WHO DRUG INFORMATION

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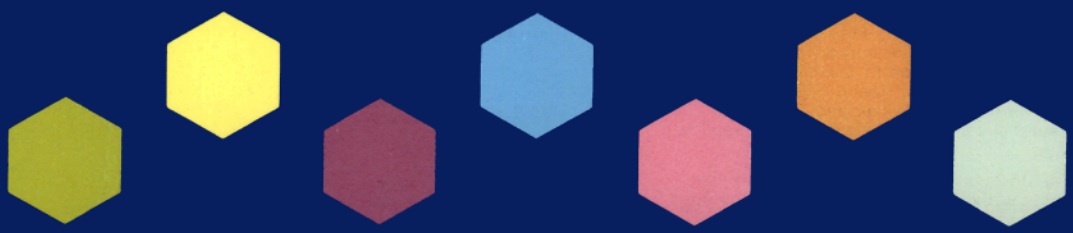
PROPOSED INN LIST 66

INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES



WORLD HEALTH ORGANIZATION · GENEVA

WHO Drug Information

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

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

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General Policy Topics

Microbes on the move

With the advent of AIDS, the potential for harmless commensal organisms to transform themselves into invasive pathogens when defences become attenuated has been demonstrated with unprecedented impact. Inevitably, this has tended to divert attention from some of the broader aspects of the problem. It is less widely appreciated, for instance, that in North America within the past two decades coagulase-negative staphylococci have become a highly prevalent cause of sepsis within neonatal intensive care units (1-4), or that candida species are now implicated in hospital-acquired sepsis almost as frequently as the familiar bacterial pathogens *Escherichia coli*, *Klebsiella* and pseudomonas species (5-8).

Many of these infections occur in the very young and in seriously ill patients who are dependent on life support systems and in other patients with indwelling catheters and implanted devices. It would be incautious, however, to ascribe the ascendancy of these infections solely to increased use of technically-sophisticated invasive procedures. Systemic candidiasis, for example, can result from major surgical interventions. It is also a threat not only to patients with HIV infection (8), but to intravenous drug abusers and to patients with serious burns. Moreover, there are concerns that the virulence of some strains have recently increased (9, 10). Estimated mortality rates among patients with candidaemia have recently attained levels of 40% and even 60% (11, 12).

Clearly, there is now no justification — as was once believed — for withholding antifungal agents until there is evidence of deep focal infection. Despite its toxicity, amphotericin B needs to be administered, either alone or in combination with flucytosine, to every patient at risk when there is evidence of candidaemia (8). The difficulty is that the diagnosis cannot always be made securely on the basis of blood cultures alone. Newer diagnostic approaches based on the detection of candida antigens or metabolites hold promise of greater selectivity (7, 13-15).

In contrast, mortality resulting from coagulase-negative staphylococcal bacteraemia still appears to be low, even among premature infants in centres where there is awareness of the condition and effective treatment is available (16). Untreated, however, bacteraemia can give rise to serious focal disease including skin abscesses, pleural effusion, meningitis, endocarditis and necrotizing enterocolitis (8). Many strains now collected in hospital nurseries produce beta-lactamase and some are also resistant to beta-lactamase-resistant penicillins and cefalosporins (4). Vancomycin remains the only antibiotic that is reliably effective.

These are but two examples of the ever-shifting picture of microbial disease. They demonstrate that dangers can arise even when meticulous measures are enforced to preclude infection. To what extent such dangers are faced in less developed countries where immune mechanisms are attenuated by malnutrition and parasitic disease, and where precautions to prevent spread of infection cannot be rigorously applied is uncertain, but undoubtedly grave. Warnings about multiresistant strains of highly prevalent pathogens have been signalled repeatedly in the medical press. To take but one example, effective control of acute respiratory tract infections is seriously compromised when there is no means of establishing the antibiotic resistance and serotype patterns of *Streptococcus pneumoniae* (17-19). Sixteen strains of this organism were recently isolated from nose swabs taken from childen in Romanian hospitals (20). Only two were susceptible to all the antibiotics commonly used. The prevalence of resistant strains was estimated to be: penicillin and oxacillin 25%; tetracycline 56%; erythromycin 6%; sulphamethoxazole 44%; trimethoprim 31%; chloramphenicol 6%; rifampicin 6%. None was resistant to cefotaxime. It was found, in particular, that 7 of 9 strains resistant to tetracycline had been isolated from children in one hospital where tetracycline was frequently given for deep respiratory infections, often to the very young, and under conditions that favoured patient-to-patient spread of organisms.

In the absence of microbiological facilities, precise diagnosis of serious infection is frequently impossible and selection of antibiotic therapy — when choice exists — becomes an arbitrary exercise. Abjurations about irrational use of antibiotics have no impact and little meaning in such circumstances. Infectious disease is a moving target. The virulence of known pathogens and their resistance to antimicrobials can change rapidly. The history of HIV infection shows that where diagnostic facilities are lacking, a new disease can strike and take an increasing toll of death for years without recognition. The retrovirus, of course, would have eluded basic laboratory tests, but precise microbiological identification of the unique constellation of associated opportunisitic infections would surely have provided earlier warning in Africa of an unprecedented epidemic of immunosuppressive disease.

The development of microbiological reference laboratories in regions where the risk of infectious disease remains greatest would operate to the benefit of people everywhere. The establishment of effective systems of monitoring and controlling antibiotic resistant bacteria is as essential as the provision of the necessary antibiotics. The Expert Committee responsible for maintaining the WHO Model List of Essential Drugs underscored the importance of these facilities when, in1989, it admitted for the first time a category of reserve antimicrobials (21). Its forthcoming report will again focus on this need. Times are hard. On every hand, consternation is expressed about shortfalls in funding to meet immediate needs in the public health sector. However, serious deficiencies in the infrastructure of health-services exacerbate tomorrow's problems as well as today's. Microbiological facilities should feature high on lists of priorities wherever the necessary capital expenditure can be contemplated.

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Reports on Individual Drugs

Mini-dose warfarin: limitations in prevention of venous thrombosis

Prevention of deep vein thrombosis remains problematic. Even brief surgery in young adults carries risk, and this is greatly increased when more extensive interventions are undertaken in elderly or obese patients (1). The greatest risk occurs in patients with shaft fractures of long bones (2) and those who have had major surgery involving the pelvis or the hip (3). Subclinical pulmonary emboli are common (4) and cases of massive fatal embolism occur even where standards of care are exemplary (5). Fatal pulmonary embolism has been found on autopsy — often unexpectedly — in as many as 10% of patients who die in hospital (6, 7) and, in highly-developed countries, massive embolism remains the most common cause of maternal death associated with childbirth (8).

Prevention is dependent upon anticoagulant therapy with heparin or warfarin coupled, when available, with the use of full-length graduated compression stockings (9, 10). Whereas heparin acts immediately, warfarin needs to be administered for several days before it becomes fully effective. Heparin also holds advantage during pregnancy in that it does not cross the placenta. Warfarin, in contrast, is potentially teratogenic, although it is still recommended in pregnant women with diseased or prosthetic heart valves (11).

Low-dose subcutaneous heparin (5000 units 2-3 times daily) has been estimated to reduce to about one half the incidence of both deep vein thrombosis and pulmonary embolism in patients undergoing general or orthopaedic surgery (12). However, discrepant experiences have been reported in patients undergoing hip surgery (13-17) and rebound thrombosis has been described following withdrawal of therapy (18).

Anticoagulant therapy instituted before elective surgery using full doses of warfarin is almost fully effective in averting thrombosis (13), but it has never been generally accepted because of the increased risk of bleeding (5). A more promising approach in high-risk situations, that holds the advantages of simplicity and relative safety, appeared to have been devised when warfarin, administered perioperatively in a small fixed adult dose of 1 mg daily, was reported to be effective in preventing leg vein thrombosis after elective gynaecological surgery (19). More recently, the technique has been shown to protect against thrombosis in the subclavian vein during the insertion of an indwelling catheter (20). However, reports of two recent small prospective studies indicate that it provides scant, if any, protection against complications of thromboembolism in patients undergoing hip replacement (21, 22).

Reconstructive hip surgery offers a formidable test of antithrombotic therapy. The overall rate of thrombotic complications associated with these operations remains high (22), yet many orthopaedic surgeons do not employ antithrombotic measures routinely (23). If an efficient, simple and relatively safe antithrombotic regimen were to satisfy their needs it would undoubtedly be extensively used. With cautious adjustment of dosage, warfarin might yet provide a clinically useful regimen without undue risk of haemorrhage.

In a broader context, these problems serve as a reminder that, five years after its introduction, the rationale for mini-dose warfarin therapy still seemingly rests on the results of a few small trials. Given the considerable population of patients that might benefit from its wider acceptance, and its applicability to modestly-equipped surgical services, exploration of its use in a wider range of settings could still prove rewarding.

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Low-dose acetylsalicylic acid in hypertensive pregnancy disorders

Hypertensive disorders of pregnancy are among the most important causes of maternal and perinatal mortality, of retarded intrauterine growth and premature birth (1, 2). They are also highly prevalent. It has been estimated that, in varying degree, raised blood pressure complicates between 5% and 15% of all pregnancies. Why this problem should arise is far from adequately explained, but various mechanisms have been suggested including enhanced susceptibility to endogenous vasopressor substances (3), and placental insufficiency resulting from imbalance in the production of the vasoactive prostaglandins, thromboxane A and prostacyclin (4, 5).

Since it has been established that acetylsalicylic acid is a potent antithrombotic agent, presumably because it selectively inhibits synthesis of platelet thromboxane A_2, investigation of its use in low doses in an attempt to prevent hypertensive disorders of pregnancy has inevitably attracted attention (5-10). Approaches have been cautious, however, because this action might at the same time predispose to neonatal and excessive maternal bleeding (11).

All the trials as yet undertaken have been small in scale and in no case has the daily dose of acetylsalicylic acid exceeded 150 mg throughout the second and third trimesters of pregnancy. The two largest studies report a significantly reduced

incidence in proteinuria associated with hypertension among the treated women. Two studies suggest that acetylsalicylic acid reduces the overall incidence of hypertension. In other respects, including the effects of treatment on birth weight, Caesarian section and perinatal mortality, the results have been discrepant.

Three of the studies involved less than 50 patients, and none included more than 100. Lack of statistical power may consequently have resulted in failure to demonstrate some important drug-related effects. In these circumstances, pooling of results of comparable trials in accordance with the still-evolving rules of meta-analysis, is claimed — given important assumptions regarding statistical homogeneity — to provide more reliable estimates of treatment effects (12-14). Such an analysis, which embraces all 6 published trials, has recently been published (15). In essence, the conclusion is that low-dose acetylsalicylic acid reduces by two to threefold not only the incidence of pregnancy-induced hypertension and very low birth weight, but also the need for Caesarian section. No adverse effects were ascribed to therapy among almost 200 women who received acetylsalicylic acid, nor were clinically-significant drug-related differences detected in either maternal or neonatal bleeding.

The results imply that, on average, 4 to 5 high-risk women would need to be treated to prevent one case of pregnancy-induced hypertension. None the less, the authors of the meta-analysis caution that considerably more experience is required before consideration can be given to using acetylsalicylic acid routinely during pregnancy. Risk factors for hypertensive disease of pregnancy need to be more precisely identified (16); screening for adverse effects — and excessive bleeding in particular — needs to be undertaken in greater numbers of patients; and prospective dose-ranging studies need to be arranged. This constitutes a challenge to set up one or more large multicentre trials. The inherent organizational problems are daunting, but the preliminary results offer a persuasive stimulus for action.

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ACE inhibitors: a third pillar in the management of heart failure?

Routine management of heart failure has been based, predominantly, on treatment with digoxin and diuretics. However, ever since it was first suggested almost 40 years ago that the output of the failing heart might be increased by reducing impedance to left ventricular ejection (1, 2), there has been awareness that vasodilators could well enhance the therapeutic response in chronic congestive failure (3, 4).

With the development of new vasodilator substances, this hypothesis has been borne out repeatedly in a variety of therapeutic settings. Initially, it was shown that both the alpha adrenoreceptor blocking agent, phentolamine (5), and the non-specific vasodilator, sodium nitroprusside, alleviated acute congestive heart failure by reducing ventricular overload. More than a decade later the clinical value of this approach was confirmed by a demonstration that mortality among patients in severe chronic heart failure was significantly reduced, firstly by a combination of hydralazine and isosorbide dinitrate (6) and, subsequently, by the angiotensin-converting enzyme (ACE) inhibitor, enalapril (7).

Now, information on the performance of these two regimens in mild to moderate heart failure has been obtained within the context of two additional prospective, multicentre, randomized studies (8, 9). In the first of these, which was placebo controlled, the addition of enalapril to conventional therapy was associated within the follow-up period — which ranged from 22 to 55 months — with a reduction in overall risk of mortality of some 16% and a somewhat larger reduction in risk of fatal progressive heart failure. In the second study, the effect of 20 mg enalapril daily was compared under double-blind conditions with a daily dose of 300 mg hydralazine and 160 mg isosorbide dinitrate in patients who were also receiving conventional therapy. After one year, enalapril reduced mortality to 9%, as compared with 13% among patients receiving hydralazine/isosorbide dinitrate and 20% among historical controls who received placebo in an earlier trial (6). This reduction in mortality, which was not evident in subsequent years, reflected a lower incidence of sudden death rather than a difference in the incidence of progressive ventricular failure. This, it has been suggested, results from the blocking effect of ACE inhibitors on the synthesis of angiotensin II which prevents a self-potentiating spiral of falling output and increased peripheral resistance as atrial pressure is lowered (4).

This is not the end of the research trail. It has already been suggested that the use of ACE inhibitors might be explored in fully compensated heart failure, or — because enalapril and hydralazine/isosorbide dinitrate act through different mechanisms — that there might be advantage in using them in combination (3). It is generally agreed, however, that any such initiatives should be deferred until the results are available of two additional trials involving the use of ACE inhibitors which are now nearing completion. If, as it now seems, prolonged use of these drugs comes to be widely accepted in patients with a relatively good prognosis, continued oversight of their potential longer-term adverse effects will also assume importance. Functional renal insufficiency has already been described among patients treated for heart failure (10) and in one trial (8) a statistically nonsignificant excess of cancers of the gastrointestinal tract, liver, gall bladder and pancreas has been interpreted as "troublingly reminiscent of observations in some of the lipid lowering trials (11) in which deaths from cardiovascular causes decreased but cancer occurred more frequently" (3).

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Postmenopausal estrogen therapy: checks and balances

Over the past three decades, postmenopausal estrogen replacement has become one of the most widely practised medical interventions among older women in many countries within the developed world. Almost half of a cohort of more than 48 000 postmenopausal women aged up to 63 years old included in prospective study recently completed in the USA had taken, or were still taking, conjugated estrogens (1). The immediate therapeutic objective is usually to relieve perimenopausal symptoms or to attenuate osteoporosis and the risk of hip fracture (2). Estrogens, however, have other important metabolic effects. They induce changes in lipid metabolism — an increment in high-density lipoprotein cholesterol and a reduction in low-density lipoprotein cholesterol — that have been shown to be protective against coronary atherosclerosis (1, 3). But their use also has important adverse consequences. Unopposed by the action of progestagens, estrogens induce hyperplasia of the endometrium that results, following sustained use over several years, in a substantially increased risk of cancerous change (4-7), and there may also be a slight increase in the incidence of breast cancer (8).

