PROPOSED INN LIST 72
INTERNATIONAL NONPROPRIETARY NAMES
FOR PHARMACEUTICAL SUBSTANCES

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

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

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WHO Drug Information
Volume 8, 1994: Index

A
ACE inhibitors, cardiac infarction, (1) 4
cardiogenic shock, (1) 4
Acetylsalicylic acid, (4) 218
antiplatelet therapy, (2) 45
myocardial infarction, (1) 24
Aciclovir, herpes zoster, (4) 203
Adjuvant therapy, breast cancer, (1) 23
cancer, (2) 58
ADR information transfer, (1) 1
Adverse drug-related events, information, (1), 1
Adverse effects reporting, (4) 212
Albendazole, (4) 197
Albumin, placental derived, (1) 29
Alpiderm, hepatotoxicity, (2) 65
Angiography, (4) 207
Antacyclines, (3) 145
Antidepressants, hyponatraemia, (3) 152
Antineoplastic agents, exposure, (1) 20
Antiarrythmic agents, (4) 213
Azapropazone, (3) 153

B
BCG vaccine, (2) 46
Bioethics, (3) 162
Biphosphonate pamidronate, (3) 150
Birth control, (4) 189
Blood and plasma screening, (2) 65
transmission, (3) 153
Botulinum toxin, dysphagia, (2) 65
Bovine spongiform encephalitis, (1) 29
Bromocriptine, lactation, (3) 153

C
Caffeine, pregnancy, (2) 46
Captopril, diabetic renal disease, (1) 30
Carbamazepine, (4) 220
Carotene supplementation, (1) 3
Cell line management, (1) 24
Clomiphene, (4) 200
Clozapine, (2) 66

myocarditis, (4) 212
Contraceptives, oral, diabetes, (3) 135
oral, ovarian cancer, (3) 136
Corticosteroids, (4) 197
chickenpox, (1) 34
osteoporosis, (3) 149
Counterfeits, (3) 154
Cyproheptadine, (2) 66
Cysticidal drugs, (4) 197

D
d-Sotalol, (4) 213
Development of medicines, (4) 189
Diarrhoeal disease, (1) 36
Distribution practices, (1) 26
Dithranol, (3) 162
Donations, (4) 195
Dornase alfa, cystic fibrosis, (1) 26
Drug resistance, (4) 226
pneumococcal infections, (3) 148
Drugs secreted in human milk, (1) 21

E
Ergotamine, (4) 217
Estrogen therapy, (2) 66
breast cancer, (3) 137
Ethical criteria for medicinal drug promotion, (3) 157
Ethylene oxide, (2) 67
European Pharmacopoeia, China, (3) 156

F
Factor VIII, (2) 50
Felbamate, anaemia, (3) 154
Fluoxetine, (4) 213
Fluvoxamine, theophylline, (3) 156
Furosemide, (4) 207

G
Gangliosides, (1) 31
Good practices in drug distribution, (1) 26

H
Haemophilia treatment, (2) 50
Hepatitis B vaccine, (2) 52
High-lipase pancreatins, (2) 68
HIV vaccine trials, (3) 152, (4) 213
HIV vaccines, (3) 128
Homoeopathic products, (2) 67
Hydrocortisone, (1) 38

I
ICDRA, (2) 43
IFPMA code of marketing practices, (3) 125
Import procedures, guidelines, (4) 222
Influenza vaccine, (4) 202
formulations, (1) 32
Interchangeability, (2) 71
International Nonproprietary Names (INN)

Proposed list 71, (2) 85
Proposed list 72, (4) 227
Recommended list 34, (3) 165
Iron supplementation, pregnancy, (2) 54

L
L-asparaginase, (3) 143
L-tryptophan, depression, (1) 35
   eosinophilia myalgia, (1) 18
Lactation, drugs, (1) 21
Lidocaine, (3) 134
Lipid-lowering agents, (4) 204
Lovastatin, (4) 204

M
Malaria vaccine, (1) 8, (4) 198
Management of leukemia, (3) 143
Mannitol, (4) 207
Manufacture of drugs, (1) 42
Mercaptopurine, (3) 143
Methotrexate, (3) 27
Migraine and headache, (4) 215
Moxisylyte, hepatitis, (2) 67
Multi-source products, marketing, (2) 71
Multidrug-resistant tuberculosis, (2) 60

N
Neuroleptic sensitivity, (3) 155
Nicotine patches, (2) 68
Nicotine substitution, (3) 140
Nonoxynol-9, (1) 11
Nonsteroidal anti-inflammatory drugs, (3) 155
NSAIDs, (3) 155

O
Oral rehydration salts, (1) 36
Over-the-counter medicines, (4) 208

P
P-glycoproteins, (3) 145
Pancreatins, (2) 68
Paracetamol, (4) 219
Pentamidine, (1) 10
Phenformin hydrochloride, (1) 27
Pneumocystis prophylaxis, (1) 9
Post-marketing trials, guidelines, (1) 32
Pravastatin, (4) 204
Praziquantel, (4) 197
Prednisolone, (1) 39, (3) 143, (3) 150
Promotion, ethics, (3) 123
Psoriasis, (3) 161

Q
Quinine, tetanus, (4) 200

R
Remoxipride, (2) 69
Resistance, drug, (4) 226
   pneumococcal infections, (3) 148
Rifabutin and uveitis, (1) 34
Rifampicin, fixed-dose combinations, (1) 27
Royal jelly, allergy, (1) 27

S
Safety of OTC products, (4) 208
Salicylic acid, (3) 162
Samples, drugs, (3) 156
Silicone oil, retinal reattachment, (4) 214
Simvastatin, (4) 204
Small-scale drug manufacture, (1) 42
Sotalol, (3) 134, (4) 213
Spermicides, (1) 11
Sulfasalazine, (1) 40

