WHO Drug Information

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

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

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Personal Perspectives

Acceptance speech to the World Health Assembly

Dr Hiroshi Nakajima, Director-General Elect
World Health Organization

It is not easy for me to find words to adequately express my feelings on being elected Director-General of the World Health Organization by the Forty-first World Health Assembly. I am deeply moved by the confidence you show in me by this act and the honour which you bestow on me personally and on my country as well.

But it is also no less an honour to the Member States of the Western Pacific and South-East Asian Regions and to my colleagues there with whom I have had the privilege to work over the past nine years. Equally important, it is a vindication of the democratic process that the World Health Organization has the good fortune to enjoy.

The World Health Organization has emerged unscathed from the scrutiny which is being cast on all the United Nations system and has been judged as one which is doing a good job and moving in the right direction. This surely reflects the correctness of our common goals, the wisdom of our policy-makers, the dedication and loyalty of our staff, the inspired leadership of our past Directors-General, particularly Dr Halfdan Mahler, the commitment of the Regional Directors, and the steadfast support and cooperation of all our Member States.

In accepting the position of Director-General I am inspired by the achievements of WHO in the forty years of its existence. I am also influenced by my own experience as a young man in Japan, growing up amidst the misery and tragedy of war in contrast to the prosperity and development that have been achieved in the years of peace which have followed. It has strengthened my conviction that the pathway to social development is directly related to our success in maintaining peace in the world. I have lived half of my life outside the country of my birth and this experience will certainly help me to discharge my responsibilities over the next five years in a manner worthy of the trust you have shown in me. I am mindful of the challenges which lie ahead.

We live in fragile times. The gap between the "have"s and "have nots" has not narrowed. If we, Member States and WHO, are to achieve our goal of Health for All in the spirit of social equity we must establish new partnerships and engage in different dialogues involving the world community — not only with North-South but also East-West participants. But our dialogues must be followed by concerted and timely action. Talk alone is no longer enough.

Even before we win our battle against communicable diseases which has engaged us since our earliest days, many countries must now, in addition, face the burden of aging and the chronic and degenerative diseases. At the same time still too many people in the world live without the benefit of safe drinking water and sanitation. And with each passing day threats to the environment from man-made pollution make more tenuous our very survival. On the top of this sad recitation we are more recently assailed by a new terrible disease — AIDS — for which there is yet no cure.

The solution to any of these problems would tax the resources of even the rich countries but I regret to say that, in the midst of these realities, world economic recovery is slow and remains uncertain.

But there are encouraging signs about us that our common desire for peace may soon be achieved. I am optimistic that this will result in more resources being channelled towards health and social development and will lead us closer to our goal of Health for All.

In all humility I pledge to you that I shall spare no effort to maintain the proud image of your organization. With the continuing support of all of you, our Member States, working as equals in the spirit of friendly cooperation, we, the WHO Secretariat, with the strongest support of the Regional Directors, dedicate ourselves to achieving our common health goals. In so doing, we shall surely be leading the World Health Organization towards even greater excellence and making our own contribution to world peace.
Rational use of drugs

Dr Halfdan Mahler, Director-General
World Health Organization

1988 marks an anniversary of great significance for WHO and, for those of us who have spent many years in the service of the Organization, it provides occasion to take stock of its achievements and of the challenges that lie ahead. Forty years ago, in the aftermath of war and in a new spirit of internationalism, the creation of the World Health Organization by the founder members of the United Nations identified the right to health care as a fundamental tenet of civilized society in a world at peace. Ten years ago the international community, in an expression of commitment to the underserved majority of the world's population, rallied to the call contained in the Declaration of Alma-Ata for urgent action by all governments, and all health and development workers to provide, by the year 2000, through the development of primary health care, a level of health for all peoples of the world that will permit them to lead socially and economically productive lives. Today, as I prepare to step aside after fifteen years at the helm of the Organization, we seem to be propelled ever faster toward the threshold of the next millennium. Does time remain to attain these objectives? Are the turbulent, uncharted waters ahead securely navigable?

Clearly a world desperately striving to regain economic equilibrium is weakly equipped to accommodate all of yesterday's aspirations. Yet much that is tangible and lasting has been achieved, not least in one of the most potentially contentious of all domains, that of national drug policies. In 1984 the World Health Assembly called for a meeting of experts drawn from all the concerned parties, including governments, pharmaceutical industries and patients' and consumers' organizations, to discuss ways of ensuring the rational use of drugs. This occasion which, in prospect, threatened to debase into banal confrontation provided, in the opinion of the participants, a unique opportunity for constructive dialogue. Better mutual understandings were created between people facing different problems and viewing matters in quite different perspectives. Three years later I am secure in my conviction that the "spirit of Nairobi" generated more than a transient mood of euphoria. The areas of agreement were too fundamental to be casually discarded. There was general acceptance of the need for governments to display the political will to formulate and implement rational drug policies incorporating an appropriate informational component. There was strong support for strengthening national drug regulatory mechanisms, or for setting them up where they do not exist. The importance of ensuring good quality drugs for all at the lowest possible cost was stressed again and again, particularly for developing countries. Nobody contested the need to ensure ethical standards in drug advertising, although there were differing opinions about the best ways of doing it. The importance of rational prescribing was agreed by all. The need for improved drug distribution systems was similarly acknowledged, and there was universal support for the development and implementation of national essential drugs programmes.

But where is the solid evidence that these expressions of commitment, inspired by the principle of social equity, are being translated into effective action? Are there truly valid signs that the manifestly underprivileged — the urban slum-dwellers and the rural poor — have more secure access to the drugs that they so desperately need? At Nairobi, it was agreed that WHO's Model List of Essential Drugs — a "common core" of basic needs which has universal relevance and applicability — should be used more widely by interested countries and that WHO should take the necessary steps to make it generally available. For countries overwhelmed by the obligations of debt repayment and weighed down by a burden of endemic transmissible disease that reduces the average life expectation to little more than forty years, rationalization of health care has to be immediately cost-effective to be feasible. Nonetheless, aided in their search for appropriate strategies by the WHO Action Programme on Essential Drugs, 109 countries have already developed national lists of essential drugs and more than 40 are engaged in efforts to implement comprehensive programmes founded on WHO concepts. Even the most affluent of countries, faced with calls for retrenchment in the public sector and an obligation to define priorities based on need, reveal a determination to reduce drug costs, not only through direct price controls and selective registration but also through selective reimbursement of prescription costs, compulsory generic licensing, and promotion of generic prescribing and dispensing. The dilemma that emerges for all governments is to reduce public expenditure on drugs as far as is practicable without eroding the standards of the health services they
provide and yet assuring a socially-productive investment in new drug development.

At a time when the advent of AIDS has shattered previous optimism about prospects for the eventual containment of transmissible disease, yet when advances in bioengineering continue to extend the horizons for therapeutic intervention in ways that were unimaginable a few years ago, the pharmaceutical industry is subjected to unprecedented test and challenge. Its innovative performance in recent years in producing recombinant hepatitis B vaccine, in exploring promising leads for totally new vaccines and in creating valuable new drugs for treating the parasitic diseases including the benzimidazoles, praziquantel, ivermectin, mefloquine, halofantrine and polyamine inhibitors, leaves no doubt that it is within society's grasp to bring about no lesser change in the developing world than was realized elsewhere when bacterial disease was so successfully contained during the early antibiotic era.

Sadly, however, too much time and energy has been directed in recent years to accusations of disingenuous promotion of drugs that are irrelevant to real health needs, and to claims that, even in the developing world, promotional power has sometimes been callously misdirected to exploit rather than to serve the consumer. Pharmaceutical companies hold a vital key to the implementation of effective drug policies. It is their products that are at issue. Their acceptance as worthy partners in serving the world community depends upon their commercial objectives being not only attuned but subjugated to their public health responsibilities. Their ethical standards will be more readily judged and the complaints of their critics more readily vindicated or rejected in the light of WHO's newly-promulgated Ethical Criteria for Medicinal Drug Promotion. Once they are seen to be honouring these commitments, governments — out of vital self-interest — will be bound to assure their viability and research capability.

The indivisibility of "care" and "cost" has implications not only for industrial interests, but for everyone involved in the delivery of health care in the public sector. Socioeconomic as well as health-oriented responsibilities impinge at every level. Standards of individual care must remain sacrosanct, but health care professionals who neglect to provide cost-effective treatment are as culpable in their duties as those who fail in their immediate responsibilities to their patients. Efficient management of resources has relevance in virtually every educational setting from postgraduate training in therapeutic management to the instruction of health-care workers in village dispensaries. But, all too frequently, it is simply overlooked or misrepresented as an infringement of professional freedom. It is also a vital consideration in the provision of independent drug-related information, in the determination of drug procurement policies and in the quality control and storage of products in the distribution system. As much professionalism is required to assure the quality of pharmaceutical products as is needed to assure their safe administration. The attention that the World Health Assembly confers on the WHO Certification Scheme attests not only to the important economies that generic purchasing of pharmaceutical products can offer; it also unfortunately reveals the urgent need to exercise spurious and substandard products from international channels of supply.

Health for all by the year 2000 demands governmental involvement and intervention. But it cannot be realized without wholehearted commitment from everyone contributing to the vast infrastructure of health care delivery. Small economies effected through individual initiatives collectively become highly significant. The health care professions of medicine, nursing and pharmacy are the trustees of standards of practice. Their overt support for WHO's objectives is imperative if the last phase of our odyssey toward the year 2000 is to be confronted with assurance. Their concerns must be directed to health coverage as well as to its quality. They must look outward to influence and improve the integral infrastructure of health care as well as focusing an inward-looking eye on standards within their own professions. Primary health care and the rational use of drugs are issues that have profound relevance to the well-being of society everywhere. The engagement of the health professions in promoting them will be a crucial determinant of the progress that is made. WHO will always remain warmly responsive to their commitment to Health for All.
Halofantrine in malaria

From a global perspective, the need for new, rapidly-acting antimalarial agents has posed one of the foremost pharmaceutical challenges of modern times (1). Over the past twenty-five years Plasmodium falciparum malaria has threatened to escape from effective therapeutic control, initially in South America and south-east Asia (2) and latterly in Africa (3), following the emergence of parasites resistant to chloroquine and other rapidly-acting blood schizontocides. In the worst affected areas a virtual collapse in antimalarial therapy has been averted only by resorting to quinine, which earlier had been discarded in the routine management of uncomplicated, acute malaria, both because of its toxicity and the need for protracted administration. In recent years, however, reported failure rates with quinine used alone have surpassed 50 per cent in some areas of south-east Asia (4-6). Until recently, the only available strategy for stemming the rising tide of malaria-related deaths lay in protecting the therapeutic value of quinine, and some success was claimed in suppressing the continued emergence of resistant strains by using it routinely in combination with tetracyclines.

Given this situation, the recent and ongoing development of three new, highly-potent antimalarial substances holds profound significance for the communities at risk. Of these, mefloquine, an arylaminoalcohol and a 4-quinoline derivative, has been in routine use since 1984 in those countries where multiple drug resistance is most prevalent. After early clinical trials had established its efficacy in chloroquine-resistant P. falciparum in non-immune patients (7), cure rates as high as 97 per cent were obtained with single oral doses in early field studies in Thailand (8). This success has focused interest on the development of another candidate arylaminoalcohol, halofantrine, while independent research in China has centred much attention on derivatives of artemisinin, a sesquiterpene-lactone with a cyclic peroxide group that is obtained from the leaves of the shrub Artemisia annua (9, 10) and that is chemically unrelated to other known antimalarials.

Halofantrine (Halfan®, Smith, Kline & French), one of three phenanthrene methanol derivatives which was initially investigated for schizontocidal activity within the United States Army Antimalarial Drug Program, was selected for further development because, in a variety of models, it was comparable in its activity to mefloquine (11, 12). Toxicological screening (13) has provided no evidence of genotoxic or teratogenic activity, nor of adverse effects on fertility or fecundity. However, it does have an embryotoxic potential at dosages deleterious to the mother. In non-pregnant animals, single oral doses greatly in excess of the therapeutic requirement were well tolerated, but specific changes became evident on repeated daily dosage over four weeks, notably thyroid hyperplasia in rats receiving 10 mg/kg daily, and myositic changes in dogs receiving 25 mg/kg daily. These were accompanied by less specific changes in haematological and hepatic function. No evidence of toxicity, aside from transient elevation of liver enzymes and mild gastrointestinal symptoms, has been reported either in human volunteers or in patients treated for malaria (14, 15). As yet, the feasibility of using halofantrine over more extended periods in the prophylaxis of malaria has not been established and it remains contraindicated, on the basis of the animal studies, in the treatment of both pregnant women and nursing mothers.

Halofantrine is largely insoluble in water. Its systemic absorption from the currently available tablet and suspension formulations is unpredictably variable, but these differences are ameliorated when dosage is divided. The apparently critical importance of the dosage regimen was strikingly demonstrated during early clinical studies, particularly within a trial involving non-immune military recruits: 1500 mg produced satisfactory parasite clearance in 95 per cent of cases when it was given in three doses of 500 mg at intervals of six hours, but when the first two doses were combined and administered concurrently the response rate fell to 65 per cent (16). Continued efforts are being made to develop both improved oral dosage forms and an injectable solution. However, highly satisfactory results are claimed with the existing formulations in semi-immune patients when 1500 mg (or 24 mg/kg for children) is administered in three six-hourly doses (13). In all, the clinical and parasitological response to halofantrine has been evaluated in almost 1000 patients with acute
The irreplaceable contribution of mefloquine and halofantrine to the management of multidrug-resistant falciparum malaria imposes a need for every reasonable precaution to be taken now to inhibit the emergence of resistant strains. High levels of resistance to both drugs can readily be induced experimentally in *P. berghei*, which produces malaria in rodents (17, 18) and, under field conditions, the long plasma half-life of mefloquine may predispose to this risk. Indeed, resistance to mefloquine has already been reported in a clinical context from Thailand (19), the Philippines (20), Tanzania (21) and Indonesia (22) and within an experimental study involving infection with multidrug-resistant organisms (23). Concerns have also recently been expressed on the basis of *in vitro* evidence that, even prior to the introduction of mefloquine in West Africa, ambient strains of *P. falciparum* may be inherently resistant to the compound (24). Although cross-resistance with halofantrine was sought — but not found — in the latter study, it can reasonably be anticipated having regard to its structural and functional similarity to mefloquine (17, 25, 26). Indeed, cross-resistance has already been observed clinically and induced experimentally in the rodent model (18). Particularly disconcerting is a report of a strain of *P. berghei* rendered resistant to halofantrine which showed cross-resistance not only to mefloquine but also to the structurally-unrelated artemisinin (18).

Thus far, the value of every schizontocidal compound introduced into routine use has been compromised, sooner or later, by the selection of resistant strains of *P. falciparum* within the exposed pool of organisms. The medical community bears an onerous responsibility to devise and employ approaches to antimalarial therapy that — without compromising individual patient care — will reduce as far as is practicable the selection pressure that determines the emergence of resistance. There is no prospect of immediate consensus on how this might be attained. Long-established views have recently been challenged by the suggestion that, instead of exhausting the therapeutic potential of one or two compounds in a given area, it may be preferable to promote the concurrent use of a wider spectrum of antimalarials (27). The potential protective benefit to be derived from using schizontocides in combination or in conjunction with gametocytocides is already being further explored (18). In any event, national strategies aimed at reducing the emergence of resistance need to be explicitly defined as an aspect of public health policy, and intensive monitoring of profiles of drug resistance needs to be instituted wherever antimalarials are widely used.

References


General Information

Nebulizers for home use: bacterial contamination

United Kingdom — Jet nebulizers used for bronchodilator treatment at home are often contaminated with environmental bacteria of low pathogenicity. It has been shown that this can be substantially diminished by thorough washing after use and dry storage. Drying is readily effected by using the compressor to blow air through the tubing and nebulizer.


Amodiaquine resistance in Plasmodium falciparum

Brazil — Eight spontaneously-reported cases of failure of chloroquine-resistant Plasmodium falciparum to respond to amodiaquine have been notified. In a prospective evaluation of the drug involving eighteen patients in an area where chloroquine had previously been used extensively, a full course of treatment was curative in only one instance. A transient reduction in parasitaemia was obtained in 12 patients and, in the remainder, "no clinical or parasitological improvement was demonstrated".


Phenothiazines: extrapyramidal reactions

United Kingdom — Abnormally high concentrations of products of lipid peroxidation have recently been demonstrated in the cerebrospinal fluid of patients receiving phenothiazines, and particularly those with extrapyramidal adverse reactions, which are of particular concern since the effects are sometimes irreversible. This suggests these reactions may result from drug-induced structural oxidative damage to membrane lipids in neural tissue. One possibility is that phenothiazines induce translocation of copper ions from neural tissue into the cerebrospinal fluid and that resultant copper-albumin and copper-histidine complexes then catalyse the process of lipid peroxidation. The hypothetical value of chelating agents in inhibiting the catalytic activity is discussed, but the authors suggest that, as an initial step, the therapeutic and protective potential of a lipid-soluble antioxidant such as vitamin E (tocopherol) might be explored.


Methotrexate: suspected interaction with trimethoprim

United Kingdom — A case is reported of an elderly patient with psoriasis who developed necrotic skin ulcers and pancytopenia when treated concurrently with methotrexate, trimethoprim and naproxen. This may have been due to synergistic inhibition of folate metabolism by methotrexate and trimethoprim, and the authors suggest that the effect could have been further potentiated by the displacement of methotrexate from protein-binding sites by naproxen. Naproxen may also have competitively impaired the renal clearance of methotrexate.

Ulcerative lesions are very rare when methotrexate is administered alone within the recommended therapeutic dose range and the authors conclude that careful consideration of possible interactions is required before a decision is taken to administer other drugs concurrently.

Insect repellants: toxicity after accidental ingestion

**Canada** — Five cases of serious poisoning, two of which were fatal, have recently been reported in individuals who had accidentally or deliberately ingested proprietary preparations of the insect repellant N,N-diethyl-m-toluamide (DEET). This has heightened concern previously aroused by occasional cases of toxic encephalopathy attributed to repeated excessive applications in children, and the need is questioned for the recent introduction of highly-concentrated proprietary preparations (up to 100%) of this widely used compound. It is suggested that 75% solutions are acceptably efficacious and that these products be sold in child-resistant containers bearing a warning against excessive application to small children who are at increased risk from percutaneous absorption because of their relatively large surface-to-body weight ratio.