This knowledge provides an onerous challenge to the epidemiologist and a dilemma for the prescribing physician. The objective must be to refine the evidence to provide a secure framework on which to base objective therapeutic strategies. A commentary recently published in the *New England Journal of Medicine* leads clinicians a substantial way toward this goal (9). It makes the case that the clinical decision to recommend estrogen should be driven largely by its effect on ischaemic heart disease. It bases this conclusion on two considerations. Firstly, within the target population of women over 50, the cumulative risk of death from ischaemic heart disease is some 10-fold greater than death resulting from breast cancer or hip fracture, and 40 to 50 fold greater than death resulting from endometrial cancer (10, 11). Secondly, with one important exception (12), a consensus of epidemiological reports has indicated that extended postmenopausal estrogen therapy reduces the incidence of ischaemic heart disease by as much as 40 – 50% (1, 13, 14).

If the protective effect of estrogen is sustained throughout the full period of treatment, even a small reduction in the risk of ischaemic heart disease would overwhelm all adverse effects of treatment. In no circumstance, however, can the risk of estrogen-induced cancers be disregarded. Treatment evokes a commitment not only to regular physical examination, but also arguably to periodic mammography (15) and — in women who have not undergone hysterectomy — endometrial biopsy (16). Early detection through close observation greatly decreases the risk of mortality from endometrial cancer (15), but this risk can be very largely averted by supplementary treatment with a progestagen for 10 days or more in each induced menstrual cycle (17, 18). None the less, even if this aim were to be achieved, the net benefit in terms of mortality would be more than offset if the progestagen were shown to attenuate the protection afforded by estrogens against ischaemic heart disease by as little as 5 – 10% (10).

The weight of the epidemiological evidence that has been brought to bear on the consequences of estrogen replacement therapy is now considerable. As yet, however, no confirmation of these findings has been obtained within the context of a prospective randomized controlled trial. Given the current state of knowledge, ethical considerations could well preclude the enrolment in such a study of women with clinically significant osteoporosis or increased risk of ischaemic heart disease. But,

given the extent to which estrogens are now prescribed, the case for a large-scale, placebo-controlled prospective study among women at lesser risk still merits careful consideration (9) and a commitment to address the challenge has now, it seems, been accepted by the US National Institutes of Health (19).

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Intravenous immune globulin: a case study in cost-effectiveness

Within the span of a few years the use of intravenous immune globulin has soared in many highly developed countries (1). Initially, its use was largely confined to two relatively rare disorders: primary immunodeficiencies and antibody-mediated diseases such as immune thrombocytopenic purpura. It is now also used in many other conditions, including symptomatic HIV infection in children (2), other secondary immunodeficiencies (3), a wide range of autoimmune diseases, some chronic inflammatory conditions, and chronic lymphocytic leukaemia (4). Its value is also being explored as an adjunct in the treatment of cytomegalovirus pneumonia in patients with diseases other than HIV infection (5-7); in combination with antibiotics in the treatment of sepsis in premature

infants; in the management of various neurological and muscular conditions including Guillain-Barré syndrome and myasthenia gravis; and even in the treatment of steroid-dependent asthma (1).

As a result, intravenous immune globulin has become one of the most costly items in some hospital drug budgets (1). Its use in chronic conditions incurs particularly onerous expenses, since it has to be given in high dosage and at frequent intervals. It has been estimated, not only that the drug cost for continuous treatment of an average adult patient with chronic lymphatic leukaemia is in excess of US$ 15 000 per year, but that this buys no extension of life — only an average of less than one additional day of good quality life each year (4). Nor has intravenous immune globulin been demonstrated to prolong the lives of children with HIV infection, although among children with relatively high CD4 lymphocyte counts it does reduce the incidence of serious infections and cumulative time spent in hospital (2).

These sums of money are astronomic when they are compared with the pittances available for health care in less favoured countries. They leave no doubt, however, that the cost-effectiveness of health care is now a live and urgent issue everywhere. Unless priorities are identified and workable criteria are respected for the use of the most expensive products of health care technology, the health care infrastructure must inevitably collapse under the strain. As far as use of intravenous immune globulin is concerned, it might reasonably be emphasized that it has no proven value in patients able to synthesize antibody in normal amounts and that, in this circumstance, it may even inhibit endogenous production of immunoglobulin. The least that can be expected — as has been emphasized during a recent consensus conference organized by the US National Institutes of Health (8) — is that the decision to prescribe intravenous immune globulin on a long-term basis should always be taken in the light of a thorough immunologic evaluation.

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Penicillin, allergy and rheumatic heart disease

Rheumatic heart disease, resulting from recurrent attacks of rheumatic fever, remains the most common cause of cardiovascular death in developing countries. Prophylactic use of antibiotics has consistently been shown to be effective in preventing the streptococcal respiratory infections that are responsible for cardiac lesions (1-3). WHO, which has helped to establish prevention programmes in many countries, recommends long-term monthly injections of benzathine benzylpenicillin, 1.2 million units, for all patients with a history of rheumatic fever (4). However, the acceptance of penicillin preparations has been compromised in some countries by concerns among doctors and patients that the incidence of serious allergic reactions may be raised in this population of patients (5).

Early investigation of the use of benzathine benzylpenicillin for this purpose gave no support to these concerns (6), and the doubts that have since been raised have been based largely on anecdotal evidence. Recently, however, the results of a study involving 1790 patients on long-term prophylaxis drawn largely from developing countries in the Far

East, southern Asia and South America, have provided the data necessary to offer firm reassurance (7). The incidence of allergic reactions among these patients was found to be about 2.5% — no greater, in fact, than the incidence recorded among patients receiving short courses of benzathine benzylpenicillin for sexually transmitted disease (8). In all, 4 episodes of anaphylaxis associated with a total of 32 430 injections were encountered within the study. One of these episodes was fatal, but none occurred in the 600 children in the cohort under 12 years of age. Again, this closely matches experience on the incidence of allergy to penicillin in other populations of patients (9, 10).

Notwithstanding these reassuring results, the authors of the international study suggest that, in order to reduce the already low risk of a fatal reaction, a skin test for penicillin allergy might reasonably be performed on all patients who already have severe heart disease before they are first offered prophylactic penicillin. It has been suggested that anaphylactic reactions may be more hazardous in these patients (11) and this underscores the need for resuscitation facilities to be immediately available. However, the long-term benefits of prophylaxis greatly outweigh the risk of a serious allergic reaction to penicillin (8).

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Poliomyelitis: setbacks in the timetable for eradication?

A perplexing and serious outbreak of paralytic poliomyelitis has recently been reported from 6 of the 7 administrative regions of Oman (1). It was attributed to a recently imported type 1 strain, and it occurred in a sparsely populated, predominantly rural setting where the proportion of childen immunized with 3 doses of oral poliovirus vaccine during the first year of life had recently been raised from 67% to 87%. In all, a total of 118 cases of paralytic disease were reported, and half of the afflicted children had previously received 3 doses of oral vaccine. The vaccine was of the required potency and there was no evidence of failure of the cold chain.

The factors that determined the outbreak are uncertain, but several are at issue:

- the rapid increase in vaccination coverage before the outbreak may have reduced the reservoir of endemic strains and diminished the contribution of natural infection to immunity in the local population;

- the proportion of susceptible infants was presumably high because, whereas the target age for primary immunization is 3.5 months, many children remained unvaccinated until they were 7 months of age;

- the clinical efficacy of 3 doses of the vaccine was lower, at 91%, than is typically achieved in industrialized countries, and serological studies indicated that 50% of vaccinated children had no detectable antibody against poliovirus type 3; and
- the diffuse geographic nature of the outbreak suggests that many fully vaccinated children must have been involved in the chain of transmission.

Earlier experiences are on record of lower than expected humoral immunity against poliovirus types 1 and 3 resulting from use of oral vaccine in developing countries (2-5). These findings raise doubts about the degree of secretory immunity conferred by oral poliovaccine, which has previously been considered to hold advantage in that it normally prevents intestinal infection and subsequent excretion of poliovirus (6, 7). It now seems that, where standards of sanitation are low, an inoculum of wild poliovirus may be large enough to overcome the levels of secretory antibody that would otherwise protect vaccinated children from infection (1).

Whereas it now seems probable that fully immunized individuals can be involved in wild poliovirus transmission, this should not limit achievement of the global target of polio eradication by the year 2000 (8). In Oman, the major determinant of widespread dissemination of infection was a delay of several months between the onset of the outbreak and its subsequent detection and control. Once this was initiated, the epidemic was rapidly terminated.

WHO recommends that in countries likely to be subject to importation of wild poliovirus, effective surveillance should be established to assure early detection of any cases of acute flaccid paralysis. These cases should be investigated expertly and supplementary mass immunization instituted as soon as the clinical diagnosis is confirmed. This involves giving two doses of oral poliovaccine within a short period of time to all children at risk in the area on a house-to-house basis.

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Thiomersal: time for a reassessment?

Thiomersal is a weak antibacterial agent that has long been used as a preservative in vaccines, eye and nose drops, and contact lens solutions. Although ethylmercury residues are potentially neurotoxic and long sequestered after systemic absorption of thiomersal, the small quantities used for these purposes were considered unlikely to pose a hazard. In 1981, however, delayed hypersensitivity was demonstrated to constitute a problem for some patients who stored their contact lenses in solutions containing thiomersal as an antibacterial (1). Clinically, the condition was expressed as intolerance to lens wear, conjunctival hyperaemia and punctate epithelial keratopathy which resolved within a few weeks after the last exposure.

Some 7% of adult patients with chronic blepharitis who have not used soft contact lenses have also been shown to be sensitized to thiomersal on skin patch (2) and intradermal (3) testing — presumably through ophthalmic preparations containing thiomersal. Among younger adults, the prevalence may be higher (2). In these patients continued exposure to thiomersal will eventually aggravate

inflammatory changes. An isolated case of acute laryngeal obstruction has also been reported in a previously sensitized patient who used a throat spray preserved with thiomersal (4).

Local reactions are unlikely to result from injections that are administered subcutaneously or intramuscularly. Reports of hypersensitivity reactions to vaccines are rare, even though several products, including recently developed hepatitis B vaccines, are preserved with thiomersal. None the less, severe reactions are on record (5, 6).

Other antiseptic substances, including chlorhexidine, are also claimed to have induced cell-mediated immunity, albeit with a far lower incidence than thiomersal (3). It is not surprising, having regard to the scale of the problem as it is encountered in ophthalmic practice, that the case for using non-preserved eye drops and contact lens care solutions in sterile, single-dose containers continues to be persuasively restated (3).

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General Information

What patients need to know

Few would now contest that patients have a right to develop a questioning attitude towards medical advice and particularly about drugs that are prescribed for them. The debate is still intensively engaged, however, on how much information should be shared and how it should be presented.

There is no argument about basic essentials: the importance, for instance, of storing tablets of acetylsalicylic acid out of the reach of children, or the need routinely to complete the full prescribed course of an antibiotic. Beyond this, however, and particularly in the management of the chronically ill, the duty of conveying information to the patient can become far more demanding. This is the consensus that permeated the proceedings of a nationally-oriented symposium held in the United Kingdom in 1990 (1-4), and the message has been reinforced recently by the Office of Psychiatric Services in the Australian state of Victoria which has formed a working party to review needs for patient information on psychoactive drugs (5). They define the following principles that everyone engaged in preparing such materials needs to bear in mind.

1. They must be written so that they can be understood by at least 85% of the target population of patients (6).

2. They must be aimed to encourage patients to ask questions of those involved with their treatment about their condition and the drugs that they receive. Patient information leaflets should be designed to promote dialogue, not to inhibit it (7).

3. Any single leaflet on a drug or a group of drugs may not be suited, or even relevant, to every patient under treatment. Individual patients differ in their needs and expectations. Prescription instructions can be influenced by the severity and stage of the treated condition, the period of time over which the drug has been taken, and by other conditions that the patient may already have contracted or is at risk of developing.

4. New leaflets should not be widely distributed until they have been field tested and revised in the light of comments provided by representative patients. The fact that 18 months of consultation and re-writing was required by the Office of Psychiatric Services to produce a series of patient leaflets on psychotropic medicines in accordance with these principles is proof enough that their observance is demanding of both time and effort (5). Many other groups have been engaged in similar initiatives over the past few years. Their experience constitutes a valuable resource. WHO plans shortly to compile an annotated inventory of their activities as a service to others embarking on similar tasks. Those with relevant experience or materials to offer are invited to contact the *WHO Drug Information*.

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Acute poisonings: referral patterns in Zimbabwe

Few reliable statistics have been gathered on the patterns of acute poisoning that prevail in developing countries. The publication of a

retrospective analysis of all such admissions recorded over the past decade by the six largest hospitals in Zimbabwe offers an unusually comprehensive insight into the nature of the problem (1). An average of slightly more than 600 cases were recorded annually. Of these, some 20% resulted from acts of intentional self-poisoning but only 4.5% of the patients died.

Admissions were most prevalent among children under 5 years (35% of all cases) and adults aged between 20 and 30 years (over 20% of cases). It was in the latter group that most cases of intentional poisoning were recorded. Heading the list of causal agents were traditional medicines (23% of the total), followed closely by household chemicals, modern therapeutic drugs, agrochemicals and snake or insect bites. Prominent within these various categories were paraffin, which is often sold in used soft drink bottles; and organophosphates, which were implicated in a substantial number of cases of self-poisoning as well as in occupational exposure.

It is conspicuous that, in the latter years of the decade, traditional medicines were cited as causes of involuntary poisoning with increasing frequency. A similar trend has previously been reported from central Africa (2). It seems probable that this change is in part artefactual since doctors are becoming increasingly aware of the biological activity of traditional medicines. The circumstances of such poisonings often remain vague and patients rarely disclose how they obtained the medicine under suspicion (3, 4). Patterns of toxicity are also highly varied. Intestinal irritation is common when poisoning is acute, and signs are frequently referable to the lungs, the liver and the central nervous system (5). A history of preceding illness can sometimes provide an important diagnostic clue. In Zimbabwe, it is claimed, traditional medicines are used in children mostly to treat diarrhoea, constipation and seizures. Men commonly use them for sexually transmitted diseases and for aphrodisiac purposes; while, women frequently employ them either to promote fertility or as abortifacients. The large doses of aloes that are still frequently used to induce abortion carry a risk of death that is associated far more frequently with post-abortion septicaemia than with acute poisoning (6).

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A new global children's vaccine initiative

Inspired by the success of the Expanded Programme on Immunization in raising to 80% the proportion of the world's children who are protected against poliomyelitis, measles, tuberculosis, diphtheria, pertussis and tetanus, a new global initiative — the Children's Vaccine Initiative — has been launched to develop new and improved vaccines which, if successful, could reduce mortality among children under 5 by as much as one-third by the year 2000.