T
Tamoxifen, (1) 12, (2) 69
Tar products, (3) 162
Teratogenic risk, guidelines, (4) 210
Theophylline, fluvoxamine, (3) 156
Thymoxamine, (2) 70
Tiaprofenic acid, (3) 155
Tobacco control, (2) 63
Trimethoprim/sulfamethoxazole, (1) 10

V
Vaccination, (4) 190
Vaccine, BCG, (2) 46
   hepatitis B, (2) 52
   HIV, (3) 128, (4) 214, (3) 152
   influenza, (4) 202
   malaria, (1) 8, (4) 198
   varicella, (1) 29
Varicella vaccine, (1) 29
Vincristine, (3) 143, (4) 214
Visceral leishmaniasis, (2) 60
Vitamin K, (1) 16

W
WHO Certification Scheme, USA/Russian Federation, (1) 33

Z
Zidovudine, (2) 57, (3) 130
   pregnancy, (3) 157
   vertical transmission, (3) 130
WHO Drug Information

Contents

General Policy Topics
Socially-responsive development of medicines
   I. Preventive care 189

Personal Perspectives
Private donations for former Yugoslavia 195

Reports on Individual Drugs
When should cysticidal drugs be prescribed in cerebral cysticercosis? 197
Malaria vaccination: further encouraging results 198
Intramuscular quinine and the risk of tetanus 200
Ovulation-stimulating agents: an association with ovarian tumours? 200
Influenza vaccination: a cost-effective intervention 202
Herpes zoster and aciclovir 203
Lipid-lowering agents: where is the evidence of increased survival? 204

General Information
Angiography: reducing the risk of nephrotoxicity 207
Home medicines: much promotion but little enlightenment 208
Teratogenic risk: need for guidance on management of exposed pregnancies 210

Regulatory Matters
Reporting adverse effects: new FDA rules 212

Consultative Document
Guidance for small national regulatory authorities: Draft guidelines on import procedures for pharmaceutical products 222

Recent Publications
Drug resistance: fast gathering clouds 226

Proposed International Nonproprietary Names: List 72 227
Socially-responsive development of medicines

Never has it been more important, throughout the evolution of modern medicine, to take stock of the challenges ahead. In two short decades, confidence that infections and transmissible disease could be effectively contained has been replaced by apprehension about the emergence of new infections and of multidrug-resistant organisms.

The antibiotic era may be in irreversible decline. Defensive strategies need to be developed as a matter of urgency, within a global context, that embrace both public and private sector interests.

A series of commentaries on different aspects of the underlying situation will be included in future issues of WHO Drug Information.

John Dunne, Editor
WHO Drug Information

I. Preventive care

It would be artificial to consider drug needs in developing countries in isolation from the economic and social context in which they are used. The countries that are most in need of drugs are also most in need of effective water management, reliable and adequate food supplies, sources of energy that do not impoverish the environment, effective transport and communications services, and educational systems that provide young people with a reasonable chance of attaining their potential in life. Where too little money is available to support social services harsh political decisions have to be taken to determine priorities.

Medicines form a vital component of every health care system and WHO has developed the essential drugs concept as an aid to defining priorities. Essential drugs are collectively defined as those drugs that have been shown to be widely required, to hold value in a variety of medical settings, and that should be immediately available to everyone in need. The WHO Model List of Essential Drugs provides a template for drug prescribing and for procurement and reimbursement strategies at every level of the health care system. At the same time, it provides a stimulus for new product development for it displays in uncompromising simplicity the precariously slender resources — and in some instances the manifest inadequacy of the resources — now available to protect against or to provide cures for some of the world's most feared diseases.

It is now evident that innovative efforts will continue to be required simply to retain the benefits derived from hard-won gains of the past. Populations continue to escalate in regions of existing deprivation and political instability; antimicrobial-resistant strains of established pathogens are emerging at a rate that presages the demise of the antibiotic era (see also p. 226) while hitherto unknown infections threaten to emerge in environments already overcrowded; and, in the longer term, climatic changes threaten substantially to extend the areas of endemicity of transmissible tropical diseases. This article examines the potential for developing new preventive strategies, and immunological approaches in particular, in response to these threats.

The challenge of birth control

The implications for subsequent generations of the burgeoning global population has emerged as an issue of profound political importance. Contraception is but one vital element within a broad and fundamental ethical and socioeconomic construct. Whereas use of contraceptives has expanded considerably over the past 30 years, it is estimated that, as yet, some 50% of sexually-active women in
developing countries remain without any reliable form of birth control (1). Induced abortion, so often conducted under conditions that result in high morbidity and significant mortality, remains commonplace.

New formulations of existing steroidal contraceptives still appear from time to time that provide for safer, lower dosage regimens or more extended periods of effectiveness. However, the commercial incentive to explore novel approaches has long since evaporated. Litigation arising from thromboembolic disease associated with early high-dose estrogen products was dissuasively costly. Moreover, the existing products are safe enough and reliable enough to discourage expenditure of high risk capital on alternative innovative approaches which, in the final analysis, may not match up to what is already available.

Without doubt, there is both need and potential to develop new approaches to birth control. The objective is to devise methods that do not produce the endocrine and metabolic disturbances and the concerns about hormone-dependent malignancies associated with steroidal preparations; do not have to be taken every day; do not pose the problems of storage and disposal associated with barrier methods; do not have to be surgically inserted, are relatively long-lasting but not permanent, and are inexpensive to manufacture and of low cost to the user. In less developed countries, in particular, the logistic advantage of long-acting injectable contraceptive products is irrefutable. However, hostile reactions to such methods among women's groups active elsewhere in the world demonstrate a deep-rooted antipathy to any contraceptive method that cannot be "turned off" at will.