Elastomers containing stannous octoate: potential toxicity

It has recently been shown that 2-ethylhexanoic acid (2-EHA), a substance with teratogenic and carcinogenic potential in rodents, is formed in small amounts in various elastomers and other plastics in which stannous octoate is used as an initiator. These materials are components of foam dressings for wounds and various slow-release systems used in steroid contraceptives, including subcutaneous implants and vaginal rings.

The Toxicological Advisory Group of WHO's Special Programme for Research, Development and Research Training in Human Reproduction, which has recently reviewed the potential toxicity of 2-EHA, considers that the absolute amounts formed in currently-available implantable devices are too small to be of toxicological significance, particularly since no more than 10% is likely to be leached out in normal circumstances. The maximal possible exposure resulting from use of a vaginal ring, assuming the total content of 2-EHA is absorbed over a 24-hour period, is estimated to be 40 mg or 0.7 mg/kg. In rodents, more than 100 mg/kg of 2-EHA is required daily to induce peroxisomal proliferation, the mechanism likely to account for its toxic effects.

The Group concluded, on these grounds, that currently-available contraceptive devices containing 2-EHA present no toxicological risk to the user.


Acetylsalicylic acid in breast milk

**United Kingdom** — Paediatric preparations of acetylsalicylic acid were withdrawn in the United Kingdom in 1986 following demonstration of an association between cases of Reye's syndrome and use of acetylsalicylic acid in children with chicken pox and other febrile conditions.

Evidence — thus far based on one case only — has now been presented that acetylsalicylic acid is readily excreted into breast milk. The serum salicylate concentration of a nine-week-old breast-fed infant attained one-third that of the mother who was taking high doses of acetylsalicylic acid for adult Still's disease.

This has prompted a suggestion that products containing acetylsalicylic acid should be avoided during lactation, and that their labelling should bear a warning to this effect.


Anabolic steroids: evidence of increasing abuse

**United States of America** — The Food and Drug Administration has expressed concern about the growing use of anabolic steroids by an increasingly young population to improve athletic performance.
Sex-dependent adverse effects in men include breast enlargement; testicular atrophy with consequent sterility or decreased sperm count and abnormal motility and morphology; impotence, and enlargement of the prostate. Analogous changes in women include clitoral enlargement; beard growth; baldness; deepened voice and diminution of breast tissue.

In addition both sexes are vulnerable to a range of other hazards including increased aggression and antisocial behaviour; increased risk of coronary heart disease, stroke or obstructed blood vessels; liver tumours, peliosis hepatis (blood-filled cysts), and jaundice. Moreover, in children and adolescents, acne frequently develops and accelerated bone maturation can lead to permanent stunting of growth.

An additional risk is posed by illegally-imported or manufactured steroids that have not been approved and that are consequently not subjected to quality control. Non-sterility and pyrogenicity are of particular concern. The Agency is organizing educational campaigns in high schools and universities and it has asked manufacturers and distributors to take every precaution to ensure that these drugs are not diverted from authorized channels of distribution. It has also asked doctors to report any adverse effects believed to have arisen as a result of this abuse.


**Recommended composition of influenza virus vaccines for 1988-1989 season**

The World Health Organization recommends that vaccines prepared for the 1988-1989 season be trivalent and contain the following antigens:

- an A/Singapore/6/86(H1N1)-like antigen
- an A/Sichuan/2/87(H3N2)-like antigen
- a B/Beijing/1/87-like antigen.

As previously, the specific virus used in each country should be approved by the national control authorities.

Most of the population is likely to have been infected with influenza A(H3N2), influenza A(H1N1) and influenza B viruses in recent years. As a consequence, one dose of inactivated vaccine should be immunogenic for individuals of all ages except young children. Previously unvaccinated children should receive two doses of the vaccine, with an interval between doses of at least 4 weeks.

Reagents for use in laboratory standardization of inactivated vaccine may be obtained from the Division of Viral Products, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, Herts EN6 3QG, United Kingdom, or from the Division of Virology, Center for Biologies Evaluation and Research, Food and Drug Administration, Building 29A, 8800 Rockville Pike, Bethesda, Maryland 20892, USA.

A review of the prevalence of influenza viruses in the world is scheduled for publication in the *Weekly Epidemiological Record* on the last Friday in October 1988 as a basis for determining the composition of inactivated virus vaccines for use in the southern hemisphere.


**Testing for HIV antibody required for blood and blood products**

**United States of America** — The Food and Drug Administration is amending its biologics regulations to require that each unit of human blood — and all components of human blood intended for use in preparing a product for administration to patients — be tested and demonstrated to be negative for antibodies to human immunodeficiency virus (HIV).


**EEC: proposed extension of pharmaceutical directives**

The Commission of the European Communities has recently put forward proposals, to be implemented by 1 January 1991, to extend the scope of the community pharmaceutical directives to cover immunological medicinal products (including sera, vaccines, toxins and allergens), medicinal products derived from human blood, radiopharmaceuticals and non-proprietary (generic) medicinal products. Several other amendments of a general nature are also proposed relating to product information for patients, manufacturing standards and the export of
pharmaceutical products to developing countries.


**Orphan drugs and “truly new” pharmaceuticals or biologicals licensed in 1987**

**United States of America** — In 1987, the Food and Drug Administration approved the following eight orphan drug products — the highest number since the Orphan Drug Act was first implemented in 1983:

- **Alpha-1 proteinase inhibitor**
  - Selected cases of protein deficiency
  - Prolastin®, Cutter Laboratories

- **Etidronate disodium I.V.**
  - Hypercalcaemia
  - Didronel IV®, Norwich Eaton

- **Mitoxantrone**
  - Selective anti-leukaemic agent
  - Novantrone®, Lederle Labs

- **Pentastarch**
  - Adjunct in leukopheresis
  - Pentaspan®, DuPont Critical Care

- **Sodium benzoate and sodium phenylacetate**
  - Elevated ammonia levels in metabolic deficiencies
  - Ucephan®, Kendall McGray Laboratories

- **Somatropin**
  - Growth hormone deficiency
  - Humatrope®, Eli Lilly Co.

- **Teriparatide acetate**
  - Diagnosis of hypocalcaemia
  - Parathar®, Rorer Pharmaceuticals

- **Zidovudine**
  - Acquired immune deficiency disease
  - Retrovir®, Burroughs Wellcome Co.

In reviewing all products approved during 1987 the FDA cites the following as some of the most highly innovative:

**Molecular entities:**

- **Mesalamine**
  - Nonsteroidal anti-inflammatory
  - Rowasa®, Reid-Rowell

- **Ursodiol**
  - Biliary antilithic
  - Deursil®, Gipharmex

- **Aplonidine**
  - Adrenergic antagonist for postsurgical control of blood pressure
  - Iopidine®, Alcon

- **Carprofen**
  - Nonsteroidal anti-inflammatory
  - Rimadyl®, Hoffmann-LaRoche

- **Cefmenoxime HCl**
  - Cefalosporin antibiotic
  - Cefmax®, Tap Pharmaceuticals

- **Iofetamine**
  - (123I) radio-contrast medium
  - Spectamine®, Medi-Physics Inc.

- **Lisinopril**
  - ACE inhibitor antihypertensive
  - Prinivil®, M. S. & D.

- **Lovastatin**
  - Antihyperlipidaemic agent
  - Mevacor®, M. S. & D.

- **Mebrofenin**
  - Hepatobiliary diagnostic agent
  - Choletec®, Squibb Diagnostics

- **Milrinone**
  - Cardiac stimulant
  - Corotrope®, Sterling-Winthrop

- **Mometasone**
  - Topical corticosteroid
  - Elocon®, Schering Corporation

- **Mupirocin**
  - Topical antibiotic
  - Bactroban®, Beecham

- **Penbutolol sulfate**
  - Antihypertensive
  - Levatol®, Eli Lilly Co.

- **Terazosin**
  - Antihypertensive
  - Hytrin®, Abbott

- **Terconazole**
  - Topical antifungal
  - Terazol 7®, Ortho Pharmaceuticals

- **Ciprofloxacin HCl**
  - Antibacterial
  - Cipro®, Miles Pharmaceuticals

- **Fluoxetine HCl**
  - Antidepressant
  - Prozac®, Eli Lilly Co.

**Biological products:**

- **Alteplase (TPA)**
  - Thrombolytic agent
  - Activase®, Genentech Inc.
A new Salk-type vaccine manufactured using human cell cultures

**United States of America** — By taking advantage of advances in cell culture technology and of improved methods of purification of vaccine components based upon techniques developed within the National Institute of Public Health in the Netherlands, Connaught Laboratories of Canada has created a more potent inactivated poliovirus vaccine.

The original Salk-type vaccine, which was raised in monkey kidney cells, has been largely superseded by the oral vaccine. This is cheaper and simpler to administer, is more immunogenic particularly in the gastro-intestinal tract, and - through subsequent spread of the virus - offers some protection to unimmunized contacts. However, use of the live vaccine very occasionally results in cases of paralytic poliomyelitis. Inactivated vaccine consequently remains of value for protecting groups considered to be at higher risk of vaccine-associated paralysis, including unimmunized adults who are travelling to areas where poliomyelitis is endemic or who are household contacts of children receiving the oral vaccine, and for immunocompromised children. It has recently been licensed for these indications by the US Food and Drug Administration.


Biotechnology patents: 20 per cent increase in 1987

**United States of America** — The number of biotechnology patents issued by the US Patent and Trademark Office increased by 20% in 1987. The total number awarded was 1476 and, of these, over half concerned pharmaceutical and health-care products.


Traditional drugs in Japan

**Japan** — Self-medication in Japan, according to recently-published estimates, remains firmly based on herbal products, many of which stem directly from

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**Factor VIII**

Monoclonal antibody derived antihaemophilic factor

Inactivated polio vaccine

Haemophilia B-conjugate vaccine

HIV Western Blot test kit


**Monitoring of ciclosporin blood levels**

**United States of America** — Serious adverse reactions, including nephrotoxicity and hepatotoxicity, frequently occur when ciclosporin is used as an immunosuppressant during allogenic transplantation. These reactions have been attributed to high serum concentrations which occur unpredictably and complicate the clinical management of these patients. The development of a radioimmunoassay kit, recently approved by the Food and Drug Administration, that enables rapid serial estimations to be made of ciclosporin blood levels promises to simplify post-operative management.


**New clotting agent**

**United States of America** — The Food and Drug Administration has approved a preparation of human antihaeomophilic factor (Monoclate® Factor-VIII-C, Armour Pharmaceuticals) which is extracted from normal human blood using monoclonal antibodies. This highly specific method for separating factor-VIII complex from extraneous plasma proteins results in a product of greater purity than those available previously and it is anticipated that this will reduce the risk of transmission of pathogenic agents.

the medicines of ancient China. Their lack of potent pharmacological properties coupled with apparently safe usage over two millennia and sustained strong consumer demand has resulted in their reimbursement for insurance purposes since 1976. Quality assurance is vested in approved standards for the formulation of Chinese medicines that were established by the Ministry of Health in 1972. These standards also serve to identify the products as "household remedies" which can be sold or otherwise supplied by people without professional qualifications or knowledge of medicine.


Reye’s syndrome: decline in reported incidence

United States of America — The Centers for Disease Control have completed a review of 101 cases of Reye’s syndrome reported to the National Reye Syndrome Surveillance System in 1986. Despite widespread prevalence of influenza-B, the estimated incidence of Reye’s syndrome was about one half to one third of that reported in previous years with high influenza-B activity. Moreover, the number of cases known to be associated with varicella infection was the lowest since the present surveillance scheme was introduced.

Seventy-four per cent of the cases occurred during January, February and March, the peak months of influenza B activity. Thirty-eight per cent of the patients were 0-4 years of age; 12% 5-9 years; 34% 10-14 years; 15% 15-19 years and 2% 20 or over.

It is considered unlikely that the decline in the number of cases could be an artifact resulting from decreased reporting, and the trend is interpreted as reflecting a true decline in the use of acetylsalicylic acid in children with influenza-like disease or varicella. This is corroborated by a preliminary review of 1987 surveillance data which indicates a further decrease in the number of reported cases. Health care professionals are urged to continue reporting all cases to the Centers for Disease Control and the importance is emphasized of ensuring that not only doctors, but all parents and older children, are made aware of the association between the use of acetylsalicylic acid and Reye’s syndrome.

References:

Post-exposure prophylaxis of rabies

United States of America — Prompt treatment with rabies immune globulin and human diploid cell rabies vaccine does not offer complete protection against the disease. The causes of treatment failure, based upon two illustrative cases, are discussed in a recent issue of the Journal of the American Medical Association. In both cases the vaccine was given in the gluteal area where subcutaneous fat may have interfered with the immunogenicity response. Both patients were bitten in dangerous locations — the finger and the face respectively — where the rich innervation is known to favour the development of rabies, yet in one case the bite wounds were cleansed only with saline solution. It is stressed that care must always be accorded to proper wound management including cleaning with soap and water, which has significant antiviral action, and that up to half of the rabies immune globulin should be infiltrated around the wound. The remainder should be given intramuscularly in the gluteal area or lateral thigh, whereas the deltoid is the preferred site for injection of the vaccine.


Enalapril and atenolol equally effective in mild to moderate hypertension

Canada — The angiotensin-converting enzyme (ACE) inhibitors are attracting interest as an additional therapeutic option in the management of mild to moderate essential hypertension. The results of a comparative multicentre Canadian trial, in which regimens of once daily doses of enalapril (10-40 mg) and the beta-adrenoreceptor blocking agent atenolol (50-100 mg) were evaluated under randomized double-blind conditions, are of particular interest in this regard. The study involved 180 patients with diastolic pressures of 95 to 115 m Hg. After a placebo run-in period each patient received increasing dosages of
For and against generic prescribing

United Kingdom — A recent article in the Drug and Therapeutics Bulletin reviews the case for generic prescribing from the perspective of a country where standards of quality in marketed pharmaceutical products are effectively assured through a rigorous licensing system. For over 25 years the Department of Health and Social Security and its advisers have advocated the use of generic drug names by prescribers. Nonetheless, in the year ending February 1987, only 36% of general practitioners’ prescriptions in England and Wales were written generically. The Drug and Therapeutic Bulletin cites the following advantages of generic prescribing:

- Generic names usually indicate the therapeutic or chemical class to which the drug belongs.
- The exclusive use of a single name for a drug reduces confusion.
- In undergraduate and postgraduate teaching, as well as in most medical and scientific publications, generic names are almost universally used.
- Pharmacists could reduce their stocks if generic prescribing were general.
- Overall, generic prescribing costs are less than those of brand-name prescribing.

Against this, it perceives a number of disadvantages:

- Brand names are often simpler, more euphonious and more easily pronounced, spelled and remembered than generic names.
- The quality of generic products has been claimed to be inferior to that of branded products. However, apart from occasional well-documented problems, most of the evidence for this is anecdotal and the current extent of the problem is unknown.
- Different preparations of a drug, whether branded or generic, often differ in shape, size, colour or taste. These differences may matter to patients, particularly the elderly, who identify their medicines by appearance.
- Excipients may differ between a branded product and its various generic equivalents.
- The source of a generic product often cannot be identified once it has been dispensed.
• The research-based pharmaceutical industry claims that extensive generic prescribing would reduce the resources available for investment in new drug development.

In presenting a value judgement on the situation the article concludes that the case for generic prescribing outweighs the case against it. Prescribers are counselled, whenever possible, to use generic names rather than brand names and an appeal is made to medical teachers explicitly to support this policy.

An important caveat would doubtless have been added had the article been written from the viewpoint of a country largely dependent upon imported pharmaceutical products. Generic products, like their branded counterparts, can be used with confidence only if their quality has been adequately assured. Provision of this assurance is the objective of WHO's Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce.


Testing of an experimental vaccine against AIDS

United States of America — The Food and Drug Administration has announced that an experimental vaccine against AIDS will be tested on 30-60 healthy homosexual volunteers at the Pacific Medical Center. The vaccine is produced by Bristol-Myers Co. from vaccinia virus into which the genes for the surface proteins from HIV have been inserted by recombinant DNA techniques. The FDA Commissioner expresses hope for the future, having regard to the vast resources accorded both by government and the private sector to the search for a successful vaccine. However, he emphasizes that the vaccine is in the earliest stage of clinical testing and that even the most optimistic experts predict that an AIDS vaccine will not be in general use before the 1990s. This is the second experimental vaccine approved for clinical testing. The first, an insect-cell culture-derived vaccine manufactured by MicroGeneSys Inc. was approved for human trials in August 1987.


Cocaine: a dangerous drug

United Kingdom — Earlier in this century, cocaine was widely reputed to be a relatively harmless, or even beneficial, recreational drug. In the face of massively-increasing production in South America, and the availability of more potent preparations, the time for complacency is long past. In addition to cocaine hydrochloride crystals, which are often snuffed or occasionally injected, chemically-modified versions of cocaine are now available including cocaine paste, "crack" and freebase. These preparations are intended to be smoked or inhaled in order to produce a more rapid rise in blood concentration and a more powerful subjective response. They are inevitably more likely to produce greater degrees of dependence leading to larger requirements and sometimes to intravenous administration which is highly hazardous. Some users, it seems, are able to keep their use of cocaine under control, but others become as dependent as heroin addicts. There is no way of predicting who will be able to maintain control or who will become dependent. Moreover, the acute dangers of cocaine use confront everyone that experiments with the drug. Non-addicted novices are at risk of acute myocardial infarction, ventricular tachycardia and fibrillation. Higher doses raise blood pressure, induce seizures and invoke a risk of sudden death from respiratory or cardiac arrest, while poorly-prepared samples can contain traces of corrosive chemicals capable of causing irreversible lung damage.

Recent editorial comment in the British Medical Journal emphasizes that in no circumstances can cocaine be regarded as a safe recreational drug: its dangers are substantial, immediate and manifold.

Regulatory Matters

Drugs for human use

Alcohol-containing drugs contraindicated for nursing mothers

Federal Republic of Germany — The Federal Health Office now requires that the product information for pharmaceuticals containing more than 0.5 g alcohol (ethanol) in each dosage unit (or more than 3.0 g in the maximum recommended individual dose) must contain a warning against use by nursing mothers. Alcohol passes readily into breast milk and the possibility that this may cause harm to the infant cannot be excluded.


Alginic acid in over-the-counter preparations

United States of America — The Food and Drug Administration has refused to approve the labelling claim “foam-forming floating antacid” for products containing alginic acid indicated in acid indigestion. The agency recognizes that such products may form a floating layer on top of the stomach contents but it considers that insufficient evidence has been presented that this contributes to clinical effectiveness.


Allethrin-containing insecticides: warning for asthmatics

Brazil — The National Health Secretariat has decided that the product information for preparations of the household insecticide allethrin should carry a warning advising that patients with asthma or other respiratory diseases should avoid exposure to the product.