The initiative — which is being pursued jointly by WHO, the United Nations Children's Fund, the United Nations Development Programme, the World Bank and the Rockefeller Foundation — has already attracted support from bilateral aid programmes, public and private foundations and pharmaceutical companies. Its mandate is to focus and coordinate the efforts of international organizations, governments, donors and industry to promote the development of new and improved vaccines and to ensure their use for the benefit of children worldwide. The immediate goals are to develop three specific products: a single-dose tetanus vaccine; a thermostable oral poliovirus vaccine; and a measles vaccine that can be administered earlier in infancy.

Later, it is planned to foster the development of entirely new vaccines, including dengue, hepatitis A and respiratory syncytial viruses; and of polyvalent vaccines active against several diseases using

either sophisticated micro-encapsulation techniques or genetically manipulated live-vaccine carriers.

The range of illnesses which still cause substantial mortality in children and which may ultimately yield to preventive immunization remains impressive. Aside from a wide spectrum of viral and bacterial infections, are several major parasitic diseases in which a measure of naturally-induced immunogenic protection is evident. Conspicuous among these is malaria which continues to cause up to one million deaths annually, mainly among young children in Africa.

Source: WHO Press Release, WHO/63 17 December 1991.

New approaches to carcinogenicity testing

Doubts continue to resurface about the reliability and efficacy of life-time dosing studies in rodents as indicators of carcinogenicity in man. Inevitably, these doubts fuel concerns that the length of these tests adds substantially to the time schedule for new drug development, a consideration that holds implications for patients as well as manufacturers when important new products are at issue. If, in the last analysis, the results are of dubious relevance to the intended clinical use of the product, an innovation of potential therapeutic value may be unjustifiably lost for ever (1, 2).

The issues are twofold. Firstly, does daily life-time administration of test substances at or near the maximum tolerated dose induce tissue damage that itself invokes a risk of carcinogenicity? Secondly, to what extent do organ-specific tumours induced by non-genotoxic mechanisms of carcinogenicity reflect derangement of metabolic processes that hold no relevance for man?

Little direct information is available about sub-morphological toxicity and rates of cell turnover during carcinogenicity testing, and evidence of a causal link between organ toxicity and tumour development is meagre. In a recent survey of some 50 known carcinogens undertaken by the United States National Institute of Environmental Health Sciences such a correlation was demonstrated in only 7 instances (3). None the less, the possibility is still canvassed that sub-morphological toxicity may accelerate cell turnover (4). If so, the resulting increase in mitogenesis might then proportionately increase the risk of DNA mutations that favour carcinogenesis. However, such an effect is likely to be evident only when the test substance is administered at or near the maximum tolerated dose. Demonstration of a graduated tumour-inducing response across a range of subtoxic doses still provides a firm indication of a direct carcinogenic action (5).

Even when a clear dose response is demonstrated, the question remains as to whether the carcinogenic effect is relevant to the proposed use of the product. Much depends on the length of time and the cumulative frequency with which the drug will be administered clinically and the purpose for which it will be used. Also at issue, however, is whether the mechanism of carcinogenesis in the rodent model has predictive relevance to man. It is believed, for instance, that tumours of the lung are induced in rodents solely by mutagenesis (or genotoxicity). However, in other tissues, disruption of specific metabolic processes provides the stimulus for carcinogenic change; and some of these processes have no precise analogy in man (4, 6). The liver, the kidney, bone marrow and the thyroid have been identified as tissues in which carcinogenic changes are commonly invoked by nongenotoxic mechanisms rather than by specific damage to DNA (5, 7). Insight into these mechanisms is important for a better understanding and design of carcinogenicity studies, not least because identical tumours occur spontaneously and with widely varying incidence in control animals (8).

A commentary recently published in *Nature* concludes that experimental techniques already available are sufficiently developed to provide for exploration of a more rational and expeditious approach to carcinogenicity testing (8). This thesis builds on knowledge that combined use of the *in vitro* salmonella mutagenicity assay and the mouse bone marrow micronucleus assay, or a similar *in vivo* test, will identify a high proportion of proven human carcinogens (9). In the first instance, it is suggested, the structure of new chemicals should first be inspected for configurations known to be associated with genotoxicity. They should then be tested *in vitro* for mutagenicity (including screening for the few *Salmonella*-negative genotoxins). Given that not all genotoxins are carcinogenic (8), the challenge is then to discriminate between carcinogenic and non-carcinogenic genotoxins in rodents without resorting to life-time bioassays. The authors

are optimistic that newly-developed transgenic rodent mutation assays could be used in this context to amplify organ-specific mutations at successive stages in a classical bioassay (10). It then remains to evaluate the carcinogenic potential of nongenotoxic compounds using as indicators an array of some 15 acute toxic effects associated with rodent carcinogenesis, many of which can be monitored in the same animal (11-14).

The authors accept that it would be premature at present to discard classical life-time carcinogenicity studies in the investigation of new synthetic compounds of unknown biological activity. More experience needs to be gained, in particular, about the possible species specificity of some of the indicators of nongenotoxic carcinogenicity. They estimate, none the less, that their scheme would identify more than 95% of some 300 carcinogens characterized in the data base of the US National Toxicology Program, and they question — given the possible exaggerated risk estimations for low-level human exposure — how long high-exposure life-time studies will remain the first, rather than the last resort, for routine screening purposes (10).

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Pre-emptive therapy for immunocompromised patients

The fundamental concern in the management of immunocompromised patients is to protect them against infection from the many viral, bacterial and parasitic diseases to which they are particularly vulnerable. The most direct approach is to provide polyvalent antimicrobial prophylaxis to everyone at risk on an open-ended basis. This is a solution that fails, however, not only on grounds of cost and logistics, but also because of the hazards of drug toxicity and selection pressures that favour the emergence of drug-resistant pathogens.

One approach, in these circumstances, is to develop indicators of early preclinical infection that will enable pre-emptive — as distinct from prophylactic — therapy to be offered on a selective basis in a timely way. That this is feasible, at least in relation to pulmonary infection by cytomegalovirus, has recently been demonstrated among recipients of allogeneic bone-marrow transplants (1). The incidence of cytomegalovirus pneumonia among these patients while they remain on immunosuppressive therapy approaches 20% and, until recently, the associated mortality has been about 90% (2-4). Ganciclovir administered in combination with intravenous immune globulin has been shown in several studies to improve survival in patients with established pneumonia (5-7) but, because of its toxic effects on myeloid cells and the kidney, it is unsuitable for prolonged prophylactic administra-

tion. Both polyclonal immunoglobulin preparations (8, 9) and high-dose aciclovir (10) have been used for this purpose, but without striking effect.

An important advance has now been achieved with broncho-alveolar lavage and cell culture to identify early cytomegalovirus infection in these patients and then to institute treatment with ganciclovir while the disease remains subclinical (1). In a controlled study involving 40 culture-positive patients pre-emptive treatment resulted in a threefold reduction in the incidence of interstitial pneumonia, and no patient who received ganciclovir — 5mg/kg intravenously twice daily for two weeks and then 5 times weekly for 15 weeks — subsequently developed cytomegalovirus infection.

In an accompanying commentary in the *New England Journal of Medicine* this strategy is described as "a paradigm of a new approach to the antimicrobial treatment of immunocompromised hosts" (11). It entails a definition of the clinical and laboratory features that are highly correlated with the occurrence of a life-threatening infection, and use of this knowledge to formulate an effective pre-emptive antimicrobial regimen. The concept is not entirely original, but its realization is now a major challenge to those who care for the rapidly-increasing population of immunocompromised patients.

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Hypertension in the elderly: the case for active intervention

Isolated systolic hypertension, which results from decreased elasticity and atherosclerosis of the arterial tree, becomes increasingly prevalent with age. It is the most common type of hypertensive disease in the elderly (1, 2) and epidemiological studies have shown consistently that, like diastolic hypertension, it is associated with increased risk of stroke and major cardiovascular events (4-6). However, whether these patients are likely to benefit from antihypertensive treatmenthas remained uncertain. Concern has been expressed that even cautious reduction of cerebral perfusion pressure might precipitate stroke and that the untoward metabolic effects of diuretic therapy might be particularly troublesome in this age group (7, 8). This uncertainty has now been settled decisively by a 5-year trial conducted in 16 centres distributed throughout the USA (9). Nearly 5 000 patients aged over 60 years with resting systolic blood pressures ranging from 160 to 219 mmHg and normal diastolic pressures were randomly allocated either to

stepped antihypertensive therapy or to placebo. The initial daily regimen for the treated patients was chlorthalidone 12.5 mg. This was augmented, when the response was considered inadequate to chlorthalidone 25 mg daily, after which atenolol 25 mg, and subsequently 50 mg, was added as required.

Throughout the period of observation active treatment reduced the incidence of stroke by more than one third. In absolute terms, this represented a decrease of 30 cerebrovascular incidents over the 5 year period for every 1000 patients in the trial. As might be anticipated from the results of treatment of diastolic hypertension, other major cardiovascular events, including coronary heart disease, were also reduced in incidence (10). Overall, the death rate from all causes was reduced by 13% in the treated group. These results are the more remarkable in that about one third of the patients assigned to placebo were taking other antihypertensive medicines at the completion of the trial.

It is important to recognize, however, that only 10% of patients meeting the stipulated blood pressure criteria were admitted to the trial. Excluded were patients at high risk for the conditions selected as end points. A study on unselected elderly patients might well have produced less decisive results. None the less, the impressive performance — and the relatively low price — of chlorthalidone in this context has not passed unremarked. An independent commentary on the outcome of the trial concludes confidently that "...it seems prudent to apply the current wisdom of treatment of diastolic hypertension in elderly patients to the treatment of isolated systolic hypertension — that is, use a thiazide diuretic unless a compelling reason, particularly concurrent illness such as angina pectoris or diabetes mellitus, indicates another choice" (8).

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Asthma: newly detected allergens have implications for treatment

The rising number of deaths that have been attributed to asthma over the past decade in many western countries has generated much debate in the medical press (1). This has resulted in a major reassessment, not only of the principles of treatment, but of the basic pathology of the disease. The condition is now regarded as primarily inflammatory in nature rather than simply as a bronchospastic phenomenon (2). Regular use of inhaled corticosteroids is now widely favoured, while opinion is shifting towards the use of beta-agonist bronchodilators only in the management of acute exacerbations.

Whereas therapeutic strategies may well require adjustment, the rising death rate recorded in recent years may also simply reflect that asthma is becoming more common (3-5). For a while it seemed that the apparent increase in the prevalence of the disease might result from changes in diagnostic criteria, more sensitive diagnostic tests, or greater utilization of health services. To some extent these factors may have contributed. However, they cannot explain marked peaks and troughs in the prevalence of the disease that have

been recorded within a few years in several countries (1), less still the existence of discrete geographical foci in which mortality from asthma is particularly high (6).

If, as seems evident, asthma is triggered by bronchial inflammation, these perturbations in its incidence could well reflect increasing exposure to environmental allergens or pollutants (7). Patterns of occupational asthma demonstrate that a wide range of allergens can invoke hyperresponsiveness of the airways (8). None the less, house dust mites are a dominant cause of sensitivity, particularly among asthmatic children (9), and it is possible that other specific sensitizing agents of high prevalence remain to be discovered. Indeed, recently published evidence suggests that two ubiquitous microorganisms may be of major importance.

One of these is a mold, *Alternaria alternata*. Positive skin tests and IgE antibodies to its spores have been consistently detected in 11 patients who developed respiratory arrest during an exacerbation of asthma. In contrast, they were found in only one third of 99 matched asthmatic patients who had never experienced such an episode (10).

The other organism, *Chlamydia pneumoniae*, has only recently been identified as a cause of acute pneumonic infection, although 30% to 50% of adults worldwide have serological evidence of previous infection (11). A recent survey indicated that patients with serologically-confirmed *Chlamydia pneumoniae* infection were sixfold more likely to develop subsequent bronchial asthma than patients with microbiologically confirmed infection who remained seronegative (12).

It is premature to speculate on the extent to which these findings might contribute to the current historically high incidence and mortality of asthma, but they do create possibilities for new protective and therapeutic approaches to its management. No formal comparative trials have yet been undertaken, but preliminary experience with doxycycline suggests that antimicrobial therapy may have a significant place in the management of cases associated with recent chlamydial infection (12, 13).

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Regulatory Matters

Parenteral gangliosides and Guillain-Barré syndrome

Germany — It was reported in this journal in 1989 that the Federal Health Office had suspended the marketing authorization for parenteral preparations containing mixed bovine brain gangliosides as a result of their possible association with Guillain-Barré syndrome — a condition characterized by mixed polyradiculitis and progressive paralysis which can involve the respiratory muscles, and which may not be reversible.

These preparations remain banned in Germany where, it seems, motor neurone disease with the characteristics of either the Guillain-Barré syndrome or amyotrophic lateral sclerosis has supervened in at least 20 of some 14 000 treated patients (1, 2). Of these, 5 are known to have died. In one instance, the patient developed an immunogenic reaction with fever, shock, and rapidly progressive tetraparesis within 3 days of completing a course of treatment (3).

Delayed-type hypersensitivity and sensitization to gangliosides has been described both in laboratory animals (4) and in at least one patient (5). More recently, anti-G_{M1} ganglioside antibodies have been detected in patients with Guillain-Barré syndrome following heliobacter infection (6), and anti-G_{M1} and anti-G_{M2} ganglioside antibodies have been reported respectively in single patients who developed neurological complications following parenteral treatment with gangliosides (7, 8). It has been disputed whether gangliosides are themselves immunogenic (9), but the circumstantial evidence is now persuasive that they can develop sensitizing potential, possibly when complexed to serum or tissue proteins (7).

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Glafenine reassessed and further restricted

Spain — The National Pharmacovigilance Committee has responded to advice recently issued by the European Communities by withdrawing all combination products containing glafenine and subjecting remaining preparations to prescription control. Indications are restricted to the symptomatic control of pain when the use of other analgesics is inappropriate. Contraindications include known hypersensitivity to glafenine or one of its derivatives, antrafenine and floctafenine, and renal or hepatic insufficiency.

The reassessment was prompted by concern regarding adverse reactions, and particularly allergic phenomena including cases of anaphylactic shock.

Source: National Pharmacovigilance Commission, Communication to WHO, 23 July 1991.

Loperamide: dangers in young children

France — The Ministry of Health has restricted the approved indications for preparations containing the antidiarrhoeal agent, loperamide, to exclude their use in children under two years of age. It is emphasized that loperamide should never be used in place of oral or intravenous rehydration when the criteria for such treatment are satisfied and that, in all instances, doctors should consider the severity of the diarrhoea, age of the patient and the environmental situation before prescribing these products.

Source: *La Revue Prescrire*, **11**: 293 (1991).

