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 includes the lists of proposed and recommended International Nonproprietary Names for Pharmaceutical Substances (INN). Its contents reflect, but do not present, WHO policies and activities and they embrace socioeconomic as well as technical matters.

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

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## WHO DRUG INFORMATION

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General Policy Topics

Postmarketing surveillance: what is being achieved?

It has long been recognized within national drug regulatory authorities that at the time a newly-developed drug is accorded a product licence, there is need for further investigation of its performance under routine conditions of use. This arises because premarketing clinical studies are typically undertaken for relatively short periods of time on a cumulative total of no more than one or two thousand carefully selected patients (1).

Whereas the resulting data provide a satisfactory basis for assessing efficacy and dose-related toxicity, other important aspects of the drug's performance remain to be explored. There may be need to review the consequences of long-term treatment, the potential for abuse and the management of overdosage in the light of extended experience. It is also imperative to institute some form of monitoring to ensure that rare but potentially serious adverse reactions and drug interactions are identified or excluded with reasonable certainty, not only in the target population of patients as a whole but in specific groups such as the very old and the very young. In particular, insofar as pregnant and lactating women are treated, the implications of fetal and perinatal exposure may have to be assessed.

Earlier this year, a working group of representatives of major drug regulatory authorities and multinational research-based pharmaceutical companies, meeting under the aegis of the Council for International Organizations of Medical Sciences, published proposals intended to harmonize requirements for the submission of these supplementary data (2). At present, some 12 national authorities formally require manufacturers to reassess periodically the safety of their licensed products (3). Two-thirds of 27 prospective studies that were reviewed were judged to be unsatisfactory as a basis for evaluating adverse events; they were uncontrolled; selection bias was not effectively excluded; and no study met the target of extending the number of patients in whom the drug had been formally studied by 5-fold or more. In general, it was felt that companies had been slow to provide the generated information and that existing national guidelines on what is required are too vague (4).

The changes now being considered within the United Kingdom invoke issues of fundamental principle. There is recognition that refinement of observational cohort studies is necessary if the prevailing inadequacies in experimental design are to be overcome, and that the scale of the studies must be substantially increased if meaningful information is to be gained on infrequent events. It is also accepted that an array of independent studies may be required to examine all aspects of safety inherent in a particular drug, and that each needs to be selected with regard to signals of possible toxicity generated within preclinical and clinical studies.

The hope must be that these changes can be implemented using computerized data storage and retrieval facilities without a burdensome increment in drug development costs. Logistics suggest that the whole gamut of activities embraced within postmarketing drug safety assessment will soon have to be addressed on a broader international basis.

References

Personal Perspectives

Pharmaceutical Inspection Convention (PIC)

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Wherever pharmaceutical products are manufactured, the national regulatory authority has a responsibility to ensure that Good Manufacturing Practices (GMP) are observed through inspection of production areas and operations. This is the responsibility of the national pharmaceutical inspectorate. An underlying tenet of international trade in pharmaceuticals — and, more specifically, of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce — is that trading countries should have comparable inspection procedures and apply equivalent standards. The Pharmaceutical Inspection Convention, described below, was created within Europe with this objective. The scheme stands as a model to national trading partners wishing to develop similar procedures in other regions.

The Convention for the Mutual Recognition of Inspection in respect of the Manufacture of Pharmaceutical Products (the name of which has since been shortened to Pharmaceutical Inspection Convention or PIC) was signed in October 1970. The Convention was initiated in the European Free Trade Area (EFTA) and was signed by all the EFTA countries of the time (Austria, Denmark, Finland, Iceland, Liechtenstein, Norway, Portugal, Sweden, Switzerland and the United Kingdom).

From the outset, the Pharmaceutical Inspection Convention was intended to be limited exclusively to EFTA Member States, but has since become open to any country that can show it has a developed inspection system comparable to that of the signatories. Since its entry into force, several such countries have joined the Convention: Hungary, Ireland, Romania, Germany, Italy and Belgium. Several others are now engaged in the accession process: Australia, France, Czechoslovakia, the Netherlands and Turkey. Others have indicated their interest in joining: Canada, Japan, Luxembourg and South Africa.

The Convention and its operation
In essence, the Convention provides that an inspection of a pharmaceutical plant, from which products are intended to be exported to one of the contracting states, is carried out by its national authority and shall be regarded and assessed by the health authority of the country of importation as if it had been carried out by its own inspectors.

In practice, the procedure functions as follows: the health authority of a member country wishing to obtain information concerning a product which has been or is to be imported, requests information from the national authority of the exporting country about the standards of GMP applied in the producing firm and specific standards appropriate to the manufacture and control of the product in question. The inspectorate in the exporting country sends an inspection report to its counterpart in the importing country which is then in a position to determine whether or not there are any breaches of GMP that would warrant blocking or cancelling importation.

The interests of the manufacturers are safeguarded in that they are entitled to withhold consent for the transmission of the report. Moreover, the information contained in the report may only relate to manufacture and control and exclude any information that might be commercially confidential, such as data concerning technical know-how or financial and commercial matters.

The main advantage of the Convention is that where domestic production is concerned, national systems and standards are not perturbed by having foreign inspectors with slightly different standards coming into the plant. Moreover, efficiency is promoted in that inspections are performed by inspectors who are best acquainted with the firm.

The Convention is based on mutual confidence in the standards of the respective inspection systems.
of the contracting states, in the competent national authorities and, even more important, in the persons who actually carry out the inspections and provide the inspection reports.

Committee of officials
A permanent committee of officials, appointed to supervise the operation of the Convention, deals with all technical matters that arise from the Convention. This committee is made up of representatives from the member countries' inspectorates. The committee's tasks are to exchange experience on methods of achieving effective inspections, to promote common training requirements for inspectors, and to make recommendations on matters relating to the implementation of the Convention. A chairman and deputy chairman are elected by the committee to serve a two-year term of office. The committee meets whenever necessary, but at least twice a year.

Good manufacturing practices
The basic principle underlying the whole Convention is that member countries have comparable inspection systems and apply equivalent standards. At a very early stage it was recognized that a common basis of reference would be required for the preparation and exchange of inspection reports. It was necessary to ensure a common language to be used by all inspectors when referring to technical matters relating to the manufacture of pharmaceutical products. Basic standards of GMP were therefore elaborated and adopted in 1972 by the committee of officials. Later, various guidelines were developed to supplement the basic standards: on the manufacture of sterile products, on the handling of starting materials, on manufacture and analysis under contract, on packaging and labelling, on the manufacture of active ingredients and on good practices in control laboratories.

The PIC basic standards and additional guidelines, were issued in the form of recommendations. At the time of their elaboration they represented a goal. Since then, they have become minimum standards acceptable to and applied by all the authorities under the Convention. This evolution provides concrete proof, if any is needed, of the long-term and wide-ranging harmonizing effect of the chosen approach.

It is interesting to note that the PIC standards of GMP have also served as the main basis for the elaboration of the new Economic Community Guide to GMP. In a spirit of cooperation and in order to provide for one single set of standards in all European countries, the PIC guide to GMP has been aligned with that of the EC. Such harmonization will also extend beyond Europe since Australia is soon to become a PIC member and keen interest in the Convention has been expressed by other overseas countries.

Inspector training
A system such as that represented by the Pharmaceutical Inspection Convention can only function on the basis of mutual confidence between the national health authorities concerned and with the assurance that all inspectors reach and maintain comparable degrees of competence and knowledge, and apply the same principles when carrying out inspections. It was thus essential to ensure a common understanding of GMP rules among all inspectors of the Convention's countries. Seminars are therefore organized regularly so that inspectors have the possibility of considering technical topics of current interest and of discussing means and methods of achieving effective inspections. These seminars contribute substantially to creating, through close personal contacts, the climate of mutual confidence needed for the good functioning of the Convention. Industry representatives are sometimes invited to participate in some of the seminars, and thanks to their contribution, there are useful discussions on various practical aspects and new technology in the manufacture of pharmaceuticals. Another development is the organization of joint visits to manufacturers by small groups of inspectors (normally three) from different countries. This has proved very successful in promoting harmonization by upgrading and approximating the knowledge of the inspectors as well as their approach to manifold problems.

Conclusion
As intended, the Convention has become fully independent from EFTA since its entry into force even if, for practical and historical reasons, support has so far been provided by the EFTA secretariat. The Convention celebrated its 20th anniversary in 1991 and for the past five years more than 200 inspection reports have been exchanged annually. There is no doubt that it has most successfully achieved the objectives originally set for it. Mutual confidence has been created between the competent authorities, and the degree of cooperation established has far exceeded the expectations of the founding members.
Control of _Ascaris lumbricoides_: selective or community therapy?

It is probable that as many as 25% of people throughout the world are host to the nematode, _Ascaris lumbricoides_ (1). The large majority of infected persons harbour only one or two worms and — because these do not multiply within the host — they induce no symptoms. The one million cases of ascaris disease that are estimated to occur each year (2) are the consequence of repeated ingestion of ascaris eggs, which exist in large numbers in endemic areas both in the soil and the environment at large. At greatest risk are children in the exposed communities — particularly those who, because of malnutrition or deficiency of vitamin A, are susceptible to pneumonia and diarrhoeal disease (3-4).

The intensity of this contamination has been claimed to correlate with the quality of sanitation and with broader measures of socioeconomic development (5). However, within these communities, the worm load is considerably greater in some individuals than in others exposed to comparable risk (6). Because of the rapidity at which reinfection occurs, mass chemotherapy has to be sustained for long periods and to be linked with other control measures if tangible results are to be obtained (7). It has consequently been proposed that selective treatment of the intensively infected minority is more rational, notwithstanding the cost of identifying these individuals, than indiscriminate mass treatment (8).

None the less, convincing evidence has recently been obtained to show that selective chemotherapy does not offer a viable approach to control where it is most needed (9). With the aim of studying the prevalence and intensity of reinfection among people living in Dhaka, Bangladesh, a sample of 880 adults and children were treated with a single dose of pyrantel pamoate (11 mg/kg body weight) on 3 occasions at 6-month intervals. This regimen has been estimated to cure 90-95% of ascaris infections (10). After each treatment, the worms expelled by each subject were counted and weighed. The most notable conclusion to emerge from the analysis of the results was that rapid recurrence of heavy infections was common, and that such recurrences did not tend to develop in the same subgroup of patients after each round of treatment. Indeed, nearly two-thirds of all subjects — and more than 70% of schoolchildren — were shown to be heavily reinfected on at least one occasion within the context of the study.

If this pattern of infection proves to be typical, the absence of any definable subgroup of individuals “predisposed” to heavy infection will imply that selective chemotherapy can never be efficiently targeted. Mass treatment, particularly of children — whose health and development are now recognized to be seriously compromised by intestinal parasites (11) — merits high priority wherever these diseases are endemic. The development of albendazole and other less expensive benzimidazoles as single-dose, broad-spectrum anthelmintics promises to bring a simple and practicable system of community-based treatment to the school-age population in many countries.

References


Ofloxacin: promise as an anti-leprosy agent

Antimicrobial resistance has resulted in multidrug therapy becoming standard practice in the treatment of leprosy. Regimens based on rifampicin, clofazimine and dapsone are the most practicable and reliable that have yet been devised. However, since clofazimine and dapsone are only weakly active against Mycobacterium leprae, it is important to search for new bactericidal agents with novel mechanisms of action. Their addition to such regimens might not only increase efficacy and further shorten the duration of treatment (1), they might also curb the continued emergence of strains of M. leprae resistant to the currently-used drugs, and to rifampicin in particular.

Ofloxacin, which is a member of a new generation of fluorinated quinolones structurally related to nalidixic acid, has been identified as a promising candidate for this purpose. Like other quinolones, it inhibits the enzyme DNA gyrase, which controls supercoiling of DNA in bacteria (2), and it has a broad spectrum of antibacterial activity which embraces most Gram-negative bacteria, many Gram-positive bacteria and some anaerobes. Of three quinolone derivatives tested (ciprofloxacin, ofloxacin and pefloxacin), ofloxacin alone exhibited significant bactericidal activity against M. leprae in the mouse footpad system (3-6). This activity has been confirmed in small-scale trials in leprosy patients (7, 8). Indeed, the results have been encouraging to the extent that a large-scale, multicentre, field trial has been organized under the aegis of WHO, with a view to comparing the efficacy, safety and acceptability of combined regimens containing ofloxacin with the regimens currently recommended by WHO in patients with both multibacillary and paucibacillary leprosy.

Opioids for chronic pain?

There is no dispute that opioid drugs are frequently needed to provide effective relief from the pain of terminal malignant disease. Controversy still persists, however, regarding their place in the management of chronic nonmalignant pain (1, 2). Because of their addictive potential, such use is often portrayed as potentially dangerous for both the patient and society (3, 4). This argument finds support in claims that nonmalignant pain — and neuropathic pain, in particular — is intrinsically resistant to opioids in subanaesthetic doses (5, 6) and in assertions that any relief these drugs may offer is likely to result from elevation of mood and hence to be essentially addictive in nature.

It is important that these claims be further explored. For many doctors they constitute grounds for withholding opioids from large numbers of patients with severe chronic pain who do not obtain satisfac-
tory relief from other analgesics. Yet they are held in contention by others persuaded that morphine and other opioids, given in sufficient dosage and with due caution can sometimes be irreplaceable in controlling severe chronic pain of other cause (7). Various studies are cited by each side to support their viewpoints (5-9) but, for the most part, their design leaves the conclusion vulnerable to criticism (10).

The introduction of patient-controlled analgesia — an infusion technique enabling the recipient to vary opiate dosage on demand within predetermined limits (11) — has created the possibility of obtaining precise dose-response data from patients receiving opiates. The method has recently been used in a small, double-blind study in which the effects of morphine infusions at 2 strengths were compared in 10 patients with severe intractable pain (10). The pain was described as nociceptive (associated with tissue-damage) in 4 patients and neuropathic in 6. All patients with nociceptive pain and 3 of 6 with neuropathic pain were judged to have obtained substantial relief during the infusions. At first sight these results provide strong support to the thesis that both types of pain are commonly responsive to opioids. However, they must be interpreted with reservation. The author's definition of neuropathic pain is too broad to meet with consensus (12); doubts have been raised about the therapeutic relevance to non-terminal conditions of a treatment that resulted, in some cases, in intravenous doses as high as 300 mg morphine within a matter of hours (13) and, in the absence of a placebo control, observation of a dose-dependent effect in only one of the patients claimed to have neuropathic pain leaves doubt about the extent to which a pharmacological effect was demonstrated (12).

The authors' conclusion that opioids should be considered for relieving severe, otherwise-unresponsive chronic pain of any cause, provided the patient is informed and agrees, thus remains open to question. Given the importance of the issue to countless patients and the difficulties of setting up a decisive clinical experiment within accepted ethical norms, there is a need to learn much more from relevant clinical practice. The WHO international data base of adverse drug reactions is virtually silent on the issue. It would be helpful if experiences were shared as freely as opinions.

References

Spermicides and sexually transmitted diseases
Nonoxinol-9, which has been used as a contraceptive for over 30 years, has been shown more recently to have antimicrobial activity in vitro against organisms causing some of the most
prevalent sexually transmissible diseases, including gonorrhoea and chlamydial infections, trichomoniasis, genital herpes and syphilis (1). Several clinical studies and surveys have confirmed that commercially-available spermicides enhance the protection provided by condoms against gonorrhoeal and chlamydial infections (2-7).

Since these two diseases may increase the vulnerability of women to HIV infection (8) it has been suggested that nonoxynol-9 should be used routinely by women at high risk of HIV infection (7). However, used frequently, nonoxynol-9 is itself irritant to the vaginal and cervical epithelium (9) and these inflammatory and ulcerative lesions may well operate to increase any risk of HIV transmission (10, 11). Warnings have been sounded that further studies are needed to determine whether such a risk may exist before recommendations for using nonoxynol-9 to protect against sexually transmitted diseases can be accepted (12). Condoms alone, when used correctly and consistently, reduce the risk of transmission of gonorrhoea and are without known significant toxic effects (13).

References

Pralidoxime salt: is it really of value in organophosphorus poisoning?

Organophosphorus insecticides, which are widely used as crop sprays, are a frequent cause of poisoning in many developing countries. Some cases result from occupational exposure but it is claimed that more are due to attempted suicide (1, 2). The products are potent neurotoxins which irreversibly inactivate cholinesterase. A potentially fatal acute cholinergic crisis which occurs after some 24 hours is often preceded by muscular weakness, most evident in the neck, the proximal limbs and the respiratory muscles (3). Atropine, which competitively antagonizes the muscarinic action of acetylcholine, and which is cheap and widely available, is the mainstay of treatment. However, the "cholinesterase reactivator" pralidoxime salt — which has been claimed to bind and inactivate organophosphorus molecules (4) — is also commonly employed, when it is available, in cases of moderate to severe poisoning.

The rationale for using pralidoxime is based upon demonstration of an atropine-sparing action in laboratory animals, toxicological evidence that it reverses the effects of organophosphorus compounds in the central nervous system, and a potential to reactivate blood cholinesterase in vitro (5-7). However, no controlled trials have ever been undertaken to assess its value in the treatment of
It is generally accepted that more reliable information is needed on the clinical value of pralidoxime, not least because it is costly and is itself toxic. Controlled studies have been precluded on ethical grounds, but opportunity for a retrospective comparison recently arose in Sri Lanka as a result of temporary exhaustion of stocks within the country. The clinical response to treatment of 45 patients admitted to a general medical facility within 24 hours of poisoning with an organophosphorus compound was studied over two successive 6-month periods (8). Pralidoxime, which was infused in a dose of 4 g in the first 24 hours and 1 g daily thereafter, was used routinely in addition to atropine to treat the 24 patients who presented during the first 6-month period, but it was subsequently not available to the hospital. The severity of the cases admitted during each period and the poisons implicated were closely comparable. The majority of cases were attributed to malathion, methamidophos, and fenthion. Slightly less than 30% of the patients within each group died, and no important difference was demonstrated in any other measure of outcome. These included the amount of atropine required to maintain its full effect, the number of days that atropine was administered, the need for intensive care and for assisted ventilation, and the length of stay in hospital.