This mistrust, and the manifestly real concern that contraception must never be imposed through subjugation, accounted for the tardy acceptance of depot medroxyprogesterone acetate subsequent to its initial inclusion in WHO's Model List of Essential Drugs in 1980 (2, 3). More recently, this mistrust has resulted in the outright condemnation by a women's rights group (4) of WHO's commitment to support the development of a vaccine directed against chorionic gonadotrophin, a hormone that is produced exclusively in embryonic tissues and that is essential for successful implantation (2, 6, 7).

The common concern is to provide every woman with a safe and effective means to have only the number of children she wants. Because innovation can never be entirely dissociated from risk, it is essential that every promising scientific lead directed to this end be submitted to searching public debate. But progress towards common objectives will surely be frustrated if alarmist appeals come to be regarded as a legitimate substitute for scientific discussion, and if innovators are perceived as a legitimate target for penal sanction whenever their products are found to be associated with unanticipated risk.

The challenge of infectious and transmissible disease
The concept of the planned family is least persuasive where child mortality is greatest. Far from exacerbating population growth, the prospect of most children surviving through to adulthood could well exert a stabilizing influence on family size. In developed countries, immunization has already virtually eliminated the scourge of acute infectious disease in infancy and childhood. Indeed, vaccines are perceived as the most cost-effective intervention to prevent death and disease (8–11). Yet, worldwide, infectious diseases remain the foremost cause of mortality (12). The history of smallpox offers indelible proof that vaccination can eradicate endemic disease from developing as well as from developed countries. Hope is still expressed that by the turn of the century poliomyelitis may have become a relic of medical history (13). But does current progress generally give cause for satisfaction?

Almost 10 years ago, the US Institute of Medicine issued a report which identified the development of effective vaccines against malaria, the respiratory infections caused by Streptococcus pneumoniae and respiratory syncytial virus, and the severe diarrhoea caused by rotavirus and Shigellae, as projects of the greatest importance to developing countries (14). Whereas advances in immunology, molecular biology, biochemistry and vaccine delivery systems have since resulted in the introduction of new products which have filled a profitable niche in the vaccine market in developed countries, the priorities of the developing world have remained largely unsatisfied. Indeed, the emergence of HIV infection and the associated resurgence of pulmonary tuberculosis has further engulfed many of the least developed countries in a public health crisis of unparalleled proportions.

The potential of childhood vaccination
About one child in five born into the world today is never fully vaccinated. Every year, several millions die from measles and respiratory illnesses that
could readily be prevented by currently-available vaccines. Much reliance is now placed in the alliance of international agencies that has created the Children’s Vaccine Initiative (CVI). Launched in 1990 at the World Summit for Children in New York, the primary aim of the initiative is to increase global coverage of existing immunization programmes. At present, every child requires at least six vaccinations during the first two years of life to obtain full protection against diphtheria, tetanus, pertussis, measles, poliomyelitis and, less securely, against tuberculosis. Most of these vaccines are administered by injection, while measles and polio vaccines must be supplied through a cold chain. The aim is to reduce to the minimum the cost of delivering this protection. The ideal solution would be an oral vaccine protective against all of these diseases (15). No one can yet be sure that this is feasible. Even if the fundamental immunological problems are satisfactorily resolved, difficulties will be encountered in formulating a stable broad-spectrum combination product.

The immediate concern, however, is financial. It has recently been reported that the CVI has raised 10 million of the US$ 300 million estimated to be required to catalyse the necessary research and development (16). Meanwhile, interest among major research-based pharmaceutical companies is said to be muted by slender profit margins. It is estimated that the global vaccine market generates no more than US$ 3 billion each year. Some 80% of manufactured stock is currently sold at discount through UNICEF to developing countries — an arrangement that is vital to the continuance of immunization programmes throughout the world. Recently, however, profit margins have been further trimmed in the wake of price controls introduced in developed countries. Of fourteen companies in the United States that manufactured vaccines at the beginning of the 1980s, less than one-third remain active today and few newcomers have entered the field (17).

Safety aspects of vaccination programmes

Diminishing profits have not been the only impediment. Most of these companies moved out of vaccine development in the early 1980s amid concerns that whole-cell pertussis vaccines used for the previous 50 years may have caused cases of encephalopathy sometimes resulting in permanent neurological damage and death (18). Memories of the situation before the vaccine era, when several thousand young children were recorded to have died from pertussis each year within the USA alone, were cast aside (19). It is now generally accepted that the incidence of serious acute encephalopathy following DTP vaccination is no greater than 10 cases per million immunizations (20, 21). Permanent neurological sequelae cannot be excluded in such cases (22) but, whereas this risk is acknowledged, it is now generally regarded as admissible. Governments accept the vast health benefits that derive from national vaccination programmes and several are now underwriting the cost of caring for the unfortunate few that sustain vaccine-related injuries through "no-fault" health insurance schemes in an attempt to relieve the burden of liability on manufacturers (23).

Manufacturers, however, retain full responsibility for the quality of their products. Raw materials, and especially those of human origin, may be contaminated with transmissible agents, including HIV, hepatitis viruses and slow viruses. Attenuated pathogens contained in vaccines may revert back to more virulent strains. Application of recombinant DNA technology serves to reduce these hazards. Subunit vaccines, selected to contain specific immunogenic epitopes, are both highly purified and nonviable. Acellular pertussis vaccines containing inactivated pertussis toxin and other protein constituents of Bordetella pertussis will supersede cellular products (24); recombinant preparations of hepatitis B now compete with plasma-derived products (25); and conjugated capsular polysaccharide vaccines are being developed as a result of the emergence of antibiotic-resistant strains of Streptococcus pneumoniae, Streptococcus B, and Haemophilus influenzae (26, 27). Not least, two recombinant subunit HIV vaccines are destined soon to be assessed in large-scale phase-3 trials in developing countries (28).