Reference: Portaria no. 18 of 14 July 1987, Ministry of Health, Brazil.

Canthaxanthin: withdrawal

Ireland — Having regard to reported ocular toxicity associated with long-term use, the National Drugs Advisory Board has informed manufacturers that the skin-tanning agent canthaxanthin will no longer be permitted as a constituent of medicinal products.


Cell therapy: prohibition

Austria — The Ministry of Health has informed doctors and pharmacists that the use of deep-frozen cell preparations in the practice of “cell therapy” is no longer permitted. A similar measure has also recently been taken in the Federal Republic of Germany where a number of fatalities associated with cell-therapy have been notified to the health authorities.


Clebopride: warning on extrapyramidal symptoms

Japan — Following reports of three cases of extrapyramidal disturbances and other central nervous symptoms associated with the anti-ulcer drug clebopride (Amicos®: Banyu; Clast®: Meiji Seika), the Ministry of Health and Welfare has decided that the adverse effects cited in the product information should be extended to include numbness of lips and tongue and, in rare cases, salivation and stiffness of the neck. A warning is also added that treatment must be discontinued should such symptoms occur.

Contact lens cleaning fluid: warning on eye injury

United States of America — The Food and Drug Administration has modified the product information for contact lens cleaning solutions to include a more explicit warning that failure to observe approved product information on lens care may result in serious injury to the eye.


Enoxacin/fenbufen: convulsions due to interaction

Japan — The Ministry of Health and Welfare has received seven reports of convulsions in patients taking both the quinolone antibiotic enoxacin (Flumark®: Dainippon) and the nonsteroidal anti-inflammatory agent fenbufen (Napanol®: Lederle). The product information for both drugs has consequently been revised to contain a warning that they should not be administered concomitantly.


Famotidine: revised product information

Japan — The Ministry of Health and Welfare has received reports of three cases of reversible mental confusion in patients using the H2-antihistamine anti-ulcer agent famotidine. The product information has been revised accordingly. Reference to this effect is already contained in the product information for the other H2-antihistamines cimetidine and ranitidine.


FD&C Red No. 3 colorant: adverse reactions in animal study

United States of America — The colouring agent FD&C Red No. 3 has been definitively approved by the Food and Drug Administration for use in food and orally-administered drugs and provisionally approved for the colouring of cosmetics and externally-applied drugs. Since, in a long-term study in rats, exposure to this colorant was associated with thyroid tumours, the agency is requesting manufacturers to provide quantitative and qualitative information on its use both to assess potential exposure and to determine allowable safe uses if this is deemed appropriate. Manufacturers are also required to provide justification for its use in drugs or cosmetics and to propose possible alternative colorants to assist the agency in determining its relative importance in specific products.


FD&C Yellow No. 6 colorant: listing on beverage labels

United States of America — The Bureau of Alcohol, Tobacco and Firearms has proposed an amendment to existing regulations that will require the mandatory disclosure of the colouring agent FD&C Yellow No. 6 in wine, distilled spirits and malt beverages. This action is taken in the light of reports associating this colour additive with allergic reactions.


Fenfluramine: withdrawal

Tunisia — The Ministry of Public Health has informed WHO that fenfluramine (Ponderal®: Biopharma) has been withdrawn from the market. It was found that after fenfluramine had been scheduled as a narcotic substance, doctors discontinued prescribing the product.

Flunarizine: adverse effects

Belgium — The Centre for Adverse Drug Reaction Monitoring has received 32 reports of depression associated with the use of flunarizine (Sibelium®: Janssen) in patients with cerebral insufficiency and migraine. Six cases of extrapyramidal symptoms which resolved on withdrawal of flunarizine are also on record.

The maximum recommended dose for elderly patients has been reduced to 5 mg per day and the product is additionally contraindicated in patients with a history of depression or pre-existing symptoms of parkinsonism.


Glafenine and floctafenine: under prescription control

Belgium — The General Inspectorate of Pharmacy of the Ministry of Public Health and Environment has informed WHO that, having regard to the potential of products containing glafenine (Glifanan®: Roussel) or floctafenine (Idalon®: Roussel) to cause severe anaphylactic shock, they may now be obtained only on medical prescription.


Flupentixol decanoate: refusal of registration

Australia — The Drug Evaluation Committee has refused to approve registration of the tranquilizing agent flupentixol decanoate (Fluanxol Depot®: Fisons, injection fluid 20 mg/ml and concentrate 100 mg/ml) on grounds of inadequate pharmaco-kinetic studies and human safety data.


Ibuprofen: warning label

New Zealand — The Department of Health has informed WHO that, after consultation with the manufacturer, it has been agreed that products containing ibuprofen (Nurofen®, Brufen®; Boots) for over-the-counter sale should bear the following warning on the label:

"If symptoms persist for more than three days, consult your doctor. If you are receiving medication from your doctor you should seek his or her advice before taking Nurofen or any other pain reliever. If you suffer from a stomach ulcer or any other stomach disorder you should not take Nurofen or any other pain reliever. You should consult your doctor before taking Nurofen if you are asthmatic or aspirin-sensitive as there may be an increased risk of breathing difficulties."


Ganciclovir: refusal of registration application

United States of America — The Anti-Infectives Drug Advisory Committee of the Food and Drug Administration has recommended that consideration of an application to register ganciclovir, an antiviral agent indicated for the treatment of cytomegalovirus retinitis in AIDS patients, be deferred until more reliable clinical data are provided.

The Committee considered that the available data, in which reliance is vested in historical rather than concurrent control groups, do not allow an adequate evaluation of safety and efficacy.


Inactive ingredients: labelling requirements

Ireland — The National Drugs Advisory Board has recommended that the inclusion of various ingredients used in the formulation of pharmaceutical products, which may cause adverse effects in susceptible patients, should be stated on the label. These substances include sucrose, alcohol, parabens and gluten.

Insulin: no longer indicated in insulin shock therapy

**Japan** — Within the context of its periodic revision of product licences, the Ministry of Health and Welfare has deleted reference to insulin shock therapy in schizophrenia from the indications for a currently marketed preparation of soluble insulin (Insulin Actrapid MC®: Novo Yakuhin). The product remains available exclusively for the treatment of insulin-dependent diabetes.


Isotretinoin: birth defects

**United States of America** — The Dermatological Drugs Committee of the Food and Drug Administration has reviewed recent data on birth defects and abortions associated with the use of isotretinoin (Accutane®: Hoffman La Roche), a drug approved in 1982 for severe recalcitrant cystic acne unresponsive to conventional therapy. Since its introduction isotretinoin has been contraindicated for use in pregnant women because it causes birth defects in experimental animals. Despite numerous warnings to physicians and consumers issued both by the Food and Drug Administration and the manufacturer, 62 birth defects attributed to isotretinoin have now been notified to the Agency.

The committee, which was informed that isotretinoin is probably being used by thousands of US women of child-bearing age with relatively mild acne even though it is intended solely for patients at risk of disfigurement from deep pitting scars, made the following recommendations:

- The Food and Drug Administration and the manufacturer should increase the prominence and strength of warnings and contraindications through new packaging that will provide more explicit information about the degree of risk.

- Isotretinoin should be recommended only for women of child-bearing capacity who have had a negative pregnancy test.

- Educational efforts aimed at physicians, pharmacists and patients should be intensified.

- Before the drug is prescribed a written acknowledgement should be obtained from each patient that she has been informed of its potential adverse effects.

In addition, the committee suggested that consideration be given to other, more direct ways of further limiting the availability of the product including:

- restricting the right to prescribe isotretinoin to certain designated or certified physicians, and

- restricting its availability by excluding patients who are likely to ignore cautionary advice, or by requiring a second opinion before it can be prescribed to them.

It also emphasized the need to sustain ongoing activities to monitor the use of isotretinoin, and any associated birth defects in order to assess the efficacy of any preventive measures that are implemented.


Lormetazepam: registration refusal

**Australia** — The Drug Evaluation Committee has refused registration of lormetazepam (Loramet®: Wyeth; Noctamid®: Schering) capsules and tablets containing 0.5, 1, and 2 mg for use as a sedative and hypnotic on grounds of insufficient human safety data.


Nonsteroidal anti-inflammatory agents: restrictions

**Japan** — The Ministry of Health and Welfare has decided that the recommended dosages for some nonsteroidal anti-inflammatory agents should be reduced and that the product information should be revised as follows:

- diclofenac suppositories: 25-50 mg daily (formerly 50 mg); an advisory note is required that dosage should be adapted to the age of the patient and be the lowest that provides adequate relief of symptoms;

- indometacin suppositories: 25-50 mg daily (formerly 25-100 mg);
- metamizole sodium injection: 250 mg (formerly 250-500 mg), not more than twice daily.

Products containing any of these substances must bear a warning that they should be used only when other antipyretics are contraindicated or likely to be inadequately effective.

A warning against hypothermic shock must be included in the data sheet of suppository preparations of all three substances and of injectable preparations of metamizole sodium.

Labelled warnings are also required stating that, save for slow-release preparations, oral formulations of these substances should not be taken on an empty stomach.

Kebuzone and feprazone are newly subjected to prescription control and the registered indications are limited to pain relief of acute exacerbations of inflammation, and pain in rheumatoid arthritis and related conditions when these fail to respond to other NSAIDs. Duration of treatment should not exceed one week.


Oxeladin and promethazine available over-the-counter in France

France — The Ministry of Health has exempted the antitussive oxeladin from prescription control. An antitussive syrup containing oxeladin and a combination syrup preparation containing oxeladin and promethazine are now available over-the-counter from pharmacies.


Paracetamol and acetylsalicylic acid: dispensing regulations

Belgium — WHO has been informed of newly-introduced measures to regulate the dispensing of pharmaceuticals containing either paracetamol or acetylsalicylic acid.

Products containing more than 500 mg per unit or more than 10 g per package of either compound, and products containing two or more analgesic compounds, or one analgesic in combination with caffeine, will only be dispensed on presentation of a written request, dated and signed by the patient or his representative.


Parenteral vitamin preparations: limited duration of treatment

Japan — Within the context of its periodic review of product licences, the Ministry of Health and Welfare has decided that the maximum recommended duration of treatment with an intravenous multivitamin preparation be limited to three weeks. The product in question (MVI Injection®: SS Pharmaceuticals) contains retinol, ergocalciferol, tocopherol acetate, thiamine hydrochloride, riboflavin phosphate, pyridoxine hydrochloride, nicotinamide, dexpantenol and ascorbic acid.


Phenacetin withdrawn

Austria — Having regard to the risk of carcinogenicity and nephrotoxicity associated with chronic use of the analgesic, phenacetin, the Director-General of Public Health of the Federal Chancellery has prohibited its use in pharmaceutical products.


Piperazine: available without prescription in the United Kingdom

United Kingdom — The Licensing Authority, having recently reviewed the efficacy and toxicity of the
anthelmintic drug, piperazine, has decided to exempt it from prescription control. Registered preparations may now be obtained from pharmacies without prescription on the understanding that the product information will include the following advice to the patient:

"If you are pregnant or think you may be pregnant, or if you are currently taking any other medicine, do not take this product without the advice of your doctor. Do not take this product if you have kidney disease or have ever suffered from epilepsy."


Postmarketing reporting of adverse drug reactions: revision of rules to improve patient safety

United States of America — As a condition of marketing a drug in the United States the licence-holder now assumes a statutory obligation to inform the Food and Drug Administration within 15 days of any serious adverse experience that comes to its knowledge regardless of where the incident occurred.

A serious adverse experience embraces any event that results in death, congenital anomaly or cancer and was initially defined as an event that is “life-threatening, permanently disabling or requires prescription drug therapy”. The Agency has now deleted the last of these criteria from the definition since it resulted in the submission of large numbers of reports that did not warrant official review.


Propionic acid: restrictions in use

Federal Republic of Germany — A Committee of Experts convened by the Federal Health Office to review the toxicological properties of the preservative propionic acid found no conclusive evidence of carcinogenicity in experimental animal models. However, in the rat, high dosages induced papillomata and other proliferative lesions as well as dysplasia of the secretory mucosa.

Diffuse hyperplasia was also demonstrated in the gastrointestinal mucosa of dogs. On the basis of the Committee’s advice, the use of propionic acid as a preservative has been severely restricted and its use in bread has been prohibited.


Psoralens: under prescription control

Belgium — The General Inspectorate of Pharmacy has informed WHO that the antipsoriatic compounds 8-methoxypsoralen and trioxysalen have been subjected to prescription control. This results from concern that their use during ultraviolet therapy carries a risk of chronic phototoxicity and skin cancer.


Sulfites: prohibited in parenteral preparations

Ireland — The National Drugs Advisory Board has decided that it will no longer approve amino acid solutions for parenteral nutrition if they contain sulfite preservatives. It considers that the risk of these preparations is unacceptable, particularly in the routine long-term management of pre-term infants and other metabolically-compromised patients. Intake of sulfites has been associated with severe adverse reactions including anaphylaxis, predominantly in asthmatics. Experimental evidence also suggests that bisulfites are mutagenic.


Theophylline and aminophylline: sustained-release preparations

Ireland — The National Drugs Advisory Board has informed doctors that different formulations of sustained-release theophylline and aminophylline have different release characteristics and are not freely interchangeable.
A doctor wishing to transfer a patient from one to another brand of these products is advised to use a conventional dosage form for a short interim period before attempting to adjust the dosage of the alternative sustained-release formulation to individual requirements.


**Ticlopidine: warning of granulocytopenia and liver dysfunction**

*Japan* — The Ministry of Health and Welfare has received several reports of granulocytopenia and liver dysfunction in patients receiving the antithrombotic agent ticlopidine. These are now listed as contraindications to further exposure to the substance. Elderly patients, especially women, seem to be at greatest risk and doctors are advised that treatment should be suspended immediately if signs suggestive of the following conditions occur:

- agranulocytosis;
- aplastic anaemia;
- thrombocytopenia and other causes of an abnormal bleeding tendency; and
- liver dysfunction, presenting as jaundice, pruritus, nausea, vomiting, anorexia and lassitude, or elevation of serum transaminase.


**Tranexamic acid: refusal of additional indications**

*Australia* — The Australian Drug Evaluation Committee has rejected a proposed extension of the indications for tranexamic acid (Cyclokapron®: Pharmacia) to include the treatment of epistaxis and menorrhagia. An application for approval to market an intravenous formulation (100 mg/ampoule) was also refused on grounds of inadequate data.


**Tridihexethyl chloride + meprobamate withdrawn**

*United States of America* — The Food and Drug Administration has withdrawn from the market a fixed combination product containing tridihexethyl chloride 25 mg and meprobamate, 200 and 400 mg per tablet (Trihexamate®: Lord Laboratories; TCM-200® and TCM-400®: Zenith Laboratories) on grounds of lack of substantial evidence of effectiveness.


**Urokinase: warning against shock**

*Japan* — The Ministry of Health and Welfare has received four reports of shock in patients receiving preparations of the thrombolytic enzyme urokinase derived from cultured human kidney cells (Cultokinase®: Kyorin; Abbokinase®: Dainippon). The product information has consequently been revised to warn that administration should be discontinued immediately and appropriate symptomatic treatment instituted should such a reaction occur.


**Vaccines: anaphylactic reactions**

*Belgium* — The Centre for Adverse Drug Reaction Monitoring has received two reports of shock and eight reports of anaphylactic reactions to Pluserix® (SK-RIT), a trivalent vaccine containing attenuated measles, mumps and rubella virus. A proportionately similar number of reactions has been reported in association with MMR Vax® (MS&D) which is less widely used. Doctors have been alerted to the risk of reactions, particularly in children with known allergy to egg protein or neomycin, two sensitizing excipients contained in these products. It is emphasized that children should be routinely monitored for several hours following vaccination and that any infectious ailment should be regarded as a contraindication.

Veterinary drugs

Chloramphenicol banned in food animals

Canada — The Ministry of Health and Welfare has decided that chloramphenicol is no longer acceptable for administration to food-producing animals. Sale of meat, milk or eggs containing any residue of chloramphenicol is prohibited.


Decoquinate: use in breeding animals

United States of America — The Food and Drug Administration has issued a final rule rescinding prohibition of the use of the coccidiostatic agent decoquinate in breeding animals. Its use in dairy cows remains prohibited.


Model veterinary drug code: guideline

United States of America — In collaboration with the Food and Drug Administration, the Association of Food and Drug Officials has adopted a model code on the use of veterinary drugs. This is designed to support the legal apparatus most States already possess for regulating veterinary drugs and particularly to enforce existing provisions. The Association hopes that eventually the code will be officially adopted as a uniform Federal standard for veterinary drug distribution.


Tiamulin: approval for treatment or control of swine dysentery

United States of America — The Food and Drug Administration has approved the use of tiamulin (Denagard®: Fermenta Animal Health) in swine feed in a concentration of 35 g per ton for control of dysentery caused by Treponema hyodysenteriae and in a concentration of 10 g per ton for increased weight gain. Swine being treated with tiamulin should not have access to feeds containing polyether ionophores, such as lasalocid, monensin, narasin or salinomycin. It should not be used in swine heavier than 250 pounds (114 kg) and it should be withdrawn two days before slaughter.


Trout vaccine: removal from prescription control

United Kingdom — The Veterinary Products Commission has decided that Ermogen® (Vetrepharm), a vaccine derived from Yersinia ruckeri that offers protection against enteric redmouth, a disease endemic in rainbow trout stocks in the United Kingdom, will no longer be subject to prescription control. It will be made available as a pharmacy-only medicine.

Advisory Notices

**Almitrine: polyneuropathy**

**Belgium** — The Centre for Adverse Drug Reaction Monitoring has received reports of two cases of polyneuropathy associated with the use of the piperazine analogue almitrine (Vectarion®) indicated for the treatment of respiratory insufficiency. Doctors have been advised that treatment should be discontinued whenever symptoms suggestive of neuropathic lesions occur.


**Analytical control: the need for alternative methods**

**Ireland** — The National Drugs Advisory Board has requested manufacturers to include in their applications for product licences analytical specifications that can be checked using standard laboratory instrumentation. In recent years the analytical equipment used by pharmaceutical companies for in-process control has, in many instances, become too expensive for independent standard control laboratories. The alternative methods proposed by the manufacturer should, wherever possible, be based on the same principles as those employed for in-process control and, in all cases, they should be validated experimentally.


**Benzylpenicillin for suspected meningitis**

**United Kingdom** — In 1987 over 1000 cases of meningococcal meningitis were reported within the United Kingdom and 158 patients died. At least as many cases are anticipated this year. Most will occur in children under four years and in young adults in the 15 to 24 age group.