Because of uncertainty about its therapeutic value, pralidoxime has not held a secure position within the WHO Model List of Essential Drugs. The results obtained in Sri Lanka intensify pre-existing doubts. But, as the authors themselves emphasize, they should not be regarded as conclusive. A severely poisoned adult may require an infusion of as much as 500 mg/hour (9). However, the study is of prime importance, since it both provides justification and demonstrates a need for prospective controlled studies of the clinical efficacy of a very expensive antidote.

References


Rubella immunization prevention policies

Rubella infection during pregnancy results in a high incidence of abortions, stillbirths and characteristic birth defects, including serious ophthalmic, auditory, cardiovascular, and neurological lesions, known collectively as the congenital rubella syndrome (1). With the advent of an effective vaccine in 1969, eradication of this risk through mass immunization of schoolchildren became a feasible, if costly, objective which received high priority in the United States in the 1980s (2, 3). In 1984 it was estimated that eradication could in time be achieved — on the assumption that the vaccine was 95% effective — if immunization coverage were maintained year-by-year above 92% (4).

Within a few years of its full implementation, the programme appeared to be on the verge of success. Only 2 cases of congenital rubella syndrome were formally reported within the United States in 1989 (5). Since then, however, more cases have been notified that have tempered early optimism and led to a restatement of national policy (6). A recent cluster of 21 cases in southern
California included both women who escaped immunization at school because of their age and women who had first entered the United States after completing their schooling (7). Opportunity had arisen in more than half the cases for rubella screening and immunization either at the time of marriage, or during previous contacts with the health services.

In contemporary mobile societies, it is suggested, eradication of congenital rubella syndrome cannot be based exclusively on universal immunization of infants with measles-mumps-rubella vaccine. Supplementary antibody testing of women likely to be susceptible to infection needs to be carried out in diverse settings. It needs to be considered during postpartem and postabortion examinations, and during attendances at family planning clinics, student health centres, clinics for sexually transmitted diseases, and drug rehabilitation programmes. A commitment is needed within the health services at large to ensure that rubella screening and immunization is undertaken whenever women who may be at risk to seek medical care and advice.

References

Herbal medicines: need for regulatory oversight

The need for cautious oversight of the market in herbal medicines has been repeatedly voiced in recent years (1, 2) and new examples of the inclusion of potentially toxic substances in such products continue to come to light. A herbal slimming product available in the United Kingdom has recently been found to contain a recommended daily dose of approximately 120 mg sparteine (3). This, the authors warn, is a quinolizidine alkaloid with oxytocic properties obtained from Broom (Cytisus scoparius) that has been used both as a diuretic and, at an intramuscular dose of 150 mg, for induction of labour. No adverse effects are known to have been reported to the product in question. However, a minority of some 10% of caucasians are likely to metabolize sparteine slowly, since it is oxidized in the same way as debrisoquine (4), and these will be particularly vulnerable to its pharmacological actions. Concern centres upon its potential effect on the gravid uterus, but in excessive dosage it seems that serious acute systemic reactions might also occur to the individual, including circulatory collapse, respiratory arrest, cramps, diarrhoea, diplopia, blurred vision, anorexia, headache and nausea (3).

All national drug regulatory authorities clearly need to maintain and update national listings of substances prohibited for inclusion in herbal products sold directly to the public.

References

Vitamin D fortification: the case for quantitative monitoring

At the turn of this century, the vast majority of children living in northern industrial towns were afflicted with rickets. Only in the 1920s was it
appreciated that exposure to sunlight could cure the disease (1) and not until many years later was it realized that adequate stores of vitamin D — which is synthesized in skin from 7-dehydrocholesterol during exposure to ultraviolet light — are vital to normal skeletal growth and mineralization. Deficient stores of vitamin D result in impaired calcium absorption, stunted growth, soft bones, muscle weakness, secondary hyperparathyroidism and pathological fractures. Excessive reserves of the vitamin are also dangerous, however, since they induce hypercalcaemia, extraskeletal calcification, renal impairment and stone formation.

Rickets was rapidly eradicated from western Europe and North America during the 1930s by fortification of milk with vitamin D, but excessive supplements resulting in outbreaks of vitamin D intoxication brought the practice into disrepute in some countries. Withdrawal of fortified products, however, has invariably resulted in a rapid resurgence of rickets in the past (2, 3), and the current preference for low-fat milk products in many countries has rendered reliance on natural dietary sources of vitamin D even more tenuous.

The problem of assuring correct supplementation is not simply a matter of history. As recently as this year, cases of vitamin D intoxication were reported from the United States as a consequence of the distribution of milk from one outlet that contained 500 times the labelled content of vitamin D (5.0 IU per litre) (4). Further investigation of the situation nationally has shown that only 12 of 42 samples of 13 brands of milk and none of 10 samples of 5 brands of infant formula contained vitamin D in amounts within ±20% of the labelled concentration (5). Over 60% of the milk samples contained lesser amounts, and in 3 of these, no vitamin D was detectable. Conversely, 7 of the 10 samples of infant formula contained between 2 and 4 times the labelled amount.

Notwithstanding these findings, the risk of clinically-evident vitamin D intoxication from excessive fortification of foods is probably remote (6), and there can be no doubt that the benefits of supplementation greatly outweigh the risks. The benefits are not realized exclusively in temperate latitudes. Indeed, reports of vitamin D deficiency now frequently emanate from regions with abundant sunshine where people avoid direct exposure to solar irradiation and where there is no fortification of foodstuffs (7-10). There is consequently a strong case for assuring wider availability of fortified products but, at the same time, provision needs to be made for checking the care and accuracy with which they are prepared. Fortunately, the necessary monitoring technique is now relatively simple since precise chromatographic methods have superseded the cumbersome bioassays that were used in the recent past.

References

Ritodrine: does it really prevent preterm labour?
Ritodrine, a beta₂-adrenergic agonist with tocolytic activity, was developed specifically for obstetric use (1), and for the past 15 years it has been used widely in many countries to inhibit preterm labour. The results of both an overview of early published trials (2) and a recent multicentre trial undertaken in Canada involving some 700 pregnancies (3) leave
no doubt that contractions are rapidly inhibited and that the risk of delivery within 48 hours of treatment is substantially reduced. However, in the longer term, this immediate advantage has not been shown in randomized controlled trials to be associated with any reduction overall in the incidence of preterm delivery, low birth weight, or perinatal morbidity and mortality (3-6).

This does not necessarily imply, however, that tocolytic therapy is entirely without value. It is possible, for instance, that its use in threatened termination before 28 weeks' gestation might delay delivery long enough to assure viability. Indeed, the results of the Canadian study support this possibility (3). Later in pregnancy, the rationale for suppressing contractions rests on whether anything else of value can be done in the time saved (3). This might simply constitute the transfer of the mother to a tertiary care facility or, perhaps, the administration of corticosteroids with a view to promoting pulmonary maturation in the fetus (7).

Such use can only be contemplated if tocolytic therapy is essentially without hazard. Concerns were raised in the United States in the early 1980s about an association between use of these drugs and potentially fatal maternal pulmonary oedema. This complication has recently been restated to develop with an incidence of 3% to 9% in treated patients (6). However, this does not reflect the current situation. Adverse reaction reports contained in WHO's international data base show that 66 of a total of 69 reports of pulmonary oedema associated with ritodrine originated in the USA and, of these, 46 were reported between 1981 and 1983. Reports of oedema associated with infusion of terbutaline followed a similar trend. In 1983 a warning was issued by the manufacturer of ritodrine to doctors within the USA emphasizing the danger of fluid overload during preterm labour and of using saline solution as the diluent for ritodrine infusion (8). Despite continued wide usage of ritodrine, the median annual number of such cases reported to WHO between 1984 and 1988 was 3; since 1989 only such one case has been notified.

References


General Information

Drug information centres

The time is decisively past when busy practising doctors could expect to prescribe simply on the basis of experience and memory alone. It is reassuring that some highly developed national health administrations are still able to issue formularies that slip easily into the pocket of a white coat. But occasions inevitably arise when a clinician is confronted with a need for specific drug-related information that is not readily accessible in order to resolve a pressing clinical problem.

To respond to this need, some of the larger hospital pharmacies in North America and Europe started some 30 years ago to organize themselves as centres of technical information (1-4). A recent survey of independent drug information centres within Europe (5) shows that it is not unusual for well-established hospital centres to deal with some 10 to 20 specific inquiries each day. Some have developed teaching commitments, others issue drug bulletins, and many offer a vital resource to institutional drug and therapeutics committees.

Disappointingly, the results of the survey suggest that such centres remain the exception rather than the rule within teaching and regional hospitals, and that they remain unevenly distributed from country to country. Of almost 1900 hospitals and other institutions contacted, replies were received from 277 and completed questionnaires from only 110. Almost 90% of the questionnaires were returned from 4 countries: the United Kingdom, France, the Netherlands and Spain. None was returned from any country in eastern Europe. Even in those countries where centres are most generously distributed, a need for a corporate identity is strongly felt. Most of the responses to the questionnaire supported the concept of creating a European network of centres. Some suggested that a directory of existing centres be published, and others proposed that guidelines be prepared setting out the resources, staffing and training required to establish a centre.

The development of a corporate image could obviously do much to advance the fortunes of information centres. It might even dispel current inertia and encourage the creation of a second generation of centres. There is obviously much potential still to be mobilized within Europe and North America. Elsewhere, the need has hardly been addressed. Yet, inevitably, it is in the countries of the developing world where information is most grievously lacking and where efficient organization of the slender resources that are available is most urgently needed. Should a corporate international body ever be set up to represent the interests of information centres, it should not overlook the needs of less favoured countries.

References


Expensive drugs and cost containment

Debates about prices demanded for recently-introduced pharmaceutical products are not new. For two decades or more, attention was directed primarily at innovative antibiotics — especially penicillins with an extended spectrum of activity and the third-generation cefalosporins. Treatment costs, sometimes in excess of US$ 1000 for a routine course of therapy, provided an important stimulus for the creation of institutional drug and therapeutics committees. Now, with techniques of biological synthesis able to generate complex polypeptide and protein compounds virtually on demand, pharmaceutical manufacture has moved into a new
era. However, new technology is rarely placed on offer at bargain prices. It no longer engenders surprise when a manufacturer introduces a monoclonal antibody or a product derived from recombinant DNA synthesis with a price tag of US$ 4 to 5000 for a single cycle of therapy (1).

In part, these onerous charges doubtless reflect the daunting capital costs involved in bringing new techniques and new generations of pharmacologically-active substances into the market place. However, as months and years pass without any sign of remission in sight, the debate intensifies on how such expensive treatments can be offered within a system of health care reliant upon either general taxation or private insurance. Clearly, products placing a significant strain on the health care budget can never be lightly prescribed, and, as more of them become registered for general use, searching conditions will inevitably need to be satisfied before they can be accepted into routine use for the treatment of common ailments.

A number of conditions that will be widely seen as qualifying for further consideration have been proposed by Dr Robert Meyer, writing in a recent issue of Clinical Pharmacology and Therapeutics (2). He accepts that new drugs will continue frequently to enter into use on the basis of physiological or pharmacological indicators of activity rather than definitive evidence of reduced morbidity or mortality. But he emphasizes that rigorous cost-benefit assessments of drug performance need to be put in hand promptly in the post-marketing period. By way of example, he points to the history of tissue plasminogen activator (alteplase, t-PA). Much pharmacological evidence was generated early in the development of the product that its lytic activity would be confined to sites of pre-existing thrombus. This apparent selectivity of action generated an enthusiasm which was subsequently reinforced by radiological demonstration of t-PA's superiority over other thrombolytic agents in establishing vessel potency in post-infarction patients at a single relatively early point in time (3, 4). Five years elapsed before it was shown that a human tissue-type (alteplase) loses its apparent advantage when vessel potency is monitored over a longer time span (5), and before comparative studies showed it to be indistinguishable in clinical performance from the less costly streptokinase (6, 7).

When acute mortality is not at issue, rigorous cost-benefit assessments become both more complex and more controversial. Meyer focuses attention on the use of erythropoietin to treat the anaemia of chronic renal insufficiency. It has been estimated that the annual purchase costs of epoetin alfa for the treatment of patients on long-term haemodialysis will shortly exceed US$ 1 billion within the United States alone (8). If only 50% of these patients were transferred from androgen therapy to epoetin alfa (erythropoietin), it is predicted that a net increase in costs of US$ 650 million would be sustained over a period of 5 years (8). In part, this would be offset by a considerable reduction in transfusion requirements (9, 10), but no dramatic improvement can be expected either in the functional status of the patients (11-14) or in their rate of return to partial or full-time employment (13, 14). "More than 2 years after its introduction into widespread clinical use", Meyer concludes, "we are only now beginning to assess whether [erythropoietin's] benefits are as great as we had hoped and whether the costs for these benefits are reasonable".

As enthusiasm for the initial approved indication for erythropoietin becomes tempered, its application — often at significantly higher doses — in a wide range of unrelated conditions is being explored. Among these are chemotherapy-induced anaemia (15), anaemia of malignancy (16), multiple myeloma (17), rheumatoid arthritis (18), anaemia of prematurity (19), zidovudine anaemia (20), and myelodysplastic syndrome (21). Scientifically-based clinical investigation of newly-marketed drugs carried out within accepted norms of ethics, followed by publication of the results, is integral to the continued evolution of clinical medicine.

Meyer questions the idea, however, that once a drug is approved for use, it may be used routinely outside the context of a formal trial for a non-approved indication. He dismisses the notion that the individual doctor at the bedside is a source of major therapeutic innovation, and he calls for a re-examination of the policy that all physicians may prescribe any approved drug. He also pleads for the biotechnology industry to accept limits on its investment return. The basic techniques necessary for the production of these new compounds, he claims, were developed in large part as a result of publicly-funded research, and not by industry-funded efforts (8).

Whether such measures would significantly diminish the cost constraints now evident wherever medicine is practised remains open to question. More fundamentally, Meyer observes, "rationing among patients now occurs on the basis of unequal financial resources and variable access to care. The real question is whether this is the best way for rationing to take place" (22).
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Parental attitudes towards children’s medicines: a case study

Theophylline remains commonly used in the control of childhood asthma despite widespread belief among doctors and parents that it can adversely affect both behaviour and learning (1). Because of its reputation, a large proportion of parents probably fail to give it to their children regularly (2).

However, it now seems that much of this concern may be ill-founded. One study undertaken in the United States suggests that theophylline can be taken regularly by more than 9 out of 10 children of school age without psychological disturbance (3). More secure estimates applicable to both school and pre-school children may shortly be obtained from a multicentre survey sponsored by the American Academy of Allergy and Immunology (4).
In the meantime, the importance of suggestibility in parental attitudes has been impressively demonstrated in two complementary studies involving US families. Almost half of some 200 parents who collaborated believed that their asthmatic child became restless and hyperactive while taking theophylline (5). These perceptions did not correlate with tests of behaviour and mood in the treated children which were largely normal, and it was subsequently shown that the same parents were unable to distinguish between the effects of theophylline and placebo given to their child in a cross-over study under blind conditions (6).

It is possible that the one-week sequential treatment periods that were used in this study were too short to allow full development of any psychological disturbance, but the results confirm similar findings obtained in several unselected groups of asthmatic children (7-10). This does not deny that severe psychological reactions to theophylline may occur. Persuasive case reports citing stammering, depression and even psychosis have been published (6-11). Associations with impulsive behaviour (12, 13), and impairment of memory and concentration (13-15) have also been described in various controlled studies. However, the detection of isolated, inconsistent, and often marginal anomalies within an array of otherwise normal indicators has dubious clinical significance.

Whatever reassessment may be made of the place of theophylline in the treatment of childhood asthma it is by no means certain that this will have much effect on parental attitudes (16). Much more remains to be learned about how patients' and parents' beliefs influence patterns of use of prescribed medicines by children (17).

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“First-dose” anaphylactoid reactions

Australia — Over a recent 2-month period of observation, more than 2% of some 1200 suspected adverse drug effects reported by doctors in Australia to their national centre were found to have occurred subsequent to the first dose of a newly-acquired, orally-administered medicine. Although only 5 of the 28 reported incidents were classified as characteristically anaphylactoid in nature, various other urticarial and exanthematous reactions are likely to have resulted from the same immunogenic mechanisms. Among a variety of other less-frequently notified reactions were nausea and vomiting, dizziness, tremor, agitation, insomnia, weakness, increased sweating, and localized oedema, particularly of the face.

Preparations sold over the counter in pharmacies as well as prescription medicines were represented within the sample and, in some instances, there was no history of previous exposure to the product. Almost one-third of the reports implicated trimethoprim, administered either alone or in combination with sulfamethoxazole. Nonsteroidal anti-inflammatory agents were also prominent.