Inevitably, this sophisticated technology creates new challenges:

1. Whereas subunit peptides or polysaccharides can induce a brisk antibody response, they rarely stimulate potent cellular immunity. Short-lived immunogenicity has been reported with several such products (26, 27, 29, 30), although promising approaches to enhancing and extending the period of protection are emerging.

2. The subunits are selected from immunogenic epitopes specific to a genetic subtype of the targeted pathogen. Vaccines developed against
strains of Streptococcus pneumoniae that typically cause ear infections in North America and Europe may not offer effective protection against the strains responsible for the pneumonia that is the leading cause of death among young children in developing countries (31, 32). Similarly, experimental subunit HIV vaccines derived from epitopes contained in the B subtypes of the retrovirus that predominate in Europe and the United States (33, 34), may not be ideally constituted for use in Africa where some of the early large-scale HIV vaccine trials are likely to take place.

3. Subunit vaccines are costly to develop and to manufacture. Currently available hepatitis B vaccines cannot be delivered in the quantities required to the communities in sub-Saharan Africa and south-east Asia where most children become infected within the first few weeks of life. Subsequently, most of these become chronic carriers of the virus, and many are condemned to die from chronic hepatitis, cirrhosis or primary hepatocellular carcinoma. Similarly, given the current cost of conjugated polysaccharide vaccines, immunization against capsular forms of Haemophilus influenzae and streptococci seems destined to remain virtually unattainable in those countries where young children are most at risk of bacterial pneumonia and meningitis, and where strains resistant to the first-line antibiotics are doubtless emerging most rapidly.

It is vital that such developmental work should be maintained and extended. Much innovation in the vaccine field now takes place outside the commercial sector, and some of this has produced highly promising results. Attenuated strains of Vibrio cholerae have been developed in which the genes encoding for essential determinants of virulence, including cholera toxin, have been deleted, and an innocuous subunit of the toxin has been shown to have valuable immunogenic potential (35). Promising progress has similarly been made with candidate rotavirus vaccines based upon live rhesus strains reassorted with genes from one or more human serotypes (36).

**The promise of an antimalaria vaccine**

The apparent promise of an antimalaria vaccine synthesized in Colombia from portions of the circumsporozoite protein of Plasmodium falciparum linked to short peptides derived from the blood-stages of the parasite is an issue of immediate interest (see also p. 198) (37). Trials both in Colombia (38) and very recently in Tanzania (39) have shown not only that the vaccine is immunogenic and apparently well tolerated, but that it may reduce the risk of clinical malaria among children exposed to intense falciparum transmission by as much as one third. Many questions remain to be answered before a full assessment of these findings can be made, but the results provide a considerable stimulus for further developmental studies. Given the relentless advance of multidrug-resistant malaria in hyperendemic areas — reflected within the past few months in outbreaks causing many deaths in India and Sudan — even a vaccine offering this relatively modest degree of protection might well merit acceptance.

This accomplishment, together with the discovery and development within China of the antimalarial artemisinin derivatives (40, 41), could well presage and encourage the establishment of a formidable pharmaceutical research capability in developing countries. Ultimately, commitment from within may prove to be decisive in alleviating the burden of hyperendemic infectious and transmissible disease in many of these countries.

**The challenge to national administrations**

As these new players are entering the scene, the established research institutions of the industrialized world seem to be retiring from the stage. Unprecedented retrenchment and restructuring is taking its toll of research programmes in many of the major multinational pharmaceutical companies. Teams involved with the development of antimicrobial products have been among the first to be disestablished. Some outstanding contributions have been made to the management of parasitic tropical diseases within the past decade. The microfilaricide ivermectin effectively suppresses the progression of onchocerciasis; injectable eflornithine is the first effective treatment of late-stage African trypanosomiasis; praziquantel is an effective and remarkably well tolerated schistosomicide. Other projects, still ongoing, are now in jeopardy.

The underlying difficulty is that lack of finance and of health care infrastructure has frustrated delivery of therapeutic community-based care in the countries where these drugs are most needed. Few of the many millions of patients with schistosomiasis have access to praziquantel, and lack of a tangible market no doubt explains why ivermectin has never been developed for the management of lymphatic filariasis.

Sooner rather than later, society will be bound to recognize that some fields of pharmaceutical research cannot be left to sink or swim in a market
driven economy. There is scant commercial incentive, for example, to satisfy the need to develop a reserve antimicrobial. Financial return on capital investment cannot realistically be deferred indefinitely to such time as the product is widely needed to stem the emergence of an otherwise unresponsive pathogen. Yet the treatment of infectious disease remains secure only for as long as effective second-line drugs remain in reserve to treat cases unresponsive to routine therapy.

The advent of AIDS should surely serve as a bellwether to alert society to the reality that infectious disease is a moving target (42), and that a state of alert needs to be maintained the world over if the emergence of new pathogens and changing patterns of microbial susceptibility are to be successfully contained. This calls for the institution of internationally organized networks of microbiological laboratories as well as the preservation of an efficient pharmaceutical research capability directed to projects of fundamental social relevance. For as long as these precautions remain in default, civilization is left singularly vulnerable to every adverse biological perturbation. Tangible precautions are worthy of discussion. Their relevance should not be dismissed as a consequence of short-sighted indulgence in complacency.

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Personal Perspectives

Private donations for former Yugoslavia

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In the face of disaster and witness of suffering, there is a natural human impulse to reach out and help those in need. The survival of thousands of people endangered by the conflict in former Yugoslavia is hinged upon the assistance extended by governments, institutions, and private individuals. Without this assistance, the casualties of this conflict would be far higher.

Within former Yugoslavia, WHO has seven offices in daily contact with other humanitarian agencies and local health authorities. These agencies are either governmentally or privately funded and all depend upon donations of some kind to operate.

In-cash donations
Exchangeable currency constitutes the ideal donation. It supports the procurement of essential supplies and their distribution through a well-established system. However, this type of funding is generally time-limited and cannot be relied upon to support long-term projects.