At present, there is no vaccine against the causative group B meningococci, and doctors have recently been reminded in a circular letter issued by the Government's chief medical officer of the importance of ensuring that any patient with suspected meningococcal meningitis — particularly when there is a haemorrhagic rash already evident — should be given benzylpenicillin immediately and before transfer to hospital is arranged.


**Benzodiazepines: limitation in duration of treatment**

**Ireland** — Having regard to the potential of benzodiazepines to induce dependence, particularly during prolonged usage, the National Drugs Advisory Board has advised doctors that duration of treatment should not exceed 4 to 6 weeks and that the lowest effective dose should be used to reduce the incidence of agitation, restlessness and anxiety on withdrawal.


**Bioavailability: revised registration requirements**

**Ireland** — The National Drugs Advisory Board has decided that, as a general rule, results of dissolution tests will be required in marketing applications for new drug products. In addition, it will require evidence of in vivo bioavailability for the following categories of products:

1. All dosage forms with a novel or unconventional mechanism for delivery of the active ingredient to the patient. This includes percutaneous and buccal delivery systems, oral medications claiming sustained or controlled rate of release, and implanted products.
2. All anti-infective agents presented in a dosage form other than solution.
3. Dosage forms containing an active ingredient which is highly potent, short-acting, or with a low therapeutic ratio.
4. Dosage forms differing significantly in their formulation from the conventional standard.

In the case of products intended for repeated administration, the Board may require information on multiple-dose studies in which steady-state kinetics have been achieved as well as information on single-dose studies.


Buprenorphine abuse

**United Kingdom** — Buprenorphine (Temgesic®: Essex) is an opioid analgesic that has a low dependence liability in standard experimental models. However, the Northern Regional Health Authority has recently received several reports of buprenorphine abuse and it has requested doctors and pharmacists to remain alert to such cases. Reconsideration of the legal status of buprenorphine is suggested. At present it is available on prescription only and is not subject to control as a narcotic. Such controls have already been applied in Austria, the Federal Republic of Germany and New Zealand.

Reference: Northern Regional Health Authority, Drug Newsletter, No.44 (1987).

Controlled-release dosage forms: therapeutic equivalence

**United States of America** — Pharmaceutical manufacturers developing controlled-release products (tablets, capsules and injections) rarely employ the same approach to formulation. The Food and Drug Administration has consequently indicated that it does not consider controlled-release dosage forms containing the same active ingredient in equal strength as therapeutically equivalent “unless such equivalence between individual products for both rate and extent has been demonstrated through appropriate bioequivalence studies”.


Dextromethorphan: adverse reactions and abuse

**Federal Republic of Germany** — Reported adverse reactions to the centrally-acting antitussive, dextromethorphan, include various effects on the central nervous system such as confusion, fatigue, fear, sleep disturbances, headache, mydriasis, dysuria, nausea, cardiac dysrhythmia and, rarely, skin reactions.

The Federal Health Office is aware that abuse of medicines containing dextromethorphan has been reported from other countries but no such cases are on record in the Federal Republic of Germany. It has requested relevant information, particularly from pharmacists, since antitussives are purchased predominantly over-the-counter.


Procaine: allergic reactions

**Federal Republic of Germany** — The Federal Health Office has requested doctors to report all allergic reactions to procaine-containing products following the receipt of several reports of anaphylactoid reactions in patients receiving procaine parenterally.

The Agency emphasizes that procaine should be administered by this route only when absolutely necessary and that facilities for emergency resuscitation must always be available.

Essential Drugs

Malaria

More than 90 million cases still occur each year

Malaria is endemic in more than 100 countries in Africa, Asia, Oceania, Central and South America, and in certain Caribbean islands. It is estimated that over 90 million cases occur each year and, in its socioeconomic impact, it is the most important of the transmissible parasitic diseases.

Types of malaria

Human malaria, which is transmitted by anopheline mosquitoes (and rarely by congenital transmission, transfusion of infected blood or use of contaminated syringes among drug addicts), is caused by four species of plasmodial parasites. *Plasmodium vivax* is the most extensively distributed and causes much debilitating disease. *P. falciparum*, which is also widespread, results in the most severe infections and is responsible for nearly all malaria-related deaths. *P. ovale*, which is mainly confined to Africa, is less prevalent, while *P. malariae*, which causes the least severe but most persistent infections, also occurs widely.

Sporozoites produced in the mosquito vectors from sexual forms of the parasite migrate to the salivary glands. When injected into the blood stream of man they rapidly penetrate the parenchymal cells of the liver where they transform and grow into large tissue schizonts containing considerable numbers of merozoites (tissue schizogony). These begin to rupture after 5 to 20 days, according to the species, and the released merozoites invade circulating erythrocytes. The subsequent rapid intraerythrocytic multiplication of the merozoites (blood schizogony) culminates in the rupture of the host cells, the release of another generation of merozoites and the cyclical invasion of further erythrocytes which, in turn, are destroyed. The destruction of red blood cells and the release of the parasites' waste products produce the episodic chills and fever that characterize the several variants of the disease. Because some merozoites develop into male or female gametocytes the host becomes a reservoir of infection for mosquitoes and completion of the transmission cycle is assured. Certain tissue forms of *P. vivax* and *P. ovale* which persist in the liver for many months and even years (hypnozoites) are responsible for the relapses characteristic of these forms of malaria. Such latent forms are not generated by *P. falciparum* or *P. malariae*. Recrudescence of these infections results from persisting blood forms in inadequately treated or untreated patients.

Clinical manifestations

The clinical response to infection depends both on the species of the parasite and on the immunological status of the patient. Non-immune travellers to malarious areas risk severe attacks. Acute malaria also occurs where exposure is limited or seasonal and where the collective immunity is relatively low. In these circumstances it can occur in epidemic proportions and affect all age groups in the community. Acute falciparum malaria is a potentially fatal disease causing prolonged, irregular high fever, intense headache and vomiting. Severe infection, resulting from intense parasitaemia, frequently gives rise to hyperpyrexia, convulsions, stupor, collapse, copious vomiting and diarrhoea, haemolytic anaemia, and jaundice. Complications include cerebral malaria (characterized by confusion, convulsions and rapidly-progressive coma), hypoglycaemia, pulmonary oedema, acute renal failure and massive haemolysis. Chronic or repeated infection often leads to splenomegaly and progressive anaemia. Splenic rupture is a dangerous complication of vivax malaria, and *P. malariae* occasionally gives rise to a fatal nephrotic syndrome.

Pregnant women, if untreated, are at particularly high risk of death from falciparum malaria, especially where transmission is intermittent. In holoendemic areas they are partially protected by a measure of immunity. This reduces the risk of congenital infection, but it does not protect the placenta which, particularly in primigravidae, harbours large numbers of malaria parasites. The fetus is thus inevitably exposed to the effects of placental insufficiency. Largely as a result of passive transfer of maternal antibodies across the placenta, infants born to im-
mune mothers living in holoendemic areas are unlikely to acquire malaria for several months after birth. Thereafter, they risk death from severe and recurrent acute attacks during infancy and early childhood. From the age of five until adulthood the severity and frequency of these attacks decrease as immunity develops. Except among pregnant women and immunodepressed patients, clinically-significant malaria is infrequent in adults who have always lived in areas of high transmission.

**Prevention**

Hopes that malaria could be eradicated by systematic use of insecticidal sprays and drugs have been abandoned. The emergence of vectors resistant to widely-used insecticides and of parasites resistant to first-line drugs has resulted both in rising attack rates in many endemic areas and in the need to resort to more costly chemotherapeutic agents associated with greater toxicity.

Systematic insecticidal spraying is not feasible in the rural areas where it is most needed. However, where it is practicable, it is often necessary to use recently developed, and hence relatively expensive compounds such as bendiocarb, pirimphos-methyl, chlorphoxim and synthetic pyrethroids. Destruction of mosquito breeding sites by land drainage schemes and biological control using anti-larval parasites (such as *Bacillus thuringiensis* H14 and *B. sphaericus*) or larvivorous fish (such as *Gambusia*) can sometimes reduce dependence upon insecticidal chemicals, but the potential of these methods is limited.

Emphasis is now placed upon prompt diagnosis and treatment of the disease, and upon selective use of antimalarial drugs with a view to reducing the risk of emergence of drug resistance and unnecessary drug-induced toxicity. Routine prophylaxis is now generally reserved exclusively for pregnant women, special groups, such as labour teams and military personnel living in closed communities, and non-immune visitors to endemic areas.

Efforts are consequently being intensified to teach communities and individuals at risk how to reduce contact with mosquitoes and particularly on the use of bed nets, preferably impregnated with safe, long-lasting, repellent insecticides such as permethrin or deltamethrin. Vaccines against sporozoites and other forms of the parasite are under development, but none has yet been subjected to extensive clinical trial.

**Antimalarial drugs**

Various comprehensive classifications of antimalarial drugs have been proposed.* The simplified adaptation set out on the table overleaf suffices for an understanding of routine approaches to treatment and prophylaxis. In practice, the choice of treatment is influenced not only by the intrinsic properties of the drug but also by the degree to which the locally-occurring parasites have developed specific patterns of drug resistance.

**Blood schizontocides**

These are the mainstay of the treatment of acute malaria and some are also used for prophylaxis. They include the 4-aminoquinolines (chloroquine and amodiaquine) and the related arylamino-alcohols (mefloquine and quinine). They suppress the disease by destroying the asexual blood forms of the parasites but, because they are not active against intrahepatic forms, they do not eliminate *P. vivax* and *P. ovale* infections in which some of these forms remain latent for months or even years.

These schizontocidal properties are shared by various antimetabolites (including pyrimethamine, sulfonamides and sulfones) and by some antibiotics (particularly tetracyclines). Because they act more slowly, these substances are of little value when used alone. However, some antimetabolites act synergistically in combination: pyrimethamine in combination with a sulfonamide or sulfone is a potent blood schizontocide. The tetracyclines are used primarily as adjuncts to quinine where multiple drug-resistant *P. falciparum* is prevalent.

**Tissue schizontocides**

Proguanil and chlorproguanil (an analogue with a considerably longer half-life) are pro-drugs which are

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transformed in the liver into the active metabolite cycloguanil. These are widely described as causal prophylactic agents since they are active against pre-erythrocytic intrahepatic forms, particularly of \textit{P. falciparum}. Currently-used dosage schedules for both are under review and other studies are in hand to determine whether the early liver forms of \textit{P. vivax} and \textit{P. malariae} are at least transiently susceptible. The latent persistent liver forms of \textit{P. ovale} and \textit{P. vivax} are unresponsive. \textbf{Primaquine}, unlike proguanil, is effective in eliminating the latent liver forms of \textit{P. ovale} and \textit{P. vivax} which persist after suppressive treatment with chloroquine. However, because of its toxicity and particularly the risk of haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, it is not suitable for prophylaxis.

The \textbf{tetracyclines} are active against tissue forms as well as blood forms of \textit{P. falciparum}. This effect has limited clinical application, however, because of their innate toxicity, particularly in the fetus and young child, as well as their suppressive effect on the normal bowel flora. Nonetheless, doxycycline has been used for short-term prophylaxis in non-pregnant adult travellers to areas of high multiple-drug resistance.

## Drugs under development

Few other substances have been shown to have potentially useful antimalarial activity. \textit{Artemisinin} (Qinghaosu), a plant extract, and some of its derivatives, are potent, rapidly-acting blood schizontocides when administered parenterally and they have important potential in the treatment of severe and complicated malaria. Other \textit{trioxanes} chemically related to artemesinin also hold promise and are currently being subjected to toxicological screening. \textit{Halofantrine} (Halfan®, Smith, Kline & French), one of three phenanthrene methanol derivatives known to have blood schizontocidal activity, has already been subjected to clinical trial and has recently been registered in France and several countries in Equatorial Africa (see page 58). Other new synthetic compounds in various stages of development include \textit{pyronaridine} and the \textit{hydroxynaphthoquinones}.

### Locus of action of antimalarial drugs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Biological Activity</th>
<th>Blood Schizontocide</th>
<th>Tissue Schizontocide</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Aminoquinolines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chloroquine</td>
<td></td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Aryaminoalcohols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>quinidine</td>
<td>++</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>quinine</td>
<td>++</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>mefloquine</td>
<td>++</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>proguanil</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>chlorproguanil</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>pyrimethamine</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>sulfadoxine</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>sulfalene</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>dapsone</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tetracycline</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>doxycycline</td>
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<td>+</td>
<td></td>
</tr>
<tr>
<td>minocycline</td>
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<td>+</td>
<td></td>
</tr>
<tr>
<td>8-Aminoquinoline</td>
<td></td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>
Chemotherapy of acute malaria

The successful management of patients with acute malaria demands the observance of several points of principle:
- whenever possible, the diagnosis should be confirmed before treatment by examination of blood smears.

- drugs used to treat *P. falciparum* malaria must always be selected with due regard to the prevalence of specific patterns of drug resistance.

- patients should always be supervised to ensure they swallow the prescribed tablets. If they are subsequently vomited, the same dose must immediately be readministered.

- patients not at risk of reinfection should be re-examined several weeks after treatment for signs of recrudescence which may result from inadequate chemotherapy or survival of persistent hepatic forms.

Supportive therapy in patients with severe and complicated malaria is directed to reducing hyperpyrexia, controlling convulsions and correcting hypoglycaemia. Severely anaemic patients may need blood transfusion, and exchange transfusion can be beneficial when there is intense parasitaemia. Peritoneal or haemodialysis can be life-saving if acute renal failure supervenes. Steroids have no place in the management of these conditions.

Chloroquine, administered orally, is a well-tolerated, safe, inexpensive and rapidly-acting blood schizontocide. It should be used to treat acute malaria wherever the parasites remain susceptible. *P. vivax, P. ovale* and *P. malariae* still remain fully sensitive to chloroquine. However, chloroquine-resistant strains of *P. falciparum* are now widespread in South-East Asia and South America. More recently, they have also been reported from East and, latterly, West Africa.

If subsequent relapse occurs in *P. ovale* and *P. vivax* infections primaquine should be administered, after a second course of chloroquine, to eliminate the intrahepatic infection.

Amodiaquine, a related compound, is of limited value where substantial chloroquine resistance is widespread since cross-resistance is common. Cases of agranulocytosis have occurred among travellers who had taken it prophylactically for long periods and it is no longer recommended for this purpose.

Because *P. falciparum* and *P. vivax* rapidly develop resistance to *pyrimethamine* it is no longer used alone but always in combination, either with a sulfonamide, particularly *sulfadoxine* or *sulfalene*, or the sulfone, *dapsone*. Resistance is now widespread, even to these combinations, particularly in South-East Asia and South America and, more recently, in East and Central Africa. However, they retain their value in some areas of high chloroquine resistance.

Because of the need for a rapid response, severe *P. falciparum* malaria should be treated initially by slow intravenous infusion of *quinine*. When necessary, quinine may be replaced by its stereoisomer, *quinidine*, but intensive cardiovascular monitoring is then required. When neither quinine nor quinidine is available, parenteral chloroquine may offer the only effective available therapy for severe malaria but it is dangerously toxic when injected intravenously as a bolus injection. It should be administered over a period of not less than 8 hours either by continuous infusion or by small, frequent intramuscular or subcutaneous injections.

In less severe infections *quinine* may be administered orally either alone or in combination with *tetracycline*. In these circumstances, it should be reserved for infections likely to be unresponsive to other drugs. Resistance to quinine was, until recently, rare, but there are ominous indications that the prevalence of such strains is increasing in South-East Asia and South America.

Much reliance is now vested in the newly-introduced blood schizontocide, *mefloquine*. No parenteral preparations are currently available, and it is thus suitable only for patients who can take drugs by mouth. It is well tolerated and currently effective in a single dose against the blood forms of all malaria parasites. However, because of the danger of the emergence of mefloquine-resistant strains of *P. falciparum* it should be used only in areas with a high prevalence of multiple-drug resistance, and where strict governmental control of its importation, distribution and utilization has been recommended. The paramount need to suppress the emergence of resistant strains resulted in a recommendation that mefloquine be administered routinely in combination with *pyrimethamine/sulfadoxine*. Whether this regimen holds true advantage in this regard is now disputed, and, because of the associated risk of sulfonamide-induced toxicity, the World Health Organization has initiated further studies to compare the efficacy of different mefloquine-based treatment regimens more precisely.
Chemoprophylaxis

Acquired immunity offers the most reliable protection for people living permanently in endemic areas. Approaches to chemoprophylaxis for persons visiting endemic areas are maintained under constant review by the World Health Organization. For recommendations operative in specific countries the reader is referred to the current, annually-revised WHO booklet, "Vaccination Certificate Requirements and Health Advice for International Travel".

No widely available drug regimen gives assured protection to everybody, and indiscriminate use of existing antimalarials unnecessarily increases the risk of inducing resistance. Chloroquine, which is usually well-tolerated at the required dosage, is widely used where *P. falciparum* remains fully sensitive. Greater reliance may, in future, be placed on the causal prophylactic agents proguanil and chlorproguanil in areas where chloroquine resistance occurs. Simultaneous use of chloroquine and proguanil may hold advantage in areas with a marginal incidence of chloroquine-resistant *P. falciparum*. Both mefloquine and doxycycline have been used in areas where multiple-drug resistance has been reported. The value of doxycycline is compromised by its adverse effects on bone and tooth development and more information is required concerning the clinical performance of both drugs. Because of widespread resistance, pyrimethamine is no longer used alone for prophylaxis, and other drugs are associated with too great a risk of toxicity to be used in this way even when they are administered on a short-term basis.

Many travellers at risk of exposure to *P. falciparum* resistant to both chloroquine and proguanil, need to rely primarily on protection against mosquito bites and prompt treatment should fever occur. If there is a likelihood that medical attention will not be immediately available, a supply of an appropriate anti-malarial should be carried for “stand-by” treatment pending medical advice. If complete elimination of infection is to be assured a non-immune visitor leaving an endemic area should continue to take prophylactic therapy for as long as latent forms are likely to remain viable in the liver. Risk of recrudescence of *P. falciparum* and *P. malariae* infections is remote if prophylaxis is maintained for six weeks after the last risk of exposure.

