with loss of volition, depression and hypochondria.
*Adverse effects:* extrapyramidal effects, anticholinergic and neurological symptoms including anxiety, excitation, drowsiness, vertigo, headache.

**cefpimizole**
Cefalosporin antibiotic
Ajicef®: Ajimomoto, Japan
 powder for injection 0.5, 1 g/ampoule
*Indications:* septicemia, infection of respiratory, urinary and biliary tracts, peritonitis and pelvic inflammatory disease.

**cicletanine**
Peripheral vasodilator
Secletan®: Ipsen, Luxembourg
 capsule 50, 100 mg
*Indication:* essential hypertension.
*Contraindications:* severe renal or hepatic insufficiency.
*Caution* in hypokalaemic individuals. Avoid administration in renal insufficiency with creatinine clearance below 30 ml/min.

**ciclopirox olamine**
Antimycotic
Cicloche®: Novag, Spain
 cream 100 mg/g, powder 10 mg/g, solution 10 mg/g
*Indication:* topical treatment of dermal and mucosal mycoses.
*Contraindications:* hypersensitivity.
*Caution:* Not to be applied to the eyes.

**ciprofloxacin**
Broad-spectrum quinolone antibiotic
Ciproxin®: Bayer, Luxembourg
 table 100, 250, 500, 750 mg
 injection fluid 1, 2 mg/ml
*Indication:* infection due to susceptible microorganisms.

*Contraindications, cautions, warnings* as usual for drugs of this class.

**clenbuterol**
β-adrenoreceptor stimulating agent
Spiropent®: Castejon, Spain
 syrup 0.01 mg/5 ml
*Indication:* bronchial asthma, asthmatic bronchitis, spastic bronchitis.
*Contraindications, cautions, warnings* as usual for drugs of this class.

**dinoprostone**
Prostaglandin derivative
Prostin E2®: Upjohn, Netherlands
 infusion fluid (concentrate) 1, 10 mg/ml
*Indications:* induction of labour, therapeutic termination of pregnancy, "missed abortion", hydatidiform mole.
*Contraindications:* hypersensitivity; uterine scarring; fetal disproportion.

**elcatonin**
Eel calcitonin
Elcitonin®: Toyo Jozo, Japan
 injection fluid 50 IU/ml
*Indication:* hypercalcaemia, Paget's disease.
*Caution* in patients with bronchial asthma, hypersensitivity.
*Adverse effects:* anaphylactic shock, sweating, fever, hot flushes or palpitations, headache, vertigo, transient rise in serum transaminase concentration, hyponatraemia, pain at injection site. Safety of use has not been established in children, during pregnancy or lactation.

**febuprol**
Choleretic
Valbil®: Röhm Pharma, Luxembourg
 capsule 100 mg
*Indication:* gastrointestinal complaints due to insufficient biliary secretion.
*Contraindications:* severe liver dysfunction, acute exacerbation of chronic liver disease, biliary duct obstruction, intestinal obstruction, acute inflammation of liver, bile duct or intestine, gastrointestinal ulcer or tumours. Not to be taken during the first trimester of pregnancy or during lactation. Not to be used for treatment of biliary colic.

**flumazenil**
Benzodiazepine antagonist
Anexate®: Roche, Switzerland
 injection fluid 0.1 mg/ml
**Indication:** treatment of benzodiazepine overdose, reversal of benzodiazepine-induced anaesthesia.

**Contraindication:** hypersensitivity.

**Caution:** ability to drive or operate machinery may be impaired. When used to reverse anaesthesia it should not be administered whilst a muscle relaxant remains effective.

**fluoxetine**

Antidepressant
Prozac®: Lilly, Luxembourg
capsule 20, 30, 40, 60 mg

**Indication:** depression with anxiety in hospitalized or ambulatory patients.

**Contraindications:** hypersensitivity. Not to be administered to children.

**flutoprazepam**

Minor tranquilizer
Restar®: Sumitomo Chemical, Japan
tablet 2 mg

**Indications:** anxiety, depression, sleep disturbances; psychosomatic disorders, including gastrointestinal ulcer, irritable bowel syndrome.