In-kind donations
Donations of supplies, generally provided by private organizations or individuals, pose a challenge to channel effectively. Many people initially assume that virtually anything they choose to send is better than nothing, but this is far from the case.

Many private donations of medicines are channelled through the United Nations High Commission for Refugees (UNHCR) which is not a medical agency. They often arrive without warning, poorly packaged, without labels or past their labelled expiry dates, and they sometimes contain mixed or unusable drugs. Sorting and handling such supplies consumes resources, creates logistical problems and in some situations even creates environmental and other hazards.

Unfortunately, donors frequently fail to consult recipients or even to check regulations that apply to donations either in transit or in the country of destination. A donation will not be treated as such until the local government has accorded this status to the consignment. In the case of the Federal Republic of Yugoslavia, each consignment must be specifically approved by the Sanctions Committee of the Security Council in New York, a process which can sometimes take months. In many cases, transportation costs are higher than the actual value of the donation.

Perishable supplies, particularly serums, vaccines and other biological drugs and reagents require cold storage. Some diagnostics and therapeutic agents are also hazardous to transport. In all cases, proper packaging is very important. Consignments worth thousands of dollars have been lost due to damage by rain.

In a theatre of war involving three different parties, improperly manifested and marked consignments can create nightmare scenarios, especially when packages identify an intended end-user. An entire convoy was almost turned back and a driver threatened because someone "forgot" to manifest two candles in a consignment. In Sarajevo, WHO field staff have risked their lives under sniper fire trying to identify unmarked medical supplies lying on the airport runway.

Quality of donations
Sometimes, it is found that the cost of packaging and transportation have been wasted on drugs of unacceptable quality. Because of almost inevitable delays in transit, drugs often arrive at their destination after they have passed their expiry date. In Bosnia there are huge quantities of expired medicines which are scheduled for destruction, but which remain dumped because of lack of fuel. They take up valuable space, and could eventually filter into local distribution channels for want of other supplies.

In many instances donors send something that they want to be rid of, but which they feel may be useful to others, such as boxes of assorted drugs that are insufficient to cover a single course of treatment. Great frustration is met in the field when non-priority
Items finally arrive after weeks of waiting for basic necessities. Agencies in the field are always best placed to advise on priority needs.

WHO has devised emergency health kits that cover basic contingencies likely to arise within a sizeable community. This has proven to be a most efficient system of distribution of medicines in emergency situations. For donors that wish to send medicines rather than money, such kits are strongly recommended.

WHO's efforts to mould in-kind donations into useful contributions have been highly rewarding. UNHCR Frankfurt, a major transit station for supplies, reports that the proportion of useful donations has increased by some 30%. UNHCR Ancona, and field offices in former Yugoslavia have reported improvements in the quality of consignments. Very specific needs, which otherwise would have remained unidentified, have been fulfilled.

Suggestions for future operations
We have learned many lessons concerning in-kind donations. Not wanting to discourage people from sending supplies, we have sought ways of making the best of the situation, and we offer the following advice for consideration in future operations:

1. Resources should be allocated at the outset of an emergency situation to correlate assistance offered by donors with needs in recipient countries. "An ounce of prevention is worth a pound of cure."

2. Basic guidelines should be prepared and issued to the media to instruct potential donors on how they can best help in the situation.

3. Collection centres should be created in recipient countries to sort, package and distribute donations according to need.

4. Health authorities should be assisted in establishing policies and regulations relating to donations.
When should cysticidal drugs be prescribed in cerebral cysticercosis?

Cysticercosis is the commonest parasitic infection of the central nervous system, and it is endemic in Central and South America, south-east Asia, India, the Caribbean, and southern Africa (1-3). When eggs of the porcine tapeworm, *Taenia solium*, are ingested they hatch in the small intestine, burrow into venules, enter the blood stream and sequestrate either in muscle or the brain where, within a few months, they develop into mature larvae, or cysticerci (4).

Within the central nervous system the cysts, which grow to some 5-10 mm or more in diameter, may lodge in the parenchyma, the subarachnoid space, or the ventricular system of the brain. The clinical signs of infection are determined by the location of the cysts, and they result from distention, inflammation, or obstruction of the flow of cerebrospinal fluid. Parenchymal lesions cause seizures and focal deficits, while obstruction of the ventricular system results in raised intracranial pressure or hydrocephalus, and is sometimes associated with a form of chronic inflammatory meningitis (5-7).

Until the 1980s, management of the disease was limited to surgical removal of large cysts and symptomatic treatment of complications, including use of anticonvulsants to control seizures; corticosteroids to reduce raised intracranial pressure; and ventriculo-peritoneal shunts to relieve hydrocephalus. Subsequently, praziquantel, a broad-spectrum antitrematode drug initially used to treat schistosomiasis, was shown to have a specific cysticidal action. A review of some 200 patients treated in six open and uncontrolled studies with doses of praziquantel ranging from 5 to 75 mg daily for 6 to 21 days, concluded that almost 90% of patients ultimately benefited from treatment (8).

However, many of these patients experienced a transient but troublesome exacerbation of symptoms attributed to an inflammatory reaction to decomposing cysts (3-9). Corticosteroid cover attenuated these reactions, but the rationale for routine use of praziquantel to treat parenchymal cysts was challenged (10) both because these reactions were sometimes intense and because computerized tomography had shown that many parenchymal cysts resolve spontaneously within two to three years (11-13).