Given the apparently important prevalence of such incidents, the Adverse Drug Reactions Advisory Committee has reminded doctors to ensure that they are equipped to treat anaphylactoid reactions in an emergency, and it recommends that every patient should be advised by their doctor or pharmacist of the possibility, no matter how remote, that ingestion of virtually any medicine can occasionally induce an acute allergic reaction.


Fenfluramines and pulmonary hypertension

United Kingdom — Doctors have been reminded by the Committee on Safety of Medicines that fenfluramines, which are approved for use as an adjunct to the dietary management of severe obesity, should not be taken continuously for more than 3 months and that all serious adverse events associated with their use should be notified. They have been requested, in particular, to remain alert to the possibility of pulmonary hypertension developing during treatment and to advise patients taking these products to report immediately any episode of syncope, chest pain or palpitation, or any increase in breathlessness either at rest or on exertion.

Worldwide, some 25 cases of pulmonary hypertension are reported to have developed in patients taking products containing the racemic mixture of fenfluramine from the time that they were introduced in the mid 1960s. Over the past 6 years, 6 further cases — mostly reported from France — have been associated with the more recently introduced +-(S) isomer of fenfluramine. In all, 4 of these 31 cases are reported to have been fatal.

Spontaneously-occurring primary pulmonary hypertension is a rare disease that is responsible for about 100 deaths each year in the United Kingdom. It is not known how fenfluramines might promote the underlying pathological changes. However, the possibility of a causal relationship — although it remains unproven — is suggested because most cases have been associated with prolonged or repeated use of these compounds, and because several cases have been reported to regress on drug withdrawal.


Fluoxetine: association with suicide remains unconfirmed

United Kingdom — The Committee on Safety of Medicines has recently started to release selected findings from early post-marketing studies of newly-registered drugs when these cast light on previously-suspected adverse effects.

Within this context, it had earlier been suggested that fluoxetine, but not fluvoxamine, is associated with a risk of suicidal and hostile behaviour. Both these drugs, which specifically inhibit the reuptake of 5-hydroxytryptamine by nerve cells, are indicated for the treatment of depression. A comparison of
adverse reactions reported within the context of post-marketing studies in which these two drugs were examined has now been conducted by the Committee, and this has indicated that there is no important difference between the two adverse reaction profiles (1).

The Committee estimates that approximately 480,000 prescriptions have been written for fluoxetine in the United Kingdom and 280,000 for fluvoxamine. By June 1992 it had received 2422 reports citing fluoxetine and 1236 citing fluvoxamine. The only differences of any significance indicated that dermatological reactions were more frequent with fluoxetine, whereas gastrointestinal reactions were more frequent with fluvoxamine. The number of reports of attempted suicide were respectively 20 and 25 per million prescriptions for fluvoxamine and fluoxetine respectively.

These findings are consonant with the results of a recent meta-analysis of clinical trials in which comparisons between fluoxetine, tricyclic antidepressants and placebo provided no indication of an increase in suicidal behaviour in any of the observed groups (2).

References

Growth hormone and Creutzfeldt-Jacob disease
United Kingdom — The Department of Health has written to all patients within the country who received injections of growth hormone before pituitary-derived products were withdrawn in May 1985. Each has been offered counselling because of the possible risk of Creutzfeldt-Jacob disease. The decision to issue the letter was influenced by concern that organ or tissue donation by recipients of these preparations might result in further transmission of the disease. Funding has been assured to maintain a regional network of counsellors over a period of 12 months.

The first fatal case of Creutzfeldt-Jacob disease to be diagnosed in a British patient who had received pituitary-derived growth hormone was notified in 1985. To date, six cases of the disease have been confirmed and two others are suspected among the 1900 patients at risk within the UK.


Sumatriptan contraindicated in patients with ischaemic heart disease
United Kingdom — The Committee on Safety of Medicines has requested doctors to report all suspected adverse effects associated with the 5-HT receptor agonist, sumatriptan, which was registered as a subcutaneously administered formulation in September 1991 for the treatment of migraine and cluster headaches. An oral formulation is about to be introduced.

Whereas no episodes of myocardial ischaemia were demonstrated with sumatriptan during premarketing trials, angiographic studies have shown that it may induce coronary vasoconstriction and that this risk is potentiated by simultaneous administration of ergot alkaloids. Its use in combination with ergotamine and in patients with ischaemic heart disease or Prinzmetal's angina is consequently contraindicated.

Notwithstanding these warnings, and within 9 months of the introduction of sumatriptan during which some 15,000 prescriptions were written, the Committee received 34 reports of patients who complained of pain or tightness in the chest immediately following injection. Symptoms, which were sometimes severe, persisted for periods ranging from several minutes to several hours. The affected patients reflected the demographic characteristics of the target population as a whole insofar that they were typically middle-aged women. In no patient was there proof that the pain was of cardiac origin. None had a history of ischaemic heart disease; only three were receiving treatment for hypertension; and no ischaemic changes were identified in the 3 patients from whom electrocardiograms were obtained.

However, 5 of these patients developed similar symptoms on rechallenge, and two other cases of proven myocardial ischaemia following administration of sumatriptan are on record, both in men in their late forties.

**Temafloxacin: unacceptable incidence of serious adverse effects**

**United States of America** — The manufacturer of the recently-marketed quinolone antimicrobial agent, temafloxacin, has announced that it has voluntarily withdrawn the product worldwide following its association with an unusually high number of serious adverse reactions.

Among a total of some 50 reported cases, which include 3 fatalities, are instances of acute renal failure, some of which required haemodialysis; severe hypoglycaemia, particularly among elderly patients with previously impaired renal function; acute hepatic damage; anaphylactic reactions sometimes resulting in life-threatening respiratory distress; and haemolytic anaemia associated with abnormalities in formed blood elements.

The circumstances of the withdrawal are unusual in that some of these events were totally unanticipated, both in terms of experience with other quinolone antimicrobials and having regard to the performance of temafloxacin in premarketing trials in which treatment was withdrawn from less than 4% of the patients involved. At the time of its introduction, it was claimed to have a relatively low potential to cause adverse effects.


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**Tibolone and vaginal bleeding**

**United Kingdom** — Over a period of 14 months since it was first marketed in the UK, the Committee on Safety of Medicines has received 134 reports of vaginal bleeding in women receiving the synthetic steroid, tibolone. This is a compound with estrogenic, progestational and androgenic properties that is indicated for the treatment of post-menopausal vasomotor symptoms.

Blood loss has not been severe, but its timing is unpredictable since tibolone is taken continuously rather than cyclically. Most episodes occur within 2 months of starting treatment, but some are longer delayed and, in rare cases, bleeding has occurred shortly after discontinuation of therapy. This creates problems of diagnosis that sometimes require extensive investigation.

Since episodes of bleeding are most likely to occur in women who are either within 1 year of their last natural menstrual period or who have recently received estrogen replacement therapy, the Committee has recommended that tibolone should not be prescribed in these circumstances.

**Source:** Committee on Safety of Medicines. *Current Problems*, No.34, June 1992.

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**Triazolam, anxiety and amnesia**

**United States of America** — A technical advisory committee of the Food and Drug Administration has concluded that the benefits of the benzodiazepine hypnotic, triazolam outweigh the risks associated with its use (1). However, because of the unusually high rate at which reports of anxiety and memory loss are being reported among treated patients, it has recommended that:

- labelling be reviewed to ensure that the need to use the lowest effective dose of the drug for the shortest period of time is adequately emphasized, and readily understood guidance on dosage requirements be included in the package insert for patients;
- further clinical trials be conducted to determine the lowest effective dosages, and to investigate the relationships of dosage, effectiveness and unwanted effects to factors such as age, sex and body weight.

The manufacturer has since announced that a 10 000-patient study is being designed in collaboration with the FDA to compare the safety of triazolam with that of other hypnotic agents.

The outcome of the appeal made by the manufacturer against the current suspension of triazolam preparations in the United Kingdom is not yet known.

**Sources**

Essential Drugs

Diseases of the skin (continued)*

The infectious dermatoses and other skin conditions that are particularly prevalent in developing countries were discussed in the previous issue of this journal. The following account is concerned with the more diverse spectrum of dermatological diseases which occur worldwide and which, in many instances, result from immunological disturbances in predisposed individuals. The coverage is not comprehensive. Emphasis is given to those conditions which can be managed largely on an outpatient basis. Drug induced eruptions and chronic diseases, in which skin lesions are a manifestation of generalized systemic disease, will be covered in a separate account.

Acne vulgaris

Acne is an inflammatory disease of the pilosebaceous units in the skin of the face, neck, chest and upper back. Typically, it first appears during puberty when androgenic stimulation triggers excessive production of sebum. This results in abnormal follicular keratinization, colonization by a Gram-positive bacterium — Propionibacterium acnes — and local inflammation. It is possible, but not proven, that P. acnes promotes inflammation by hydrolysing lipid esters to irritant fatty acids.

Clinically, the disease varies in intensity from a trivial condition, in which a few comedones (dilated pilosebaceous cysts containing sebum, cornified epithelium, bacteria and saprophytic yeasts) leave small atrophic scars, to a severe disfiguring disease in which cysts, nodules and sinuses form in areas of intense inflammatory reaction. Scarring is sometimes followed by keloid formation, particularly among Africans. The disease has been claimed to be less common among vegetarians, but there is no evidence that the course of the disease can be influenced by dietary manipulation.

Occasionally, systemic or topical exposure to specific chemicals is implicated. These include:

- orally-administered drugs, notably corticosteroids, isoniazid, lithium carbonante, phenytoin and halogen-containing sedatives and expectorants;
- topical exposure to irritant oils or cosmetics;
- environmental exposure, even in minute amounts, to dioxin or halogenated phenolic compounds.

Management

Exposure to agents suspected of causing or aggravating the condition should be avoided or minimized.

The aims of drug therapy are to reduce secretion of sebum and follicular keratinization, and to inhibit infection and inflammation. Mild cases usually respond satisfactorily to topical therapy alone. Systemic use of antibiotics, estrogens, antiandrogens or retinoids should be reserved for severe and unresponsive cases.

Systemic treatment must be invariably sustained for several months before a response can be anticipated. During this time topical preparations should be applied concomitantly to affected areas to prevent new lesions from developing.

Topical therapy

Benzoyl peroxide, which promotes desquamation and has a potent bactericidal action, is most widely used. Gel formulations are claimed to be more effective than creams or ointments, but they are also more irritant. Treatment is usually started with a 2.5% preparation applied every other day. The strength and frequency of application is later increased as the irritant reaction subsides.

Preparations containing sulfur — which also has a bactericidal action and promotes desquamation — continue to be used, often in formulations containing salicylic acid as a keratolytic agent.

Retinoic acid is claimed to be more effective than benzoyl peroxide when applied topically, but it is considerably more expensive. It reduces follicular hyperkeratosis by stimulating turnover of epithelial cells. A variable degree of irritation is induced which is aggravated by exposure to ultraviolet light. The required dosage can be reduced by concomitant treatment with topical or systemic antibiotics or with topical benzoyl peroxide.

* The first part appeared in WHO Drug Information, 6(2): 60-74 (1992)
Topical antibiotics, although widely used when signs of inflammation are prominent, hold a disputed place in the treatment of acne. Erythromycin, tetracycline and clindamycin are widely used. Treatment must be maintained for 2 to 3 months before any benefit is obtained and this prolonged treatment carries risks of sensitization, of folliculitis due to invasion of resistant Gram-negative bacteria, and of selection and spread of antibiotic-resistant organisms.

**Systemic therapy**

Systemic administration of antibiotics, estrogens, antiandrogens or retinoids should be considered only when topical treatment fails or when severe cystic acne threatens to result in substantial scarring.

The clinical response to systemically administered antibiotics is probably not directly dependent upon the antimicrobial action. Penicillins, for instance, are likely to be effective only in cases of Gram-negative folliculitis, even though they are bactericidal to *P. acnes*. Low doses of tetracycline (0.5 to 1.0 gram daily) are most widely used and, when they are contraindicated, erythromycin is commonly substituted. To be effective, treatment has to be maintained for at least 6 months, during which time *P. acnes* can become resistant to tetracyclines and the normal bowel flora may be overgrown by *Clostridium difficile*, exposing the patient to a remote but potentially fatal risk of pseudomembranous colitis.

Estrogens and antiandrogens, which produce clinical remission by reducing secretion of sebum, can be used only in women because of their feminizing action. Combined oral contraceptives are often effective when administered at normal dosages. Products containing norethisterone are favoured because, by raising circulating concentrations of sex-hormone binding globulin, they reduce plasma concentrations of free testosterone. The antiandrogen, cyproterone acetate — administered in combination with the estrogen, ethinylestradiol, to assure a contraceptive action — has been claimed to be more effective.

The oral retinoic acid derivative, isotretinoin, which is a more potent inhibitor of sebum production, is the most effective treatment available for severe cystic acne. However, it is very expensive; it often induces signs of hypervitaminosis A, including cheilitis, dry eyes, generalized xerosis, pruritus and paronychia; and, most problematic of all, it is a proven and potent human teratogen. Even where the most rigorous precautions have been exercised both by the manufacturer and by prescribers to exclude pregnancy before treatment is instituted, and to ensure that effective contraception is practised throughout treatment and for at least three months after its withdrawal, congenital abnormalities attributed to intrauterine exposure to the drug are still occasionally reported.

**Pruritus**

Itching is thought to result from the release of histamine from mast cells in the dermis. It is a persistent and distressing symptom of many skin disorders, but it also occurs in apparently healthy people, and particularly among adults living in tropical climates.

Non-specific pruritus, unaccompanied by other evidence of skin disease, is commonly diffuse and can be aggravated by restrictive clothing. In temperate climates, it is often exacerbated by warm weather. Elderly patients, in particular, should be carefully examined to exclude specific skin conditions, incipient jaundice and other systemic causes of pruritus.

**Management**

Frequent applications of calamine lotion often provide useful relief. Hydrocortisone applied sparingly and intermittently in low concentrations sometimes provides additional relief when the sensation remains troublesome. Systemic antihistamines are justified only in severe, refractory cases.

**Urticaria**

Urticaria (hives) is a non-specific vascular response to a wide variety of stimuli. It is determined by genetic, immunologic and other largely unknown factors and it is triggered by chemical and physical stimuli including cholinergic activity, sunlight, localized pressure, heat and cold. As many as 20% of persons probably experience the condition at some time in their lives. It is characterized by cutaneous weals — erythematous pruritic papules — that blanch on pressure. Angioedema is a variant that predominantly affects the mucous membranes. Most episodes are transient but, particularly in patients with autoimmune thyroid disorders, lesions may persist for many months.

**Hereditary angioedema** is an autosomal dominant trait. Weals typically spread in annular fashion in response to trauma. A similar disorder sometimes occurs in patients with lymphoproliferative diseases; lymphosarcoma and chronic lymphocytic leukemia.
Cholinergic urticaria is common in young adults after vigorous exercise or emotional stress. It is often accompanied by other signs of cholinergic activation including abdominal cramps, dizziness and wheezing. The lesions are usually confined to the trunk. Most regress within 30-60 minutes but occasionally they are more persistent and tend to coalesce.

Solar urticaria develops within minutes of exposure to direct sunlight and resolves completely within an hour of withdrawing. Some persons are even sensitive to light that has been filtered through window glass.

Dermographism, in which weals are induced by scratching or rubbing of the skin is probably genetically determined. However, an allergic mechanism seems to be involved, since it has been transferred passively by intradermal injection of serum from affected patients.

Cold urticaria is often, but not invariably, familial. Localized pruritus, erythema, and swelling develop rapidly in response to a cold stimulus. Predisposed individuals risk shock, loss of consciousness and even death from drowning if they plunge into cold water.

Urticarial vasculitis, which is sometimes associated with systemic lupus erythematosus, shares the clinical features of other causes of urticaria but it is a totally different condition resulting from necrotizing vasculitis which is probably caused by deposition of immune complex. It cannot be managed symptomatically. It must be treated as a manifestation of systemic lupus.

Management
Urticaria, even in its more chronic forms, is usually self-limiting. Identification and avoidance of causative stimuli is the only practicable approach to prevention in most instances. Patients with any form of urticaria are often sensitive to acetylsalicylic acid and to specific foods including meats, shellfish, tomatoes, chocolate and fresh berries.

Selective desensitization, which may be directed to physical as well as chemical stimuli, is sometimes effective. Frequent hot baths for patients with cholinergic urticaria and controlled graduated exposure to UV light for those with solar urticaria sometimes induce a useful measure of tolerance.

The aim of symptomatic treatment is to deplete stores of histamine or to inhibit its release from mast cells, or to block either agonist drugs or receptor sites competitively. Antihistamines that are claimed to be non-sedating possibly hold advantage and they should be given regularly until all signs have been suppressed for at least 2 to 3 days. Patients resistant to antihistamines sometimes respond to cromoglycate sodium, which inhibits histamine release by stabilizing mast cell membranes.

Psoriasis
Psoriasis, which affects people of all ages in every country, is one of the commonest of the chronic dermatoses. It is estimated, overall, to affect about 2% of the population of the United States and northern Europe. Considerable local variations in its prevalence have been variously attributed to climatic, nutritional and ecological factors. It is recognized to be genetically determined, but the precise mode of inheritance is unknown. Various biological events may trigger its expression, including streptococcal or viral infection, an emotional crisis or pregnancy. Other cases appear to be related to the administration of specific drugs including lithium, chloroquine and beta-adrenergic blocking agents.