Moracizine: for life-threatening post-infarction dysrhythmias only

United States of America — The National Heart, Lung and Blood Institute has announced that a multicentre trial of the membrane stabilizing agent, moracizine, in non life-threatening post-infarction dysrhythmias has been discontinued because the risk of sudden death appeared to be greater among treated patients than among those receiving placebo.

Two other membrane stabilizing agents, flecainide and encainide, were withdrawn from the trial for the same reason at an earlier stage. The trial was continued as a study of moracizine alone because, at that time, it appeared to be performing better than placebo and because it had a distinctive pharmacological profile.

It now seems probable that all membrane stabilizing agents — the class-1 antidysrhythmic drugs — are associated with similar risks when used in these circumstances.

All three drugs remain available for the treatment of patients with severe, life-threatening dysrhythmias and moracizine remains under investigation for the treatment of supraventricular tachycardia.

Source: Du Pont Pharmaceuticals. Open letter to all US physicians, 9 August 1991.

Tacrine: approval refused for Alzheimer's disease

United States of America — An advisory committee to the Food and Drug Administration has refused to recommend approval of tacrine as an "investigational new drug" for Alzheimer's disease on the grounds that insufficient evidence has been presented to show that it improves cognitive function in patients with this condition. Tacrine is known to have hepatotoxic potential and a large scale study was planned, in which the hepatic function of all patients would have been closely monitored, with a view to assessing the acceptability of prolonged treatment in a general practice setting.

A special unit created within the FDA is currently assessing 12 other compounds that are each proposed for the treatment of Alzheimer's disease.

Source: US refuses approval for tacrine. *Lancet*, **338**: 244 (1991).

Terodiline and ventricular tachycardia

Worldwide — The manufacturer of terodiline, an anticholinergic agent indicated for the treatment of urinary incontinence, has withdrawn the product worldwide, following its association with various cardiac dysrhythmias including torsades de pointes, heart block, and ventricular tachycardia. Several patients required resuscitation and some needed permanent pacing.

Sources

1. Kabi Pharmacia. Open letter to doctors, 13 September 1991.

2. UK Committee on Safety of Medicines. Open letter to doctors and pharmacists, 25 July 1991.

Bovine spongiform encephalopathy (BSE)

Switzerland — In *WHO Drug Information* Volume 5, No 2, 1991, p. 60, we reported on proposals then subject to consultation that had been issued by the Intercantonal Office for Medicines Control (OICM) regarding the manufacture of medicines containing ingredients of bovine origin. Since then, WHO has been informed by the OICM of the final text of the decision. This differs substantially from the earlier text and the essential points are set out below:

1. Use of brain, spinal cord, thymus, tonsils, spleen, other lymphatic tissue, and intestines of bovine

origin (including sheep and goats) is prohibited except when the material is proven to originate from animals that:

- are less than 6 months of age at the time of slaughter;
- come from a country or a herd that is free of BSE; and
- have never been fed with products of animal origin.

The extraction procedure and the manufacturing process should be shown to exclude all possibility of contamination.

Medicinal products containing organ extracts that do not comply with these requirements must be withdrawn from the market with immediate effect.

2. Medicinal products intended for parenteral administration, ophthalmological use or for application to wounds or mucosa will be suspended from registration if the manufacturer is not able to supply adequate assurances of compliance with these requirements within a period of 3 months. The Agency may additionally require that animals over six months of age should not be used as a source of materials destined for these products.

3. Provisionally exempted from these requirements, having regard to their therapeutic importance, are products including insulin, glucagon, heparin and blood factors containing heparin.

Partially exempted from these requirements are products that contain no ingredient of animal origin other than lactose, and products such as fetal bovine serum that are chemically treated in such a way that risk of infection is essentially precluded. In all instances, however, the material must be taken from animals derived from BSE-free herds that have never been fed animal material.

4. Other tissues or organs may be included in medicines intended for oral use or application to intact skin, provided that the animals are derived from BSE-free herds.

5. The product information intended for health professionals should describe precisely the origin of the animal material, and the information intended for patients should specify the species from which the material was obtained. Exempted are products that contain no bovine ingredient other than gelatin, milk or milk constituents (including lactose).

6. Each of the above measures also applies to medicines containing material originating from sheep or goats.

Advisory Notices

Cefalosporins and haemolysis

Immune haemolytic anaemia was only very rarely associated with the earlier members of the cepfalosporin family. Serological evidence indicated that cefalothin was responsible for at least 5 cases (1-4), but the very few cases attributed to other first generation compounds were insecurely documented.

With the introduction of the second and third generation of cefalosporins such reports have increased in frequency and, it seems, in intensity (6). Since 1987 nine cases have become known to the American Red Cross Blood Services, some of which resulted in death. Among these, five were attributed to cefotetan (5).

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Dexfenfluramine and pulmonary hypertension

Switzerland — The Intercantonal Office for the Control of Medicines has notified doctors that a young woman taking dexfenfluramine as an anorectic has died from pulmonary hypertension. Although similar cases attributed to both dexfenfluramine and its racemate, fenfluramine, are on record they are extremely rare and a causal relationship has not been established with certainty. Doctors have been asked to ensure that no course of treatment is extended beyond 12 weeks and to remain alert to early signs of pulmonary hypertension, including inhabitual dyspnoea on exertion, chest pain, palpitation, syncope and signs of cardiac insufficiency.

Another anorectic agent, aminorex, was withdrawn 20 years ago when when it was found to be strongly associated with pulmonary hypertension.

Source: Intercantonal Office for the Control of Medicines. Communication to WHO. 23 August 1991.

Identification codes for tablets and capsules

United States of America — The Food and Drug Administration is now reviewing comments it has received on a proposal to require all solid oral dosage forms to be imprinted with a code that identifies both the active ingredient and the holder of the product licence. The objectives are manifold. The codes will simplify identification of tablets and capsules in cases of drug overdosage and other emergencies; they will assist patients and doctors to recognize prescribing and dispensing errors; and they will aid identification and investigation of counterfeit and defective drug products.

The proposal has the support of organizations representing manufacturers of both generic drugs and over-the-counter, non-prescription products.

Sources

1. *Federal Register*, May 15 1991 (56 CFR 22370).

2. Nightingale, S. From the Food and Drug Administration. *Journal of the American Medical Association*, **266:** 190 (1991).

Flunarizine and extrapyramidal signs

Japan — The Pharmaceutical Affairs Bureau has advised doctors that products containing the peripheral vasodilator substance, flunarizine, induce reversible extrapyramidal symptoms in

some patients. Since the products are used in the management of patients with cerebral lesions resulting from arteriosclerosis, infarction or haemorrhage, the possibility of drug-induced neurological changes can be readily overlooked. Doctors have been advised to reassess all patients receiving these products 3 months after starting treatment and at monthly intervals thereafter.

Source: Information on Adverse Reactions to Drugs, No. 109, July 1991, Pharmaceutical affairs Bureau, Ministry of Health and Welfare, Tokyo.

Iron dextran and allergic reactions

Australia — The Adverse Drug Reactions Advisory Committee has reviewed and categorized the types of sensitivity reactions that have been reported in association with parenteral administration of iron dextran. A wide diversity of immediate and delayed events is listed. Some are minor and transient; others, including anaphylactoid reactions, dysrhythmias and arthralgias, are potentially serious. The Committee suggests that a reduction in the frequency of reports in recent years may reflect the introduction of refinements in production technology. It emphasizes, however, that all patients must be carefully monitored throughout and immediately following infusion, and that doctors should remain alert to the possibility of delayed reactions.

Source: *Australian Adverse Drug Reactions Bulletin*, **10** (3): 2 (1991)

Mercury in dental amalgam

United States of America — The Food and Drug Administration, after reviewing recent animal studies, has decided to establish a special working group that will collaborate with the National Institute for Dental Research in obtaining evidence required to support a definitive assessment of the safety of mercury amalgam fillings.

Dental amalgam, which consists of a mixture of silver and mercury, is a material that has been essential to the practice of dentistry for over 150 years. The FDA emphasizes that the information currently available does not warrant removal of existing fillings or any change in current dental practice.

Source: *FDA Talk Paper*, T91-15, March 1991.

Vitamin K and anaphylaxis

Australia — Phytomenadione (vitamin K) has been associated with anaphylactoid reactions in 18 reports received by the Adverse Drug Reactions Advisory Committee. All but one of these related to intravenous administration and two were fatal. Reactions ascribed to intramuscular or subcutaneous administration were, in general, less severe and were typified by localized lesions at the site of injection, urticaria and other skin rashes. Doctors are advised that the intravenous route of administration should be used only when a rapid response is vital and that, in all cases, the injection should be delivered slowly.

Source: *Australian Adverse Drug Reactions Bulletin*, **10** (3): 2 (1991).

Quinine and thrombocytopenia

Australia — The Adverse Drug Reactions Advisory Committee has received a cumulative total of 87 reports of thrombocytopenia, 5 of which were fatal, associated with the use of quinine to prevent muscular cramps. In more than two thirds of the cases quinine was the sole suspected agent and, in one third, a causal relationship was conclusively established either by demonstrating quinine-dependent antibodies or by inadvertent positive rechallenge.

Source: *Australian Adverse Drug Reactions Advisory Committee*, **10** (3): 2 (1991).

Quinolones and allergic reactions

Belgium — The national monitoring centre has now received a cumulative total of 25 reports of anaphylactic reactions associated with the use of quinolone antibiotics, including 19 cases of anaphylactic shock and 6 cases of angioedema (1). Among other allergic reactions notified to the centre and attributed to drugs of this type are cases of urticaria, pruritus and photosensitization.

The possibility that ciprofloxacin is causally associated with 4 cases of toxic epidermal necrolysis and various adverse haematological reactions has also been raised (2).

Sources

1. *Folia Pharmacotherapeutica*, **18:** 47 (1991).

2. Tham, T., Allen, G., Hayes, D. et al. Possible association between toxic epidermal necrolysis and ciprofloxacin. *Lancet*, **338:** 522 (1991).

Tienilic acid and hepatitis

France — The antihypertensive agent, tienilic acid, was withdrawn from the market in the United States of America in 1980 after more than 350 cases of hepatitis, 24 of which were fatal, had been attributed to the drug within a short span of time. In France, where it had been most extensively used, few such cases had been reported and it was decided that it should remain available. That the risk associated with treatment is considerably lower in France has been borne out over time. From 1976, the French National System of Pharmacovigilance has received, each year, an average of 35-40 reports associating tienilic acid with hepatic damage. None the less, fatal cases of fulminant hepatitis are on record (1, 2), including 4 fatalities, and in some instances chronic hepatitis has supervened (3).

At present, about 25 000 patients in France are estimated to be taking the drug, and it has been recently questioned by the regional pharmacovigilance centre in the Saint-Antoine Hospital, Paris, whether — having regard to the cumulative evidence — its record of toxicity can still be regarded as acceptable in an antihypertensive preparation (3).

References

1. Lechevalier, L., Lebrec, D., Lam, X. et al. Hépatite fulminante due à l'acide tiénilique. *Gastroentérologie Clinique et Biologique*, **7:** 523-528 (1983).

2. Biour, M., Poujol, A., Chazouilleres, O. et al. Fulminant hepatitis due to tienilic acid. *Lancet*, **338:** 891 (1991).

3. Pariente, E., André, C., Zafrani, E. et al. Hépatite aiguë, hépatite chronique et cirrhose à l'acide tiénilique. *Gastroentérologie Clinique et Biologique*, **5:** 567-571 (1981).

Essential Drugs

WHO Model List: revised in November 1991

Section 1: Anaesthetics

1.1 GENERAL ANAESTHETICS AND OXYGEN

diazepam (1b, 2)	injection, 5 mg/ml in 2-ml ampoule
ether, anaesthetic (2)	inhalation
halothane (2)	inhalation
ketamine (2)	injection, 50 mg (as hydro chloride)/ml in 10-ml vial
nitrous oxide (2)	inhalation
oxygen	inhalation (medicinal gas)
*thiopental (2)	powder for injection, 0.5 g, 1.0 g (sodium salt) in ampoule

1.2 LOCAL ANAESTHETICS

*bupivacaine (2, 9)	injection, 0.25%, 0.5% (hydrochloride) in vial
	injection for spinal anaesthesia, 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution
*lidocaine	injection, 1%, 2% (hydrochloride) in vial
	injection, 1%, 2% (hydrochloride) + epinephrine 1:200 000 in vial
	injection for spinal anaesthesia, 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution
	topical forms, 2 - 4% (hydrochloride)
	dental cartridge, 2% (hydrochloride) + epinephrine 1:80 000

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

Explanatory Notes

When the strength of a 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:
(1) Drugs subject to international control under (a) the Single Convention on Narcotic Drugs (1961); (b) the Convention on Psychotropic Substances (1971); and (c) the Convention on Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988);
(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;
(7) Adverse effects diminish 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.

Section 2: Analgesics, Antipyretics, Non-steroidal Anti-inflammatory Drugs and Drugs Used to Treat Gout

2.1 NON-OPIOIDS

acetylsalicylic acid	tablet, 100 - 500 mg suppository, 50 - 150 mg
allopurinol (4)	tablet, 100 mg
colchicine (7)	tablet, 500 µg
*ibuprofen	tablet, 200 mg
*indometacin	capsule or tablet, 25 mg
paracetamol	tablet, 100 - 500 mg suppository, 100 mg syrup, 125 mg/5 ml

2.2 OPIOID ANALGESICS

*codeine (1a)	tablet, 30 mg (phosphate)
*morphine (1a)	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
*methionine	tablet, 250 mg (racemate)
methylthioninium chloride (methylene blue)	injection, 10 mg/ml in 10-ml ampoule
naloxone	injection, 400 µg (hydrochloride) in 1-ml ampoule
penicillamine (2)	capsule or tablet, 250 mg
potassium ferric hexacyanoferrate(II) $2H_2O$ (Prussian blue)	powder for oral administration
sodium calcium edetate (2)	injection, 200 mg/ml in 5-ml ampoule
sodium nitrite	injection, 30 mg/ml in10-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 (intravenous or rectal)
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)

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

Section 6: Anti-infective Drugs

6.1 ANTHELMINTHICS

6.1.1 INTESTINAL ANTHELMINTHICS

levamisole (8)	tablet, 50 mg, 150 mg (as hydrochloride)
*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

6.1.2 SPECIFIC ANTHELMINTHICS

albendazole	chewable tablet, 200 mg

6.1.3 ANTIFILARIALS

diethylcarbamazine	tablet, 50 mg (dihydrogen citrate)
ivermectin	scored tablet, 6 mg
suramin sodium (2, 7)	powder for injection, 1 g in vial

6.1.4 ANTISCHISTOSOMALS

metrifonate	tablet, 100 mg
oxamniquine	capsule, 250 mg
	syrup, 250 mg/5 ml
praziquantel	tablet, 600 mg

6.2 ANTIBACTERIALS

6.2.1 PENICILLINS

*amoxicillin (4)	capsule or tablet, 250 mg, 500 mg (anhydrous)
	powder for oral suspension, 125 mg (anhydrous)/5 ml
ampicillin (4)	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) (as sodium or potassium 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 ANTIBACTERIALS

*chloramphenicol (7)	capsule, 250 mg
	oral suspension, 150 mg (as palmitate salt)/5 ml
	powder for injection, 1 g (as sodium succinate) in vial
*erythromycin	capsule or tablet, 250 mg (as stearate or ethyl succinate)
	powder for oral suspension, 125 mg (as stearate or ethyl succinate)
	powder for injection, 500 mg (as lactobionate) in vial
*gentamicin (2, 4, 7)	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

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

*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)
Complementary drugs	
ciprofloxacin (B)	tablet, 250 mg (as hydrochloride)
clindamycin (B)	injection, 150 mg (as phosphate)/ml
doxycycline (B) (5, 6)	capsule or tablet, 100 mg (as hyclate)
	powder for injection, 100 mg (as hyclate) in ampoule
nitrofurantoin (B) (4, 7)	tablet, 100 mg
trimethoprim (B)	tablet, 100 mg, 200 mg

Additional reserve antimicrobials are discussed in Section 5 of Technical Report Series, No. 796 (1990).