Notwithstanding these reservations, the need for treatment cannot be lightly dismissed in communities where the disease is endemic; where as many as one in every 20 persons is infected (14); and where the disease accounts for more than half of the cases of late-onset epilepsy (15, 16). Only recently has a large comparative prospective study of cysticidal therapy been undertaken in patients with parenchymal cysticercosis associated with seizures in an attempt to resolve doubts about the extent to which antimicrobial treatment influences the long-term prognosis of cysticercosis (17). In an unblinded, unrandomized study conducted in Mexico, more than 100 patients with no discernible pericystic inflammatory responses on imaging received either praziquantel, or albendazole — which has been shown independently to be highly effective in destroying cysticerci in brain tissue (18, 19). Both drugs were administered in a daily dose of 50 mg/kg — praziquantel for 15 days, and albendazole for 30 days. The progress of this treated group was compared with that of some 50 similar patients — none of whom had radiological signs of inflammatory reaction — who were either not offered, or who refused to take cysticidal drugs.

About half the treated patients remained free of seizures throughout follow-up over three years. During this time, the annual frequency of attacks decreased from 11.3±2.0 to 0.6±0.1, and the mean number of detectable cysts fell from 5.0±0.3 to 0.9±0.2. Only some 20% of these patients required corticosteroid therapy (8 mg dexamethasone 3 times daily) for secondary reactions which included headache, vomiting, seizures, and focal neurological signs. None of these reactions was persistent or serious, all occurred within three days of cysticidal therapy, and no patient needed to remain on corticosteroids for more than a few days.

In the untreated group of patients, no significant changes were detected in the frequency of epileptic attacks over the three-year period, while the mean number of parenchymal cysts identified on imaging increased by some 15%.
However, the interpretation of these apparently decisive results is rendered less secure by the inclusion within the study of a second group of 60 patients in the study who were judged to have radiographic evidence of pericystic inflammation. None of these was treated, yet the mean annual frequency of seizures within this group regressed spontaneously over 4-5 years from $7.5\pm1.0$ to $2.7\pm0.9$, and some 30% of the patients became free of seizures during this period.

The authors conclude, none the less, that all patients with epilepsy found to be associated with parenchymal cysts should be advised to accept cysticidal therapy. Notwithstanding their demonstration that an inflammatory reaction often presages the death of a cyst, they point to evidence that the residual granulomatous scar constitutes a potential persistent epileptic focus (15, 16).

This conclusion provides an eminently practical basis for management. But its reliability is questionable, both because it is in part inferential, and because data from which it is derived are vulnerable to selection bias — particularly since it is unclear at which point in the trial the untreated patients were segregated on the basis of their inflammatory response. Confirmation of the findings within the context of a randomized, placebo-controlled study would provide a far more secure basis for determining routine therapeutic practice.

References


Malaria vaccination: further encouraging results

Two years have now passed since a chemically-synthesized subunit malaria vaccine (SPI66),
developed in Colombia and targeted empirically against blood-stage antigens of *Plasmodium falciparum* was first reported to be partially protective against clinical episodes of the disease. Partial protection was demonstrated in both adults and children living in an area of low malaria transmission on the Colombian coast (1).

A larger-scale study of the vaccine has now been completed in Africa involving 586 children aged 1–5 years living in an area of intense perennial malaria transmission in southern Tanzania (2). It was recognized that in this environment, where the community is exposed daily to the bites of infected mosquitoes, prevention of infection and parasitaemia by such a vaccine could never be attainable. The objective was to determine whether the vaccine can reduce and attenuate clinical episodes of malaria, and confer a degree of immunity analogous to that acquired naturally by the adult population in holoendemic areas (3).

Each child received a subcutaneous injection containing either vaccine (2 mg peptide in an alum adjuvant) or placebo at 0, 4 and 26 weeks. Morbidity was monitored over a period of one year, starting at the time of the first inoculation. Clinical malaria was defined as a febrile episode (>37.5°C) accompanied by a parasite density >20,000/µl in capillary blood. Blood smears were also taken in large subgroups of the children to estimate the extent to which the vaccine reduced the incidence and intensity of parasitaemia.

No adverse effects were associated with vaccination other than localized induration and, in 5 cases, transient erythema after the third dose. All children who received three doses of the vaccine had detectable anti-SPf66 antibodies. The geometric mean response was 8.3 in the vaccine group and 0.7 in the placebo group (p<0.001). The vaccine was thus highly immunogenic but, as yet, no relationship has been established to associate this response with clinical protection.

Cross-sectional surveys within the cohort indicated that the cumulative incidence of infection and median parasite density were not demonstrably influenced by vaccination until the third dose had been administered. Nor was any effect on anaemia shown throughout the duration of the trial. However, within the six-month period following the third dose, the number of episodes of clinical malaria were reduced among the vaccinated children. The average annual incidence rates of clinical malaria within the vaccinated group was 0.25 compared with 0.35 among children receiving the placebo.

A true reduction of one-third in morbidity — particularly if it were accompanied by a comparable reduction in mortality — would represent an impressive advance in the management of malaria. It is important, however, to appreciate that the difference in attack rates is only marginally significant in statistical terms (95% confidence interval 0 to 52%; p=0.046). This borderline result is a consequence of the design of the study. The intention was to detect 50% protective efficacy against symptomatic malaria with 95% confidence and 80% power. Lesser degrees of efficacy are detected in such a design with less certainty. Given the outcome of earlier studies in low transmission areas, the trial was attuned to an overly optimistic target. None the less, taken together with the outcome of the Colombian trial — which provided an estimate of protective efficacy of 39% — and recently reported studies in Ecuador (4) and Venezuela (5), the consistency of the findings is highly encouraging.

At this stage, however, fundamental questions still remain to be answered (6). Will persistent boosting by natural infection assure an enduring protective effect? Will the antigenic diversity of wild malaria parasites result in the selection of resistant strains? Could a partially protective vaccine paradoxically increase mortality by “destabilizing” the disease in areas of intense persistent transmission? (6)

Within the next year, the results of similar ongoing studies will become available. WHO plans to organize a meeting in 1995 at which these field trials will be presented and further development of the vaccine considered. By this time, clinical development of other vaccines, now emerging from phase-1 studies, will have progressed further (7). A clearer picture of the long-term potential of SPf66 and of other approaches to vaccination should then emerge.