Psoriasis vulgaris, the most common form of the disease, is characterized by erythematous, scaly plaques of varying size. These are usually confined to the scalp, elbows and knees, although disabling widespread extension, described as erythrodermic or exfoliative psoriasis, frequently occurs. Histologically, the lesions show intense proliferation and incomplete differentiation of the epidermal keratinocytes, abnormal endothelial changes in the dermal blood vessels, and infiltration of activated neutrophils and T lymphocytes into the dermis and epidermis. Acute inflammatory exacerbations characterized by a severe febrile reaction and pustule formation are commonly a consequence of inappropriate treatment. About 10% of patients develop a destructive peripheral inflammatory arthritis of the hands and feet which is sometimes associated with ankylosing spondylitis. Psoriasiform skin lesions are also seen in some patients with Reiter's syndrome and subacute cutaneous lupus erythematosus.

Guttate psoriasis, which occurs mainly in children, is characterized by the sudden appearance of smaller but widespread lesions. The condition sometimes resolves spontaneously, but most cases ultimately transform into psoriasis vulgaris.

Management
Many different approaches to treatment are used. Each has advantages and shortcomings and none reliably assures remission from relapse.
Topical applications
Localized psoriasis vulgaris can frequently be cleared, sometimes for many months, by daily applications of dithranol cream for 2 to 4 weeks. A “short contact” method in which each application is rinsed off within 30 to 60 minutes causes slight, if any, irritation or staining of normal skin. This is particularly useful for outpatient management although there is a risk of severe conjunctivitis if the paste accidentally enters the eye.

Topical corticosteroids should be reserved for short-term treatment of active lesions on the scalp, face, palms and soles. More extensive applications are inappropriate. They neither induce remission nor are they effective in clearing plaques and there is always a danger of rebound after withdrawal, resulting in a more unstable form of psoriasis. Systemic corticosteroids should not be used under any circumstance. They are not reliably effective and their withdrawal frequently induces a severe exacerbation of the disease.

Resistant lesions need to be treated in hospital either with prolonged applications of dithranol in increasing concentrations or, when lesions are widespread as in erythrodermic and guttate psoriasis, with coal tar. The latter has a wider margin of safety, but patients need to be highly motivated to tolerate the mess and smell of coal tar dressings in the home. Both liquid tar and crude coal tar are available in various solutions and ointments, some of which also contain salicylic acid as a keratolytic. Better results are often obtained when daily applications or baths are combined with ultraviolet irradiation. Preliminary results, which have yet to be confirmed, suggest that calcipotriol, a vitamin D₃ analogue, which promotes the differentiation of epidermal keratinocytes, offers promise as an effective and acceptable form of topical therapy.

Systemic treatment
Several options exist for the systemic treatment of patients unresponsive to topical therapy. Each, however, is associated with hazards. It is prudent, when treating patients who require extended systemic treatment, to change the drug regimen from time to time to reduce the risk of cumulative toxicity associated with any one agent.

Most lesions can be cleared by combining oral administration of a psoralen, methoxsalen, with 12 to 24 sessions of long-wave ultraviolet A irradiation (PUVA therapy). Light of this wave-length promotes an interaction between the psoralen and DNA in the basal cells of psoriatic plaques with the result that growth is slowed to normal. The psoralen is taken 2 hours before each session of irradiation. Clearance of lesions can be expected within 5-6 weeks when standard incremental exposure to irradiation is arranged 3 times weekly. This therapy has not been associated with serious systemic complications, although nausea, pruritus and unwanted phototoxic reactions can be troublesome. Any risk of non-melanomatous skin cancer is thought to be negligible if the aggregate life-time therapeutic exposure is no greater than 400 J/cm² UVA and it is possible that the risk may be further diminished by administering each course in fewer, more powerful doses.

In the past, reliance has been placed in the antimitabolite, methotrexate, as a treatment of last resort for patients with recalcitrant and severe cutaneous or arthritic lesions. In some cases it was highly effective, but treatment was sometimes compromised by oral ulceration and gastrointestinal intolerance. Regular monitoring of the blood count was necessary because of the risk of bone marrow suppression and serial liver biopsies were recommended for patients on long-term therapy as the only means of detecting early drug-induced cirrhotic changes. Treatment was contraindicated in patients with pre-existing liver disease or an alcoholic tendency. Several other antimitabolites and immunosuppressive agents, including hydroxychloroquine and azathioprine, have been similarly employed. However, each has been associated with systemic toxicity and, in general, they are considered to be less effective than methotrexate.

More recently, highly impressive short-term results have been reported with the immunosuppressant, ciclosporin, administered for 4 months at daily doses as low as 5 mg/kg. Ciclosporin is vasoactive to the extent that it is contraindicated in hypertensive patients and, even at these low doses, it substantially — but reversibly — reduces glomerular filtration rates. In the short term, this dose does not appear to increase the risk of incidental infection, nor does it seriously derange other physiologically important immunological responses. However, more must be known about the speed and rate of relapse after discontinuation of treatment and the possible toxicity of longer term therapy — including any risk of lymphoma or non-melanomatous skin cancer — before the use of ciclosporin can be regarded as established in the routine management of psoriasis. Those patients that are selected for ciclosporin therapy are probably best transferred back to one of the longer
established treatments for maintenance therapy. Extensive clinical experience has also confirmed that systemic administration of the synthetic retinoid, etretinate, is highly effective in many patients with severe forms of psoriasis. Its mechanism of action remains unknown, but it rapidly attenuates both inflammation and scaling and restores normal histological architecture throughout all skin layers. Most lesions clear within 8 to 12 weeks of continuous daily therapy but plaque-like lesions respond better when etretinate is used in conjunction with PUVA therapy. Etretinate is well tolerated by most patients. However, dryness of skin and mucous membranes can be troublesome, while its association with cases of hepatotoxicity and raised blood lipids render it unsuitable in some patients. Of more general concern is the drug’s proven teratogenic potential. No woman of childbearing age should receive etretinate until pregnancy has been positively excluded and — having regard to its prolonged sequestration in fatty tissues — until she has agreed to use an effective method of contraception throughout the period of treatment and for at least 2 years after the last dose is taken.

Seborrhoeic dermatitis
Dandruff, an erythematous, greasy scaling eruption primarily involving the scalp, is the mildest form of seborrhoeic dermatitis and one of the most common of the chronic skin diseases. In its more florid forms, the lesions are more extensive and the inflammatory reaction is more intense.

Pityrosporum yeasts are presumed to play at least a facultative, and possibly a causative role in the development of seborrhoeic dermatitis. Androgens may also be involved since men are more frequently affected. Other factors, including fatigue, stress and infection are claimed to trigger some cases. An association has been established with other diseases, including Parkinson’s disease, epilepsy, cardiac failure, zinc deficiency and phenylketonuria.

Management
Application of keratolytic shampoos and exposure to ultraviolet light reduce both the inflammation and scaling.

Selenium sulfide is widely used as a keratolytic agent in many proprietary shampoos. A combination of sulfur and salicylic acid, which has an additional antimicrobial action, is also active.

Topical applications of the fungicidal agent, ketoconazole, are also reported to be effective. Because of the associated risk of hepatotoxicity, systemic administration of ketoconazole is not justified in the management of a benign condition that is likely to recur within a short period of time.

Alopecia areata
Alopecia areata is relatively common everywhere. It is characterized by patchy hair loss, usually on the scalp but sometimes elsewhere, within circumscribed oedematous areas of skin. “Exclamation point” hairs can be plucked out at the margins. Diffuse thinning of hair sometimes occurs in the early stages and, in severe cases, the lesions may extend and ultimately result in total hair loss. The lymphocytic T-cells, which are reduced in number in the peripheral circulation, appear to be involved in the cytotoxic process that destroys the hair follicles.

The condition can occur at any age but, typically, it first appears in early adult life, rather more frequently in men than in women. In some patients there is an apparent hereditary predisposition and it is often associated with other diseases: one quarter of the patients have atopic syndrome and less pronounced associations have been described with vitiligo, Down’s syndrome, and various autoimmune conditions including thyroid disease and polyglandular syndromes, lupus erythematosus and lichen ruber. In two-thirds of the cases, partial or complete regrowth of hair occurs within five years. After this time spontaneous recovery is unusual.

Management
The response to drug therapy is generally disappointing. The prospect for improvement is uncertain and beneficial results are often short-lasting. Localized regrowth of hair is sometimes stimulated by application of topical corticosteroids or of irritants such as dithranol and retinoic acid. In more severe cases systemic corticosteroids have been used but, given the dangers of this treatment and the uncertain response, even at high doses, it can rarely, if ever, be justified.

Patchy hair loss is sometimes a secondary manifestation of systemic disease. It is vital, particularly before corticosteroids are administered, to exclude autoimmune disorders and infectious diseases,
including syphilis. In general, drug therapy is not warranted in children and adolescents, nor in any patient in whom the condition is stable and the likelihood of spontaneous recovery is relatively high. In most cases, a wig or other cosmetic aid provides a more satisfactory solution.

**Pityriasis rosea**

Pityriasis rosea is a common self-limiting dermatosis that is presumed to be infective in origin. A prodromal episode of malaise, headache and sore throat often precedes the appearance of the characteristic annular erythematous herald plaque on the trunk, neck or upper limb. Within a few days, a symmetric rash commonly indistinguishable from that of secondary syphilis, becomes apparent, usually on the back. In Caucasians this rash rarely lasts for more than a few weeks, but in more deeply pigmented persons it may be more persistent and more extensive, often involving the face and distal extremities. In these cases scaling of the active lesions and post-inflammatory pigmentary changes can be particularly prominent.

**Management**

Specific treatment is neither available nor necessary but a serological test to exclude the possibility of syphilis should be undertaken whenever the diagnosis is in doubt. Calamine lotion effectively relieves pruritus in most cases, but topical application of hydrocortisone acetate in a concentration not exceeding 1% is occasionally justified in severe cases.

**Photodermatoses**

Exposure of skin to solar ultraviolet irradiation is beneficial in moderation since it is vital to the synthesis of vitamin D and hence to satisfactory skeletal development. Excessive exposure, however, is hazardous, particularly in light-skinned persons who tan poorly, and in patients with pathological sensitivity to sunlight.

The damage is most immediately evident as acute sunburn or, in the longer term, as premature aging of the skin. However, excessive exposure is also a predisposing factor in the development of malignant and pre-malignant skin lesions including solar keratosis, squamous cell carcinoma, basal cell carcinoma and malignant melanoma.

The incidence of these neoplastic conditions is particularly high among light-skinned persons living in hot sunny climates. Many cases could be prevented by persuading parents and those directly at risk of the importance of avoiding sunburn and reducing their exposure to solar radiation. The use of protective clothing — tightly woven fabrics, wide-brimmed hats, long sleeves and long trousers — is highly effective. When this is not practicable or acceptable, it is important to encourage regular use of sunscreen products with a protection factor rating of at least 15.

**Pathological photodermatoses**

Some patients react idiosyncratically to sunlight, either as a result of genetic predisposition or metabolic disease, or following exposure to specific drugs or chemicals.

**Solar urticaria**, which is probably immunologically mediated, is characterized by transient weals lasting from a few minutes to one hour. These may be single or multiple, and they develop within minutes or even seconds of exposure to strong sunlight. Antihistamines are of limited value, but long-term administration of chloroquine is claimed to increase the tolerance of the skin to sunlight.

**Polymorphic light eruptions** occur in vulnerable individuals within hours or days of exposure to sunlight and usually persist for several days. Irritating papules, which may coalesce into plaques, occur on exposed sites. The lesions, which frequently become excoriated, usually subside within 2–5 days if further exposure is avoided. Systemic use of antimalarials, which were once widely used to suppress intense inflammation, has now been largely superseded by topically-applied corticosteroids. Systemic corticosteroids are sometimes needed to treat severe and widespread eruptions.

**Actinic prurigo**, which occurs among people of American and Asian descent, is probably genetically determined. It first appears during childhood, and it regresses progressively and completely during adolescence and early adult life. Recurrent patchy oedematous erythema results in the formation of persistent excoriated plaques, papules and nodules. Cheilitis is a common feature, particularly during the early phases of the disease. Vesicles and small pitted scars sometimes develop on the face, while chronic conjunctivitis and pterygium formation are common among affected children in South America. Sunscreens, when used regularly, provide a useful measure of protection. The cutaneous signs are suppressed by thalidomide and, to a lesser extent, topical corticosteroids, but they recur within a few weeks of discontinuation of treatment.
**Hydroa vacciniforme** is a disease of childhood which becomes apparent toward the end of the first ten years of life and regresses spontaneously during adolescence. It is sometimes associated with atopy and, while several members of the same family are often affected, it has no clear genetic basis. Tense necrotic blisters and papules form where exposure to intense sunlight has induced oedematous erythema. This is followed by crusting and eventually by varioliform scars. These changes occur at intervals throughout periods of exposure and, over a period of several years, they become less intense and eventually cease. Chloroquine and beta carotene are reputed to be of value in suppressing the reaction but no comparative clinical trials have been undertaken.

**Chemical photodermatoses** are phototoxic reactions caused by sensitization to a systemically or topically administered inducing agent. Sulfonamides, salicylanilides, phenothiazines, quinoxaline dioxide, tar products, dyes, psoralens, plant constituents, fragrances, animal feeding stuffs, and topical sunscreens are most frequently responsible. Following sensitization, exposure to sunlight or other sources of ultraviolet radiation results in erythema, sometimes with oedema. All exposed skin areas may be affected if the sensitizing agent is ingested. Lesions resulting from topical application are usually limited to sites of chemical contact and blistering may be extensive. Symptomatic treatment with systemic antihistamines and acetylsalicylic acid can alleviate discomfort, pruritus and erythema. Prevention is dependent upon avoidance of contact with presumed causative agents.

**Ichthyosis**

Various factors, both hereditary and acquired, are determinants of ichthyosis, which is characterized by defective desquamation of the skin.

**Ichthyosis vulgaris**, an autosomal dominant disease which occurs worldwide, is the most common of the hereditary varieties. Small, rough, dry, whitish scales, which are most apparent on the extensor surfaces of the arms and legs, and to a lesser extent on the back, typically first appear during the first few years of life and tend to regress with age. About half the patients also have atopic dermatitis and other signs of atopy. The course of the disease is largely unpredictable, but it is often exacerbated by environmental factors and particularly by cold. In severe cases the cornified layer of the epidermis is greatly thickened, but the underlying granular layer is often thinned and sometimes absent.

**Sex-linked ichthyosis**, which is a recessive disorder, becomes apparent during infancy. It differs histologically and clinically from ichthyosis vulgaris. Larger, brownish scales thicken the cornified layer, but the granular layer remains essentially normal. With the exception of the central areas of the face, the palms and the soles, virtually all skin surfaces, including flexural regions, are affected and the front of the trunk tends to be more severely involved than the back. Corneal opacities frequently develop during adulthood, but they rarely impair visual acuity.

**Acquired ichthyosis** is most prevalent in tropical climates where it is associated with nutritional deficiency disorders, long-standing lepromatous leprosy and other debilitating infectious diseases. Clinically, it resembles ichthyosis vulgaris, but it develops later in life as a secondary manifestation of other diseases, and there is no evidence of familial predisposition.

**Treatment**

Simple precautionary measures are important. Detergents and other degreasing agents should be avoided. Baths should be tepid rather than hot, and soap should be used sparingly. Adequate protective clothing should be worn in cold weather and centrally-heated premises should be humidified.

An emollient such as propylene glycol should be applied weekly, or daily in more severe cases, to affected skin. The addition of a keratolytic, such as 5% salicylic acid or lactic acid can be helpful. Occlusion therapy using 60% propylene glycol in water is more effective in less responsive patients where circumstances permit. However, it is inappropriate where the climate is hot or conditions are unhygienic and, because of the risk of secondary infection, it should always be employed sparingly. In adverse conditions, a cream containing 10% urea, which is claimed to have moisturizing, keratolytic and antimitotic properties, may prove more effective than an emollient. Sodium chloride is sometimes added to augment the moisturizing effect.

Topical or systemic administration of retinoids, which have an antiproliferative action, are unlikely to be of value except in rare forms of ichthyosis in which hyperkeratosis is a consequence of hyperproliferation rather than defective desquamation.
Bullous dermatoses

These diseases, which are characterized by the formation of multiple blisters in the epidermis and mucous membranes, result from localized destruction of intercellular cement. This process of acantholysis, which ultimately results in failure of the barrier function of the skin, is mediated by autoantibodies directed against the cell surfaces of keratinocytes. The most prevalent clinical forms, which differ in their severity and prognosis, are pemphigus and dermatitis herpetiformis.

Pemphigus

Pemphigus vulgaris and a less severe variant, pemphigus foliaceus, in which the blisters are more superficial and mucous membranes are spared, are the most common variants of this condition. Occasionally, particularly after exposure to sunlight, the lesions become confluent and give rise to a form of exfoliative dermatitis. Pemphigus vulgaris is typically a disease of middle age. It is most prevalent in eastern India, in south-east Asia and among patients of Jewish descent. Elsewhere, it is rare. Occasional cases follow exposure to penicillamine or captopril and associations have also been described with thymoma, myasthenia gravis and other immunopathic conditions. Painful erosions in the mouth often precede skin lesions by several months. Fragile flaccid blisters develop in the deeper layers of the cutaneous epidermis in non-inflamed skin, typically on the scalp, chest and intertriginous areas. They extend readily on digital pressure and they often rupture giving rise to large areas of weeping denuded skin. Ulceration of mucosal surfaces is common and can be extensive. Untreated, most patients die within 5 years from secondary sepsis, electrolyte imbalance and emaciation.