6.2.3 ANTILEPROSY DRUGS

clofazimine	capsule, 50 mg, 100 mg
dapsone	tablet, 50 mg, 100 mg
rifampicin	capsule or tablet, 150 mg, 300 mg

6.2.4 ANTITUBERCULOSIS DRUGS

ethambutol (4)	tablet, 100 - 400 mg (hydrochloride)
isoniazid	tablet, 100 - 300 mg
pyrazinamide	tablet, 500 mg
rifampicin	capsule or tablet, 150 mg, 300 mg
rifampicin + isoniazid	tablet, 150 mg + 100 mg, 300 mg + 150 mg
streptomycin (4)	powder for injection, 1 g (as sulfate) in vial
Complementary drug	
thioacetazone + isoniazid (A) (7)	tablet, 50 mg + 100 mg, 150 mg + 300 mg

6.3 ANTIFUNGAL DRUGS

amphotericin B (4)	powder for injection, 50 mg in vial
griseofulvin	capsule or tablet, 125 mg, 250 mg
*ketoconazole (2)	tablet, 200 mg
	oral suspension, 100 mg/5 ml
nystatin	tablet, 100 000, 500 000 IU
	lozenge 100 000 IU
	pessary, 100 000 IU
Complementary drug	
flucytosine (B) (4, 8)	capsule, 250 mg
	infusion, 2.5 g in 250 ml

6.4 ANTIPROTOZOAL DRUGS

6.4.1 ANTIAMOEBIC AND ANTIGIARDIASIS 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 drug	
chloroquine (B)	tablet, 150 mg (as phosphate or sulfate)

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 (isetionate) in vial

6.4.3 ANTIMALARIAL DRUGS

(a) FOR 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 (as bisulfate or sulfate)
	injection, 300 mg (as dihydrochloride)/ml in 2-ml ampoule
Complementary drugs	
mefloquine (B)	tablet, 250 mg (as hydrochloride)

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

*sulfadoxine + pyrimethamine (B)	tablet, 500 mg + 25 mg
*tetracycline (B)	capsule or tablet, 250 mg (hydrochloride)

(b) FOR PROPHYLAXIS

chloroquine	tablet, 150 mg (as phosphate or sulfate)
	syrup, 50 mg (as phosphate or sulfate)/5 ml
proguanil	tablet, 100 mg (hydrochloride)

Complementary drug

mefloquine (B)	tablet, 250 mg (as hydrochloride)

6.4.4 ANTITRYPANOSOMAL DRUGS

(a) AFRICAN TRYPANOSOMIASIS

melarsoprol (5)	injection, 3.6% solution
pentamidine (5)	powder for injection, 200 mg (isetionate) in vial
suramin sodium	powder for injection, 1 g in vial

Complementary drug

eflornithine (C)	injection, 200 mg (hydrochloride) /ml in 100 ml bottles

(b) AMERICAN TRYPANOSOMIASIS

benznidazole (7)	tablet, 100 mg
nifurtimox (2, 8)	tablet, 30 mg, 120 mg, 250 mg

6.5 INSECT REPELLENTS

diethyltoluamide	topical solution, 50%, 75%

Section 7: Antimigraine Drugs

7.1 FOR TREATMENT OF ACUTE ATTACK

acetylsalicylic acid	tablet, 300 - 500 mg
ergotamine (7)	tablet, 2 mg (tartrate)
paracetamol	tablet, 300 - 500 mg

7.2 FOR PROPHYLAXIS

*propranolol	tablet, 10 mg, 20 mg (hydrochloride)

Section 8: Antineoplastics, Immunosuppressives and Drugs Used in Palliative Care

8.1 IMMUNOSUPPRESSIVE DRUGS

*azathioprine (2)	tablet, 50 mg
	powder for injection, 100 mg (as sodium salt) in vial
ciclosporin (2)[1]	capsule, 25 mg
	concentrate for injection 50 mg/ml in 1-ml ampoule

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
cytarabine (2)	powder for injection, 100 mg in vial
dacarbazine (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
methotrexate (2)	tablet, 2.5 mg (as sodium salt)
	powder for injection, 50 mg (as sodium salt) in vial
procarbazine	capsule, 50 mg (as hydrochloride)
vinblastine (2)	powder for injection, 10 mg (sulfate) in vial
vincristine (2)	powder for injection, 1 mg, 5 mg (sulfate) in vial

Complementary drug

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

* Example of a therapeutic group. Various drugs can serve as alternatives.
[1] For organ transplantation.
[2] Drug for "rescue therapy" with methotrexate.

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)

8.4 DRUGS USED IN PALLIATIVE CARE

The essential drugs are those included in the WHO publication *Cancer Pain Relief*. WHO, Geneva, 1986.

Section 9: Antiparkinsonism Drugs

*biperiden	tablet, 2 mg (hydrochloride)
	injection, 5 mg (lactate) in 1-ml ampoule
levodopa + *carbidopa (5, 6)	tablet, 100 mg + 10 mg, 250 mg + 25 mg

Section 10: Blood, Drugs affecting

10.1 ANTIANAEMIA DRUGS

ferrous salt	tablet, equivalent to 60 mg iron
	oral solution, equivalent to 25 mg iron (as sulfate)/1 ml
ferrous salt + folic acid [3]	tablet, 60 mg + 250 µg
folic acid (2)	tablet, 1 mg, 5 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 DRUGS AFFECTING COAGULATION

desmopressin (8)	injection, 4µg (acetate)/ml in 1-ml ampoule
heparin	injection, 1000 IU/ml, 5000 IU/ml, 20 000 IU/ml in 1-ml ampoule
phytomenadione	injection, 10 mg/ml in 5-ml ampoule
	tablet, 10 mg
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 Plasma Substitutes

11.1 PLASMA SUBSTITUTES

*dextran 70	injectable solution, 6%
*polygeline	injectable solution, 3.5%

11.2 PLASMA FRACTIONS FOR SPECIFIC USE [4]

albumin, human (2, 8)	injectable solution, 5%, 25%
Complementary drugs	
*factor VIII concentrate (C) (2, 8)	(dried)
*factor IX complex (coagulation factors II, VII, IX, X) concentrate (C) (2, 8)	(dried)

Section 12: Cardiovascular Drugs

12.1 ANTIANGINAL DRUGS

glyceryl trinitrate	tablet (sublingual), 500 µg
*isosorbide dinitrate	tablet (sublingual), 5 mg
*nifedipine	capsule or tablet, 10 mg
*propranolol	tablet, 10 mg, 40 mg (hydrochloride)
	injection, 1 mg (hydrochloride) in 1-ml ampoule
Complementary drug	
atenolol (B)	tablet, 50 mg, 100 mg

12.2 ANTIDYSRHYTHMIC DRUGS

lidocaine	injection, 20 mg (hydrochloride)/ml in 5-ml ampoule

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

[3] Nutritional supplement for use during pregnancy.

[4] All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components, and Plasma Derivatives (Revised 1988). WHO Technical Report Series, No. 786, 1989.

*propranolol	tablet, 10 mg, 40 mg (hydrochloride)
	injection, 1 mg (hydrochloride) in 1-ml ampoule
verapamil (8)	tablet, 40 mg, 80 mg (hydrochloride)
	injection, 2.5 mg (hydrochloride)/ml in 2-ml ampoule
Complementary drug	
atenolol (B)	tablet, 50 mg, 100 mg
*procainamide (B)	tablet, 250 mg, 500 mg (hydrochloride)
	injection, 100 mg (hydrochloride)/ml in 10-ml ampoule
*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
*nifedipine	capsule or tablet, 10 mg
*propranolol	tablet, 40 mg, 80 mg (hydrochloride)
Complementary drugs	
atenolol (B)	tablet, 50 mg, 100 mg
methyldopa (B) (7)	tablet, 250 mg
*reserpine (A)	tablet, 100 µg, 250 µg
	injection, 1 mg in 1-ml ampoule
*sodium nitroprusside (C) (2, 8)	powder for preparing infusion, 50 mg in ampoule
*captopril (B)	scored tablet, 25 mg

12.4 CARDIAC GLYCOSIDES

digoxin (4)	tablet, 62.5 µg, 250 µg
	oral solution, 50 µg/ml
	injection, 250 µg/ml in 2-ml ampoule
Complementary drug	
digitoxin (B) (6)	tablet, 50 µg, 100 µg
	injection, 200 µg in 1-ml ampoule

12.5 DRUGS USED IN VASCULAR SHOCK

dopamine	injection, 40 mg (hydrochloride)/ml in 5-ml vial

12.6 ANTITHROMBOTIC DRUGS

acetylsalicylic acid	tablet, 100 mg
Complementary drug	
streptokinase (C)	powder for injection, 100 000 IU

Section 13: Dermatological Drugs

13.1 ANTIFUNGAL DRUGS (TOPICAL)

benzoic acid + salicylic acid	ointment or cream, 6% + 3%
*miconazole	ointment or cream, 2% (nitrate)
nystatin	ointment or cream, 100 000 IU/g
sodium thiosulfate	solution, 15%
Complementary Drug	
selenium sulfide (C)	detergent-based suspension, 2%

13.2 ANTI-INFECTIVE DRUGS

*methylrosanilinium chloride (gentian violet)	aqueous solution, 0.5%
	tincture, 0.5%
*neomycin + *bacitracin	ointment, 5 mg neomycin sulfate + 500 IU bacitracin zinc/g
mupirocin	cream, 2%
silver sulfadiazine	cream, 1%, in 500-g container

13.3 ANTI-INFLAMMATORY AND ANTIPRURITIC DRUGS

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

13.4 ASTRINGENT DRUGS

aluminium diacetate	solution, 13% for dilution

13.5 KERATOPLASTIC AND KERATOLYTIC AGENTS

benzoyl peroxide	lotion or cream, 5%
coal tar	solution, 5%
dithranol	ointment, 0.1 - 2%
fluorouracil	ointment, 5%

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

*podophyllum resin (7)	solution, 10 - 25%
salicylic acid	solution, topical 5%

13.6 SCABICIDES AND PEDICULICIDES

benzyl benzoate	lotion, 25%
permethrin	lotion, 1%

13.7 ULTRAVIOLET BLOCKING AGENTS

Complementary drugs	
p-aminobenzoic acid, SPF15 (C)[5]	cream, lotion or gel
*benzophenones, SPF15(C)	cream, lotion or gel
*zinc oxide (C)	cream, ointment

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 (as sodium or meglumine salts)/ml in 20-ml ampoule
barium sulfate	aqueous suspension
*iopanoic acid	tablet, 500 mg
*propyliodone	oily suspension, 500-600 mg/ml in 20-ml ampoule[6]
Complementary drug	
*meglumine iotroxate (C)	solution, 5 - 8 g iodine (as meglumine) in 100-250 ml

Section 15: Disinfectants and Antiseptics

15.1 ANTISEPTICS

*chlorhexidine	solution, 5% (gluconate) concentrate for dilution
hydrogen peroxide	solution, 3%
*iodine	solution, 2.5%

15.2 DISINFECTANTS

*calcium hypochlorite	powder for solution
glutaral, activated	solution, 2%

Section 16: Diuretics

*amiloride (4, 7, 8)	tablet, 5 mg (hydrochloride)
*furosemide	tablet, 40 mg
	injection, 10 mg/ml in 2-ml ampoule
*hydrochlorothiazide	tablet, 25 mg, 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
*cimetidine	tablet, 200 mg
	injection, 200 mg in 2-ml ampoule
magnesium hydroxide	oral suspension, 550 mg magnesium oxide/10 ml

17.2 ANTIEMETIC DRUGS

metoclopramide	tablet, 10 mg (as hydrochloride)
	injection, 5 mg (as hydrochloride)/ml in 2-ml ampoule
*promethazine	tablet, 10 mg, 25 mg (hydrochloride)
	elixir or syrup, 5 mg (hydrochloride)/5 ml
	injection, 25 mg (hydrochloride)/ml in 2-ml ampoule

17.3 ANTIHAEMORRHOIDAL DRUGS

*local anaesthetic, astringent and anti-inflammatory drug	ointment or suppository

* Example of a therapeutic group. Various drugs can serve as alternatives.
[5] SPF is an abbreviation for sun protection factor.
[6] This suspension is for administration only into the bronchial tree.

17.4 ANTI-INFLAMMATORY DRUGS

hydrocortisone	suppositories, 25 mg (acetate)
sulfasalazine (2)	tablet, 500 mg

17.5 ANTISPASMODIC DRUGS

*atropine	tablet, 1 mg (sulfate)
	injection, 1 mg (sulfate) in 1-ml ampoule

17.6 CATHARTIC DRUGS

*senna	tablet, 7.5 mg (sennosides) (or traditional dosage forms)

17.7 DIARRHOEA, DRUGS USED IN

17.7.1 ORAL REHYDRATION

oral rehydration salts (for glucose/electrolyte solution)	powder, 27.9 g/l

Components to reconstitute 1 litre of glucose/electrolyte solution	g/l
sodium chloride	3.5
trisodium citrate dihydrate[7]	2.9
potassium chloride	1.5
glucose	20.0

17.7.2 ANTIDIARRHOEAL (SYMPTOMATIC) DRUGS

*codeine (1a)	tablet, 30 mg (phosphate)

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, 30 µg + 250 µg
*ethinylestradiol + *norethisterone	tablet, 35 µg + 1.0 mg

Complementary drugs

depot medroxyprogesterone acetate (B) (7, 8)	injection, 150 mg/ml in 1-ml, 50 mg/ml in 3-ml vials
*norethisterone (B)	tablet, 350 µg
norethisterone enantate (B) (7, 8)	oily solution , 200 mg/ml in 1-ml ampoule

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 (as compound	injection, 40 IU/ml in 10-ml vial, 80 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial insulin zinc suspension or isophane insulin)
*tolbutamide	tablet, 500 mg

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

[7] Trisodium citrate dihydrate may be replaced by sodium bicarbonate (sodium hydrogen carbonate) 2.5g/litre. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.