References


Intramuscular quinine and the risk of tetanus

Tetanus remains an important public health problem in many developing countries. Despite the existence of active immunization programmes, protection with the necessary booster doses is commonly not maintained.

About 400 cases of the disease are admitted annually to the Centre for Tropical Diseases in Ho Chi Minh City, Vietnam. A recent survey of these cases conducted over a period of 28 months showed that some 4% were associated with intramuscular injections (1). Within this subgroup, almost two-thirds of the cases were patients recovering from a serious attack of malaria following treatment with intramuscular quinine. Despite apparently successful management of their primary illness, nearly all of these patients died.

Some 30 years ago, the adulteration of street narcotics with quinine was similarly implicated as a cause of tetanus resulting in high rates of mortality among parenteral drug abusers (2). The danger arises because quinine dihydrochloride, the widely available injectable salt of quinine, is highly acidic and corrosive. Intramuscular injection causes local vasoconstriction and necrosis which favours growth of Clostridium tetani. Meticulous attention to aseptic technique during injection could presumably reduce the incidence of infection, but it might not entirely eliminate the risk: necrosis at the injection site may provide a focus for the germination of spores inoculated into distant wounds (3).

The authors of the survey suggest that, simply by giving due heed to the precaution of diluting quinine before intramuscular injection, much necrosis and many of these infections could be averted. Tetanus has been recognized as a potential complication of intramuscular administration of quinine for more than 80 years (4). Given due care, however, this route of administration provides a relatively safe and highly practicable alternative to intravenous infusion of quinine when severe malaria is treated in a rural setting (5).

References

Ovulation-stimulating agents: an association with ovarian tumours?

As countries become more developed, a growing number of women seek careers and tend to raise families late in their reproductive years (1). Frequently, their fertility is declining by the time they plan to have children. In 1988, it was estimated that some 2 million women in the United States had taken fertility drugs at some time in their lives (2), and the use of these preparations is fast increasing. The annual number of prescriptions issued by US doctors for clomiphene is claimed to have doubled between 1973 and 1988 (3).

At the same time, concern has been generated about the safety of pharmacological stimulation of ovulation. Following publication of case-reports of ovarian tumours developing in women undergoing treatment (4-6) an analysis of 12 US case-control studies indicated that use of fertility drugs is associated with an increased risk of ovarian malignancies (7-9). This association has now been confirmed in an examination of a cohort of nearly 4000 women evaluated for infertility in a US urban community between 1974 and 1985 (10). Eleven of

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Two hypotheses have been developed to explain the possible carcinogenic action of ovulation-stimulating agents on the ovary (11). The first is mechanical: repeated and multiple ovulations may disrupt the ovarian epithelium and increase the risk of malignant transformation. The second is hormonal: persistent stimulation of the ovary by pituitary gonadotrophins might similarly promote malignancy. In the latter case, not only gonadotrophins, but also agents like clomiphene which stimulate endogenous production of gonadotrophins, would be associated with risk. As yet, no evidence has been forthcoming from any of the published studies that administration of human chorionic gonadotrophins constitutes a risk factor, but this could simply reflect lack of an adequate body of data (11).

Given the need to assure the safety of treatments approved for infertility, it is reported that the US National Institutes of Health plans to support further studies of the use of these drugs (11). Meanwhile, it is important to place the issue in broader perspective for women contemplating antifertility therapy. Ovarian tumours are uncommon. The lifetime risk among the general population of women in the United States is estimated to be less than 2%. It has been pointed out (11) that, a possible two or three fold increase in this risk resulting from exposure to ovulation-stimulating agents may be offset — in the event of a successful pregnancy — by a substantial reduction in the 12% lifetime risk of breast cancer (12).

It is also important to recognize, however, that the prognosis, in the event of ovarian cancer remains poor and has not been shown to be improved by increased surveillance or early diagnosis (13).

References

Influenza vaccination: a cost-effective intervention

Each year within the United States, between 10 000 and 40 000 deaths are attributed to influenza and its complications (1). The total economic cost associated with these epidemics has been estimated to exceed US$ 12 billion (2).

Largely because of rapid antigenic drift resulting from frequent viral mutations, the efficacy of influenza vaccine is lower than that of other widely-used vaccines and highly variable from season to season. Vaccination policy is consequently directed to reducing the incidence of lethal complications of the disease (3), rather than to reducing infection and transmission (4). Although the attack rate is greatest among children and young adults (5), elderly patients are at greatest risk (1, 6). Yet, despite repeated recommendations from the public health service that they be immunized annually against the disease (7, 8), only about one-third of the US population older than 65 years receives the vaccine (9, 10).

Since vaccination first became generally available during the 1960s many studies have been undertaken to assess its value in elderly patients, both within institutions (11–15) and in the community (16–20). Some of the results have been inconclusive, in part because of limitations in design: most of the studies have been relatively small and they have typically been observational in character. Inconsistencies in the results may also have resulted from antigenic drift in the circulating virus, or to vaccine failure resulting from inadequate storage (13).

Even conclusions drawn from some of the larger case-control studies may be unreliable because of their vulnerability to confounding. This applies particularly to studies of the effectiveness of vaccines in preventing hospitalization of older patients with presumed complications of influenza (18–20). This arises because patients with chronic cardiac and pulmonary conditions may well be vaccinated, yet also need hospital admission for an acute exacerbation of their pre-existing disease during the influenza season (21).

These deficiencies have largely been overcome in a recently published serial cohort study designed to assess the efficacy and cost-effectiveness of influenza vaccine over three consecutive seasons among elderly US patients living in the community (22). From 1990 to 1993 inclusive, information was obtained from administrative data bases on some 25 000 persons aged 65 years or over who were enrolled in a managed health care programme in a mid-western US conurbation. Immunization rates ranged from 45% to 58% in successive years.