Pemphigus vegetans is a clinically distinct variant of the disease in which skin lesions are largely limited to intertriginous areas and the scalp, and appear as crusted papillomatous lesions. In time, most cases progress to pemphigus vulgaris.

Treatment

The removal of skin debris from blistered areas is facilitated and the risk of secondary infection is reduced by regular four-hourly application of compresses soaked in either 5% aluminium diacetate or 0.1% potassium permanganate. Corticosteroids, which must be administered systemically at high dosage, offer the only means of holding the disease in check. Once the condition becomes stabilized, the dose is gradually attenuated to the minimum necessary to maintain quiescence. Commonly, prednisolone is administered orally at an initial dose of 500 mg daily. Once improvement is apparent the dose can usually be reduced rapidly to some 50 mg daily. Further cautious tapering of the dose over several months is often possible. Decrements should not exceed 5–10 mg within any 7-day period. Treatment needs to be maintained until the pemphigus antibody is no longer detectable in the blood and the initial dose should be reinstituted immediately should reactivation occur.

Concomitant use of immunosuppressive agents, such as azathioprine or cyclophosphamide, can be of value when the maintenance steroid requirement cannot otherwise be reduced to acceptable levels. The steroid sparing effect develops gradually and is rarely perceptible within 4 to 6 weeks. Corticosteroids should be withdrawn before the immunosuppressive agent is discontinued.

A high-calorie, high-protein diet is required for as long as the disease remains active. Fluid and electrolyte balance should be carefully monitored. Systemic antibiotics may be needed to treat secondary infections.

Bullous pemphigoid, which occurs in elderly patients, is less common and generally less severe than pemphigus. Spontaneous remission can occur and not all patients require systemic treatment. Tense blisters, which tend to heal spontaneously, form in inflamed skin in the axillary and inguinal folds. Their rupture does not result in large denuded areas of skin.

Treatment

Patients who need systemic therapy often respond to dapsone alone. In more severe cases corticosteroids are additionally required. As in the case of pemphigus, treatment should be continued until serum is clear of detectable antibody and then withdrawn gradually.

Dermatitis herpetiformis is a chronic, relatively benign disease that typically first appears in early adulthood and is characterized by alternating phases of activity and remission. Pruritic papular vesicles develop symmetrically on the buttocks and the extensor surfaces of the knees and elbows. The condition is often associated with gluten-sensitive
enteropathy and, in some cases at least, the disease appears to be an expression of sensitivity to dietary gluten or iodine.

**Treatment**

All patients require life-long treatment. Many respond adequately to a gluten-free diet alone, but others require long-term anti-inflammatory therapy. Most experience has been gained with dapsone which has been claimed to block the release of chemotactic factors from neutrophils. Used at an initial dose of 100 mg daily, it suppresses the formation of new lesions within 24-48 hours and dramatically reduces pruritus. However, its use is justified only when the quality of the patient's life is compromised since prolonged administration invariably induces a degree of haemolytic anaemia and methaemoglobinaemia. Dosage should be adjusted to the minimum that will suppress symptoms. In some cases the daily requirement is as high as 400 mg daily. Others remain in prolonged remission on as little as 25 mg daily.

**BENZOYL PEROXIDE**

**cream or lotion 2.5%, 5%, 10%**

Benzoyl peroxide is a keratolytic agent with bacteriostatic activity against *Propionibacterium acnes*.

It is absorbed to some extent by the skin after topical application and metabolized to benzoic acid.

**Uses**

Topical treatment of mild to moderate acne vulgaris and as an adjunct to therapy in more severe cases.

**Dosage and administration**

Apply to clean skin initially once daily, gradually increasing to twice daily as tolerance develops. It should not be applied to inflamed or broken skin.

**Contraindications**

Known hypersensitivity.

**Precautions**

Avoid contact with the eyes and mucous membranes.

**Adverse effects**

Irritation to the skin is common after topical application but subsides with continued treatment. Rarely, contact sensitivity has been reported.

**Storage**

Benzoyl peroxide should be stored in well-closed containers and should not be allowed to freeze.

**CALAMINE LOTION**

Calamine is a basic zinc oxide or carbonate coloured with ferric oxide. It has a mild astringent action on the skin.

**Uses**

Symptomatic topical treatment of mild pruritus.

**Dosage and administration**

Apply to affected skin 3-4 times daily.

**Contraindications**

Known hypersensitivity

**Precautions**

Avoid contact with the eyes and the mucous membranes of the mouth, nose, and genito-anal region.

**Storage**

Calamine lotion should be stored in well-closed containers in a cool place.

**CHLORPHENAMINE**

**tablet 4 mg (as hydrogen maleate)**

Chlorphenamine is a propylamine-derivative antihistamine. It reversibly and competitively inhibits the binding of histamine to H₁ receptors. It is well absorbed following oral administration and it is widely distributed throughout the body including the central nervous system. Plasma concentrations peak after 2-3 hours. It is metabolized in the liver and excreted in the urine, largely as metabolites.

**Uses**

Symptomatic treatment of urticaria. Severe and intractable pruritus.

**Dosage and administration**

Dosage of chlorphenamine should be adjusted according to the patient's response and tolerance. Adults and children over 12 years: 4 mg every 6 hours. Children under 12 years: 0.35 mg/kg daily administered in 4 divided doses.

**Contraindications**

Antihistamines should not be administered to neonates.

**Precautions**

The anticholinergic effects of chlorphenamine can cause drowsiness, dizziness, blurred vision and
psychomotor impairment. These effects can seriously impair the patient's ability to drive and use machinery.

Use in pregnancy
Safe use in pregnancy has not been established. Chlorphenamine should be used only when the need of the mother outweighs any possible harm to the fetus.

Adverse effects
The most common adverse effect is sedation which can vary from mild drowsiness to deep sleep but patients rapidly develop tolerance. Other unwanted central effects include dizziness, lassitude, incoordination and blurred vision. Paradoxical excitation in children and confusional states in the elderly have been reported.

Newer H₁ antagonists which do not cross the blood-brain barrier rarely produce these effects.

Gastrointestinal symptoms including anorexia, nausea, vomiting, epigastric distress, and constipation or diarrhoea are also common.

Drug interactions
Alcohol and other drugs acting on the central nervous system have an additive sedative effect. Phenytion toxicity has resulted from inhibition of its metabolism. Monoamine oxidase inhibitors intensify the anticholinergic effects.

Overdosage
Drowsiness, dizziness and ataxia are the most common symptoms of acute overdosage. Anticholinergic effects including flushing, dilated pupils and hyperthermia occur within 2 hours of ingestion. In serious cases, seizures are followed by respiratory and cardiovascular depression.

Emesis or gastric lavage followed by administration of activated charcoal is of value within a few hours of ingestion. Treatment is otherwise symptomatic and is directed to maintenance of respiration and treatment of seizures and cardiovascular abnormalities.

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

DAPSONE

*tablet 50 mg, 100 mg*

Dapsone, a sulfone, which is of prime importance in the treatment of leprosy is also used in the treatment of certain bullous dermatoses. The mechanism of action is unknown but it is claimed to block the release of chemotactic factors from neutrophils and may act as an immunomodulator.

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

Uses
Treatment of bullous pemphigoid and dermatitis herpetiformis.

Dosage and administration
*Adults:* 100 mg daily increased, as necessary, up to 400 mg daily until signs of remission are apparent. Continuous maintenance therapy, which is required in some cases, should be administered at the lowest dosage which prevents recurrence (25 mg daily).

Contraindications
Hypersensitivity to sulfones.
Pre-existing untreated severe anaemia should be treated first.

Precautions
Dapsone can induce haemolysis of varying degree, particularly in patients with glucose-6-phosphate dehydrogenase deficiency. Dose-dependent methaemoglobinaemia may supervene during the second week of treatment. Pre-existing anaemia should be corrected and the blood count must be closely monitored in susceptible patients during the first weeks of treatment.

Use in pregnancy
Safe use in pregnancy has not been established. Dapsone should be used in the treatment of dermatological disorders only when the need of the mother outweighs the potential risk to the fetus.

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

Blurred vision, paraesthesiae, reversible peripheral neuropathy, drug fever, skin rashes and psychoses have also been reported. Hepatitis, Herxheimer reactions and agranulocytosis may rarely occur.
Storage
Dapsone tablets should be kept in well-closed containers protected from light.

**DITHRANOL**
*ointment 0.1 to 2%*
Dithranol slows epidermal cell division and inhibits excessive proliferation and keratinization in patients with psoriasis. It is not significantly absorbed through the skin.

Uses
Topical management of moderately severe psoriasis.

Dosage and administration
Treatment should be started with the 0.1% ointment. After one week, the concentration may be increased to 0.25% and subsequently doubled, if necessary, at weekly intervals to a maximum strength of 2%. After application, the ointment should be left in place for up to 30 minutes.

Contraindications
Ointment should not be used on the face, on acute eruptions or excessively inflamed areas.

Precautions
If the initial treatment produces excessive soreness, or if the lesions spread, the frequency of application should be reduced, and in extreme cases discontinued.

Patients should be warned that staining of the skin and hair may occur and that some fabrics may be permanently stained.

Use in pregnancy
Safe use in pregnancy has not been established but no adverse effects have been reported.

Adverse effects
Contact with the eyes may cause conjunctivitis. Irritation is common.

Excessive erythema may occur on adjacent normal skin.

Storage
Dithranol ointment should be stored in tightly-closed containers protected from light.

**ERYTHROMYCIN**
*enteric coated tablets 250 mg (as stearate or ethylsuccinate)*

Erythromycin is a macrolide antibiotic produced by *Streptomyces erythreus*. It has a broad spectrum of bacteriostatic activity. *Inter alia*, it is active against *Propionibacterium acnes*.

Because it is inactivated by gastric juices, oral formulations are enteric-coated. It diffuses rapidly into all tissues except the brain and cerebrospinal fluid, and readily crosses the placental barrier. The plasma half-life is approximately 90 minutes. It is partially demethylated in the liver and is excreted largely via the bile and faeces.

Uses
Moderate to severe acne in patients in whom tetracyclines are contraindicated.

Dosage and administration
Adults: Initially 250 mg four times daily for 2 weeks followed by 250 mg twice daily until improvement occurs. Treatment may need to be continued for up to 6 months.

Contraindications
Known hypersensitivity.

Precautions
Hepatic function should be monitored in patients with a previous history of liver disease.

Cholestatic hepatitis, which may present with symptoms suggestive of acute cholecystitis, occasionally complicates prolonged courses of treatment. Symptoms resolve rapidly when the drug is withdrawn.

Anaphylaxis and other hypersensitivity reactions are rare.

Drug interactions
Erythromycin, chloramphenicol, and clindamycin, which have similar bacteriostatic actions tend to be mutually antagonistic when administered together. Erythromycin decreases the rate of metabolism of carbamazepine and warfarin in the liver to a degree that can warrant readjustment of dosage.

Overdosage
Symptoms of overdosage include severe nausea, vomiting, diarrhoea and hearing loss. Induction of emesis or gastric lavage may be of value if undertaken within a few hours of ingestion.
Storage
Capsules and tablets should be stored in tightly-closed containers.

ETRETINATE
capsules 10 mg
Etretinate is a synthetic, aromatic derivative of retinoic acid which inhibits keratinization, proliferation and differentiation of epithelial cells. It is especially effective in the treatment of severe forms of psoriasis, and severe congenital ichthyosis.

It is incompletely absorbed from the gastrointestinal tract after oral administration and is excreted in the urine largely as inactive metabolites. Both etretinate and its active metabolite, acitretin, have half-lives of about 100 days. They accumulate in fat and plasma after continuous administration and they have been detected in plasma 3 years after discontinuation of treatment.

Uses
Severe extensive psoriasis resistant to other forms of therapy.

Severe congenital ichthyosis.

Dosage and Administration
Because of its teratogenic potential and its prolonged sequestration, use of etretinate should only be considered for women of childbearing potential when all other treatments have been found to be ineffective.

Adults: 0.75 mg/kg daily in divided doses for 2–4 weeks. The dose may subsequently be increased, as necessary, up to 1 mg/kg. The total daily dose should never exceed 75 mg. Once signs of remission are apparent the dose should be reduced to 0.5 mg/kg daily in divided doses for a further 6–8 weeks.

Subsequent exacerbations may be treated intermittently, as necessary. Continuous maintenance therapy, which is required in some cases, should be administered at the lowest dosage which prevents recurrence (0.25–0.5 mg/kg daily).

Children: The same dosage recommendations as for adults apply but long-term maintenance therapy is not recommended.

Contraindications
Pregnancy and lactation.
Patients with hepatic or renal impairment.

Precautions
Women of childbearing potential must be informed and carefully counselled about the potentially teratogenic effects of etretinate. An effective method of contraception must be used continuously for a period extending from 2 months prior to treatment until at least 2 years after discontinuation. Liver function tests and blood lipids should be measured at the start of treatment and at 3-monthly intervals thereafter.

Diabetic patients may become unstable. Blood sugar concentrations should be checked frequently particularly at the start of therapy.

Adverse effects
Dryness of the mucous membranes, sometimes with erosion commonly involve the mouth, lips conjunctivae and nasal mucosa. Dryness of the skin may be associated with scaling, thinning, erythema and pruritus.

Reversible rises in serum levels of liver enzymes occur frequently and may necessitate dosage reduction or discontinuation of therapy. Acute hepatitis is a rare complication.

Blood lipids rise in about half the patients. Reduction of the dosage or discontinuation of therapy is often necessary in patients with other cardiovascular risk factors.

Skeletal hyperostosis and extraosseous calcification has been reported following long-term administration.

Overdosage
Symptoms of overdosage include severe headache, nausea, vomiting, drowsiness, irritability and pruritus. Emesis or gastric lavage is of value within a few hours of ingestion.

Storage
Capsules should be stored in well-closed containers, protected from light.

HYDROCORTISONE
ointment or cream 1% (acetate)
At this dosage hydrocortisone provides a topical corticosteroid preparation of low potency. Its therapeutic effects result from vasoconstriction, reduction of membrane permeability, and suppression of mitotic activity and the immune response.
Uses
Topical treatment of contact dermatitis, atopic dermatitis, lichen planus and intractable pruritus.
Phototoxic reactions, including polymorphous light eruptions and actinic prurigo.
Short-term treatment of psoriasis of the face, scalp, palms and soles.

Dosage and administration
A thin film should be applied to the affected area 1–4 times daily. When a favourable response is apparent, the frequency of application should be reduced to the minimum necessary to maintain control and avoid relapse. Treatment should be discontinued at the earliest opportunity.

The cream is suitable for most dermatoses, but ointments are often used for dry, scaly lesions. Occlusive dressings should be reserved for severe or resistant lesions; they should never be applied to weeping surfaces.

Contraindications
Known hypersensitivity.
Infections (bacterial, fungal or viral) at the intended site of application.

Precautions
Hydrocortisone is the least potent of the corticosteroids. Only when treatment with this preparation fails should the use of preparations containing more potent corticosteroids be considered.
The use of occlusive dressings facilitates penetration into keratinized lesions. Occlusion should be maintained for no longer than two days, and preferably at night only.

If secondary infection occurs the corticosteroid should be withdrawn and appropriate antimicrobial therapy should be given.

Use in pregnancy
Topical corticosteroids should not be used in large amounts or for prolonged periods during pregnancy.

Adverse effects
Corticosteroids exacerbate untreated infections. Prolonged use can induce skin atrophy, particularly on the face and in skinfolds. This is characterized by thinning of the dermis, depigmentation, dilatation of superficial blood vessels and formation of striae. Glaucoma may result after accidental contact with the eye.

Infants and young children are particularly susceptible to the local and systemic effects of topical corticosteroids. Prolonged use can result in hypercorticism and suppression of the hypothalamic-pituitary-adrenal axis.

Storage
Cream and ointment should be stored in well-closed containers.

METHOXSALEN
Capsule 10 mg
Methoxsalen is a psoralen derivative which occurs naturally in many plants but is prepared synthetically for therapeutic use. When exposed to ultraviolet A irradiation it forms photochemical conjugates with nucleic acid that inhibit DNA replication.

It is readily absorbed after oral administration and photosensitivity peaks 1–2 hours after ingestion. The drug is rapidly and extensively metabolized and is excreted in the urine.

Uses
Treatment of severe psoriasis refractory to topical therapy in conjunction with controlled exposure to UVA radiation (PUVA therapy).

Dosage and administration
Adults: 0.3–0.4 mg/kg administered 2 hours before exposure to UVA radiation. Twelve to twenty four sessions are usually necessary.

Contraindications
Hypersensitivity to psoralens.
Patients with diseases associated with photosensitivity including porphyria, acute systemic lupus erythematosus and hydroa vacciniforme.
Pregnancy.

Precautions
Treatment should be administered only under the supervision of a physician with special training in photochemotherapy.

Protective sunglasses should be worn during therapy and for the following 24 hours in order to avoid the risk of cataract formation.

Patients must be advised to avoid exposure to sunlight for at least 8 hours after therapy.

Adverse effects
Gastric discomfort occasionally occurs.
Cheilitis and transient loss of muscle coordination has been reported.

PUVA therapy carries an increased risk of cutaneous carcinoma in patients with predisposing factors.

Overdosage

Overdosage of methoxsalen or overexposure to ultraviolet light following methoxsalen administration can result in severe burning and blistering of the skin. The patient should be placed in a darkened room for at least 24 hours or until the cutaneous reaction has subsided, and supportive measures for the treatment of burns should be initiated. Emesis or gastric lavage is of value within a few hours of ingestion.