**gestrinone**

Synthetic gonadotropin antagonist
Nemestrin®: Roussel, Switzerland
capsule 2.5 mg

**Indication:** endometriosis.

**Contraindications:** pregnancy, lactation, cardiac insufficiency, severe hepatic or renal malfunction.

**gonadorelin (1)**

Synthetic gonadotropic hormone releasing factor
Lutrelef®: Ferring, Ireland, Sweden, Switzerland
powder for injection 0.8, 3.2 mg/ampoule

**Indications:** anovulatory infertility; azoospermia and severe oligospermia; induction of puberty.

Switzerland only: amenorrhoea of hypothalamic origin, support of the luteal phase after ovulation and implantation, male hypogonadism.

**gonadorelin (2)**

Synthetic gonadotropic hormone releasing factor
Cryptocur®: Hoechst, Ireland
metered-dose nasal spray 0.2 mg/dose

**Indication:** cryptorchidism.

**gonadorelin (3)**

Synthetic gonadotropic hormone releasing factor
Fertiral®: Hoechst, Luxembourg
Lutrelef®: Ferring, Switzerland

Injection fluid 0.5 mg/ml

**Indication:** hypogonadotropic hypogonadism

**Contraindications:** endometrial cysts, polycystic ovaries, amenorrhoea in women with a weight index of less than 19.5. Treatment must be discontinued if pregnancy occurs.

Switzerland: Phase I hypothalamic amenorrhoea (clomifene-positive with bleeding) should not be treated with gonadorelin.

**idebenone**

Cerebral vasodilator
Avan®: Takeda, Japan
tablet [strength not indicated]

**Indications:** sequelae of cerebral infarction or haemorrhage, cerebral arteriosclerosis.

**interferon alfa-2a**

Synthetic interferon
Roferon-A®: Roche, Luxembourg, Ireland, Switzerland
powder for injection 3 x 10^6 IU; 9 x 10^6 IU (Ireland only); 18 x 10^6 IU/ampoule

**Indications:** metastatic melanoma, Kaposi's sarcoma in AIDS patients, hairy-cell leukaemia.

**Contraindications:** hypersensitivity, severe cardiac disease, hepatic insufficiency, convulsive disorders, neurological or organic psychiatric disturbances.

**interferon alfa-2b (1)**

Synthetic interferon
Introna®: Essex, Finland
powder for injection 5 x 10^6 IU/ampoule

**Indications:** hairy-cell leukaemia, condylomata, laryngeal papilloma.

**interferon alfa-2b (2)**

Synthetic interferon
Introna®: Aesca, Austria
powder for injection 30 x 10^6 IU/ampoule

Intron A®: Essex, Australia
powder for injection 1.5, 10, 30 x 10^6 IU/ampoule

**Indications:**
Austria: hairy-cell leukaemia, multiple myeloma, Kaposi's sarcoma in AIDS patients. On a tentative basis: malignant melanoma, superficial tumours of the bladder, juvenile laryngeal papilloma, hypernephroma, leukaemia, lymphomas and viral disease such as condylomata acuminata.

Australia: hairy cell leukaemia only.

**Adverse effects:** influenza-like symptoms.
**interferon alfa-2c (1)**

Synthetic interferon
Berofor®: Bender, Austria
powder for injection 15 µg/ampoule

*Indications:* hairy-cell leukaemia, juvenile laryngeal carcinoma.
*Contraindications:* serious cardiovascular disease, bone marrow insufficiency.
*Caution:* not effective in the treatment of carcinoma of the breast, colon, or bronchus.
*Adverse effects:* influenza-like symptoms.

**interferon alfa-2c (2)**

Synthetic interferon
Berofor®: Bender, Austria
eye drops $1.5 \times 10^6$ IU/ml

*Indications:* acute epithelial herpes simplex keratitis, as an adjunct to basic therapy.
*Caution:* contact lenses should not be worn during treatment.

**iopromide**

Radiocontrast medium
Ultravist®: Schering, Netherlands
infusion fluid 499 mg/ml (240 mg iodine)

*Indications:* contrast enhancement in computer tomography, digital subtraction angiography, urography, phlebography of the extremities.
*Contraindications:* clinical hyperthyroidism, hypersensitivity.
*Caution:* not to be used for myelography.