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,[8] purified protein derivative (PPD)	injection

19.2 SERA AND IMMUNOGLOBULINS[9]

anti-D immunoglobulin (human)	injection, 250 µg in single-dose vial
antiscorpion sera	injection
*antitetanus immunoglobulin	injection, 500 IU (human) in vial
antivenom serum	injection
diphtheria antitoxin	injection, 10 000 IU, 20 000 IU in vial
immunoglobulin, human normal (2)	injection
*rabies immunoglobulin	injection, 150 IU/ml

19.3 VACCINES[10]

19.3.1 FOR UNIVERSAL IMMUNIZATION

BCG vaccine (dried)	injection
diphtheria-pertussis-tetanus vaccine	injection
diphtheria-tetanus vaccine	injection
measles-mumps-rubella 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)
	injection, 500 µg, 2.5 mg (metilsulfate) in 1-ml ampoule
suxamethonium (2)	injection, 50 mg (chloride)/ml in 2-ml ampoule
	powder for injection (chloride)

Complementary drugs

pyridostigmine (B) (2, 8)	tablet, 60 mg (bromide)
	injection, 1 mg (bromide) in 1-ml ampoule
vecuronium (C) bromide	powder 10 mg (bromide) in vial

Section 21: Ophthalmological Preparations

21.1 ANTI-INFECTIVE AGENTS

*gentamicin	solution (eye drops), 0.3%
*idoxuridine	solution (eye drops), 0.1%
	eye ointment, 0.2%
silver nitrate	solution (eye drops), 1%
*tetracycline	eye ointment, 1% (hydrochloride)

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

[8] All tuberculins should comply with the WHO Requirements for Tuberculins (Revised 1985). WHO Technical Report Series, No. 745, 1987.

[9] All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1988). WHO Technical Report Series, No. 786, 1989.

[10] All vaccines should comply with the WHO Requirements for Biological Substances.

21.2 ANTI-INFLAMMATORY AGENTS

*prednisolone	eye drops, 0.5%

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)
*timolol	solution (eye drops), 0.25%, 0.5% (maleate)

21.5 MYDRIATICS

atropine	solution (eye drops), 0.1%, 0.5%, 1% (sulfate)
Complementary drug	
epinephrine (A)	solution (eye drops), 2% (as hydrochloride)

Section 22: Oxytocics and Antioxytocics

22.1 OXYTOCICS

*ergometrine	tablet, 200 µg (hydrogen maleate)
	injection, 200 µg (hydrogen maleate) in 1-ml ampoule
oxytocin	injection, 10 IU in 1-ml ampoule

22.2 ANTIOXYTOCICS

*salbutamol (2)	tablet, 4 mg (as sulfate)
	injection, 50 µg (as sulfate)/ml in 5-ml ampoule

Section 23: Peritoneal Dialysis Solution

intraperitoneal dialysis solution (of appropriate composition)	parenteral solution

Section 24: Psychotherapeutic Drugs

*amitriptyline	tablet, 25 mg (hydrochloride)
*chlorpromazine	tablet, 100 mg (hydrochloride)
	syrup, 25 mg (hydrochloride)/5 ml
	injection, 25 mg (hydrochloride)/ml in 2-ml ampoule
*diazepam (1b)	scored tablet, 2 mg, 5 mg
*fluphenazine (5)	injection, 25 mg (decanoate or enantate) in 1-ml ampoule
*haloperidol	tablet, 2 mg, 5 mg
	injection, 5 mg in 1-ml ampoule
lithium carbonate (2, 4)	capsule or tablet, 300 mg

Section 25: Drugs Acting on the Respiratory Tract

25.1 ANTIASTHMATIC DRUGS

*aminophylline (2)	tablet, 100 mg, 200 mg
	injection, 25 mg/ml in 10-ml ampoule
beclometasone	inhalation (aerosol), 50 µg (dipropionate) per dose
epinephrine	injection, 1 mg (as hydrochloride) in 1-ml ampoule
*salbutamol	tablet, 2 mg, 4 mg (as sulfate)
	inhalation (aerosol), 100 µg (as sulfate) per dose
	syrup, 2 mg (as sulfate)/5 ml
	injection, 50 µg (as sulfate)/ml in 5-ml ampoule
	respirator solution for use in nebulizers, 5 mg (as sulfate)/ml
Complementary drugs	
*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

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

25.2 ANTITUSSIVES

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

26.3 MISCELLANEOUS

water for injection	2-ml, 5-ml, 10-ml ampoules

Section 26: Solutions correcting Water, Electrolyte and Acid-base Disturbances

26.1 ORAL REHYDRATION

oral rehydration salts (for glucose/electrolyte solution)	see section 17.7.1
potassium chloride	powder for solution

26.2 PARENTERAL

*compound solution of sodium lactate	injectable solution
glucose	injectable solution, 5% isotonic, 50% hypertonic
glucose with sodium chloride	injectable solution, 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l Cl^- 30 mmol/l)
potassium chloride (2)	11.2% solution in 20-ml ampoule, (equivalent to K^+ 1.5 mmol/ml, Cl^- 1.5 mmol/l)
sodium hydrogen carbonate	injectable solution, 1.4% isotonic (equivalent to Na^+167 mmol/l, HCO_3^-167 mmol/l)
	8.4% solution in 10-ml ampoule (equivalent to Na^+1000 mmol/l, HCO_3^-1000 mmol/l)
sodium chloride	injectable solution, 0.9% isotonic (equivalent to Na^+154 mmol/l, CL^-154 mmol/l)

Section 27: Vitamins and Minerals

*ergocalciferol	capsule or tablet, 1.25 mg (50 000 IU)
	oral solution, 250 µg/ml (10 000 IU/ml)
iodine (8)	iodized oil, 1 ml (480 mg iodine), 0.5 ml (240 mg iodine) in ampoule (oral or injectable)
	capsule, 200 mg
*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)
	oral oily solution, 100 000 IU/ml in multidose dispenser (as palmitate)
	water-miscible injection, 100 000 IU (as palmitate) (55 mg) in 2-ml ampoule
riboflavin	tablet, 5 mg
sodium fluoride (8)	tablet, 500 µg
	solution, 2% (for professional dental use only)
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.

The following changes in the WHO Model List were approved by the WHO Expert Committee on the Use of Essential Drugs which met on 18 – 23 November 1991. The report of the meeting will be published in the WHO Technical Report Series.

Deletions: lindane, sodium citrate, tetanus antitoxin, antirabies hyperimmune serum.

Additions:

Main list
ciclosporin
desmopressin
glutaral
calcium hypochlorite
rabies immunoglobulin

Complementary list
ciprofloxacin
clindamycin
eflornithine
atenolol
streptokinase
zinc oxide
vecuronium bromide

International Nonproprietary Names for Pharmaceutical Substances

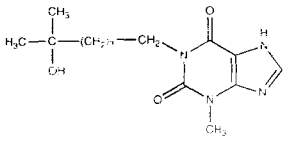
Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances (see Annexes), the following names are under consideration by the World Health Organization as Proposed International Nonproprietary Names. The inclusion of a name in the lists of Proposed International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Comments on, or formal objections to, the proposed names may be forwarded by any person to the Pharmaceuticals Unit of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for **List 66 Prop. INN not later than 31 August 1992.**

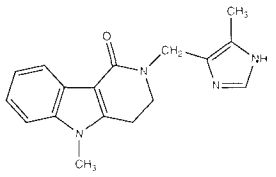
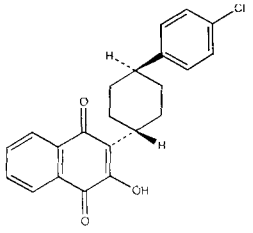
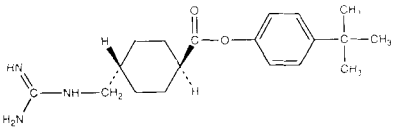
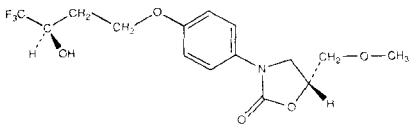
Proposed International Nonproprietary Names: List 66

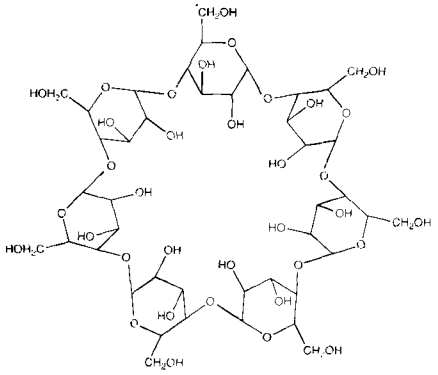
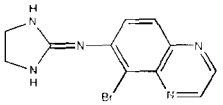
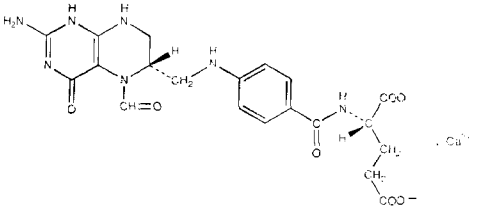
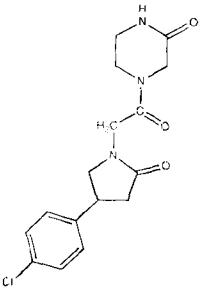
Lists of proposed (1–58) and recommended (1–27) international nonproprietary names can be found in Cumulative List No. 7, 1988.

Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS) registry number Action and Use**
albifyllinum albifylline	1-(5-hydroxy-5-methylhexyl)-3-methylxanthine $C_{13}H_{20}N_4O_3$ 107767-55-5 *polymorphonuclear neutrophil modulator*

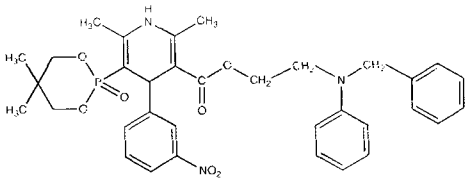
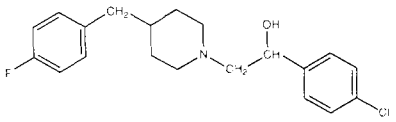
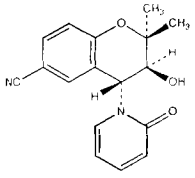
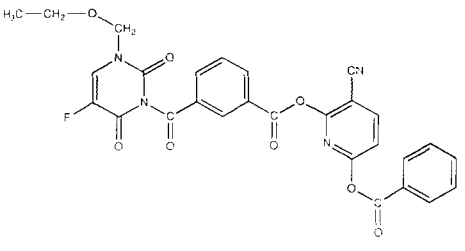


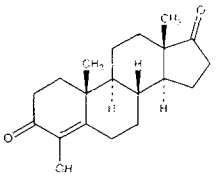
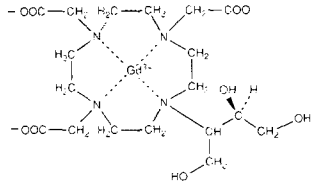
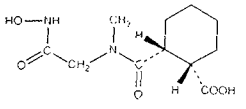
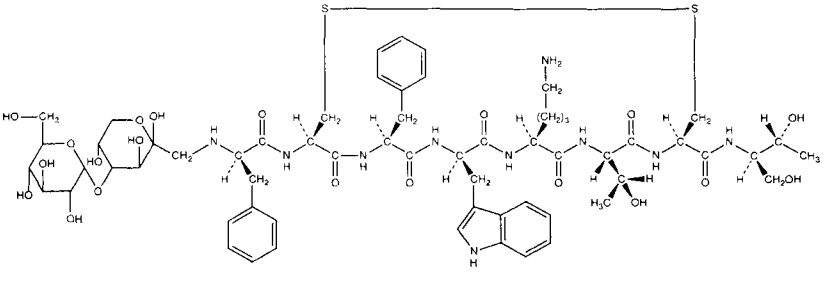
* *Action and Use: The statements in italics indicating the action and use are based largely on information supplied by the manufacturer. The information is meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names.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

Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS)[1] registry number Action and Use**
alosetronum alosetron	2,3,4,5-tetrahydro-5-methyl-2-[(5-methylimidazol-4-yl)methyl]-1*H*-pyrido[4,3-*b*]indol-1-one $C_{17}H_{18}N_4O$ 122852-42-0 *antiemetic, anxiolytic* 
atovaquonum atovaquone	2-[*trans*-4-(*p*-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone $C_{22}H_{19}ClO_3$ 95233-18-4 *antimalarial* 
batebulastum batebulast	*p-tert*-butylphenyl *trans*-4-(guanidinomethyl)cyclohexanecarboxylate $C_{19}H_{29}N_3O_2$ 81907-78-0 *antiasthmatic* 
befloxatonum befloxatone	(*R*)-5-(methoxymethyl)-3-[*p*-[(*R*)-4,4,4-trifluoro-3-hydroxybutoxy]phenyl]-2-oxazolidinone $C_{15}H_{18}F_3NO_5$ 134564-82-2 *antidepressant* 

Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS) registry number Action and Use**
betadexum betadex	β-cyclodextrin $C_{42}H_{70}O_{35}$ 7585-39-9 *pharmaceutical aid* 
biciromabum biciromab	**mouse T2G1s cell anti-human fibrin II β-chain monoclonal immunoglobulin G Fab′ fragment** *diagnostic agent*
brimonidinum brimonidine	5-bromo-6-(2-imidazolidinylidenamino)quinoxaline $C_{11}H_{10}BrN_5$ 59803-98-4 *α_2-adrenoreceptor agonist* 
calcii levofolinas calcium levofolinate	calcium *N*-[*p*-[[[(6*S*)-2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl]methyl]amino]benzoyl]-L-glutamate (1:1) $C_{20}H_{21}CaN_7O_7$ 80433-71-2 *antineoplastic* 
cebaracetamum cebaracetam	(±)-4-[[4-(*p*-chlorophenyl)-2-oxo-1-pyrrolidinyl]acetyl]-2-piperazinone $C_{16}H_{18}ClN_3O_3$ 113957-09-8 *nootropic agent* 

Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS) registry number Action and Use**
cefditorenum cefditoren	(+)-(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-[(*Z*)-2-(4-methyl-5-thiazolyl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2-(*Z*)-(*O*-methyloxime) $C_{19}H_{18}N_6O_5S_3$ 104145-95-1 *antibiotic*
cefozopranum cefozopran	(–)-1-[[(6*R*,7*R*)-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1*H*-imidazo[1,2-*b*]pyridazin-4-ium hydroxide inner salt, 7^2-(*Z*)-(*O*-methyloxime) $C_{19}H_{17}N_9O_5S_2$ 113359-04-9 *antibiotic*
cilnidipinum cilnidipine	(±)-(*E*)-cinnamyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate $C_{27}H_{28}N_2O_7$ 132203-70-4 *calcium channel blocker*
deriglidolum deriglidole	(+)-1,2,4,5-tetrahydro-2-(2-imidazolin-2-yl)-2-propylpyrrolo[3,2,1-*hi*]indole $C_{16}H_{21}N_3$ 122830-14-2 *antidiabetic, α_2-adrenoreceptor antagonist*
dexfosfoserinum dexfosfoserine	L-serine dihydrogen phosphate (ester) $C_3H_8NO_6P$ 407-41-0 *nootropic agent*

Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS) registry number Action and Use**
dorlimomab aritoxum dorlimomab aritox	ricin A chain-antibody ST 1 F(ab')2 fragment immunotoxin *immunomodulator*
efonidipinum efonidipine	2-(*N*-benzylanilino)ethyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-5-phosphononicontinate, cyclic 2,2-dimethyltrimethylene ester $C_{34}H_{38}N_3O_7P$ 111011-63-3 *calcium channel blocker* 
eliprodilum eliprodil	(±)-α-(*p*-chlorophenyl)-4-(*p*-fluorobenzyl)-1-piperidineethanol $C_{20}H_{23}ClFNO$ 119431-25-3 *N-methyl-D-aspartate antagonist* 
emakalimum emakalim	(–)-(3*S*,4*R*)-3-hydroxy-2,2-dimethyl-4-(2-oxo-1(2*H*)-pyridyl)-6-chromancarbonitrile $C_{17}H_{16}N_2O_3$ 129729-66-4 *potassium channel activator* 
emitefurum emitefur	*m*-[[3-(ethoxymethyl)-5-fluoro-3,6-dihydro-2,6-dioxo-1(2*H*)-pyrimidinyl]-carbonyl]benzoic acid, 2-ester with 2,6-dihydroxynicotinonitrile, benzoate (ester) $C_{28}H_{19}FN_4O_8$ 110690-43-2 *antineoplastic* 

Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS) registry number Action and Use**
ersoferminum ersofermin	*N*-(*N*-glycyl-L-threonyl)basic fibroblast growth factor (human clone λKB7/λHFL1 precursor reduced) $C_{775}H_{1220}N_{220}O_{223}S_7$ 111212-85-2 *growth factor*
formestanum formestane	4-hydroxyandrost-4-ene-3,17-dione $C_{19}H_{26}O_3$ 566-48-3 *aromatase inhibitor* 
gadobutrolum gadobutrol	[10-[2,3-dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)]gadolinium $C_{18}H_{31}GdN_4O_9$ 138071-82-6 *paramagnetic contrast medium* 
idraprilum idrapril	(1*S*,2*R*)-2-[[(hydroxycarbamoyl)methyl]methylcarbamoyl]cyclohexane-carboxylic acid $C_{11}H_{18}N_2O_5$ 127420-24-0 *angiotensin-converting-enzyme inhibitor* 
ilatreotidum ilatreotide	*N*-(1-deoxy-4-*O*-α-D-glucopyranosyl-D-fructopyranos-1-yl)-D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7)-disulfide $C_{61}H_{86}N_{10}O_{20}S_2$ *antiulcer agent* 

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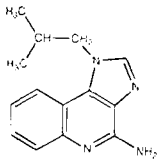
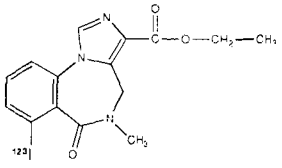
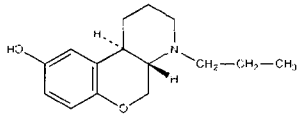
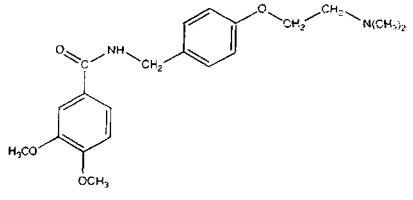
imciromabum imciromab	mouse R11D10 cell monoclonal $\varkappa$-chain containing immunoglobulin G2a, anti-human cardiac myosin heavy chain 126132-83-0 *immunomodulator*
imiquimodum imiquimod	4-amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline $C_{14}H_{16}N_4$ 99011-02-6 *antiviral* 
iomazenilum (^{123}I) iomazenil (^{123}I)	ethyl 5,6-dihydro-7-iodo-^{123}I-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate $C_{15}H_{14}{}^{123}IN_3O_3$ 127396-36-5 *benzodiazepine-receptor antagonist, diagnostic agent* 
isomolpanum isomolpan	(±)-*trans*-1,3,4,4a,5,10b-hexahydro-4-propyl-2*H*-[1]benzopyrano[3,4-*b*]pyridin-9-ol $C_{15}H_{21}NO_2$ 107320-86-5 *antipsychotic* 
itopridum itopride	*N*-[*p*-[2-(dimethylamino)ethoxy]benzyl]veratramide $C_{20}H_{26}N_2O_4$ 122898-67-3 *digestive* 

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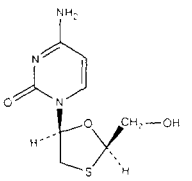
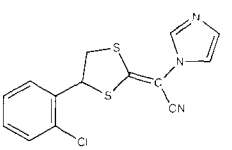
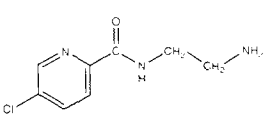
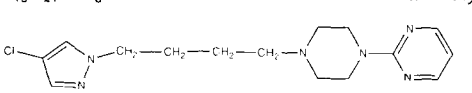
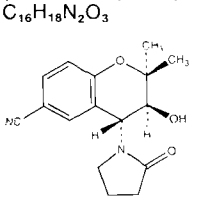
lamivudinum lamivudine	(−)-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine $C_8H_{11}N_3O_3S$ 134678-17-4 *antiviral* 
lanoconazolum lanoconazole	(±)-α-[(*E*)-4-(*o*-chlorophenyl)-1,3-dithiolan-2-ylidene]imidazole-1-acetonitrile $C_{14}H_{10}ClN_3S_2$ 101530-10-3 *antifungal, dermatological* 
lazabemidum lazabemide	*N*-(2-aminoethyl)-5-chloropicolinamide $C_8H_{10}ClN_3O$ 103878-84-8 *antiparkinsonian* 
lesopitronum lesopitron	2-[4-[4-(4-chloropyrazol-1-yl)butyl]-1-piperazinyl]pyrimidine $C_{15}H_{21}ClN_6$ 132449-46-8 *anxiolytic* 
levcromakalimum levcromakalim	(3*S*,4*R*)-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-6-chromancarbonitrile $C_{16}H_{18}N_2O_3$ 94535-50-9 *potassium channel activator* 

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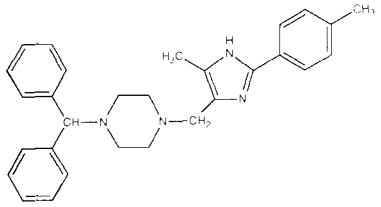
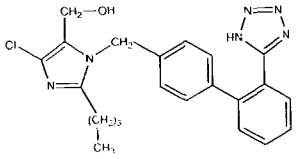
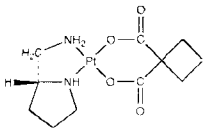
lifarizinum lifarizine	1-(diphenylmethyl)-4-[(5-methyl-2-*p*-tolylimidazol-4-yl)methyl]piperazine $C_{29}H_{32}N_4$ 119514-66-8 *vasodilator* 
losartanum losartan	2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol $C_{22}H_{23}ClN_6O$ 114798-26-4 *angiotensin II receptor antagonist* 
maslimomabum maslimomab	mouse monoclonal immunoglobulin G2b, anti-human T-cell receptor α/β chain 127757-92-0 *immunomodulator*
mecaserminum mecasermin	insulin-like growth factor I (human) $C_{331}H_{512}N_{94}O_{101}S_7$ 68562-41-4 *growth factor*
miboplatinum **miboplatin**	(–)-*cis*-[(*R*)-2-(aminomethyl)pyrrolidine](1,1-cyclobutanedicarboxylato)-platinum $C_{11}H_{18}N_2O_4Pt$ 103775-75-3 *antineoplastic* 

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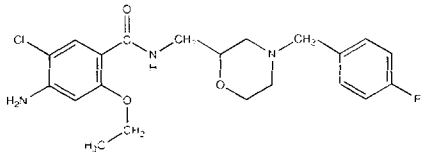
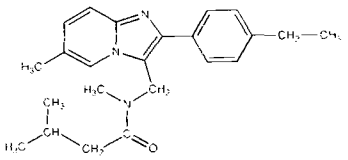
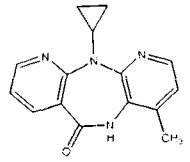
mosapridum mosapride	(±)-4-amino-5-chloro-2-ethoxy-*N*-[[4-(*p*-fluorobenzyl)-2-morpholinyl]=methyl]benzamide $C_{21}H_{25}ClFN_3O_3$ 112885-41-3 *digestive* 
nartograstimum nartograstim	*N*-L-methionyl-1-L-alanine-3-L-threonine-4-L-tyrosine-5-L-arginine-17-L-serine=colony-stimulating factor (human clone 1034) $C_{850}H_{1344}N_{226}O_{245}S_8$ 134088-74-7 *immunomodulator* *(for non-glycosylated protein)*
nebacumabum nebacumab	immunoglobulin M (human monoclonal HA-1A anti-endotoxin), disulfide with human monoclonal HA-1A κ-chain, pentameric dimer 138661-01-5 *immunomodulator*
necopidemum necopidem	*N*-[[2-(*p*-ethylphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl]methyl]-*N*,3-dimethylbutyramide $C_{23}H_{29}N_3O$ 103844-77-5 *anaesthetic* 
nevirapinum nevirapine	11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one $C_{15}H_{14}N_4O$ 129618-40-2 *antiviral* 

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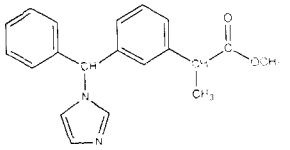
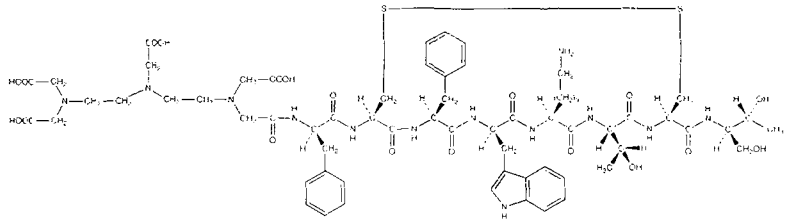
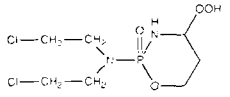
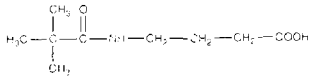
odalprofenum odalprofen	methyl (±)-*m*-(α-imidazol-1-ylbenzyl)hydratropate $C_{20}H_{20}N_2O_2$ 137460-88-9	*nonsteroidal anti-inflammatory, analgesic*
		
pentetreotidum pentetreotide	*N*-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-*N*-(carboxymethyl)glycyl-D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (3→8)-disulfide $C_{63}H_{87}N_{13}O_{19}S_2$ 138661-02-6	*diagnostic agent, antineoplastic*
		
perflubronum perflubron	1-bromoheptadecafluorooctane C_8BrF_{17} 423-55-2	*contrast medium*
	$F_3C—(CF_2)_6—CF_2Br$	
perfosfamidum perfosfamide	(±)-*cis*-2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorin-4-yl hydroperoxide, *P*-oxide $C_7H_{15}Cl_2N_2O_4P$ 62435-42-1	*antineoplastic*
		
pivagabinum pivagabine	4-pivalamidobutyric acid $C_9H_{17}NO_3$ 69542-93-4	*antiparkinsonian, anticonvulsant*
		

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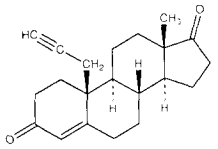
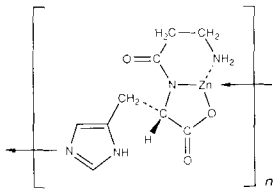
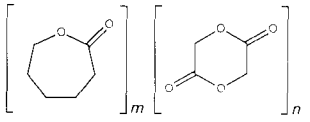
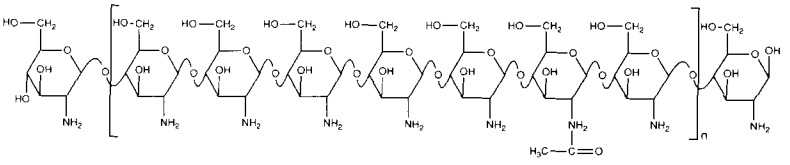
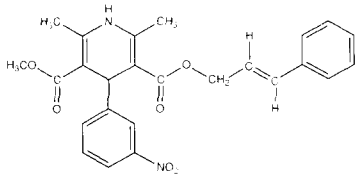
plomestanum plomestane	10-(2-propynyl)estr-4-ene-3,17-dione $C_{21}H_{26}O_2$ 77016-85-4 *antineoplastic* 
polaprezincum polaprezinc	*catena*-poly[zinc-μ-[β-alanyl-L-histidinato(2-)-*N*,N^N,*O*:N^τ]] $(C_9H_{12}N_4O_3Zn)_n$ 107667-60-7 *antiulcer agent* 
poliglecapronum poliglecaprone	2-oxepanone polymer with *p*-dioxane-2,5-dione *"m" and "n" are the numerical values representing the mol percentages of the monomers. The value of "m" should be given as a figure after the INN, e.g. "poliglecaprone 90", which means "m = 90" and "n = 10".* $(C_6H_{10}O_2)_m(C_4H_4O_4)_n$ 41706-81-4 *pharmaceutical aid* 
poliglusamum poliglusam	chitosan 9012-76-4 *haemostatic* 
pranidipinum pranidipine	(*E*)-cinnamyl methyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate $C_{25}H_{24}N_2O_6$ 99522-79-9 *calcium channel blocker* 

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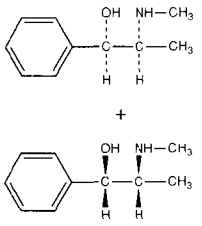
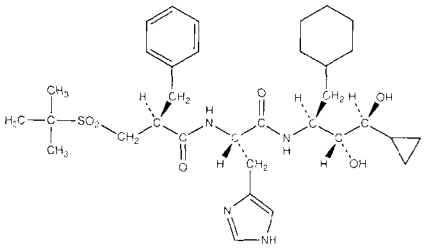
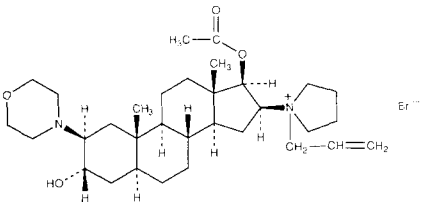
racephedrinum racephedrine	(±)-ephedrine $C_{10}H_{15}NO$ 90-81-3 *sympathomimetic*



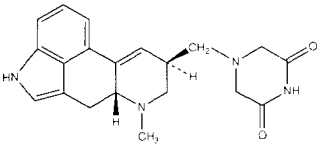
remikirenum remikiren	(*αS*)-α-[(*αS*)-α-[(*tert*-butylsulfonyl)methyl]hydrocinnamamido]-*N*-[(1*S*,2*R*,3*S*)-1-(cyclohexylmethyl)-3-cyclopropyl-2,3-dihydroxypropyl]imidazole-4-propionamide $C_{33}H_{50}N_4O_6S$ 126222-34-2 *renin inhibitor*