Storage

Capsules should be stored in well-closed containers, protected from light.

PREDNISOLONE

tablet 5 mg
injection 5 mg (as sodium phosphate or succinate) in vial

Prednisolone is a synthetic glucocorticoid with weak mineralocorticoid properties. Its therapeutic effect results from inhibition of macrophage accumulation, suppression of capillary wall permeability and oedema formation, and reduction of fibroblast proliferation and collagen deposition. It is readily absorbed from the gastrointestinal tract, is extensively protein-bound and has a plasma half-life of about 8 hours.

Uses

Bullous dermatoses
Atopic and contact dermatitis
Lichen planus
Photodermatoses pruritus

Dosage and administration

The lowest dosage to produce an acceptable clinical response should be used. Dosage is dependent upon the disease, its severity and the response to treatment.

In life-threatening conditions such as bullous dermatoses, dosage should start at 1 mg/kg daily and be raised progressively to about 5 mg/kg if a prompt response is not obtained.

In many other conditions dosages of 10–30 mg daily suffice.

During prolonged therapy, dosage may need to be incremented temporarily during periods of stress or in exacerbation of illness.

Withdrawal of treatment must be gradual to avoid adrenal insufficiency. Following prolonged treatment, decrements of as little as 1 mg monthly may be necessary.

Contraindications

Known hypersensitivity.

Prednisolone should not be used, except in life-threatening situations, in patients with active bacterial, viral or fungal infections.

Precautions

Patients must understand the importance of following dosage instructions rigorously.

Patients on long-term treatment must remain under close medical supervision. Weight, blood pressure, fluid and electrolyte balance and blood sugar should be monitored for as long as treatment is continued. Bone pain, and particularly backache, may be indicative of osteoporosis.

The response of the pituitary-adrenal axis to stress is reduced and may remain depressed for many months after withdrawal. Dosage may need to be doubled or reinstituted temporarily during this period if infection occurs.

Should a patient receiving, or having recently received long-term corticosteroid therapy require emergency surgery, parenteral hydrocortisone should be administered as follows:

- 200 mg i.m. with premedication;
- 100 mg infused i.v. in 500 ml saline during the procedure;
- 100 mg i.m. six-hourly for 72 hours.

Minor surgical procedures should be covered by 100 mg i.m. shortly before and after the intervention.

Corticosteroids should be used only for serious conditions in patients with diabetes, tuberculosis, peptic ulcer, hypertension, heart failure, epilepsy, a history of mental disorder or psoriasis. Patients with a history of tuberculosis should receive prophylactic chemotherapy during prolonged therapy.

Children on steroid therapy should receive a course of gamma globulin if they are exposed to a childhood virus infection to which they have no acquired immunity. They should not receive live virus vaccines.
Intermittent dosage regimens reduce the risk of stunted growth in children when steroid therapy is prolonged for more than six months.

**Use in pregnancy**
Corticosteroids should not be administered during pregnancy unless the need outweighs any possible risk of harm to the fetus. Adrenal development may be impaired and an association with cleft palate and other abnormalities has been described, particularly in the case of fluorinated compounds. Dosage should be kept as low as possible, but requirements may be raised slightly in replacement therapy as a result of increased binding of steroids to plasma proteins during pregnancy.

Corticosteroids are secreted into breast milk and breast-feeding should be avoided.

**Adverse effects**
Doses in excess of prednisolone 20 mg daily are immunosuppressive. Infections contracted during therapy can be overwhelming in the absence of effective treatment. Quiescent tuberculosis may be reactivated.

Continuous dosage in excess of normal physiological requirements (approximately 10 mg daily) is liable to result in:
- stunting of growth in children, which may be averted by giving corticotrophin and selecting alternate day dosage schedules;
- features of hypercorticism, including moonface, hirsutism, acne, bruising, striae, redistribution of fat, muscle wasting, hypertension;
- spinal osteoporosis and vertebral collapse, which may be retarded by calcium supplements and small doses of vitamin D;
- myopathy characterized by weakness of proximal musculature of arms and legs.

Fluid retention is not characteristic of prednisolone therapy since it has little mineralocorticoid activity.

Psoriasis may be seriously exacerbated on sudden withdrawal of corticosteroid therapy.

**Drug interactions**
Hepatic enzyme inducers including phenobarbitone, phenytoin and rifampicin may accelerate the metabolism of prednisolone.

The response to oral anticoagulants may be altered. Inhibition is characteristic, but isolated reports of potentiation are on record.

The incidence of gastrointestinal ulceration may increase when acetylsalicylic acid or nonsteroidal anti-inflammatory drugs are administered concomitantly.

The risk of hypokalaemia is increased when corticosteroids are taken concomitantly with potassium-losing diuretics.

**Overdosage**
A single large overdosage is unlikely to result in dangerous sequelae.

Symptomatic treatment is vital in the management of the adverse effects described above when they result from chronic poisoning.

**Storage**
Tablets should be stored in well-closed containers. Prednisolone sodium phosphate injection should be protected from light and freezing should be avoided.

**SELENIUM SULFIDE**

*Lotion 2.5%*

Selenium sulfide is a topical antimicrobial agent with antibacterial and mild antifungal activity. It is not absorbed following application to intact skin, but it is readily absorbed from damaged skin.

**Uses**
Topical treatment of seborrhoic dermatitis.

**Dosage**

*Seborrhoic dermatitis:*
5-10 ml of the lotion is massaged into the wet scalp and left for 2-3 minutes before rinsing off. This should be repeated twice weekly for 2 weeks.
**Contraindications**
Known hypersensitivity to selenium sulfide.
Children under 2 years.

**Precautions**
Selenium sulfide lotion should not be applied to damaged skin because of the risk of systemic toxicity.

Treatment should be discontinued if cutaneous sensitization occurs.

Contact with the eye should be avoided.

**Use in pregnancy**
Safe use in pregnancy has not been established. Treatment is best deferred until after delivery.

**Adverse effects**
Prolonged contact with the skin may cause local irritation.

Topical application to damaged skin can cause systemic toxicity characterized by tremors, weakness, lethargy, pain in the lower abdomen and occasional vomiting. These effects may be expected to resolve within 10 days of discontinuing treatment.

**Storage**
Selenium sulfide lotion should be stored in tightly closed containers in a cool place.

**SUNSCREENS**
*para-aminobenzoic acid, benzophenones*

Skin protection factor 15
Creams, lotions, gels

Sunscreens protect the cells of the skin by absorbing and reflecting solar radiation. They include *para-aminobenzoic acid* which absorbs UVB radiation only and benzophenones which absorb both UVB and some UVA radiation. The efficacy of a particular preparation is usually described as its sun protection factor (SPF). This is a ratio of the time required to produce minimal erythema with the sunscreen compared to the time without protection.

**Uses**
To prevent sunburn, actinic keratosis, premature ageing of the skin and skin cancer (basal and squamous cell carcinomas).

They may also provide some protection in photosensitive disorders.

**Dosage and administration**
Cream, lotion or gel should be applied generously, initially, to all exposed areas at least 1 hour before exposure to sunlight. It should be reapplied after swimming or profuse sweating.

**Precautions**
Contact sensitivity and photosensitivity may occur.

**Storage**
Store in well-closed containers protected from light.

**TAR PRODUCTS**
*solution 5%  ointment 1%*

Tar suppresses epidermal cell DNA synthesis and mitotic activity and restores a normal rate of proliferation.

A variety of tars, most commonly coal tar, is used to treat chronic skin disease.

**Uses**
Treatment of widespread, erythrodermic and guttate psoriasis either alone or in combination with ultraviolet light.

**Dosage and administration**
*Tar baths:* 100 ml of solution should be thoroughly mixed with bath water and the patient should soak for 10-20 minutes.

This may be repeated once every 3 days for at least 10 baths.

At least 24 hours should elapse before phototherapy is started and the tar preparation should be entirely removed from the skin.

**Contraindications**
Known hypersensitivity.

Tar preparations should not be applied to inflamed, broken or infected skin.

**Precautions**
Exposure to direct sunlight should be avoided for at least 24 hours after application because of the risk of photosensitivity reactions.

Although a potential carcinogen, there is no evidence that in the doses used therapeutically, coal tar preparations increase the risk of skin cancer.
Use in pregnancy
Safe use in pregnancy has not been demonstrated. Treatment should be deferred until after delivery whenever possible.

Adverse effects
Tar preparations are irritant and may rarely cause allergic sensitization.
Coal tar preparations produce photosensitivity reactions.
They frequently stain the skin and hair and consequently may not be well accepted by the patient.

Storage
Tar preparations should be stored in tightly closed containers, and protected from light. Freezing should be avoided.

TETRACYCLINE
capsule or tablet, 250 mg (hydrochloride) topical solution 2%

Tetracycline is a broad-spectrum antibiotic derived from a species of Streptomyces. It is selectively concentrated by susceptible bacteria and induces bacteriostasis by inhibiting protein synthesis.

Absorption from the gastrointestinal tract is always incomplete and can be further impaired by alkaline substances and chelating agents and particularly by milk and milk products, aluminium, calcium, magnesium and iron salts. Following topical application, the drug is absorbed to some extent. Peak plasma concentrations occur within 4 hours and decay with a half-life of about 8 hours. Excretion is effected primarily by glomerular filtration into the urine. Enterohepatic circulation gives rise to high concentrations in the liver and bile.

Tetracycline crosses the placenta and is excreted into breast milk.

Uses
Topical and systemic treatment of moderate to severe acne.

Dosage
Topical: Solution should be applied generously to clean affected skin twice daily.
Systemic: 250 mg four times daily for the first two weeks thereafter reducing the dose to 250 mg twice daily until the lesions are cleared. Treatment may have to be continued for up to 6 months.

As much as 2 g daily may be necessary for severe, recalcitrant acne.

Contraindications
Known hypersensitivity.
Pre-existing severe hepatic or renal damage.
Children under 8 years of age.

Precautions
Oesophagitis which can be troublesome, may be averted if the patient remains upright while the tablets are swallowed, and if they are always washed down immediately with a glass of water.

Tetracycline should be withdrawn if infective diarrhoea occurs.

Suprainfection of the bowel with resistant organisms can result in potentially fatal staphylococcal enteritis and pseudomembranous colitis.

Time-expired tetracycline capsules or tablets should be discarded. Degraded tetracycline has been reported to induce renal dysfunction indistinguishable from the Fanconi syndrome and skin lesions similar to those of systemic lupus erythematosus.

Use in pregnancy
Tetracycline is generally contraindicated in pregnancy. It impairs skeletal calcification in the fetus and can result in abnormal osteogenesis and hypoplasia of dental enamel. There is no evidence of teratogenicity with topical tetracycline, but it should be applied during pregnancy only when the need outweighs any possible harm to the fetus.

Adverse effects
Tetracycline is well tolerated following topical application. Local irritation may occur initially but subsides with continued treatment.

Following oral therapy, gastrointestinal irritation is common. So, also, is depletion of the normal bowel flora permitting overgrowth of resistant organisms. Irritative diarrhoea should be differentiated from enteritis due to suprainfection, particularly with positive staphylococci and pseudomembranous colitis due to Clostridium difficile.

Phototoxic reactions occasionally result in poikiloderma-like skin changes and pigmentation of the nails.

Pre-existing renal insufficiency may be aggravated. Acute renal failure and transient diabetes insipidus have been reported.
Skeletal deposition is a potential hazard to bone and tooth development during fetal life and childhood. Depression of bone growth is substantial, but readily reversible following short periods of exposure. Discoloration of teeth and enamel hypoplasia is permanent.

Hypersensitivity reactions are rare. Morbilliform rashes, urticaria, fixed drug eruptions, exfoliative dermatitis, cheilosis, glossitis, pruritus and vaginitis are described. Angioedema, anaphylaxis and pseudotumour cerebri have been reported.

Drug interactions
The action of oral anticoagulants may be potentiated. Severe renal failure has been reported in patients who have received a halogenated anaesthetic agent while receiving a tetracycline.

Storage
Tetracycline capsules, tablets or topical solution should be kept in well-closed containers, protected from light.
The case for self-sufficiency in drug control

Over 15 years have now passed since WHO published its first model list of essential drugs. The initiative was unanimously commended at the time by its Member States as providing a compelling and practicable basis for rationalizing drug markets throughout the developing world. However, it was cautiously acknowledged without commitment by an international industry loathe to countenance a radical constraint to the freedom of market forces.

With the passage of time, views have mellowed and the representative bodies of that industry have become increasingly supportive of the essential drugs concept both as a means of extending health coverage in developing countries and in applying the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce.

None the less, accusations remain unabated that standards of promotion by leading multinational companies frequently offend not only the truth but also basic public health interests. Distressing advertising copy is sometimes paraded to give credibility to the charges. But to what extent are these aberrations representative of prevailing standards at large in developing countries?

The message of Dr Milton Silverman and his colleagues merits particular respect. First-hand observation in a varied but representative group of developing countries has led Silverman to conclude that, all too often, improvement in drug distribution over the past few years has been more than offset by poverty and growth of populations; and that, wherever multinational companies have raised their standards, locally-based companies have emerged to exploit the situation. A decade or so after perceived dangers associated with drugs such as clioquinol, dipyrone, and phenylbutazone aroused reactive regulatory action in many industrialized countries, locally manufactured versions apparently now abound in the developing world without so much as a warning of potentially serious adverse effects.

These are accusations of fundamental importance. If they withstand the test of independent examination, they will demonstrate a reality that much consumer opinion in industrialized countries has long been reluctant to accept: countries vulnerable to abuse of their pharmaceutical markets cannot be effectively helped solely by applying exemplary pressures and boycotts on the far-distant head office of multinational companies. The countries at risk must be helped to help themselves through the development of effective pharmacy services and the creation of business-like national drug regulatory systems.

Where there are immediate and evident shortfalls in the availability of vital life-saving medicines, the call to build up national regulatory infrastructures takes second place. In the face of the widespread circulation of substandard, time-expired and fraudulently manufactured products, a measure of quality simply has to be assured if public confidence in national health care systems is not to become dangerously eroded.

The evidence that Dr Silverman now produces and the conclusions that he draws lend credence to WHO's efforts over the past years to establish practicable guiding principles for drug regulation in developing countries. Only some 25 years have passed since drug regulation in its current form started to evolve within Europe. Much was achieved in the early days with no more than a handful of motivated professionals. With the development of efficient international systems of information exchange, of national certification procedures to establish the authenticity and regulatory status of exported products, and the creation of simplified computerized information storage and retrieval systems to serve the registration process, the task has been greatly facilitated.

Much of value could stem from Silverman's analyses if he is found to be persuasive in identifying the principal targets for attention. The hope must be that he will sensitize and mobilize consumer opinion in general to the need for assisting all countries toward self-sufficiency in their responsibilities for effective drug control.

International Nonproprietary Names for Pharmaceutical Substances

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances*, the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended international Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Recommended International Nonproprietary Names (Rec. INN): List 32

Lists of proposed (1–65) and recommended (1–31) international nonproprietary names can be found in Cumulative List No. 8, 1992.