**ketanserin**

Serotonine-antagonist
Sufrexal®: Janssen, Luxembourg, Switzerland
coated tablet 20, 40 mg
injection fluid 5 mg/ml

*Indications:* acute and chronic hypertension (essential or renal); pre- or post-surgical hypertension, pre-eclampsia. As monotherapy or in combination with diuretics or β-adrenoreceptor blocking agents.
*Contraindications:* concurrent treatment with antacids or H2 antihistamines.
*Precautions:* initial dose in patients with impaired liver function may not exceed 2 x 20 mg/day.
*Adverse effects:* occasional vertigo, headache, fatigue, dry mouth.

**loxoprofen**

Nonsteroidal anti-inflammatory agent
Loxonin®: Sankyo, Japan
tablet 60 mg
granules 100 mg/g

*Indications:* pain and inflammation in rheumatic disease.
*Adverse effects, precautions* as usual for drugs of this class.

**lenampicillin hydrochloride**

Penicillin antibiotic
Varacillin®: Kanebo, Japan
Takacillin®: MECT Corporation, Japan
tablets 250 mg

*Indications:* various infections including respiratory, urinary tract, skin and soft tissue, surgical, otolaryngological, ophthalmological and dental infections due to susceptible microorganisms.

**levocarnitine**

Essential constituent of living tissues
Carnitene®: Sigma-Tau, Switzerland
tablet 330 mg
injection fluid 100, 200 mg/ml

*Indications:* myopathy due to carnitine deficiency; re-establishment of carnitine levels after dialysis.

**lisuride**

Dopamine agonist
Dopergin®: Schering, Netherlands
tablet 0.5, 1 mg

*Indications:* inhibition of lactation, galactorrhoea, amenorrhoea, acromegaly, parkinsonism.
*Contraindications:* severely impaired peripheral circulation, coronary insufficiency.

**lobenzarit sodium**

Antirheumatic agent
Carfenil®: Chugai Pharmaceutical, Japan
tablet 40, 80 mg

*Indications:* rheumatoid arthritis.

**mesalazine**

Anti-inflammatory agent
Salofalk®: Falk, Switzerland
Salofalk®: Rowell Laboratories, Netherlands
enema 4 g/60 g

*Indications:* severe distal ulcerative colitis.
*Contraindications:* impaired hepatic and renal function, gastroduodenal ulcer, bleeding diatheses, hypersensitivity to salicylates.

**metipranolol**

β-adrenoreceptor blocking agent
Glausyn®: Mann Pharma, Denmark
eye drops 3, 6 mg/g

*Indication:* wide-angle glaucoma.
micronomicin
Broad spectrum aminoglycoside antibiotic
Sagamycin®: Kyowa Hakko Kogyo, Japan
injection fluid 40, 80 mg/ml
Indication: infection due to susceptible microorganisms, in particular multiresistant strains.
Contraindications, precautions and warnings as usual for drugs of this class.

minoxidil
Vasodilator
Regaine®: Upjohn, Ireland
topical solution 20 mg
Indication: male-pattern baldness.
Caution: Application under occlusion or on shaved or abraded skin may induce systemic effects through increased absorption.

nafamostat mesilate
Enzyme inhibitor
Futhan®: Torii, Japan
powder for injection 10 mg/ampoule
Indication: acute symptoms of pancreatitis.
Adverse effects: local reaction at the injection site.

nedocromil
Antiasthmatic
Tilade®: Fisons, Ireland
inhalation suspension 2 mg/dose
Indications: reversible obstructive airways disease including bronchial asthma, asthmatic bronchitis, exercise-induced asthma, late onset asthma and bronchospasm.
Caution: Not to be used in acute attack.
Adverse effects: headache, nausea, unpleasant taste, local irritation.

nimodipine
Calcium influx blocking agent
Nimotop®: Bayer, Switzerland
injection fluid 0.2 mg/ml
Indications: cerebral vasospasm following subarachnoidal bleeding.

nizatidine
H2-receptor blocking agent
Calmaxid®: Lilly, Switzerland
capsule 150, 300 mg
Indications: gastrointestinal ulcer.

olsalazine sodium
Anti-inflammatory agent
Dipentum®: Pharmacia, Switzerland
capsule 250 mg
Indication: ulcerative colitis.
Contraindication: hypersensitivity to salicylates.
Caution: Occasionally diarrhoea occurs. Safety not established during pregnancy and lactation.