Drugs used during pregnancy

Women living in endemic areas in which *P. falciparum* remains sensitive to chloroquine should take chloroquine prophylactically throughout pregnancy. It may also be used at full dosage to treat chloroquine-sensitive infections. Proguanil can also be safely taken during pregnancy in areas where *P. falciparum* remains sensitive. Elsewhere, reliance needs to be placed upon avoidance of mosquito contact, prompt diagnosis of infection and treatment with quinine, since other widely-available drugs are both less effective and too toxic to be used prophylactically. Quinine is the only widely available drug that is accepted as suitable for treating chloroquine-resistant infections during pregnancy. The use of mefloquine for both prophylactic and therapeutic use during pregnancy in areas where multiple-drug resistance occurs remains under investigation.

Chloroquine

tablet containing 150 mg base
(as phosphate or sulfate)
syrup 50 mg base (as phosphate or sulfate) per 5 ml
injection 50 mg base (as phosphate or sulfate) per ml in 2 ml ampoule*

Policy regarding the use of this drug as an antimalarial must be determined nationally since in many areas *P. falciparum* is now resistant to chloroquine. It may still be used effectively, however, in areas where low-grade *P. falciparum* resistance is reported, especially in persons likely to have acquired a significant degree of immunity, and also wherever *P. vivax* is the predominant parasite.

Chloroquine is a 4-aminoquinoline which has marked, rapid schizonticidal activity against blood forms of *P. vivax*, *P. ovale* and *P. malariae* and against susceptible strains of *P. falciparum*. It is also gametocytocidal against *P. vivax*, *P. ovale* and *P. malariae* and immature *P. falciparum*. It is not active against intrahepatic forms.

Absorption is efficient following oral administration and peak plasma concentrations occur within 2 - 3

*No parenteral formulation is included in the WHO Model List of Essential Drugs since quinine is preferred for parenteral use.
hours. The drug and its metabolites can be detected in the plasma for up to 56 days and in the urine for up to 120 days.

**Uses**

**Treatment of acute malarial attacks:**

- *P. malariae* and susceptible *P. falciparum* infections are eliminated by treatment with chloroquine alone.

- When there is little or no likelihood of immediate reinfection, elimination of naturally-acquired *P. vivax* and *P. ovale* infections requires subsequent administration of primaquine to eliminate persistent intrahepatic forms (hypnozoites). These forms do not occur in infection acquired congenitally, or from transfusions or other contaminated injections.

Prophylaxis for pregnant women and non-immune individuals at risk.

**Dosage and administration**

All dosages are described in terms of the base.

**Treatment**

**Oral administration**

To avoid nausea and vomiting chloroquine should be administered after meals. If part or all of a dose is vomited, it must immediately be readministered.

**Adults including pregnant women:**

Total dose: 1500 mg (or approximately 25 - 30 mg/kg) given over three days.

Day 1: 900 mg (600 mg as first dose, 300 mg eight hours later)

Days 2 and 3: 300 mg in a single dose.

The three day course is sufficient to eliminate susceptible *P. falciparum* infections since effective antimalarial plasma concentrations are sustained for several weeks. No further treatment is required in patients removed from risk of reinfection.

**Children:**

Total dose: 25 mg/kg given over three days (as tablet or suspension).

This is conveniently administered in three doses:

Days 1 and 2: 10 mg/kg

and Day 3: 5 mg/kg.

However, it has been claimed that better results are obtained by boosting the first dose as follows:

Day 1: first dose 10 mg/kg; eight hours later 5 mg/kg

Days 2 and 3: 5 mg/kg.

**Parenteral administration**

Parenteral administration of chloroquine should be considered when the patient is unable to take drugs orally and when neither quinine nor quinidine is available. Excessively-rapid administration results in toxic peak plasma concentrations and a danger of fatal cardiovascular collapse.

The initial dose of 10 mg/kg should be administered over a period of not less than 8 hours, preferably by very slow intravenous infusion. This should be repeated every 8 hours until a total dose of 25 mg/kg has been given.

Infusions should be discontinued as soon as the patient is able to take chloroquine by mouth.

Where facilities for intravenous infusion are not available chloroquine can be administered by intramuscular or subcutaneous injection at a dosage of 2.5 mg/kg every 4 hours or 3.5 mg/kg every 6 hours until a total of 25 mg/kg has been given.

**Prophylaxis**

**Adults including pregnant women:** 300 mg weekly

**Children:** 5 mg/kg/weekly.

This regimen has been employed effectively even in areas of marginal resistance. However, it must be followed meticulously and be maintained in pregnant women until after delivery and for at least six weeks after the last risk of exposure in the case of non-immune individuals. This is sufficient to assure elimination of *P. falciparum* and *P. malariae*, but not of *P. vivax* and *P. ovale*, in which residual hepatic forms survive.

**Contraindications**

Known hypersensitivity to chloroquine.

Treatment of *P. falciparum* malaria which is likely to be resistant to chloroquine.
Precautions

If the condition of the patient continues to deteriorate after administration of chloroquine, resistance must be suspected and quinine must be administered intravenously as an emergency measure.

Use in pregnancy

There is no evidence that chloroquine is harmful in suppressive doses during pregnancy. Because of the susceptibility of pregnant women to falciparum malaria, it should be used at the recommended dosage for both prophylaxis and treatment wherever chloroquine-sensitive malaria is prevalent.

Adverse effects

Serious adverse effects are rare at the dosages used for malaria, but pruritus, which may be intolerable, is common among Africans and has also been reported from South and Central America and South-East Asia. It can often be alleviated by calamine lotion but because it compromises compliance it may be advisable, in the event of re-infection, to use an alternative, effective and rapidly-acting blood schizontocide. Transient headaches and gastrointestinal symptoms are occasionally troublesome.

In susceptible individuals, severe attacks of acute intermittent porphyria and of psoriasis may be precipitated. The former may simulate an attack of cerebral malaria. When the diagnosis is in doubt the urine should be tested for porphobilinogen.

Irreversible visual impairment resulting from accumulation of chloroquine in the retina is a recognized complication of long-term, high dosage therapy. It has rarely, if ever, resulted from doses recommended for malaria prophylaxis. However, it is advisable to ensure that total life-time exposure to chloroquine does not exceed 100 g of the base.

Overdosage

Acute chloroquine poisoning is often fatal: oral doses as low as 50 mg base/kg can be lethal. Nausea, vomiting and drowsiness occur rapidly and are followed by slurring of speech, agitation, breathlessness due to pulmonary oedema, convulsions, coma, impaired vision and cardiac dysrhythmias.

If the patient is seen within a few hours of the event, emesis must be induced or gastric lavage undertaken as rapidly as possible. Otherwise, treatment is symptomatic and is directed particularly to sustaining cardiovascular and respiratory function. Diazepam may help to control convulsions.

Storage

Chloroquine tablets should be kept in well-closed containers, protected from light and moisture.

Quinine

tablet 300 mg base (as bisulfate or sulfate)

injection 300 mg base (as dihydrochloride) per ml in 2 ml ampoule

Quinine, an alkaloid derived from the bark of the cinchona tree, is a blood schizontocidal agent which is more toxic than chloroquine. Its importance has become re-established because of the widespread emergence of chloroquine-resistant — and, more recently, multiple-drug-resistant strains — of malarial parasites.

Quinine is rapidly absorbed when taken orally and peak plasma concentrations are attained after 1 - 3 hours. It is highly protein-bound but it readily crosses the placental barrier and small amounts penetrate into the cerebrospinal fluid. It is metabolized in the liver, has a plasma half-life of 10 hours and is subsequently excreted in the urine, very largely as hydroxylated metabolites.

Uses

Quinine is used in the treatment of P. falciparum malaria in areas of multiple-drug-resistant P. falciparum.

- it is administered intravenously by slow infusion, in the emergency treatment of all patients seriously ill with severe or complicated malaria who cannot take drugs by mouth because of coma, convulsions, vomiting or diarrhoea.

- it is administered orally in less seriously ill patients with infections likely to be resistant to chloroquine, sometimes in combination with pyrimethamine/sulfadoxine or a tetracycline.
**Dosage and administration**

All dosages are described in terms of the base.

**Intravenous administration**

The required dose, diluted preferably in 5% glucose solution to counteract hypoglycaemia, is given in a total volume of 10 ml/kg by infusion into a large vein. In the absence of glucose, normal saline may be used. This method of administration minimizes the danger of severe hypotension and subsequent respiratory collapse and thromobphlebitis. Where facilities for intravenous infusion do not exist, quinine can be administered intramuscularly in doses of 10 mg/kg every 8 hours. This is an option of last resort, however, since quinine is highly irritant and is liable to cause focal necrosis and abscess formation.

**Adults and children:** 10 mg/kg is infused over 4 hours and repeated every 8 - 12 hours. In severely ill adults an initial infusion of 20 mg/kg may be more effective, but such high doses can be given with adequate safety only when it is certain that the patient has not already been treated with quinine or mefloquine and when cardiac monitoring can be undertaken. Pulse and blood pressure should be closely monitored during administration and the rate of infusion attenuated if dysrhythmias occur.

Infusions should be discontinued as soon as the patient is able to take quinine orally.

Maintenance dosages should be reduced threefold in patients with impaired renal function.

When quinine is not available, and provided electrocardiographic monitoring can be undertaken, quinidine may be administered. An initial loading dose of 15 mg/kg in normal saline is given over 4 hours. This is followed by a maintenance dose of 7.5 mg/kg infused every 8 hours until the patient is able to take quinidine by mouth.

**Oral administration**

Whenever practicable, quinine should be given orally. If part or all of a dose is vomited within 1 hour it must be readministered immediately.

**Adults:** 600 mg every eight hours for 3 - 7 days.

**Children:** 10 mg/kg every eight hours for 3 - 7 days.

**Contraindications**

Known hypersensitivity to quinine.

**Precautions**

Whenever possible, blood glucose should be monitored throughout treatment. Both the disease itself and the administration of quinine may promote insulin secretion and induce hypoglycaemia. This may require correction by infusion of a more concentrated (50%) glucose solution.

Haemolysis can occasionally be severe enough to warrant discontinuation of treatment; its occurrence is not apparently correlated with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

**Use in pregnancy**

Quinine should not be withheld during pregnancy, despite its alleged abortifacient properties at high dosage, since it safeguards the life of the mother. When it is administered intravenously, the infusion rate should not exceed 10 mg/kg every 8 hours.

**Adverse effects**

Serious reactions are infrequent provided the plasma concentration is not allowed to rise above 5 mg/l. Signs of mild to moderate cinchonism (tinnitus, headache, blurred vision, altered auditory acuity, nausea and diarrhoea) often supervene after the third day of treatment. These rarely, if ever, constitute grounds for withdrawal, but if, as a result of non-compliance, quinine has to be withdrawn prematurely, tetracycline must be administered for a further 7 days.

Idiosyncratic reactions can also occur, but they are uncommon. They include pruritic, urticarial or erythematous rashes, subcutaneous or submucous haemorrhage, and oedema of the eyelids, mucous membranes and lungs. Haemoglobinuria and asthma are rare.

Hypoglycaemia should be treated with supplementary glucose.

Renal damage, culminating in acute renal failure and anuria, is a frequent terminal event in malaria. Rarely, anuria is a consequence of black-water fever, a syndrome comprising massive haemolysis, haemo-
globinaemia and haemoglobinuria. Although this has been ascribed in the past to inadequate quinine therapy the supporting evidence is insecure. Black-water fever certainly occurs in patients who have not received treatment with quinine.

Dose-related adverse effects are largely limited to the cardiovascular, gastrointestinal and central nervous systems. They usually arise from excessive infusion, but accumulation can also result from oral administration.

**Overdosage**

The most frequently encountered signs of overdosage are:

- Tinnitus, decreased auditory acuity and vertigo. Permanent deafness has resulted from exposure to toxic doses.

- Amblyopia, constricted visual fields, diplopia and night blindness. Recovery is slow but usually complete.

- Quinidine-like effects resulting in hypotension, conduction disturbances, anginal symptoms and ventricular tachycardia.

- A local irritant effect on the gastrointestinal tract resulting in nausea, vomiting, abdominal pain and diarrhoea.

A single oral dose greater than 3 g is capable of causing serious and potentially fatal intoxication in adults. Much smaller doses can be lethal in children.

Dysrhythmias, hypotension and cardiac arrest can result from the cardiotoxic action and ocular toxicity can lead to blindness.

Emesis should be induced and gastric lavage undertaken as rapidly as possible. Activated charcoal should then be administered.

Supportive measures, to be employed as necessary, include intubation and ventilation, and symptomatic treatment of dysrhythmias, cardiac failure and convulsions. No specific measures of proven efficacy exist to reduce the toxicity or to promote the excretion of quinine.

**Storage**

Quinine sulfate or bisulfate tablets should be stored in tightly closed containers, protected from light. Quinine dihydrochloride injection should be stored protected from light.

**Pyrimethamine/Sulfadoxine**

tablet 25 mg/500 mg

A combination product containing two compounds that are presumed to act synergistically to inhibit folic acid synthesis: a dihydrofolate reductase inhibitor, pyrimethamine, and a dihydropteroate synthetase inhibitor, sulfadoxine. It has blood schizontocidal activity against *P. falciparum* and, to a lesser extent, *P. vivax*. The two constituents were first used in combination, following rapid development of resistance to pyrimethamine alone, to treat *P. falciparum* infections unresponsive to chloroquine. Strains of *P. falciparum* and *P. vivax* resistant to this combination are now widespread in many areas.

Both components are efficiently absorbed after oral administration. The plasma half-life of pyrimethamine is about 4 days and that of sulfadoxine about 8 days. Both substances are ultimately excreted in the urine, pyrimethamine partly as metabolites.

**Uses**

Treatment of acute attacks of malaria caused by susceptible strains of *P. falciparum*

- in areas where chloroquine-resistant organisms are known to occur, and

- in patients who, because of previous chloroquine-induced pruritus or for other reasons, are advised not to take chloroquine.

**Dosage and administration**

*Treatment of clinical attacks*

Adults: pyrimethamine 75 mg plus sulfadoxine 1.5 g (3 tablets)
Children:

31 - 45 kg: 2 tablets
21 - 30 kg: 1 1/2 tablet
11 - 20 kg: 1 tablet
5 - 10 kg: 1/2 tablet

A single dose usually suffices to eliminate infection, but quinine should additionally be given for 1 - 3 days to:

- severely infected patients since use of the combination may accelerate reduction of parasitaemia and clinical improvement;

- non-immune patients at risk of fulminating disease, having regard to the rapid emergence of pyrimethamine/sulfadoxine-resistant strains.

Contraindications

Known hypersensitivity to sulfonamides or pyrimethamine.

Pregnant women and nursing mothers.

Severe hepatic or renal dysfunction (except when no alternative treatment is available).

Precautions

Patients who develop signs suggestive of sulfonamide or pyrimethamine sensitivity should never receive drugs containing these substances again. These signs include skin rashes, evidence of haemolysis including dark urine and purpura and presumptive signs of bone marrow depression such as sore throat and mouth ulcers.

Use in pregnancy

Quinine should be used, whenever possible, to treat chloroquine-resistant malaria during pregnancy. Administration of sulfonamides can induce severe hypersensitivity reactions in the mother. They readily cross the placental barrier and their action in displacing bilirubin from protein-binding sites has given rise to concern, based on data derived from premature neonates, that they may promote kernicterus. There is no adequate direct evidence, however, that the fetus is similarly at risk.

Adverse effects

Adverse reactions to pyrimethamine are usually dose-related and reversible. Anorexia, abdominal cramps, vomiting, ataxia, tremors, seizures and megaloblastic anaemia resembling that of folic acid deficiency have been reported.

Sulfonamide-induced hypersensitivity reactions, although uncommon, can be severe. They include life-threatening cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Other infrequent reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis may occur in G6PD-deficient individuals.

Pyrimethamine/sulfadoxine is no longer recommended for routine prophylaxis or treatment of malaria sensitive to chloroquine because serious sulfonamide-induced adverse reactions have been reported to occur with an incidence of 1:5000 to 1:8000 in patients on prophylactic treatment. No comparable data are available to establish the magnitude of the risk associated with single therapeutic doses.

Drug interactions

Monitoring of the total and differential blood count is particularly important when other folate inhibitors (such as trimethoprim, methotrexate, anti-convulsants) are taken concurrently.

Overdosage

High doses of pyrimethamine are potentially fatal. Prominent symptoms of overdosage are anorexia, vomiting and seizures. Induction of emesis or gastric lavage is of value if undertaken within a few hours of ingestion. Convulsions may be controlled with parenteral diazepam.

Blood dyscrasias, which may be induced by large doses of pyrimethamine, should be treated with folinic acid.

Storage

Pyrimethamine/sulfadoxine tablets should be kept in well-closed containers protected from light and moisture.
Primaquine

tablet 7.5 mg base (as diphosphate)

An 8-aminoquinoline derivative with a potent action against the intrahepatic forms of all human malaria parasites, but which is too toxic to be used routinely for causal prophylaxis. It also has a gametocytocidal effect against all species.

Primaquine is readily absorbed when taken orally. Peak plasma concentrations occur within 1 - 3 hours and the plasma half-life is less than 5 hours. It is rapidly metabolized in the liver and only a small amount is excreted unchanged in the urine.

Uses

Elimination of intrahepatic forms of *P. vivax* and *P. ovale* (hypnozoites) after standard chloroquine therapy when risk of subsequent re-exposure is absent or slight. In areas of intense transmission, blood schizontocides alone are used to treat relapses and reinfections.

Elimination of gametocytes of *P. falciparum* following routine therapy with a blood schizontocide, particularly in areas where there is a potential for reintroduction of malaria.

Dosage

Primaquine is administered orally. All dosages are described in terms of the base.

Radical treatment of *P. vivax* and *P. ovale* malaria:

**Adults:** 0.25 mg/kg or 15 mg daily for 14 days following standard chloroquine therapy or, if G6PD deficiency is known or suspected, 0.75 mg/kg weekly for 8 weeks.

**Children over 1 year:** 0.25 mg/kg daily for 14 days as above.

**Gametocytocidal therapy:** 0.5-0.75 mg/kg in a single dose.

Contraindications

Pregnant women.

Any condition that predisposes to granulocytopenia, including active rheumatoid arthritis and lupus erythematosus.

Precautions

Blood and urine should be examined periodically for evidence of haemolysis.

Patients should be warned to stop treatment and report immediately to a doctor if they become weak, pale or notice marked darkening of the urine.

When possible, glucose-6-phosphate dehydrogenase (G6PD) deficiency should be excluded before the standard therapeutic dosage is administered. Intravascular haemolysis, when it occurs, can be severe, although it is generally mild and self-limiting even in areas where G6PD deficiency is common.

Primaquine administered as a gametocytocidal measure in a single dose is usually well tolerated. Prior testing for G6PD deficiency is not required in these circumstances.

Adverse effects

Dose-related gastrointestinal symptoms include anorexia, nausea and abdominal pain.