<table>
<thead>
<tr>
<th>Recommended International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description and Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>acidum aceneuramicum aceneuramic acid</td>
<td>(-)-5-acetamido-3,5-dideoxy-α-glycero-α-galacto-nonulosonic acid C₁₁H₁₉NO₉</td>
</tr>
<tr>
<td>adapalenum adapalene</td>
<td>6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid C₂₆H₂₅O₃</td>
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<td>aibifyllinium aibifiline</td>
<td>1-(5-hydroxy-5-methylthexyl)-3-methylxanthine C₁₉H₂₅N₄O₅</td>
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<td>alosetronum alosétron</td>
<td>2,3,4,5-tetrahydro-5-methyl-2-[(5-methylimidazol-4-yl)methyl]-1H-pyrido[4,3-B]indol-1-one C₁₇H₁₈N₄O₃</td>
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<tr>
<td>amrubicinum amrubicin</td>
<td>(±)-(7S,9S)-9-acetyl-9-amino-7-[(2-deoxy-β-D-erythro-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione C₂₃H₂₅NO₉</td>
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<td>amtolmetinum guacil amtolmetin guacil</td>
<td>N-[(1-methyl-5-p-toluoylpyrrol-2-yl)acetyl]glycine α-methoxyphosphoryl ester C₁₈H₂₂N₂O₅</td>
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<tr>
<td>araprofenum arapofen</td>
<td>(±)-p-(α-carboxyanilino)hydratropic acid C₁₆H₁₂N₂O₄</td>
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<td>atenololum atenolol</td>
<td>2-[p-(2-hydroxy-3-[[isopropylamino]propoxy]phenyl]acetamide C₁₆H₁₂N₂O₅</td>
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<table>
<thead>
<tr>
<th><strong>Recommended International Nonproprietary Name</strong></th>
<th><strong>Chemical Name or Description and Molecular Formula</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>atovaquonum atovaquone</td>
<td>2-{(\text{trans}-4-{\text{p}-\text{chlorophenyl}}\text{cyclohexyl})-3\text{-hydroxy-1,4-naphthoquinone} } C_{22}H_{19}ClO_{3}</td>
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</table>
| batebulastum batebulast | \(p\)-\text{tert-butyl}phenyl \text{trans}-4-(\text{guanidinomethyl})\text{cyclohexanecarboxylate} \} C_{24}H_{28}N_{2}O_{2} |}
| batebulastum batebulast | \((\pm)\)-1-\{\text{o}-\text{chloro-a}-\{5\text{-chloro-2-benzofuranyl}\text{benzyl}\text{imidazole} \} C_{18}H_{12}Cl_{2}N_{2}O_{2} |}
| becloconazolum becloconazole | \((R)\)-5-(\text{methoxymethyl})-3-\{\text{p}-\{(R)\}-4,4,4\text{-trifluoro-3-hydroxybutoxy}\text{phenyl}\}-2\text{-oxazolidinone} \} C_{18}H_{18}F_{3}N_{2}O_{5} |}
| becloxatonum becloxatone | mouse T2G1s cell anti-human fibrin \(\beta\)-chain monoclonal immunoglobulin G Fab' fragment |}
| biciromabum biciromab | mouse T2G1s cell anti-human fibrin \(\beta\)-chain monoclonal immunoglobulin G Fab' fragment |}
| binostronum binostrine | \((\pm)\)-N-\{2-\{1,4\text{-benzodioxan-2-ylmethyl}amino\text{ethyl}\}-1,1\text{-cyclopentanediacetimide} \} C_{26}H_{26}N_{2}O_{4} |}
| binostronum binostrine | 5-bromo-6-(2-imidazolidinylidenamino)quinoxaline \} C_{17}H_{10}BrN_{5} |}
| brimonidinum brimonidine | 5-bromo-6-(2-imidazolidinylidenamino)quinoxaline \} C_{17}H_{10}BrN_{5} |}
| calcii levofolinas calcium levofoline | calcium \text{N-\{p-[[\{(6S)\}-2\text{-aminomethyl-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl}\text{methyl}][amino]benzoyl]-L-glutamate} (1:1) \} C_{19}H_{14}CaN_{7}O_{7} |}
| calteridolum calteridol | hydrogen [(\pm)-10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate(3)]calciate(1) \} C_{31}H_{50}CaN_{4}O_{7} |}
| casokefamidum casokefamide | \(-\)-\text{tyrosyl-D-alanyl-L-phenylalanyl-D-alanyl-L-tyrosrinamide} \} C_{33}H_{40}N_{6}O_{7} |}
| cebxaratelum cebxaratam | \((\pm)\)-4-\{\text{p}-\text{chlorophenyl}\}-2-\text{oxo-1-pyrrolidinyl}[acetyl]-2-piperazinone \} C_{16}H_{18}ClN_{5}O_{5} |}
| cefditorenum cefditoren | \((\pm)\)-\{(6R,7R)-7-\{2-(2\text{-amino-4-thiazolyl})\text{glyoxylamido}\}-3-\{(Z)\}-2-(4\text{-methyl-5-thiazolyl}vinyl)-8-\text{oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,} \text{7}\{-\{(Z)\}-\text{(O-methyloxime)} \} C_{19}H_{16}N_{5}O_{3}S_{3} |}
| cefozopranum cefozopran | \((-\)-(6R,7R)-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-ylmethyl]-1H-\text{imidazol}[1,2-b]pyridazin-4-ium hydroxide inner salt, 7\{-\{(Z)\}-\text{(O-methyloxime)} \} C_{20}H_{17}N_{5}O_{3}S_{2} |}
<table>
<thead>
<tr>
<th>Recommended International Nonproprietary Name</th>
<th>Chemical Name or Description and Molecular Formula</th>
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<tr>
<td>celmoleukinum</td>
<td>interleukin 2 (human clone pTIL2-21a, protein moiety)</td>
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<td>celmoleukin</td>
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<td>$(\pm)-(E)$-cinnamyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-([m-nitrophenyl]-3,5-pyridinedicarboxylate</td>
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<td>cilnidipine</td>
<td>$C_{27}H_{32}N_2O_7$</td>
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<td>cioteronelum</td>
<td>$(\pm)-(S)$-hexahydro-4-(5-methoxyheptyl)-2(1H)-pentalenone</td>
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<td>cioteronel</td>
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<td>dapoxetineum</td>
<td>$(\pm)-(S)$-[N,N-dimethyl-α-[2-(1-naphthyl)oxy]ethyl]benzylamine</td>
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<td>dapoxetine</td>
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<td>deramciclanum</td>
<td>$N,N$-dimethyl-2-[[1R,2S,4R]-2-phenyl-2-bornyl]oxy]ethylamine</td>
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<td>deramciclane</td>
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<td>deriglidoled</td>
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<td>dexfosfoserinum</td>
<td>L-serine dihydrogen phosphate (ester)</td>
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<td>dexfosferosine</td>
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<td>dexloxiglumidum</td>
<td>$\text{(R)}$-4-(3,4-dichlorobenzamido)-N-(3-methoxypropyl)-N-pentylglutamic acid</td>
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<td>dexloxiglumide</td>
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<td>$(\pm)-(S)$-2-[2-(dimethylamino)ethyl]-3,4-dihydro-2-phenyl-1(2H)-naphthalene</td>
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<td>dexnafenodone</td>
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<td>dexverapamilum</td>
<td>$(\pm)-(R)$-5\text{-(3,4-dimethoxyphenethyl)methy lamino\text{-2-(3,4-dimethoxyphenyl\text{-2-isopropylvaleronitrile}}</td>
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<td>dexverapamil</td>
<td>$C_{25}H_{30}N_2O_4$</td>
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<td>dolasetronum</td>
<td>indole-3-carboxylic acid, ester with (8R)-hexahydro-8-hydroxy-2,6-methano-2H-quinolinizin-3(4H)-one</td>
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<td>dolasetron</td>
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<td>dorlimomab aritoxum</td>
<td>ricin A chain-antibody ST 1 F(ab')2 fragment immunotoxin</td>
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<td>dorlimomab aritox</td>
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<td>efonidipinum</td>
<td>2-(N-benzylanilino)ethyl $(\pm)$-1,4-dihydro-2,6-dimethyl 4-([m-nitrophenyl]-5-phosphonononolate, cyclic 2,2-dimethyl(trimethylene ester</td>
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<td>egualen</td>
<td>$C_{13}H_{14}O_5S$</td>
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<td>eliprodilum eliprodil</td>
<td>(±)-α-(p-chlorophenyl)-4-(p-fluorobenzyl)-1-piperidineethanol</td>
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<td>eltanolonum eltanolone</td>
<td>3α-hydroxy-5β-pregnan-20-one</td>
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<td>emakalimum emakalim</td>
<td>(−)-(3S,4R)-3-hydroxy-2,2-dimethyl-4-(2-oxo-1(2H)-pyridyl)-6-chromancarbonitrile</td>
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<td>emitelurum emitelur</td>
<td>m-[[3-(ethoxymethyl)-5-fluoro-3,6-dihydro-2,6-dioxo-1(2H)-pyrimidinyl]-carbonyl]benzoic acid, 2-ester with 2,6-dihydroxynicotinonitrile, benzoate (ester)</td>
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<td>entacaponum entacapone</td>
<td>(E)-α-cyano-N,N-diethyl-3,4-dihydroxy-5-nitrocinnamamide</td>
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<td>ersoferminum ersofermin</td>
<td>N-[N-glycyl-L-threonyl] basic fibroblast growth factor (human clone λKB7/λHFL1 precursor reduced)</td>
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<td>espatropatum espatrope</td>
<td>(R)-3-quinuclidinyl (R)-α-(hydroxymethyl)-α-phenylimidazole-1-acetate</td>
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<td>etonogestrelum etonogestrel</td>
<td>13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one</td>
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<td>exemestanum exemestane</td>
<td>6-methyleneandrosta-1,4-diene-3,17-dione</td>
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<td>fluazuronum fluazuron</td>
<td>1-[4-chloro-3-[[3-chloro-5-((trifluoromethyl)-2-pyridyl)oxy]phenyl]-3-(2,6-difluorobenzoyl)urea</td>
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<td>formestanum formestane</td>
<td>4-hydroxyandrost-4-ene-3,17-dione</td>
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<td>gadobutrolum gadobutrol</td>
<td>[16-[[1RS,2SR]-2,3-dihydroxy-1-[hydroxymethyl]propyl]-1,4,7,10-tetra-azacyclododecane-1,4,7-triacetato(3-)]gadolinium</td>
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<tr>
<td>galocitabinum galocitabine</td>
<td>N-[1-(5-deoxy-β-α-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinyl]-3,4,5-trimethoxybenzamide</td>
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<td>ganirelixum ganirelix</td>
<td>N-acetyl-3-[2-naphthyl-5-alanyl-4-chloro-3-phenylalanyl-3-(3-pyridyl)-α-alanyl-l-seryl-lysyl]-N6-(N,N-diethylamidino)-N-lysyl-l-leucyl-N6-(N,N-diethylamidino)-N-lysyl-l-prolyl-S-alaninamide</td>
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<tr>
<td>Recommended International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description and Molecular Formula</td>
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<tr>
<td>---------------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
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</tbody>
</table>
| idraprilum | idrapril | (1S,2R)-2-[[hydroxycarbamoyl]methyl]methylcarbamoyl]cyclohexane = carboxylic acid  
\[C_{11}H_{16}N_2O_3\] |
| ilatreotidum | ilatreotide | \(N\)-(1-deoxy-4-O-\(\alpha\)-D-glucopyranosyl-\(\alpha\)-fructofuranos-1-yl)-\(\alpha\)-phenylalanyl-\(\gamma\)-cysteinyl-\(\gamma\)-phenylalanyl-\(\gamma\)-tryptophyl-\(\gamma\)-lysyl-\(\gamma\)-threonyl-\(N\)-(1\(R\),2\(R\))-2-hydroxy-1-(hydroxymethyl)propyl]-\(\gamma\)-cysteinamide cyclic (2\(\rightarrow\)7)-disulfide  
\[C_{61}H_{86}N_{10}O_{20}S_2\] |
| imciromabum | imciromab | mouse R11D10 cell monoclonal \(\kappa\)-chain containing immunoglobulin G2a, anti-human cardiac myosin heavy chain |
| imiquimodum | imiquimod | 4-amino-1-isobutyl-1\(H\)-imidazo[4,5-c]quinoline  
\[C_{14}H_{12}N_4\] |
| iomazenilum (\(^{123}\)I) | iomazenil (\(^{123}\)I) | ethyl 5,6-dihydro-7-iodo-\(^{123}\)I-5-methyl-6-oxo-4\(\text{H}\)-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate  
\[C_{15}H_{14}I_{23}N_3O_3\] |
| isomolpanum | isomolpan | \((\pm)-\text{trans-1,3,4,4a,5,10b-hexahydro-4-propyl-2H-[1]benzopyrano[3,4-b]pyridin-9-ol}\)  
\[C_{15}H_{21}NO_2\] |
| itopridum | itopride | \(N\)-[p-[2-(dimethylamino)ethoxy]benzyl]veratramide  
\[C_{16}H_{26}N_2O_4\] |
| ketaminum | ketamine | 2-(o-chlorophenyl)-2-(methylamino)cyclohexanone  
\[C_{13}H_{16}CINO\] |
| lamivudinum | lamivudine | \((-\text{-1-}[2(R,5R)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine}\)  
\[C_{9}H_{11}N_{3}O_{3}\] |
| lanoconazolum | lanoconazole | \((\pm)-\alpha-[4-(\text{o-chlorophenyl})-1,3-dithiolan-2-ylidene]imidazole-1-acetonitrile\)  
\[C_{16}H_{10}CIN_{6}S_{2}\] |
| lazabemidum | lazabamide | \(N\)-(2-aminoethyl)-5-chloropicolinamide  
\[C_{8}H_{9}ClN_{3}O\] |
| lesopitronum | lesopitron | 2-[4-[4-(4-chloropyrazol-1-yl)butyl]-1-piperazinyl]pyrimidine  
\[C_{19}H_{21}ClN_{6}\] |
| levromakalium | levromakalim | \((35,4R)-3\text{-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-6-chromancarbonitrile}\)  
\[C_{19}H_{18}N_2O_{3}\] |
| levcycloserinum | levcycloserine | \((S)-4\text{-amino-3-isoxazolidinone}\)  
\[C_{3}H_{4}N_{2}O_{2}\] |
| levdobutaminum | levdobutamine | \(4\text{-}[2\text{-}[[S]-3\text{-}[(\text{p-hydroxyphenyl})\text{-1-methylpropyl}]amino]ethyll]pyrocatechol}\)  
\[C_{14}H_{19}NO_{3}\] |
<table>
<thead>
<tr>
<th>Recommended International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description and Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>lexithromycinum lexithromycin</td>
<td>erythromycin 9-[(O-methyloxime)</td>
</tr>
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<td></td>
<td>C_{26}H_{39}N_{12}O_{13}</td>
</tr>
<tr>
<td>lifarizinum lifarizine</td>
<td>1-(diphenylmethyl)-4-[(5-methyl-2-p-tolylimidazol-4-yl)methyl]pipерazine</td>
</tr>
<tr>
<td>linarotenum linarotene</td>
<td>5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl-2'-acetanaphthone (E)-[p-(methysulfonyl)phenyl]hydrazone</td>
</tr>
<tr>
<td></td>
<td>C_{27}H_{39}N_{2}O_{5}</td>
</tr>
<tr>
<td>lintopridum lintopride</td>
<td>4-amino-5-chloro-N-[(1-ethyl-2-imidazolin-2-yl)methyl]-o-anisamide</td>
</tr>
<tr>
<td>lobarplatinum lobarplatin</td>
<td>cis-[trans-1,2-cyclobutanedis(methylamino)][(S)-lactato-O',O']platinum</td>
</tr>
<tr>
<td>lobarplatin</td>
<td>C_{32}H_{27}ClN_{4}O_{2}</td>
</tr>
<tr>
<td>losartanum losartan</td>
<td>2-butyl-4-chloro-1-[p-((o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol</td>
</tr>
<tr>
<td>lufenuronum lufenuron</td>
<td>1-[2,5-dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-3-(2,6-difluorobenzoyl)urea</td>
</tr>
<tr>
<td></td>
<td>C_{20}H_{17}ClF_{15}N_{2}O_{3}</td>
</tr>
<tr>
<td>marbofloxacinum marbofloxacin</td>
<td>9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[3,2,1-ij][4,1,2]benzoxadiazine-5-carboxylic acid</td>
</tr>
<tr>
<td></td>
<td>C_{17}H_{19}FN_{4}O_{4}</td>
</tr>
<tr>
<td>maslimomabum maslimomab</td>
<td>mouse monoclonal Immunoglobulin G2b, anti-human T-cell receptor αβ chain</td>
</tr>
<tr>
<td>mecaserminum mecaserin</td>
<td>insulin-like growth factor I (human)</td>
</tr>
<tr>
<td></td>
<td>C_{215}H_{321}N_{54}O_{91}S_{7}</td>
</tr>
<tr>
<td>miboplatinum mibopatin</td>
<td>(−)-cis-<a href="1,1-cyclobutanedicarboxylato">(R)-2-(aminomethyl)pyrrolidine</a> = platinum</td>
</tr>
<tr>
<td></td>
<td>C_{11}H_{18}N_{2}O_{4}Pt</td>
</tr>
<tr>
<td>mirimostimun mirimostim</td>
<td>1-214-colony-stimulating factor 1 (human clone p3ACSF-69 protein moiety reduced), homodimer</td>
</tr>
<tr>
<td></td>
<td>C_{1008}H_{185}N_{337}O_{345}S_{14}</td>
</tr>
<tr>
<td></td>
<td>(for non-glycosylated protein)</td>
</tr>
<tr>
<td>modipafantum modipafant</td>
<td>ethyl (+)-(R)-4-((o-chlorophenyl)-1,4-dihydro-6-methyl-2-([p-2-methyl-1H-imidazo[4,5-c]pyridin-1-yl]phenyl)-5-(2-pyridylcarbamoyl)nicotinate</td>
</tr>
<tr>
<td></td>
<td>C_{33}H_{44}ClN_{8}O_{8}</td>
</tr>
<tr>
<td>mosapridum mosapride</td>
<td>(±)-4-amino-5-chloro-2-ethoxy-N-[(4-(p-fluorobenzyl)-2-morpholinyl) = methyl]benzamidie</td>
</tr>
<tr>
<td></td>
<td>C_{21}H_{25}ClFN_{3}O_{8}</td>
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<tr>
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<tr>
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<td>--------------------------------------------------</td>
</tr>
<tr>
<td>nafamostatum nafamostat</td>
<td>6-amidino-2-naphthyl p-guanidinobenzoate or p-guanidinobenzoic acid, ester with 6-hydroxy-2-naphthamidine C_{13}H_{17}N_{4}O_{2}</td>
</tr>
<tr>
<td>naglivanum naglivan</td>
<td>bis[2-amino-3-mercaptop-5-octylpropionamidato(1-)-S]oxovanadium C_{22}H_{46}N_{6}O_{4}S_{2}V</td>
</tr>
<tr>
<td>nartograstimum nartograstim</td>
<td>N-[4-methionyl-1-L-alanine-3-L-threonine-4-L-tyrosine-5-L-arginine-17-L-serine = colony-stimulating factor (human clone 1034) C_{809}H_{1344}N_{226}O_{245}S_{8} (for non-glycosylated protein)</td>
</tr>
<tr>
<td>nebacumabum nebacumab</td>
<td>immunoglobulin M (human monoclonal HA-1A anti-endotoxin), disulfide with human monoclonal HA-1A a-chain, pentameric dimer</td>
</tr>
<tr>
<td>necopidenum necopidem</td>
<td>N-[2-(p-ethylphenyl)-6-methylimidazo[1,2-a]pyridin-3-yl]methyl]-N,3-dimethylbutyramide C_{23}H_{29}N_{3}O</td>
</tr>
<tr>
<td>nelfinavirum nelfinavir</td>
<td>2-oxo-1-pyrrolidineaceto-2',6'-xylidide C_{14}H_{18}N_{2}O_{2}</td>
</tr>
<tr>
<td>nevirapinum nevirapine</td>
<td>11-cyclopropyl-5,11-dihydro-4-methyl-5H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-8-one C_{14}H_{16}N_{4}O</td>
</tr>
<tr>
<td>orlistatum orlistat</td>
<td>N-[formyl-L-leucine, ester with (3S,4S)-3-hexyl-4-[(2S)-2-hydroxytridecyl]-2-oxetanone C_{29}H_{52}NO_{4}</td>
</tr>
<tr>
<td>paracetamolum paracetamol</td>
<td>3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5-isopropylimidazo[1,5-a]quinoxalin-4(5H)-one C_{19}H_{18}N_{4}O</td>
</tr>
<tr>
<td>paracetamol paracetam</td>
<td>(±)-4'-[(2-methyl-4-oxo-1,3-benzodioxan-2-yl)oxy]acetanilide C_{17}H_{18}NO_{3}</td>
</tr>
<tr>
<td>perflubronum perflubron</td>
<td>1-bromoheptadecafluorocyclooctane C_{4}BrF_{17}</td>
</tr>
<tr>
<td>perflubron perflubron</td>
<td>(±)-cis-2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorin-4-yl hydroperoxide, P-oxide C_{19}H_{14}O_{3}N_{6}P</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Recommended International Nonproprietary Name (Latin, English)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>pirsidominum pirsidomine</td>
<td>( N\text{-p-anisoyl-3-(cis-2,5-dimethyl(piperidino)sydnone imine} ) C_{17}H_{29}N_{6}O_{6}</td>
</tr>
<tr>
<td>piva gabuminum piva gabine</td>
<td>4-pivalamidobutyric acid C_{9}H_{15}NO_{3}</td>
</tr>
<tr>
<td>plomestanum plomestane</td>
<td>10-(2-propynyl)estr-4-ene-3,17-dione C_{29}H_{30}O_{2}</td>
</tr>
<tr>
<td>polaprezincum polaprezinc</td>
<td>\text{catena-poly[zinc-\mu{-[\beta\text{-alanylL-histidinato(2\text{-})\text{-N,N,N',O:N'}}}] (C_{6}H_{12}N_{4}O_{3}Zn)_{n}}</td>
</tr>
<tr>
<td>polifeprosanum polifeprosan</td>
<td>4.4\text{-}(trimethylenedioxy)\text{ibenoic acid, polymer with sebacic acid} \text{“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”.} (C_{17}H_{16}O_{8})<em>{m}(C</em>{10}H_{18}O_{4})_{n}</td>
</tr>
<tr>
<td>poliglecapronum poliglecaprone</td>
<td>2-oxepanone polymer with p-dioxane-2,5-dione \text{“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_{6}H_{10}O_{2})<em>{m}(C</em>{4}H_{4}O_{4})_{n}</td>
</tr>
<tr>
<td>poliglusamum poliglusam</td>
<td>chitosan</td>
</tr>
<tr>
<td>pranidipinum pranidipine</td>
<td>(E)-cinnamyl methyl (\pm\text{-})-1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyrildenedicarboxylate C_{20}H_{24}N_{4}O_{6}</td>
</tr>
<tr>
<td>racephedrinum racephedrine</td>
<td>(\pm\text{-})-ephedrine C_{10}H_{15}NO</td>
</tr>
<tr>
<td>remikirenun remikiren</td>
<td>\text{(αS)\text{-α-[(αS)\text{-α-[(tert-butylsulfonyl)methyl]hydrocinnamamido}-N-[(1S,2R,3R)-1-cyclohexylmethyl]-3-cyclopropyl-2,3-dihydroxypropyl]imidazole-4-propionamide} C_{33}H_{50}N_{4}O_{6}S</td>
</tr>
<tr>
<td>remiprostolum remiprostol</td>
<td>\text{(±\text{-})-methyl (Z)-7-[(1R,2R,3R)-2-[(1E,5E)-(4RS)-6-(1-cyclopanont-1-yl)-4-hydroxy-4-methyl-1,5-hexadienyl]-3-hydroxy-5-oxocyclopentyl]-4-heptenoate} C_{28}H_{30}O_{5}</td>
</tr>
<tr>
<td>repaglinidium repaglinide</td>
<td>\text{(±\text{-})-2-ethoxy-α-[(3S,4R)-3-hydroxy-2,2-dimethyl-6-(phenylsulfonyl)-4-chromanyl]-2-pyrrolidinone} C_{27}H_{22}NO_{5}S</td>
</tr>
<tr>
<td>riilmakalimun riilmakalin</td>
<td>\text{(±\text{-})-1-[3(S,4R)-3-hydroxy-2,2-dimethyl-6-(phenylsulfonyl)-4-chromanyl]-2-pyrrolidinone} C_{27}H_{22}NO_{5}S</td>
</tr>
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<tr>
<td>-----------------------------------------------------</td>
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</tr>
<tr>
<td>rocuronii bromidum rocuronium bromide</td>
<td>1-allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-androstan-16β-yl)pyrrolidinium bromide, 17-acetate C_{28}H_{43}BrN_{2}O_{4}</td>
</tr>
<tr>
<td>rogletimidum rogletimide</td>
<td>(±)-2-ethyl-2-(4-pyridyl)glutarimide C_{11}H_{14}N_{2}O_{2}</td>
</tr>
<tr>
<td>rolafagrelum rolafagrel</td>
<td>5,6-dihydro-7-imidazol-1-yl-2-naphthoic acid C_{13}H_{20}O_{2}</td>
</tr>
<tr>
<td>romergolinum romergoline</td>
<td>4-[(9,10-didehydro-6-methyl Ergolin-8β-yl)methyl]-2,6-piperazinedione C_{20}H_{22}N_{4}O_{2}</td>
</tr>
<tr>
<td>sargramostinium sargramostim</td>
<td>23α-leucine colony-stimulating factor 2 (human clone pHG25 protein moiety) C_{329}H_{1002}N_{168}O_{196}S_{8} (for non-glycosylated protein)</td>
</tr>
<tr>
<td>seproxetinum seproxetine</td>
<td>(S)-3-phenyl-3-[[a,a,a-trifluoro-p-tolyloxy]propylamine C_{16}H_{16}F_{3}NO</td>
</tr>
<tr>
<td>sevirumabum sevirumab</td>
<td>human monoclonal immunoglobulin G1, x-chain, anti-cytomegalovirus</td>
</tr>
<tr>
<td>sitaprazinium sitapazine</td>
<td>1-methyl-4-[(a-phenyl-o-tolyl)piperazine C_{16}H_{22}N_{2}</td>
</tr>
<tr>
<td>sitleplasum sitleplase</td>
<td>N-[M-(N-glycyl-L-alanyl)-L-arginyl]plasminogen activator (human tissue-type protein moiety reduced), glycoform C_{2250}H_{3948}N_{752}O_{784}S_{40} (for non-glycosylated protein)</td>
</tr>
<tr>
<td>simendanum simendan</td>
<td>mesoxalonitrile (±)-[p-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazone C_{14}H_{12}N_{6}O_{8}</td>
</tr>
<tr>
<td>somfaseporum somfasepor</td>
<td>8-190 growth hormone (pig) C_{92}H_{148}N_{27}O_{27}S_{6}</td>
</tr>
<tr>
<td>tacalcitolum tacalcol</td>
<td>(+)-[5Z,7E,24R]-9,10-secocholesta-5,7,10(19)-triene-1α,3β,24-triol C_{27}H_{44}O_{3}</td>
</tr>
<tr>
<td>tacrolimusum tacrolimus</td>
<td>(±)-(3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-8-allyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26a-hexadecahydro-5,19-dihydroxy-3-[(E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxy-cyclohexyl]-1-methyl-vinyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxa-azacyclotricosine-1,7,20,21(4H,23H)-tetraone C_{44}H_{69}NO_{12}</td>
</tr>
<tr>
<td>tamolarizinum tamolarizine</td>
<td>(±)-a-(3,4-dimethoxyphenyl)-4-(diphenylmethyl)-1-piperazineethanol C_{27}H_{45}N_{2}O_{5}</td>
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<tr>
<td>telimomab aritoxum</td>
<td>ricin A chain-antibody T 101 Fab fragment immunotoxin</td>
</tr>
<tr>
<td>telimomab aritox</td>
<td></td>
</tr>
<tr>
<td>terdecamycin</td>
<td></td>
</tr>
<tr>
<td>terlakirennum</td>
<td>isopropyl ((\alpha R,\beta S))-\alpha-hydroxy-\beta-[(\alpha R)-3-(methylthio)-2-[(S)-\alpha-4-morpholinecarboxamidohydrocinnamamido]propionamido] = cyclohexanebutyrate</td>
</tr>
<tr>
<td>terlakiren</td>
<td></td>
</tr>
<tr>
<td>tetrofosminum</td>
<td>ethylenebis([\text{bis}(2\text{-ethoxyethyl})\text{phosphine}])</td>
</tr>
<tr>
<td>tetrofosmin</td>
<td></td>
</tr>
<tr>
<td>tinzaparinum natricum</td>
<td>Sodium salt of depolymerized heparin obtained by heparinase from \textit{Flavobacterium heparinum} (heparin lyase: EC 4.2.2.7) degradation of heparin from pork intestinal mucosa: the majority of the components have a 2-O-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2,6-O-disulfo-D-glucosamine structure at the reducing end of their chain; the relative molecular mass is 4500 \pm 1500, 70 per cent of which ranging between 1500 and 10 000; the degree of sulfatation is 2 to 2,5 per disaccharide unit.</td>
</tr>
<tr>
<td>tinzaparin sodium</td>
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</tr>
<tr>
<td>tolcaponum</td>
<td>3,4-dihydroxy-4'-methyl-5-nitrobenzophenone</td>
</tr>
<tr>
<td>tolcapone</td>
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</tr>
<tr>
<td>tolterodinum</td>
<td>((+\cdot)(R)-2-[\alpha-{2\text{-diisopropylamino} \text{ethyl}} \text{benzyl}] \text{p-cresol})</td>
</tr>
<tr>
<td>tolterodine</td>
<td></td>
</tr>
<tr>
<td>tretinoinum tocoaferium</td>
<td>((\pm\cdot)(2R^<em>))-2,5,7,8-tetramethyl-2-[(4R^</em>,8R^*)]-4,8,12-trimethyltridecyl]-6-chromanyl retinoate</td>
</tr>
<tr>
<td>tretinoin tocoaferil</td>
<td></td>
</tr>
<tr>
<td>trimegestonum</td>
<td>(17\beta^-{S}-\text{lactoyl}-17\text{-methyl}-\text{estra}-4,9\text{-dien}-3\text{-one})</td>
</tr>
<tr>
<td>trimegestone</td>
<td></td>
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<tr>
<td>tucaresolum</td>
<td>(\alpha-{2\text{-formyl}-3\text{-hydroxyphenoxy}}-\text{p-toluic acid})</td>
</tr>
<tr>
<td>tucaresol</td>
<td></td>
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<tr>
<td>tuvirumabum</td>
<td>human monoclonal immunoglobulin G1, (\lambda)-chain, anti-hepatitis B virus surface antigen</td>
</tr>
<tr>
<td>tuvirumab</td>
<td></td>
</tr>
<tr>
<td>unoprostonum</td>
<td>((+\cdot)(Z)-7\cdot{1R,2R,3R,5S}-3,5\text{-dihydroxy}-2\cdot{3\text{-oxodecyl}}\text{cyclopentyl}} \text{5-ho}</td>
</tr>
<tr>
<td>unoprostone</td>
<td></td>
</tr>
<tr>
<td>utibaprilatum</td>
<td>((S)-\text{2-tert-butyl}-4\cdot{\text{S}}^-\text{N}-{\text{S}}^-\text{carboxy}-3\text{-phenylpropyl} \text{alanyl}-\text{d}^\text{3}-1,3,4-thiadiazolene} \text{5-carboxylic acid})</td>
</tr>
<tr>
<td>utibapril</td>
<td></td>
</tr>
<tr>
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</tr>
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<td>---------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>velaresolum velaresol</td>
<td>5-(2-formyl-3-hydroxyphenoxy)valeric acid C\textsubscript{18}H\textsubscript{14}O\textsubscript{5}</td>
</tr>
<tr>
<td>verlukastum verlukast</td>
<td>3-[((\alpha)R)-m-[(E)-2-(7-chloro-2-quinolyl)vinyl]o-[[2-(dimethylcarbamoyl)ethyl]thio]benzyl]thio]propionic acid C\textsubscript{26}H\textsubscript{27}ClIN\textsubscript{2}O\textsubscript{3}S\textsubscript{2}</td>
</tr>
<tr>
<td>voglibosum voglibose</td>
<td>3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epi-inositol C\textsubscript{16}H\textsubscript{31}NO\textsubscript{3}</td>
</tr>
<tr>
<td>zalcitabinum zalcitabine</td>
<td>2',3'-dideoxycytidine C\textsubscript{6}H\textsubscript{13}N\textsubscript{3}O\textsubscript{3}</td>
</tr>
<tr>
<td>zaldaridum zaldaride</td>
<td>(±)-1-[[4-(methyl-4H,6H-pyrrolo[1,2-d]imidazol-4-yl)ethyl]methyl]-3,5-pyridinedicarboxylate C\textsubscript{26}H\textsubscript{28}N\textsubscript{4}O\textsubscript{2}</td>
</tr>
<tr>
<td>zoniclezolum zoniclezole</td>
<td>5-chloro-3-(1-imidazol-1-ylethyl)-1,2-benzoisoxazole C\textsubscript{12}H\textsubscript{15}ClIN\textsubscript{2}O</td>
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**AMENDMENTS TO PREVIOUS LISTS**