pinaverium bromide
Spasmolytic agent
Dicetel®: Triosol, Luxembourg
tablet 25, 50 mg
Indication: irritable colon.
Contraindication: paralytic ileus.

piretanide
Diuretic
Diurax®: Cusi, Spain
tablet 6 mg
Indication: oedema, hypertension.
Contraindications: renal insufficiency with oliguria or anuria, severe electrolyte deficiency, hepatic precoma or coma.
Caution: Not to be used in the first trimester of pregnancy or during lactation. It is excreted in the milk and may decrease milk production. Nephrotoxicity and ototoxicity of cefalosporin and aminoglycoside antibiotics may be potentiated.

pranoprofen
Nonsteroidal anti-inflammatory agent with anti-pyretic activity
Niflan®: Yoshitomi, Japan
capsule 75 mg
Indications: pain and inflammation in rheumatic disease, upper airways inflammation, dental procedures, trauma.
Adverse effects, precautions as usual for drugs of this class.

roxatidine
H2-receptor blocking agent
Altat®: Teikoku Hormone, Japan
capsule 75 mg
Indication: gastroduodenal ulcer, Zollinger-Ellison syndrome, reflux oesophagitis, pre-anaesthetic medication to prevent aspiration pneumonia.

somatropin
Synthetic human growth hormone
Humatrope®: Lilly, Sweden
powder for injection 4 IU/ampoule
Indication: pituitary dwarfism.
Caution: in diabetes mellitus, malignant disease.
somatrem
Synthetic methionyl growth hormone (human)
Somatonorm®: Fides, Spain
powder for injection 4 IU/ampoule
Indication: short stature due to deficient growth hormone secretion.
Contraindication: diabetes mellitus.

sufentanil
Narcotic analgesic
Sufenta®: Janssen, Austria
injection fluid 0.05 mg/ml
Indication: induction and maintenance of anesthesia in extensive surgery.
Caution: safety during pregnancy and lactation has not been established. Obstetric use should be avoided because sufentanil passes the placenta and may cause respiratory depression in the neonate.

thymopentine
Synthetic pentapeptide
Immunox®: Cilag, Luxembourg
injection fluid 10, 100 mg/ml
Indications: Di George syndrome (absence or immaturity of the thymus gland), severe herpes labialis or genitalis not responding to other antiviral agents.
Contraindications: hereditary hyper-IgE syndrome.
Caution: Local skin reactions may occur. Leukocyte count should be monitored.

tizanidine
Central muscle relaxant
Sirdalud®: Sandoz, Finland
tablet 2, 4, 6 mg
Indications: painful muscle spasms, spasticity due to neurological disorders.

trazodone
Antidepressant
Molipaxin®: Roussel, Ireland
tablet 150 mg
Indication: anxiety, depression.
Warnings: Use in children is not recommended. Safety of use during pregnancy and lactation has not been established. Ability to drive or operate machinery may be impaired.
Caution: in patients with renal or hepatic dysfunction and in epileptic patients.

trimazosin
Vasodilator
Cardiovar®: Pfizer, Ireland
tablet 50, 100, 150 mg
Indication: hypertension, moderate to severe congestive cardiac failure unresponsive to other measures, under direct medical supervision in the hospital.
Contraindication: hypersensitivity.

triptorelin
Synthetic luteotropic hormone releasing factor
Decapeptyl®: Ferring, Switzerland
micro-encapsulated powder for injection
3.75 mg/ampoule
Indication: advanced hormone dependent prostatic cancer.
Contraindications: proven non-hormone dependent carcinoma; after surgical castration.
Caution: Initial exacerbation of symptoms may occur.

zidovudine (1)
Antiviral agent
Retrovir®: Wellcome, Netherlands
infusion fluid (concentrate) 200 mg/10 ml
capsule 100 mg
Contraindications: hypersensitivity, neutropenia, anaemia.
Caution: Only to be administered by experienced specialists.

zidovudine (2)
Antiviral agent
Retrovir®: Wellcome, Sweden, Switzerland
capsules 100, 250 mg
Indication: severe manifestations of infection with HIV virus.