Acute haemolytic anaemia occurs most frequently in patients with G6PD deficiency. It is usually self-limiting but in severe cases blood transfusion may be necessary.

Methaemoglobinemia, haemoglobinuria, agranulocytosis, granulocytopenia and leukopenia occur rarely.

Drug interactions

Primaquine should not be administered concurrently with any other drug that is likely to induce haemolysis or bone marrow depression.

Overdosage

Gastrointestinal symptoms, weakness, methaemoglobinemia, cyanosis, haemolytic anaemia, jaundice and bone marrow depression may occur. There is no specific antidote and treatment is consequently symptomatic.
Storage
Primaquine tablets should be kept in well-closed containers, protected from light.

Mefloquine hydrochloride
Tablets containing 250 mg base (as hydrochloride)

Mefloquine, a 4-aminoquinoline methanol, is a relatively new blood schizontocide which, like chloroquine, is active against the asexual blood stages of all malaria parasites. It is also active against the gametocytes of P. vivax, P. ovale and P. malariae.

Absorption from the gastrointestinal tract is rapid. The compound is almost completely bound to plasma proteins and plasma concentrations decay with a half-life varying from 15 to over 30 days. Very little of the administered dose is excreted unchanged in the urine.

Uses
Treatment of acute attacks of malaria due to multiple-drug-resistant strains of P. falciparum.

Prophylaxis for travellers to areas with a high prevalence of multiple-drug resistant P. falciparum.

Dosage
All dosages are described in terms of the base.

Treatment
Adults: 18 - 20 mg/kg (750 - 1250 mg), either as a single dose or, above 750 mg, in two divided doses.

Children: 25 mg/kg as a single dose.

Prophylaxis
Adults and children of more than 45 kg: 250 mg weekly.

Contraindications and precautions
Mefloquine-containing preparations should be used only where multiple-drug resistance has been reported.

It is contraindicated in persons taking cardioactive drugs, particularly beta-adrenoceptor and calcium-channel-blocking agents since it has been associated with asymptomatic sinus bradycardia.

As yet there is no clinical experience with the use of mefloquine in infants and young children.

Use in pregnancy
The prophylactic and therapeutic use of mefloquine during pregnancy remains under investigation. At present, it should be used in early pregnancy only if alternative drugs are either not available or unlikely to be effective.

Adverse effects
Mefloquine is, in general, well tolerated but dose-related adverse effects, including nausea and dizziness, can be severe. Mild to moderate reactions include disturbed sense of balance, vomiting, diarrhoea, abdominal pain and loss of appetite. Other rare effects include headache, bradycardia, rash, pruritus, feeling of weakness and neuropsychiatric manifestations.

Drug interactions
Concurrent use of quinine can potentiate the dose-related adverse effects of mefloquine. In general mefloquine should not be administered within 12 hours of the last dose of quinine.

Overdosage
Induction of emesis and gastric lavage are of value if undertaken within a few hours of ingestion.

Storage
Mefloquine hydrochloride tablets should be kept in well-closed containers protected from moisture.
Tetracycline hydrochloride

capsule or tablet 250 mg

Tetracycline is a broad-spectrum antimicrobial antibiotic which has a potent but slow action against the asexual blood stages of all plasmodial species. It is also active against the primary intrahepatic stages of *P. falciparum*. The closely related substances doxycycline and minocycline share the same actions.

Absorption of tetracycline from the gut 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.

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.

Tetracyclines cross the placenta and are excreted into breast milk.

**Uses**

It is employed primarily as a supplement to quinine in the treatment of *P. falciparum* malaria when resistance to quinine has been reported and in patients in whom pyrimethamine/sulfadoxine is contraindicated because of hypersensitivity to sulfonamides.

Because of its slow time-course of action tetracycline should never be used alone in the treatment of malaria. Neither is it suitable for extended prophylactic use which could promote the development of resistance not only in plasmodial species, but also in a wide variety of susceptible bacteria. However, preliminary studies in non-pregnant adults indicate that the related compound, doxycycline 100 mg daily, may be of value for short-term prophylaxis in areas of high transmission for *P. falciparum* where other drugs are likely to be ineffective.

**Dosage**

Tetracycline should always be administered orally in the treatment of malaria.

**Adults and children over 8 years:**

Orally 250 mg 4 times daily for 7 - 10 days.

**Contraindications**

Known hypersensitivity to tetracyclines.

Pre-existing severe hepatic or renal damage. Doxycycline, which is not excreted significantly in the urine, is preferred in patients with renal impairment.

Children under 8 years of age, in whom tetracyclines cause hypoplasia of dental enamel, permanent brown discoloration of teeth and retardation of bone growth.

**Precautions**

Oesophagitis, which can be troublesome, may be averted if the patient is propped up for a few minutes while the tablets are swallowed, and if they are always washed down immediately with a glass of water. Other symptoms of gastrointestinal irritability can be reduced if tetracycline is taken with a meal, but milk products must be avoided since they reduce absorption.

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. However, in regions where *P. falciparum* infections are not reliably responsive to quinine alone, the benefits of concomitant tetracycline therapy can outweigh the risks.

**Adverse effects**

Gastrointestinal irritation is common. So, also, is depletion of the normal bowel flora permitting over-
growth of resistant organisms. Irritative diarrhoea should be differentiated from enteritis due to suprainfection, particularly with coagulase positive staphylococci, and from pseudomembranous colitis due to Clostridium difficile.

Phototoxic reactions occasionally result in porphyria-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 due to 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 pseudotumor 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 taking tetracyclines.

Storage

Tetracycline capsules or tablets should be kept in well-closed containers, protected from light.

Proguanil tablet 100 mg

Proguanil is a synthetic biguanide derivative of pyrimidine which is highly active against the preerythrocytic intrahepatic forms of P. falciparum. Its effect on the primary intrahepatic forms of other species is less well documented. There is evidence that it may be effective in P. vivax only immediately after the initial infection. It has no activity on the latent intrahepatic forms (hypnozoites) of P. vivax and P. ovale. It also has some schizontocidal activity, but this effect is slow and has no established clinical application.

Foci in which P. falciparum is resistant to proguanil and related compounds occur everywhere that malaria is endemic and particularly where it has previously been employed in mass prophylaxis.

Absorption from the gastrointestinal tract is rapid and peak concentrations are attained in the plasma about 4 hours after administration. It has a plasma half-life of 12 - 16 hours and is excreted in the urine and faeces both unchanged and as its active metabolite, cycloguanil.

Uses

Prophylaxis for pregnant women and non-immune individuals at risk of exposure.

It is often used together with chloroquine for short-term prophylaxis in travellers to areas with a marginal incidence of chloroquine-resistant P. falciparum.

Dosage and administration

Adults (including pregnant women): 200 mg daily.

Children: < 1 year 25 mg daily
1 - 4 years 50 mg daily
5 - 8 years 75 mg daily
9 - 12 years 100 mg daily

This regimen is generally effective even in areas where breakthrough resistance has been reported with previously recommended lower dosage regimens. However, the recommended treatment schedule must be followed meticulously and be sustained until after delivery in the case of pregnant women and for 6 weeks after the last risk of exposure to infected mosquitos in the case of non-immune individuals. This is sufficient to assure elimination of P. falciparum and P. malariae, but not of P. vivax and P. ovale in which residual hepatic forms often survive for long periods.

Contraindications and precaution

Proguanil should not be used in areas with known resistance either to proguanil or pyrimethamine since cross-resistance readily occurs.
Because haematuria has been reported following overdosage, the use of proguanil should be carefully considered in patients with renal impairment.

Use in pregnancy

There is no evidence that proguanil is harmful in suppressive doses during pregnancy. Because of the vulnerability of pregnant women to falciparum malaria, it should be used at full prophylactic dosage wherever the disease is prevalent and likely to be responsive to proguanil, if chloroquine is not available or is unlikely to be effective.

Adverse effects

Occasionally patients develop mouth ulcers during treatment but, at the recommended prophylactic dosage, proguanil is generally well tolerated.

Overdosage

Gross overdosage gives rise to abdominal pain, vomiting, diarrhoea and haematuria. No specific antidote exists and symptoms should be treated as they arise.

Storage

Store in well-closed containers.
Newly Registered Products

**alfacalcidol**
1-alpha-hydroxy vitamin D
One-alpha®: Leo, Ireland
oral solution 0.2 µg/ml
*Indications:* uraemic bone disease, hypo- and hyperparathyroidism, osteoporosis, rickets; prophylactic and therapeutic use in infants of low birth weight.

**alteplase**
recombinant tissue plasminogen activator (TPA), a glycoprotein which promotes conversion of plasminogen to plasmin.
Activase®: Genentech, USA
Actilyse®: Boehringer Ingelheim, Austria, Luxembourg
powder for injection 20 mg/ampoule
*Indication:* fibrinolytic therapy in acute coronary thrombosis.
*Contraindications:* increased bleeding tendency, internal bleeding, cerebral bleeding, severe cardiovascular disease, recent trauma or major surgery, uncontrolled severe hypertension, bacterial endocarditis, acute pancreatitis, severe diabetes mellitus, diabetic retinopathy, sickle-cell anaemia.
*Caution:* safety not established during pregnancy and lactation or in children.
*Adverse effects:* spontaneous bleeding, cardiac dysrhythmias.

**aztreonam**
lactamase-resistant antibiotic
Azactam®: Squibb, Austria, Finland
powder for injection 1 g/ampoule
*Indications:* infections due to susceptible microorganisms.
*Caution:* For hospital use only.

**benzbromarone**
uricosuric agent
Besuric®: Labaz, Luxembourg
tablet 100 mg
*Indications:* gout, idiopathic hyperuricaemia.

**betaxolol**
beta-adrenoreceptor blocking agent
Alcon®: Alcon-Fin, Finland
eyedrops 5 mg/ml
*Indication:* open-angle glaucoma.

**bisoprolol fumarate**
beta-adrenoreceptor blocking agent
Emconcor®: Merck, Belgium
coated tablet 10 mg
*Indications:* hypertension, angina pectoris, cardiac dysrhythmia.

**budesonide**
glucocorticosteroid
Pulmicort®: Astra, Austria
aerosol 0.2 mg/puff
*Indications:* bronchial asthma and chronic obstructive bronchitis.

**buserelin**
synthetic analogue of luteinizing hormone releasing factor
Suprefact®: Behringwerke, Austria
Boehringer Ingelheim, Iceland
Hoechst, Ireland
**** injection fluid 0.1, 1 mg/ml
**Indications:** advanced prostatic cancer when suppression of testicular hormones is required.

**cadexomer iodine**

disinfectant
Iodosorb®: SK-RIT, Belgium
powder 100/
**Indications:** dressing for decubitus ulcer.

**carboplatin**
cytostatic
Paraplatin®: Bristol, Belgium
powder for injection 50, 150, 450 mg/ampoule
**Indications:** ovarian cancer, small-cell lung cancer, carcinoma of the head and neck.

**carteolol**
beta-adrenoreceptor blocking agent
Caltidren®: Liphar, Belgium
tablet 20 mg
**Indications:** mild to moderate hypertension, angina pectoris.

**cefamandole**
cefalosporin antibiotic
Kefadol®: Lilly, Ireland
powder for injection 750 mg
**Indications:** infections with susceptible microorganisms, prophylaxis in surgery.

**cefmenoxime**
cefalosporin antibiotic
Cemix®: Erga, Belgium
powder for injection 0.5, 1 g/ampoule
**Indications:** severe infections in adults due to susceptible microorganisms.
**Contraindication:** meningitis.

**ceftizoxime**
cefalosporin antibiotic
Cefizox®: Wellcome, Netherlands
powder for injection 0.5, 1, 2 mg/ampoule
**Indications:** infections due to susceptible microorganisms.

**ciclopirox olamine**
antimycotic
Batrafen®: Hoechst, Ireland
solution 1%
**Indication:** topical treatment of skin infection.

**ciprofloxacin**
quinolone antibiotic
Ciproxin®: Bayer
Australia: tablet 250, 500, 750 mg
Austria: coated tablet 100, 250, 500, 750 mg;
capsule 250 mg; injection fluid 1, 2 mg/ml
Finland: capsules 250 mg; injection fluid 10 mg/ml
**Indications:** infections due to susceptible microorganisms involving the genitourinary tract, respiratory and gastrointestinal tract, skin and soft tissues, bones and joints; recurrent exacerbation of severe infections in patients with mucoviscidosis; peritonitis; active chronic otitis media; panophthalmitis; prophylaxis in immunocompromised patients. Gonorrhoea.

**clemastine**
antihistamine
Allereze®: Intercare, Ireland
elixir 0.1 mg/ml
**Indications:** allergic conditions.

**collagen (equine)**
Tachotop®: Hormon-Chemie, Austria
desiccated foam pads
**Indication:** treatment of bleeding resulting from dental surgery and small wounds.

**dacarbazine**
cytostatic
Dacatic®: Orion, Finland
powder for injection 100 mg/ampoule
**Indications:** malignant melanoma, sarcoma, Hodgkin's disease.

**deflazacort**
glucocorticosteroid
Flantadin®: Lepetit, Italy
tablet 6 mg, 30 mg
**Indications:** adrenocortical insufficiency, rheumatic disease, collagen and selected skin diseases, allergic conditions, selected respiratory and ocular disease, haematologic disorders, selected malignancies, oedema, gastro-intestinal disease.
Contraindications: active tuberculosis, peptic ulcer, herpetic eye infection, systemic mycotic infection, psychoses.

Precautions, warnings and adverse effects as usual for other drugs of this class.

**desogestrel + ethinylestradiol**
oral contraceptive
Desolett®: Organon, Sweden
tablet 0.15 mg + 30 µg
*Indications*: contraception, functional dysmenorrhoea.

**diacerein**
nonsteroidal anti-inflammatory agent
Artrodar®: Proter, Italy
capsule 25, 50 mg
*Indication*: osteoarthritis.
*Contraindication*: hypersensitivity.
*Caution* in patients with a history of enterocolitis. Safety not established during pregnancy or lactation.

**doxefazepam**
benzodiazepine tranquilizer
Doxans®: Schiapparelli, Italy
capsule 10 mg
*Contraindications, precautions and warnings* as for other drugs of this class.

**enflurane**
inhalation anaesthetic
Allyrane®: Anaquest, Ireland
liquid 100%
*Indication*: induction and maintenance of general anaesthesia.

**flumazenil**
benzodiazepine antagonist
Anexate®: Roche, Austria, Luxembourg
injection fluid 0.5, 1 mg/ml
*Indications*: reversal of the central effect of benzodiazepines, as required, during anaesthesia and intensive care.

**flutamide**
antiandrogenic cytostatic
Flugerel®: Essex, Austria
Drogenil®: Essex, Ireland
tablet 250 mg

*Indications*: palliative treatment of advanced prostatic carcinoma.

**ipratropium bromide (1)**
anticholinergic
Atrovent®: Boehringer Ingelheim, Ireland
solution 5 mg/ml
*Indication*: reversible airways obstruction.

**ipratropium bromide (2)**
anticholinergic
Bitrop®: Boehringer Ingelheim, Luxembourg
Itrop®: Boehringer Ingelheim, Switzerland
tablets 10 mg, injection fluid 0.5 mg/ml
*Indications*: sinus bradycardia of vagal origin, atrial fibrillation, bradycardia with sinoatrial block, atrioventricular block.
*Contraindications*: glaucoma, prostatic hypertrophy, gastrointestinal stenosis, megacolon, tachycardia.

**leuprorelin**
synthetic analogue of luteinizing hormone releasing factor
Lupron®: Abbot; Iceland, Sweden
injection fluid 5, 25 mg/ml
*Indications*: advanced prostatic cancer when orchidectomy is not indicated.

**lidocaine + prilocaine**
local anaesthetic
Emla®: Astra, Netherlands
cream 25 + 25 mg/g
*Indications*: analgesia of intact skin.
*Caution*: apply at least one hour and no more than two hours before surgical intervention.

**meclofenamic acid**
nonsteroidal anti-inflammatory agent
Meclomen®: Parke-Davis, Austria
capsule 100 mg
*Indications*: inflammatory and degenerative rheumatic disease.
*Contraindications, precautions and warnings* as for other drugs of this class.

**mitoxantrone**
cytostatic
Novantrone®: Lederle, Sweden
solution (concentrate) for infusion 2 mg/ml
*Indication*: advanced metastatic breast cancer.
mupirocin
antibiotic
Bactroban®: Beecham, Ireland
ointment 2 g/100 g
*Indication:* acute primary skin infection due to susceptible bacteria.

nabumetone
nonsteroidal anti-inflammatory agent
Mebutan®: Bencard, Luxembourg
tablet 500 mg, syrup 100 mg/ml
*Indications:* rheumatic and other inflammatory conditions of joints.

naloxone
opioid antagonist
Nalorex®: Dupont, Ireland
tablet 50 mg
*Indications:* adjunct in management of opiate withdrawal.

omeprazole
inhibitor of gastric acid secretion.
Losec®: Astra, Luxembourg
Parfenac®: Vital Pharma, Luxembourg
capsule 20 mg, containing enteric coated granules
*Indications:* duodenal ulcer, Zollinger-Ellison syndrome.
*Adverse effects:* occasional nausea, headache, diarrhoea.
*Caution:* Possible interaction with phenytoin, diazepam and other drugs metabolized by the liver.

podophyllotoxin
a component of podophyllin with antimitotic and cytolytic properties.
Condyline®: Gist-Brocades, Netherlands, Norway
Wartec®: Conpharm: Norway
liniment 5 mg/ml
*Indication:* condyloma acuminata.
*Contraindications:* pregnant or lactating women, children.
*Warnings, precautions:* Not to be used in combination with other podophyllin preparations. Avoid contact with the eyes. Do not apply to large epithelial surfaces.

propofol
anaesthetic
Diprivan®: ICI, Netherlands
injection fluid 10 mg/ml
*Indication:* induction and maintenance of anaesthesia.

rilmenidine
Centrally-acting alpha-2-adrenoreceptor antagonist
Rilmenidine Servier®: Servier, France
Hyperium®: Biopharma
tablet 1 mg
*Indication:* essential hypertension.
*Contraindications:* severe depressive states, severe renal insufficiency (creatinine clearance <15 mg/min).
*Precautions and warnings:* Treatment must not be discontinued abruptly. Monitoring required following a recent vascular accident. Safety has not been established during pregnancy and in children. Since it is excreted in breast milk, it should not be taken during lactation.

simvastatin
antihyperlipidaemic, which increases HDL and decreases LDL cholesterol concentration.
Cholesolvin®: Yoshitomi, Japan
capsule 250 mg, granules 50 mg/g
*Indications:* hyperlipidaemia associated with atherosclerosis, cerebral atherosclerosis, coronary arteriosclerosis, hypertension, diabetes.
*Caution:* in concurrent treatment with anticoagulants. Periodic monitoring of hepatic function is recommended during long-term treatment.

somatrem
methionyl growth hormone
Somatonorm®: KabiVitrum, Australia
powder for injection 4 IU/ampoule
*Indication:* short stature due to growth hormone deficiency.

somatropin
human growth hormone
Humatrope®: Lilly, Norway
Genotropin® KabiVitrum, Sweden
Norway: powder for injection 4, 12 IU/ampoule
Sweden: 12 IU/ampoule
*Indication:* growth retardation due to pituitary insufficiency.
Newly Registered Products


spiramycin
macrolide antibiotic
Rovamycine®: Rhone-Poulenc, Luxembourg
tablet 500 mg
powder for injection 500 mg/ampoule
*Indications*: infections due to susceptible microorganisms.

tenoxicam
nonsteroidal anti-inflammatory agent
Tilcotil®: Roche, Luxembourg
coated tablet 20 mg
*Indications*: rheumatic disease, arthritis, gout.

terlipressin
precursor of lypressin
Glypresin®: Ferring, Ireland
powder for injection 1 mg/ampoule
*Contraindication*: pregnancy.
*Caution* in patients with hypertension, renal dysfunction or cardiac insufficiency.
*Adverse effects*: abdominal pain including colic, peripheral blanching, headache, hypertension, antidiuretic effect.

terodiline
anticholinergic
Terolin®: KabiVitrum, Ireland
Mictrol®: KabiVitrum, Norway
tablet 12.5 mg
*Indication*: urinary incontinence in patients with detrusor instability or neurogenic bladder.

tertatolol
beta-adrenoreceptor blocking agent
Artex®: Servier, Luxembourg
tablet 5 mg
*Indications*: hypertension, angina pectoris.

tianeptine
tricyclic antidepressant
Stablon®: Servier, Luxembourg
tablet 12.5 mg
*Indications*: neurotic depression, anxiety with somatic overlay, alcohol withdrawal.