_Supplement to WHO Chronicle Vol. 35, No. 5, 1981_

**Recommended International Nonproprietary Names (Rec. INN): List 21**

p. 5  felodipinum  felodipine  _replace the chemical name by the following:_

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

_Supplement to WHO Chronicle, Vol. 39, No. 5, 1985_

**Recommended International Nonproprietary Names (Rec. INN): List 25**

p. 7  glimepiridum  glimepiride  _replace the chemical name by the following:_

1-[[p-[[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea
Supplement to WHO Chronicle, Vol. 40, No. 6, 1986

Recommended International Nonproprietary Names (Rec. INN): List 26

p. 10    teceleukinum  
         teceleukin

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

N-L-methionylinterleukin 2 (human)

C_{388}H_{1127}N_{175}O_{204}S_8

WHO Drug Information, Vol. 1, No. 4, 1987

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

p. 5     limaprostum  
         limaprost

replace the description and the molecular formula by the following:

(E)-7-[(1R,2R,3R)-3-hydroxy-2-[(E)-(3S,5S)-3-hydroxy-5-methyl-1-nonenyl]-5-
oxocyclopentyl]-2-heptenic acid

p. 8     ramoplaninum  
         ramoplanin

replace the description and the molecular formula 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}C_{21}N_{21}O_{35-40}


Recommended International Nonproprietary Names (Rec. INN): List 29

p. 14    niguldipinum  
         niguldipine

replace the chemical name by the following:

(-)-(S)-3-(4,4-diphenylpiperidino)propyl methyl 1,4-dihydro-2,6-dimethyl-
4-(m-nitrophenyl)-3,5-pyridinedicarboxylate


Recommended International Nonproprietary Names (Rec. INN): List 31

p. 4     cibobradinum  
         cibobradine

replace the chemical name by the following:

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

p. 4     daltopristinum  
         daltopristin

replace the chemical name by the following:

(3R,4R,5E,10E,14S,26R,26aS)-26-[[2-(diethylamino)ethyl]sulfonyl]-
8,9,14,15,24,25,26,26a-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3H-
21,18-nitrolo-1H,22H-pyrrolo[2,1e][1,8,4,19]dioxadiazacyctetrasosine-
1,7,15,22(4H,17H)-tetraone

p. 6     fantofaronum  
         fantofarone

replace the molecular formula by the following:

C_{31}H_{38}N_{2}O_{5}S

p. 14    terikatantum  
         terikatant

replace the chemical name by the following:

(-)-(S)-1-[2-(4-chromanyl)ethyl]-4-(3,4-dimethoxyphenyl)piperidine
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<th>Pages</th>
<th>Price</th>
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<tbody>
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<td>The use of essential drugs</td>
<td>1990</td>
<td>57</td>
<td>8.00</td>
</tr>
<tr>
<td>WHO model prescribing information: drugs used in anaesthesia</td>
<td>1989</td>
<td>53</td>
<td>11.00</td>
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<tr>
<td>WHO model prescribing information: drugs used in parasitic diseases</td>
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<tr>
<td>WHO model prescribing information: drugs used in mycobacterial diseases</td>
<td>1991</td>
<td>40</td>
<td>9.00</td>
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<tr>
<td>Guidelines for developing national drug policies</td>
<td>1988</td>
<td>iv + 52</td>
<td>11.00</td>
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<tr>
<td>The International Pharmacopoeia, third edition</td>
<td>1979</td>
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<tr>
<td>Basic tests for pharmaceutical dosage forms</td>
<td>1991</td>
<td>v + 129</td>
<td>24.00</td>
</tr>
<tr>
<td>International Nonproprietary Names (INN) for Pharmaceutical Substances, Cumulative List No. 8</td>
<td>1992</td>
<td>xlvi + 692</td>
<td>140.00</td>
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</tbody>
</table>

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

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