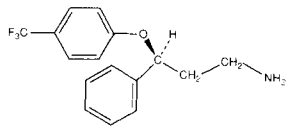
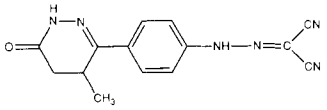
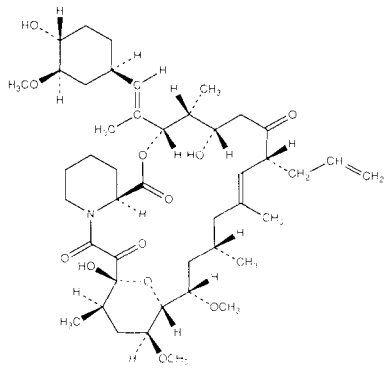


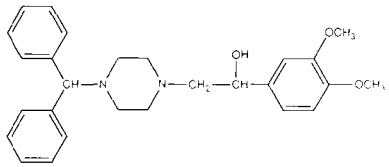
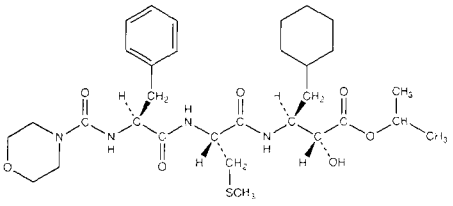
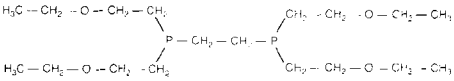
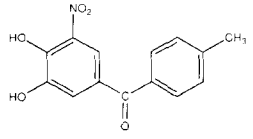
rocuronii bromidum rocuronium bromide	1-allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-androstan-16β-yl)pyrrolidinium bromide, 17-acetate $C_{32}H_{53}BrN_2O_4$ 119302-91-9 *neuromuscular receptor antagonist*

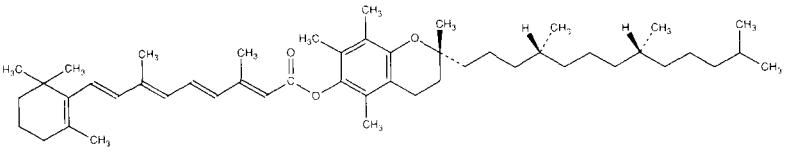
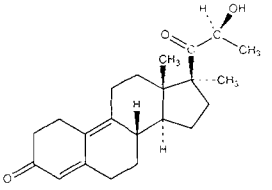
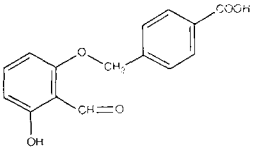
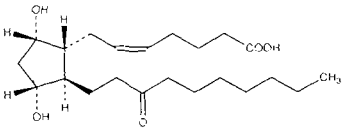


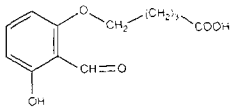
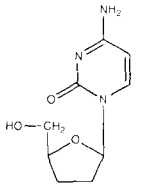
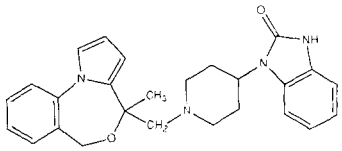
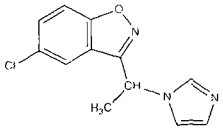
romergolinum romergoline	4-[(9,10-didehydro-6-methylergolin-8β-yl)methyl]-2,6-piperazinedione $C_{20}H_{22}N_4O_2$ 107052-56-2 *antiparkinsonian, antipsychotic*



Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS) registry number Action and Use**
sargramostimum sargramostim	23-L-leucinecolony-stimulating factor 2 (human clone pHG25 protein moiety) $C_{639}H_{1002}N_{168}O_{196}S_8$ 123774-72-1 *immunomodulator* *(for non-glycosylated protein)*
seproxetinum seproxetine	(*S*)-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine $C_{16}H_{16}F_3NO$ 126924-38-7 *antidepressant* 
sevirumabum sevirumab	human monoclonal immunoglobulin G1, ϰ-chain, anti-cytomegavirus *immunomodulator*
simendanum simendan	mesoxalonitrile (±)-[*p*-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazone $C_{14}H_{12}N_6O$ 131741-08-7 *cardiac stimulant* 
somfaseporum somfasepor	8-190 growth hormone (pig) $C_{938}H_{1465}N_{257}O_{278}S_6$ 129566-95-6 *growth hormone (vet.)*
tacrolimusum tacrolimus	(–)-(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-8-allyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(*E*)-2-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxa=azacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone $C_{44}H_{69}NO_{12}$ 104987-11-3 *immunosuppressant* 

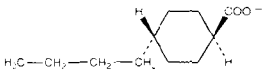
Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS) registry number Action and Use**
tamolarizinum tamolarizine	(±)-α-(3,4-dimethoxyphenyl)-4-(diphenylmethyl)-1-piperazineethanol $C_{27}H_{32}N_2O_3$ 128229-52-7 *nootropic agent* 
telimomabum aritoxum telimomab aritox	ricin A chain-antibody T 101 Fab fragment immunotoxin 117305-33-6 *immunosuppressant*
terlakirenum terlakiren	isopropyl {α*R*,β*S*)-α-hydroxy-β-[(*R*)-3-(methylthio)-2-[(*S*)-α-4-morpholinecarboxamidohydrocinnamamido]propionamido]=cyclohexanebutyrate $C_{31}H_{46}N_4O_7S$ 119625-78-4 *renin inhibitor* 
tetrofosminum tetrofosmin	ethylenebis[bis(2-ethoxyethyl)phosphine] $C_{18}H_{40}O_4P_2$ 127502-06-1 *diagnostic agent* 
tolcaponum tolcapone	3,4-dihydroxy-4′-methyl-5-nitrobenzophenone $C_{14}H_{11}NO_5$ 134308-13-7 *antiparkinsonian* 

Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS) registry number Action and Use**
tretinoinum tocoferilum tretinoin tocoferil	(±)-(2*R**)-2,5,7,8-tetramethyl-2-[(4*R**,8*R**)-4,8,12-trimethyltridecyl]-6-chromanyl retinoate $C_{49}H_{76}O_3$ 40516-48-1 *vitamin* 
trimegestonum trimegestone	17β-(*S*)-lactoyl-17-methylestra-4,9-dien-3-one $C_{22}H_{30}O_3$ 74513-62-5 *progestogen* 
tucaresolum tucaresol	α-(2-formyl-3-hydroxyphenoxy)-*p*-toluic acid $C_{15}H_{12}O_5$ 84290-27-7 *antianaemic* 
tuvirumabum tuvirumab	human monoclonal immunoglobulin G1, λ-chain, anti-hepatitis B virus surface antigen *immunomodulator*
unoprostonum unoprostone	(+)-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoic acid $C_{22}H_{38}O_5$ 120373-36-6 *antiglaucoma* 

Proposed International Nonproprietary Name (Latin, English)	*Chemical Name or Description, Molecular and Graphic formulae Chemical Abstracts Service (CAS) registry number Action and Use**
velaresolum velaresol	5-(2-formyl-3-hydroxyphenoxy)valeric acid $C_{12}H_{14}O_5$ 77858-21-0 *antianaemic*
	
zalcitabinum zalcitabine	2′,3′-dideoxycytidine $C_9H_{13}N_3O_3$ 7481-89-2 *antiviral*
	
zaldaridum zaldaride	(±)-1-[1-[(4-methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)methyl]-4-piperidyl]-2-benzimidazolinone $C_{26}H_{28}N_4O_2$ 109826-26-8 *antidiarrhoeal*
	
zoniclezolum zoniclezole	5-chloro-3-(1-imidazol-1-ylethyl)-1,2-benzisoxazole $C_{12}H_{10}ClN_3O$ 121929-20-2 *anticonvulsant*
	

Names for Radicals and Groups

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

buciclas buciclate	*trans*-4-butylcyclohexanecarboxylate $C_{11}H_{19}O_2$
	

Supplement to WHO Chronicle, Vol. 34, No. 9, 1980

Proposed International Nonproprietary Names (Prop. INN): List 44

p. 12 felodipinum
felodipine

replace the chemical name and the CAS registry number by the following:

(±)-ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate
86189-69-7

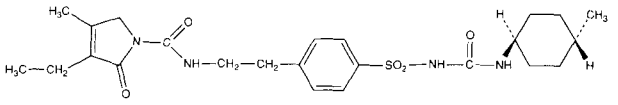
Supplement to WHO Chronicle, Vol. 39, No. 5, 1985

Proposed International Nonproprietary Names (Prop. INN): List 53

p. 12 glimepiridum
glimepiride

replace the chemical name and the graphic formula by the following:

1-[[*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) = ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea



WHO Drug Information, Vol. 1, No. 2, 1987

Proposed International Nonproprietary Names (Prop. INN): List 57

p. 104 ramoplaninum
ramoplanin

replace the description, molecular formula and CAS registry number by the following:

glycopeptide antibiotic produced by *actinoplanes* species ATCC33076
Ramoplanin is a complex antibiotic consisting of a main component designated as ramoplanin A_2 and a small amount of related substances, ramoplanin A_1 and A_3.
$C_{112-120}H_{142-156}ClN_{21}O_{35-40}$ 76168-82-6

WHO Drug Information, Vol. 2, No. 4, 1988

Proposed International Nonproprietary Names (Prop. INN): List 60

p. 15	*delete*	*insert*
	orlipastatum orlipastat	orlistatum orlistat

Proposed International Nonproprietary Names (Prop. INN): List 62

p. 6 epoetinum alfa
epoetin alfa

replace the description by the following:

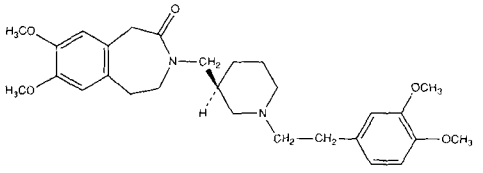
human 1-165-erythropoietin, glycoform α

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

p. 4 cilobradinum
cilobradine

delete the CAS registry number and replace the chemical name and the graphic formula by the following:

(+)-(*S*)-3-[[1-(3,4-dimethoxyphenethyl)-3-piperidyl]methyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one



Proposed International Nonproprietary Names (Prop. INN): List 64

p. 7 corticorelinum
corticorlin

replace the description, molecular and graphic formula by the following:

corticotropin-releasing factor; the species specificity should be indicated in brackets behind the name e.g.:

corticorelin (human)
$C_{208}H_{344}N_{60}O_{63}S_2$

H — Ser — Glu — Glu — Pro — Pro — Ile — Ser — Leu — Asp — Leu — Thr — Phe — His — Leu — Leu — Arg — Glu — Val — Leu — Glu — Met — Ala — Arg — Ala — Glu — Gln — Leu — Ala — Gln — Gln — Ala — His — Ser — Asn — Arg — Lys — Leu — Met — Glu — Ile — Ile — NH_2

corticorelin (ovine)
$C_{205}H_{339}N_{59}O_{63}S$

H — Ser — Gln — Glu — Pro — Pro — Ile — Ser — Leu — Asp — Leu — Thr — Phe — His — Leu — Leu — Arg — Glu — Val — Leu — Glu — Met — Thr — Lys — Ala — Asp — Gln — Leu — Ala — Gln — Gln — Ala — His — Ser — Asn — Arg — Lys — Leu — Leu — Asp — Ile — Ala — NH_2

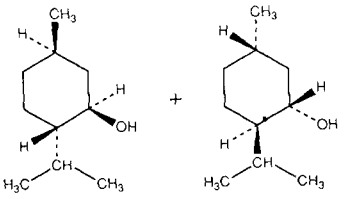
p. 12 lenograstimum
lenograstim

insert the following CAS registry number:

135968-09-1

p. 20 racementholum
racementol

replace the graphic formula by the following:



p. 27 fendizoatum
fendizoate

delete the CAS registry number:

p. 27 loprazolamum
loprazolam

replace the CAS registry number by the following:

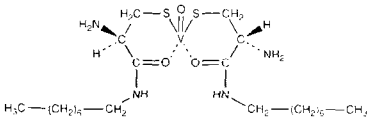
61197-73-7

WHO Drug Information, Vol. 5, No. 2, 1991

Proposed International Nonproprietary Names (Prop. INN): List 65

p. 9 naglivanum
naglivan

replace the graphic formula by the following:



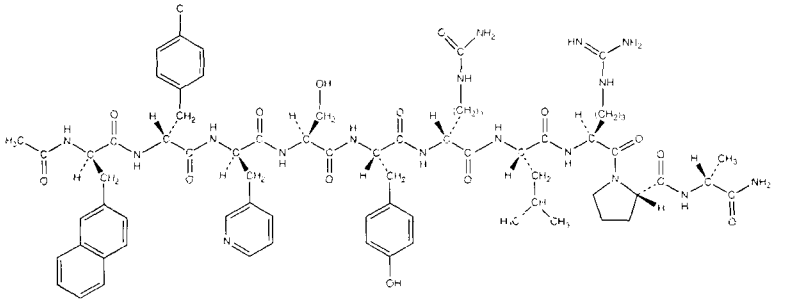
p. 10 polifeprosanum
polifeprosan

add the following:

"m" and "n" are the numerical values representing the mass percentages of the monomers. The value of "m" should be given as a figure after the INN, e.g. "polifeprosan 20", which means "m = 20" and "n = 80".

p. 17 cetrorelixum
cetrorelix

replace the graphic formula by the following:



p. 19 terikalantum
terikalant

replace the chemical name by the following:

(−)-(*S*)-1-[2-(4-chromanyl)ethyl]-4-(3,4-dimethoxyphenyl)piperidine

Procedure and Guiding Principles

The text of the *Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances* and *General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances* appeared in list 65 of proposed INN and will appear again in the next list.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

	Price* (Sw. fr.)
The use of essential drugs Fourth report of the WHO Expert Committee WHO Technical Report Series, No. 796 1990 (57 pages)	8.–
WHO model prescribing information: drugs used in anaesthesia 1989 (53 pages)	11.–
WHO model prescribing information: drugs used in parasitic diseases 1990 (128 pages)	21.–
WHO model prescribing information: drugs used in mycobacterial diseases 1991 (40 pages)	9.–
Guidelines for developing national drug policies 1988 (iv + 52 pages)	11.–
The International Pharmacopoeia, third edition Volume 1: general methods of analysis. 1979 (223 pages) Volume 2: quality specifications. 1981 (342 pages) Volume 3: quality specifications. 1988 (407 pages)	 24.– 36.– 64.–
Basic tests for pharmaceutical substances 1986 (vi + 204 pages)	34.-
Basic tests for pharmaceutical dosage forms 1991 (v + 129 pages)	24.–
International Nonproprietary Names (INN) for pharmaceutical substances, cumulative list no. 7 1988 (xviii + 617 pages)	65.-

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

** prices in developing countries are 70% of those listed here.*