Contraindications: children younger than 15 years; patients undergoing treatment with MAO inhibitors.

tiaprofenic acid
nonsteroidal anti-inflammatory agent
Surgamyl®: Roussel, Finland
tablet 600 mg
*Indications*: rheumatoid arthritis, osteoarthritis.

tixocortol pivalate
corticosteroid
Pivalone®: ACF Farma, Netherlands
nose spray 10 mg/ml
*Indications*: allergic and vasomotor rhinitis.

zuclopenthixol
neuroleptic
Clopixol-Acutard®: Lundbeck, Luxembourg, Switzerland
Cisordinol-Acutard®: Austria, Sweden
injection fluid 50 mg/ml
*Indications*: acute psychoses and exacerbations of chronic psychoses, particularly schizophrenia.
*Contraindications*: acute alcohol, barbiturate or opioid intoxication, coma. To be used in pregnancy and lactation only when absolutely necessary.
*Caution* in epileptic patients.
Recent Publications

Onchocerciasis control: a progress report

This report of the WHO Expert Committee on Onchocerciasis provides a comprehensive review of the socioeconomic impact of the disease and of recent advances in related clinical, scientific, and epidemiological issues.

In particular, it reviews the status of vector control and the chemotherapy of the disease in the light of the recent introduction of ivermectin. This has, at last, created a prospect for acceptable and practicable suppressive therapy. There is also hope that, by reducing the microfilarial population in patients, it will reduce transmission. This is particularly heartening in the face of evidence that the disease is spreading in some areas of South America. Ultimately, however, a drug is needed that will destroy the adult worms. It would be counter-productive if the unquestioned value of ivermectin were to slacken the search for one. The Expert Committee report provides a comprehensive and authoritative overview of the situation.


Chemotherapy of tropical diseases

This book offers considerably more than a timely update on recent advances in the management of the transmissible tropical diseases. It analyses the major influences that have determined research on the chemotherapy of these conditions from the time of Ehrlich's work on trypanosomiasis to the present day and points to the imperative need for the innovative effort to be sustained.

No drug yet exists, for example, that is effective against adult filarial worms or the chronic stage of Chagas' disease. Nor are private companies offered adequate incentive to invest in research directed to products that are unlikely ever to recuperate their development costs. Independent financial sponsorship is seen as a vital stimulus to engage the commitment of research teams in academia and industry. The initiative taken by WHO, the World Bank and the United Nations Development Programme in setting up WHO's Special Programme for Research and Training in Tropical Diseases is depicted as a model in this regard. In setting out to identify priority research goals, the book leaves no doubt that rich rewards in terms of public health are attainable if the resources are forthcoming.


Biotechnological products: the scientific basis of their regulation

The rapid development of biotechnology has created challenges not only for pharmaceutical manufacturers but also for national regulatory authorities. Fundamentally new approaches to the production of biologically-derived substances establish a need for new approaches to their control and a timely conference organized by Interscience in Paris in September 1987 brought together experts from industry and academia and regulatory officials from Europe, Japan and North America to review current practices and to discuss prospects for harmonization of regulatory requirements. It was agreed that, where guidelines can be justified on a sound scientific basis, these should be generally adopted.

It was recognized, however, that the further evolution of production techniques will inevitably raise new issues regarding the quality and safety of finished products. Somewhere, it was felt, an international forum needs to be created to encourage informal discussion of these technical problems as they arise.

International Nonproprietary Names for Pharmaceutical Substances

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

Comments on, or formal objections to, the proposed names may be forwarded by any person to the Pharmaceuticals unit of the World Health Organization within four months of the date of their publication in WHO Drug Information, e.g., for List 59 Prop. INN not later than 31 December 1988.

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

Action and Use
The statements in italics indicating the action and use are based largely on information supplied by the manufacturer. The information is meant to provide an indication of the potential use of new substances at the time they are accorded proposed INNs. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature these descriptors will not be included in the Cumulative Lists of INNs.

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

Comprehensive information on the INN programme can be found in: WHO Technical Report Series, No. 581, 1975 (Nonproprietary Names for Pharmaceutical Substances. Twentieth Report of the WHO Expert Committee), ISBN 92 4 120581 4 (price: Sw. fr. 6.–); an account of this publication will be found in Annex 2 of the present List. All names from Lists 1–47 of Proposed International Nonproprietary Names, together with a molecular formula index, will be found in International Nonproprietary Names (INN) for Pharmaceutical Substances. Cumulative List No. 6, 1982, World Health Organization, Geneva (ISBN 92 4 056013 0) (price: Sw. fr. 55.–). This publication consists, in the main, of a computer printout which groups together all the proposed and recommended international nonproprietary names (INN)—in Latin, English, French, Russian, and Spanish—published up to April 1982. The printout also indicates in which of the 47 individual lists of proposed names and 21 lists of recommended names each INN was originally published, and gives references to national nonproprietary names, pharmacopoeia monographs, and other sources. In addition, the list contains molecular formulae and Chemical Abstracts Service registry numbers. For easy reference, national nonproprietary names that differ from INN, molecular formulae, and Chemical Abstracts Service registry numbers are indexed in a series of annexes. A final annex describes the procedure for selecting recommended INN and outlines the general principles to be followed in devising these names. All the textual material published in this volume appears in both English and French.

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

2 Other lists of proposed and recommended international nonproprietary names can be found in Cumulative List No. 6, 1982.
<table>
<thead>
<tr>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>acidum butedronicum butedronic acid (diphosphonomethyl)succinic acid</td>
<td>bone imaging agent</td>
</tr>
<tr>
<td>acidum gadotericum gadoteric acid hydrogen [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetato(4-)]-gadolinate(1-)</td>
<td>paramagnetic contrast medium</td>
</tr>
<tr>
<td>acidum pamidronicum pamidronic acid (3-amino-1-hydroxypropylidene)diphosphonic acid</td>
<td>inhibitor of tumor-induced hypercalcaemia</td>
</tr>
<tr>
<td>alfadexum alfadex</td>
<td>α-cyclodextrin</td>
</tr>
<tr>
<td>alteplasum alteplase plasminogen activator (human tissue-type 2-chain form protein moiety)</td>
<td></td>
</tr>
<tr>
<td>ambasilidum ambasilide 3-(p-aminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane</td>
<td>antidysrhythmic</td>
</tr>
<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>aminoacida</strong></td>
<td>see general statement on nomenclature of amino acids under <em>amendments</em></td>
</tr>
<tr>
<td><strong>amino acids</strong></td>
<td></td>
</tr>
<tr>
<td><strong>anistreplasum</strong></td>
<td>anisoylated (human) lys-plasminogen streptokinase activator complex (1:1)</td>
</tr>
<tr>
<td><strong>anistreplase</strong></td>
<td></td>
</tr>
<tr>
<td><strong>apraclonidinum</strong></td>
<td>2-[(4-amino-2,6-dichlorophenyl)imino]imidazolidine</td>
</tr>
<tr>
<td><strong>apraclonidine</strong></td>
<td>$\text{C}<em>9\text{H}</em>{10}\text{Cl}_2\text{N}_4$</td>
</tr>
<tr>
<td><strong>arpromidinum</strong></td>
<td>(±)-1-[3-(p-fluorophenyl)-3-(2-pyridyl)propyl]-3-(3-imidazol-4-ylpropyl)-guanidine</td>
</tr>
<tr>
<td><strong>arpromidine</strong></td>
<td>$\text{C}<em>{21}\text{H}</em>{25}\text{F}\text{N}_6$</td>
</tr>
<tr>
<td><strong>beraprostum</strong></td>
<td>(±)-(1$R^<em>,2R^</em>,3aS^<em>,8bS^</em>$)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(E)-(3S$^*$)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1H-cyclopenta[b]benzofuran-5-butyric acid</td>
</tr>
<tr>
<td><strong>beraprost</strong></td>
<td>$\text{C}<em>{24}\text{H}</em>{30}\text{O}_5$</td>
</tr>
<tr>
<td><strong>brivudinum</strong></td>
<td>(E)-5-(2-bromovinyl)-2'-deoxyuridine</td>
</tr>
<tr>
<td><strong>brivudine</strong></td>
<td>$\text{C}<em>{11}\text{H}</em>{9}\text{BrN}_2\text{O}_3$</td>
</tr>
</tbody>
</table>
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)
Chemical Abstracts Service (CAS) registry number
Action and use

**Cefcanelum**

(6R,7R)-7-[(R)-mandelamido]-3-[[5-methyl-1,3,4-thiadiazol-2-yl]thio][methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

\[
\text{C}_{19}\text{H}_{18}\text{N}_{4}\text{O}_{5}\text{S}_{3} \quad 41952-52-7 \quad \text{antibiotic}
\]

**Cefcanel**

\[
\begin{align*}
\text{C}_{19}\text{H}_{18}\text{N}_{4}\text{O}_{5}\text{S}_{3} \\
\end{align*}
\]

**Cefcanelum Daloxatum**

2,3-dihydroxy-2-butenyl (6R,7R)-7-[(R)-mandelamido]-3-[[5-methyl-1,3,4-thiadiazol-2-yl]thio][methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, cyclic 2,3-carbonate, ester with L-alanine

\[
\text{C}_{27}\text{H}_{27}\text{N}_{5}\text{O}_{9}\text{S}_{3} \quad 97275-40-6 \quad \text{antibiotic}
\]

**Cefquinomum**

1-[[6(R,7R)-7-2-[(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-5,6,7,8-tetrahydroquinolinium hydroxide, inner salt, \(\text{7}^+\)-(2)-(O-methyloxime)

\[
\text{C}_{29}\text{H}_{24}\text{N}_{6}\text{O}_{5}\text{S}_{2} \quad 84957-30-2 \quad \text{antibiotic}
\]

**Cisconazolum**

(±)-cis-1-[[3-[(2,6-difluorobenzyl)oxy]-5-fluoro-2,3-dihydrobenzo[b]thien-2-yl]methyl][imidazole

\[
\text{C}_{19}\text{H}_{15}\text{F}_{3}\text{N}_{2}\text{O}_{5} \quad 104456-79-3 \quad \text{antifungal}
\]

**Clarithromycinum**

6-O-methylerythromycin

\[
\text{C}_{38}\text{H}_{69}\text{NO}_{13} \quad 81103-11-9 \quad \text{antibiotic}
\]
<table>
<thead>
<tr>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Proposed International Nonproprietary Name (Latin, English)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3β-hydroxy-5α-cholesta-8(14)-en-15-one</td>
<td>colestolone</td>
</tr>
<tr>
<td>C$<em>{27}$H$</em>{44}$O$_{2}$</td>
<td>50673-97-7</td>
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</table>

<table>
<thead>
<tr>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>50673-97-7</td>
<td>hypolipidaemic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>( + )-4-[((R)-α,2,3-trimethylbenzyl)imidazole</th>
<th>dexmedetomidinum</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$<em>{13}$H$</em>{16}$N$_{2}$</td>
<td>113775-47-6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(-)-2-acetamido-N-(3,4-dihydroxyphenethyl)-4-(methylthio)butyramide bis(ethyl carbonate) (ester)</th>
<th>docarpaminum</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$<em>{21}$H$</em>{30}$N$<em>{2}$O$</em>{8}$S</td>
<td>74639-40-0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1-[(1-isobutoxymethyl)-2-[(1-(1-propynyl)cyclohexyl)oxy]ethyl]pyrrolidine</th>
<th>dopropidilum</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$<em>{26}$H$</em>{32}$NO$_{2}$</td>
<td>79700-61-1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>27-L-leucine-44a-glycinegrowth hormone-releasing factor (human)</th>
<th>dumorelinum</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$<em>{218}$H$</em>{362}$N$<em>{72}$O$</em>{68}$</td>
<td>105953-59-1</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Proposed International Name (Latin, English)</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>edelfosinum</td>
<td>choline hydroxide, (±)-2-methoxy-3-(octadecyloxy)propyl hydrogen phosphate, inner salt or 2-O-methyl-1-O-octadecyl-rac-glycero-3-phosphocholine</td>
<td>C_{27}H_{58}NO_{6}P 70641-51-9</td>
<td>antineoplastic</td>
</tr>
<tr>
<td>edelfosine</td>
<td>C_{27}H_{58}NO_{6}P</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| efaroxanum                                  | (±)-2-(2-ethyl-2,3-dihydro-2-benzofuranyl)-2-imidazoline | C_{13}H_{16}N_{2}O 89197-32-0 | α₂-adrenoreceptor antagonist |
| efaroxan                                   | | | |

| elnadipinum                                 | isopropyl (-)-(S)-4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-5-(1,3,4-oxadiazol-2-yl)nicotinate | C_{19}H_{19}Cl_{2}N_{3}O 103946-15-2 | Calcium antagonist |
| elnadipine                                 | C_{19}H_{19}Cl_{2}N_{3}O | | |

| emedastinum                                 | 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)benzimidazole | C_{17}H_{26}N_{4}O 87233-61-2 | histamine antagonist |
| emedastine                                 | C_{17}H_{26}N_{4}O | | |

<p>| etrabaminum                                 | 4,5,6,7-tetrahydro-6-(methylamino)benzothiazole | C_{6}H_{12}N_{2}S 70590-58-8 | antidepressant |
| etrabamine                                  | C_{6}H_{12}N_{2}S | | |</p>
<table>
<thead>
<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Nonproprietary Name (Latin, English)</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>flacitabinum</td>
<td>flacitabine</td>
<td>antiviral</td>
</tr>
<tr>
<td>1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine</td>
<td>$C_{9}H_{11}F_{1}N_{3}O_{4}$</td>
<td>69123-90-6</td>
</tr>
<tr>
<td>flecrobuterolum</td>
<td>flecrobuterol</td>
<td>β-adrenoreceptor agonist</td>
</tr>
<tr>
<td>$\alpha-[(t$-butylamino)methyl]-o-fluorobenzyl alcohol</td>
<td>$C_{12}H_{18}FNO$</td>
<td>82101-10-8</td>
</tr>
<tr>
<td>fronedipilum</td>
<td>fronedipil</td>
<td>antidysrhythmic, anti-ischaemic</td>
</tr>
<tr>
<td>1-[1-(isobutoxymethyl)-2-[1-methyl-1-phenyl-2-propynyl]oxy]ethyl]pyrrolidine</td>
<td>$C_{21}H_{31}NO_{2}$</td>
<td>79700-63-3</td>
</tr>
<tr>
<td>galtifeninum</td>
<td>galtifenin</td>
<td>diagnostic aid</td>
</tr>
<tr>
<td>$[[[(2,6$-diethyl-3-iodophenyl)carbamoyl[methyl]iminodiacetic acid</td>
<td>$C_{16}H_{21}IN_{2}O_{9}$</td>
<td>106719-74-8</td>
</tr>
<tr>
<td>gapromidinum</td>
<td>gapromidine</td>
<td>histamine $H_{2}$-agonist</td>
</tr>
<tr>
<td>1-(3-imidazol-4-yl)propyl]-3-[2-(2-pyridylamino)ethyl]guanidine</td>
<td>$C_{14}H_{12}N_{3}$</td>
<td>106686-40-2</td>
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</tbody>
</table>
### Proposed International Nonproprietary Name (Latin, English)

#### Chemical Name or Description, Molecular and Graphic Formulae

<table>
<thead>
<tr>
<th>Name</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>granisetronum</strong></td>
<td>1-methyl-(N)-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1(H)-indazole-3-carboxamide</td>
<td></td>
</tr>
<tr>
<td><strong>granisetron</strong></td>
<td>(\text{C}<em>{18}\text{H}</em>{24}\text{N}_{4}\text{O}) 109689-09-0</td>
<td>serotonin antagonist</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Granisetron structure" /></td>
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</tr>
<tr>
<td><strong>imirestatum</strong></td>
<td>2,7-difluorospiro[fluorene-9,4'-imidazolidine]-2',5'-dione</td>
<td></td>
</tr>
<tr>
<td><strong>imirestat</strong></td>
<td>(\text{C}<em>{15}\text{H}</em>{8}\text{F}<em>{2}\text{N}</em>{2}\text{O}_{2}) 89391-50-4</td>
<td>aldose reductase inhibitor</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Imirestat structure" /></td>
<td></td>
</tr>
<tr>
<td><strong>inaperisonum</strong></td>
<td>((\pm\text{-})4'-\text{ethyl-2-methyl-3-{1-pyrrolidinyl}propiophenone})</td>
<td></td>
</tr>
<tr>
<td><strong>inaperisone</strong></td>
<td>(\text{C}<em>{16}\text{H}</em>{23}\text{NO}) 99323-21-4</td>
<td>centrally acting muscle relaxant</td>
</tr>
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<td></td>
<td><img src="image" alt="Inaperisone structure" /></td>
<td></td>
</tr>
<tr>
<td><strong>ioxilanum</strong></td>
<td>(N)-(2,3-dihydroxypropyl)-5{(\text{N)-(2,3-dihydroxypropyl)acetamido)-(\text{N)-(2-hydroxy-ethyl)})-2,4,6-triidoisophthalamide)</td>
<td></td>
</tr>
<tr>
<td><strong>ioxilan</strong></td>
<td>(\text{C}<em>{18}\text{H}</em>{24}\text{N}<em>{2}\text{O}</em>{6}) 107793-72-6</td>
<td>contrast medium</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Ioxilan structure" /></td>
<td></td>
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</tbody>
</table>
isbogrelum
isbogrel

(E)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid
C₁₈H₁₉NO₂ 89667-40-3 thromboxane A₂-synthetase inhibitor

lornoxicamum
lornoxicam

6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide
C₁₃H₁₀ClN₃O₄S₂ 70374-39-9 nonsteroidal anti-inflammatory

manidipinum
manidipine

6300

2-[4-(diphenylmethyl)-1-piperazinyl]ethyl methyl (±)-1,4-dihydro-6,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate
C₃₅H₃₈N₄O₆ 89226-50-6 Calcium antagonist

muroderminum
murodermin

urogastrone (mouse salivary gland) or epidermal growth factor (mouse salivary gland)

H — Asn — Ser — Tyr — Pro — Gly — Cys — Pro — Ser — Ser — Tyr — Asp — Gly —
| Hs — Met — Cys — Val — Gly — Asn — Leu — Cys — Tyr |
| Ile — Glu — Ser — Leu — Asp — Ser — Tyr — Thr — Cys — Asn — Cys — Val — Ile — Gly — Tyr |

muromonabum-CD3
muromonab-CD3

A biochemically purified IgG₂κ immunoglobulin consisting of a heavy chain of approx. 50,000 daltons and a light chain of approx. 25,000 daltons. It is manufactured by a process involving the fusion of mouse myeloma cells to lymphocytes from immunized animals to produce a hybridoma which secretes antigen-specific antibodies to the T3 antigen of human T-lymphocytes.

immunomodulator
<table>
<thead>
<tr>
<th>Product Code</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>nebracetamun</td>
<td>(±)-4-(aminomethyl)-1-benzyl-2-pyrrolidinone</td>
<td>nootropic agent</td>
</tr>
<tr>
<td>nebracetam</td>
<td>C_{12}H_{16}N_{2}O</td>
<td>97205-34-0</td>
</tr>
<tr>
<td>nelezaprinum</td>
<td>(E)-9-chloro-11-[3-(dimethylamino)propylidene]-6,11-dihydr-5H-pyrrolo[2,1-b][3]benzazepine</td>
<td>centrally acting muscle relaxant</td>
</tr>
<tr>
<td>nelezaprine</td>
<td>C_{18}H_{21}CIN_{2}</td>
<td>69624-60-8</td>
</tr>
<tr>
<td>noberastinum</td>
<td>3-(5-methylfurfuryl)-2-(4-piperidylamino)-3H-imidazo[4,5-b]pyridine</td>
<td>histamine H_{1}-antagonist</td>
</tr>
<tr>
<td>noberastine</td>
<td>C_{17}H_{21}N_{5}O</td>
<td>110588-56-2</td>
</tr>
<tr>
<td>nuvenzepinum</td>
<td>6,11-dihydro-11-(1-methylisonipecotoyl)-5H-pyrido[2,3-b][1,5]benzodiazepin-5-one</td>
<td>antiulcer, gastric antisecretory</td>
</tr>
<tr>
<td>nuvenzepine</td>
<td>C_{19}H_{20}N_{4}O_{2}</td>
<td>96487-37-5</td>
</tr>
<tr>
<td>ondansetronum</td>
<td>(±)-2,3-dihydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl]carba-zol-4(1H)-one</td>
<td>serotonin antagonist</td>
</tr>
<tr>
<td>ondansetron</td>
<td>C_{18}H_{19}N_{3}O</td>
<td>99614-02-5</td>
</tr>
</tbody>
</table>
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)
Chemical Abstracts Service (CAS) registry number
Action and use

pentisomidum  
pentisomide  
$(\pm)-\alpha-[2-(diisopropylamino)ethyl]-\alpha\text{--isobutyl-2-pyridineacetamide}$
$C_{19}H_{33}N_3O$  
96513-83-6  
antidysrhythmic

phenylpropanolaminum  
phenylpropanolamine  
$(\pm)-norephedrine$  
$C_9H_{13}NO$  
14838-15-4  
sympathomimetic

piroxantronum  
piroxantrone  
$5-[(3\text{--aminopropyl)amino}]-7,10\text{--dihydroxy-2-[2-[2-hydroxyethyl]amino]-}
\text{ethyl]anthra[1,9-cd]pyrazol-6(2H)-one}$  
$C_{21}H_{25}N_9O_4$  
91441-23-5  
antineoplastic

prifelonum  
prifelone  
$3,5\text{--di-} \text{tert}-\text{butyl-4-hydroxyphenyl 2-thienyl ketone}$  
$C_{19}H_{24}O_2S$  
69425-13-4  
nonsteroidal anti-inflammatory

ridogrelum  
ridogrel  
$(E)-5-[[\alpha-3\text{--pyridyl-}m\text{--(trifluoromethyl)benzylidene]amino}oxy]\text{valeric acid}$  
$C_{18}H_{17}F_3N_2O_3$  
110140-89-1  
thromboxane synthetase inhibitor

rosterelonum  
rosterelone  
$17\text{--hydroxy-1a-methyl-17-propyl-5a-androstan-3-one}$  
$C_{23}H_{36}O_2$  
79243-67-7  
antiandrogen
Proposed International Chemical Name or Description, Molecular and Graphic Formulae

Nonproprietary Name (Latin, English)  
Proposed International Chemical Name or Description, Molecular and Graphic Formulae  
Chemical Abstracts Service (CAS) registry number  
Action and use

roxindolum  
roxindole  
3-[(4-(3,6-dihydro-4-phenyl-1(2H)-pyridyl)butyl]indol-5-ol  
C_{23}H_{26}N_{2}O  
112192-04-8  
presynaptic dopamine agonist

saperconazolum  
saperconazole  
(±)-1-sec-butyl-4-[p-[4-[p-[[2R^*,4S^*]-2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]- \Delta^2-1,2,4-triazolin-5-one  
C_{35}H_{38}F_{2}N_{6}O_{4}  
110588-57-3  
antifungal

sarmazenilum  
sarmazenil  
ethyl 7-chloro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo-[1,5-a][1,4]benzodiazepine-3-carboxylate  
C_{15}H_{14}ClN_{3}O_{3}  
78771-13-8  
benzodiazepine antagonist

sitalidonum  
sitalidone  
(+)-2-chloro-4'-hydroxy-5-(2-hydroxy-1-methyl-5-oxo-2-pyrrolidinyl)-3',5'-diisopropylbenzenesulfonanilide  
C_{22}H_{24}ClN_{2}O_{5}S  
108894-39-9  
diuretic, hypolipidaemic

sumatriptanum  
sumatriptan  
3-[2-(dimethylamino)ethyl]-N-methylindole-5-methanesulfonamide  
C_{14}H_{21}N_{2}O_{2}S  
103628-46-2  
serotonin agonist
Proposed International Nonproprietary Name (Latin, English)
Chemical Name or Description, Molecular and Graphic Formula
Chemical Abstracts Service (CAS) registry number
Action and use

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Latin, English</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>CAS registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>tazanolastum</td>
<td>tazanolast</td>
<td>butyl 3'-(1H-tetrazol-5-yl)oxanilate</td>
<td>C₁₃H₁₅N₅O₃ 82989-25-1</td>
<td>antiallergic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>technetium (⁹⁹mTc) sestamibi</td>
<td>technetium (⁹⁹mTc) sestamibi</td>
<td>hexakis(2-methoxy-2-methylpropyl isocyanide)[⁹⁹mTc]technetium(1 +)</td>
<td>C₃₆H₆₆N₆O₆⁹⁹mTc 109581-73-9</td>
<td>radioactive diagnostic agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tedisamilum</td>
<td>tedisamil</td>
<td>3',7'-bis(cyclopropylmethyl)spiro[cyclopentane-1,9'-[3,7]diaza-bicyclo[3.3.1]nonane]</td>
<td>C₁₉H₃₂N₂ 90961-53-8</td>
<td>anti-ischaemic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tomelukastum</td>
<td>tomelukast</td>
<td>2'-hydroxy-3'-propyl-4'-(4-(1H-tetrazol-5-yl)butoxy)acetophenone</td>
<td>C₁₅H₂₂N₂O₃ 89107-10-2</td>
<td>antiasthmatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>troxolamidum</td>
<td>troxolamide</td>
<td>3-[[2,3-dihydroxy-1-((hydroxymethyl)propyl)carbamoyl]-2,2,5,5-tetramethyl-1-pyrrolidinyl]ox</td>
<td>C₁₇H₂₃N₂O₅ 97546-74-2</td>
<td>paramagnetic contrast medium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonproprietary Name (Latin, English)</td>
<td>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
<td>Action and use</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>vinmegallatum vinmegallate</td>
<td>17,18-didehydro-3α,16α-eburnamenine-14-methanol 3,4,5-trimethoxybenzoate (ester)</td>
<td>83482-77-3</td>
<td>antipsoriatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C$<em>{30}$H$</em>{32}$N$_2$O$_5$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>zardaverinum zardaverine</td>
<td>6-(4-(difluoromethoxy)-3-methoxyphenyl)-3(2H)-pyridazinone</td>
<td>101975-10-4</td>
<td>bronchospasmolytic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C$<em>{12}$H$</em>{10}$F$_2$N$_2$O$_3$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Names for Radicals and Groups

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

\[
digolilum \\
digolil
\]

\[
2\text{-}(2\text{-hydroxyethoxy})\text{ethyl} \\
C_4H_9O_2 \\
\text{HO} \cdots \text{CH}_2 \cdots \text{CH}_2 \cdots \text{O} \cdots \text{CH}_2 \cdots \text{CH}_2
\]

AMENDMENTS TO PREVIOUS LISTS

Nomenclature of aminoacids:

During the Seventeenth Consultation on INNs held in Geneva from 29 April to 1 May 1987 the following was agreed:

Names for the L-form should be the names of the aminoacids without a prefix as is present practice in INNs. When there is a need to name the D- and o-forms the INNs of the respective aminoacids should be prefixed with D- and o- respectively. This approach is in agreement with established IUPAC practices in structural formulae for aminoacids where in the abbreviations Arg, Lys etc. the configuration is not indicated for the usual L-form but only when the aminoacid is in the o-form and then it is indicated as o-.


Proposed International Nonproprietary Names (Prop. INN): List 1

p. 299 acidum glutamicum glutamic acid

replace the chemical name by the following:

L-glutamic acid


Proposed International Nonproprietary Names (Prop. INN): List 4

p. 32 methioninum methionine

replace the chemical name by the following:

L-methionine

In Cumulative List No. 6 replace CAS registry number by: 63-68-3

114
Proposed International Nonproprietary Names (Prop. INN): List 13

p. 394 levoglutamidum
levoglutamide
replace the chemical name by the following:
\( \text{\( \ L-glutamine \) } \)

WHO Chronicle, Vol. 18, No. 11, 1964

Proposed International Nonproprietary Names (Prop. INN): List 14

p. 433 acidum asparticum
aspartic acid
replace the chemical name by the following:
\( \text{\( \ L-aspartic \text{ acid} \) } \)

Cumulative List No. 3, 1971

International Nonproprietary Names (INN) for Pharmaceutical Substances

p. 17 aprotininum
aprotinin
replace the chemical name and the molecular formula by the following:
Arg-Pro-Asp-Phe-HCys-Leu-Glu-Pro-Pro-Tyr-Thr-Gly-Pro-HCys-Lys-Ala-Arg-Ile-Ile-Arg-Tyr-Phe-Tyr-Asn-Ala-Lys-Ala-Gly-Leu-HCys-Arg-Thr-Val-Tyr-Gly-Gly-HCys-Arg-Ala-Lys-Asn-Phe-Lys-Ser-Ala-Glu-Asn-HCys-Met-Arg-Thr-HCys-Gly-Ala cyclic (5\( \rightarrow \)55), (14\( \rightarrow \)38), (30\( \rightarrow \)51)-tris(disulfide)
\( \text{\( C_{284}H_{432}N_{84}O_{79}S_7 \) } \)

p. 117 quinbolonum
quinbolone
replace the chemical name by the following:
17\( \beta-(1\)-cyclopenten-1-yloxy)androsta-1,4-dien-3-one

WHO Chronicle, Supplement to Vol. 33, No. 9, 1979

Proposed International Nonproprietary Names (Prop. INN): List 42

p. 6 ceftizoximum
ceftizoxime
replace the graphic formula by the following:
Proposed International Nonproprietary Names (Prop. INN): List 46

p. 3  avilamycinum
      avilamycin

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

Consists mainly of avilamycin A or O-(1R)-4-C-acetyl-6-deoxy-2,3-O-methylenedioxy-D-galactopyranosylidene-(1→3)-2-O-(2-methyl-1-oxopropyl)-α-L-lyxopyranosyl O-2,6-dideoxy4-O-(3,5-dichloro-4-hydroxy-2-methoxy-6-methylbenzoyl)-β-D-arabinohexopyranosyl-(1→4)-O-2,6-dideoxy-α-arabinohexopyranosylidene-(1→3)-O-2,6-dideoxy-3-C-methyl-β-D-arabinohexopyranosyl-(1→3)-O-6-deoxy-4-O-methyl-β-D-galactopyranosyl-(1→4)-2,6-di-O-methyl-β-D-mannopyranoside

prop. INN: List 53

p. 14  delete
       midalcipranum
       midalcipran

insert
       minacipranum
       minacipran

p. 17  pimelauidum
       pimelauidide

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

threeo-6-carbamoyl-N²-N-(N-lauroyl-L-alanyl)-D-γ-glutamyl-N⁶-glycyl-D-lysine
Proposed International Nonproprietary Names (Prop. INN): List 55

p. 11 pirarubicinum
pirarubicin

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

\((8S,10S)-10-[3\text{-}amino\text{-}2,3,6\text{-}trideoxy\text{-}4\text{-}O\text{-}(2R\text{-}tetrahydro\text{-}2H\text{-}pyran\text{-}2\text{-}yl)\text{-}\alpha\text{-}\text{L}\text{-lyxo\text{-}hexopyranosyl}\text{oxy}]\text{8}\text{-}glycoloyl\text{-}7,8,9,10\text{-}tetrahydro\text{-}6,8,11\text{-}trihydroxy\text{-}1\text{-}methoxy\text{-}5,12\text{-}naphthacenedione}\)

\[
\begin{align*}
\text{HO} & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OH} \\
\text{CH}_3 & \quad \text{OH}
\end{align*}
\]

Proposed International Nonproprietary Names (Prop. INN): List 56

p. 3 delete
bermastinum
bermastine

insert
barmastinum
barmastine

p. 6 eбиратидум
ebiratide

replace the chemical name by:

\(\text{L}\text{-methionyl}\text{-}\text{L}\text{-glutamyl}\text{-}\text{L}\text{-histidyl}\text{-}\text{L}\text{-phenylalaninyl}\text{-}\text{o-lysyl}\text{-}\text{N}\text{-}(8\text{-}amino\text{-}octyl}\text{-}\text{L}\text{-phenylalaninamide}\text{S,S-dioxide}}\)

p. 15 seganserinum
seganserin

replace the molecular formula by the following:

\(\text{C}_{29}\text{H}_{27}\text{F}_{2}\text{N}_{3}\text{O}\)

p. 16 somatropinum
somatropin

replace the molecular formula by the following:

\(\text{C}_{930}\text{H}_{1528}\text{N}_{262}\text{O}_{300}\text{S}_{7}\)

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

p. 96 clopidogrelum
clopidogrel

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

methyl \((+)-(\text{S}\text{-}\text{a-(o-chlorophenyl)}\text{-}6,7\text{-dihydrothieno[3,2-c]pyridine-5(4H)}\text{-acetate}}\)

113665-84-2

p. 97 dramedilolum
dramedilol

replace the graphical formula by the following:

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

p. 177 delete
bendacololum
bendacolol

p. 178 delete
clipoxaminum
clipoxamine

p. 180 insert
doreptidum
doreptide

replace the graphic formula by the following:

\[
\text{Cl} - \text{CH}_2 - \text{CH}_3 \\
\text{ON} - \text{N} - \text{C} - \text{NH} - \text{CH} - \text{P} - \text{OC}_2 \text{H}_5
\]

Annex 1

PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

The following procedure shall be followed by the World Health Organization in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with the World Health Assembly resolution WHA3.11:

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

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

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

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

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

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

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

name during the period it is under consideration by the World Health Organization.

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

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

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

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

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

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:
A. request that it be recognized as the nonproprietary name for the substance; and
B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or trade-name.

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

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

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

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

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

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

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-ac</td>
</tr>
<tr>
<td>-actidum</td>
<td>-actide</td>
</tr>
<tr>
<td>-adolum</td>
<td>-adol</td>
</tr>
<tr>
<td>-adol-</td>
<td>-adol-</td>
</tr>
<tr>
<td>-astum</td>
<td>-ast</td>
</tr>
<tr>
<td>-astinum</td>
<td>-astine</td>
</tr>
<tr>
<td>-azepamum</td>
<td>-azepam</td>
</tr>
<tr>
<td>-bactamum</td>
<td>-bactam</td>
</tr>
</tbody>
</table>

- anti-inflammatory agents of the ibufenac group
- synthetic polypeptides with a corticotrophin-like action
- analgesics
- anti-asthmatic, anti-allergic substances not acting primarily as antihistaminics
- antihistaminics
- substances of the diazepam group
- \( \beta \)-lactamase inhibitors
ANNEX 2
NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES: TWENTIETH REPORT OF THE WHO EXPERT COMMITTEE

In its twentieth report, the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant recent change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic "stem" indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed. Also reported is the intention to change the practice with regard to the nomenclature of individual members of polymeric series.

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

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

1 A more extensive listing of stems is contained in the working document Pharm S/Nom 15 which is regularly updated and can be requested from Pharmaceuticals, WHO, Geneva.