Although chronic respiratory and cardiac disease was more prevalent among vaccinees, vaccination was associated with reductions of 39% to 54% in mortality from all causes during each of the three years. Vaccinees were also admitted to hospital less frequently than non-vaccinated persons with pneumonia and influenza (−46% to −57%; p ≤0.002) or other chronic respiratory conditions (−27% to −39%; p ≤0.01) throughout the influenza seasons. During an epidemic outbreak of influenza A, vaccination was also associated with a reduction in admissions for congestive heart failure (−37%; p=0.04). It is estimated that, within the full cohort, vaccination resulted in savings in hospital inpatient costs of some US$ 5 million over the three year period.

These are substantial benefits and they have persuaded one of the largest US health insurance organizations to add vaccination against influenza to its list of reimbursable services for the elderly (22). There is no doubt that the elderly gain most benefit from protection against influenza, but vaccination of younger age groups with the aim of reducing morbidity and loss of working hours resulting from infection may also in time prove to be a cost-effective investment (23).

References


**Herpes zoster and aciclovir**

Herpes zoster infection is common in elderly patients. It is caused by viral infection of a posterior nerve root causing pain followed by rash over the cutaneous distribution of the affected nerve and subsequent local scarring. The complications can be severe. Occasionally, the virus invades the spinal cord or brain, giving rise to myelitis or encephalitis. Persistent local complications are vastly more common. Infection of the ophthalmic division of the trigeminal ganglion can lead to corneal ulceration. Involvement of the eighth nerve may cause deafness or vertigo. Segmental muscle wasting may occur. Most highly prevalent, particularly among older patients, is intractable post-herpetic neuralgia which may last for months or years, and which may recur after apparent remission.
The antiviral compound, aciclovir, has been reported to be effective in treating the acute rash when administered either intravenously (1, 2) or topically (3), but it has remained uncertain whether it can prevent post-herpetic neuralgia and ocular complications. Remarkable results have now been reported, however, from a five-year follow-up of patients included in a randomized comparison of high-dose oral aciclovir (800 mg five times daily for seven days) and placebo administered in the acute phase of the illness (4). Of 74 patients originally seen, 57 were contacted five years later, 30 of whom had received aciclovir and 27 placebo. The two groups were considered to be comparable in age, sex, and distribution of signs and symptoms, and all were immunologically competent.

Ocular signs, which were reported prior to treatment in a total of 14 patients, resolved in all 8 patients who received the antiviral, whereas all 6 patients given placebo required additional therapy to prevent worsening of the condition. Post-herpetic neuralgia — defined as pain persisting for more than one month after the original infection — occurred in only two (7%) of the patients who received aciclovir, and in ten (37%) of those in the placebo group.

Aciclovir is costly. However, because post-herpetic neuralgia can be incapacitating and because there is no effective treatment for the established condition, a proven preventive measure would offer not only a cost-effective approach to management of herpes zoster infections, but also an important contribution to the quality of life. Given the decisive advantage associated with antiviral therapy within this small number of patients, prospective comparisons of treated patients with historical controls could well prove adequate to confirm these encouraging findings.

References

Lipid-lowering agents: where is the evidence of increased survival?

Over the past 20 years pharmaceutical companies have invested on a massive scale in the development of lipid-lowering agents in the expectation that they would reduce death rates from coronary heart disease by slowing or even reversing the progression of coronary atheroma.

The scientific basis of this expectation has long received endorsement from the medical establishment (1, 2). There is an impressive correlation between hypercholesterolaemia and excess risk of coronary heart disease (2). There is ample evidence that lipid-lowering agents can rapidly and substantially reduce the concentration of atherogenic lipoproteins in blood, by reducing total cholesterol, reducing the ratio of low-density to high-density lipoprotein components of cholesterol, and by lowering serum concentrations of triglycerides and apolipoprotein-B. Evidence has also accrued over the past five years from randomized, placebo-controlled trials (3-12) indicating that sustained reduction in serum cholesterol induced by 3-hydroxy-3-methylglutoryl coenzyme A (HMG CoA) reductase inhibitors (statins) slows the progression of diffuse and focal coronary atherosclerosis.

However, amid this wealth of data, evidence that lipid-lowering agents either extend or improve the quality of life has been slow to emerge (13). Results of several primary and secondary prevention studies in which patients taking lovastatin (9, 10), pravastatin (11) or simvastatin (12) were followed for periods ranging from two to four years, raised queries as to whether the magnitude of radiologically-observed regression of coronary atherosclerosis is sufficient to hold clinical relevance (12). These doubts were assuaged in some degree by evidence from meta-analysis, involving records of many thousands of patients treated with a variety of lipid-lowering agents, that sustained treatment over periods of five years or more has been associated with a significant reduction in the incidence of coronary events (14) and of deaths from coronary heart disease (15). But offsetting this latter effect, treatment was associated in the second of these analyses with increased deaths from other causes — notably cancer, suicide, accident and violence.

In the face of these equivocal findings, the future of
lipid-lowering therapy will eventually be determined by the outcome of large-scale mortality studies. The first of several ongoing long-term multicentre studies has now been completed in Scandinavia and the results are singularly encouraging (16). Simvastatin produced highly-significant reductions in the risk of death and morbidity in patients with coronary heart disease followed for a median of 5.4 years, relative to patients receiving standard care.

In all, 4444 patients with previous myocardial infarction (80%) or angina pectoris (20%) and with serum cholesterol levels ranging from 5.5 to 8.0 mmol/l while on a lipid lowering diet, were randomized under double-blind conditions to receive treatment with either simvastatin or placebo. Simvastatin produced changes in total cholesterol, low-density-lipoprotein cholesterol, and high-density-lipoprotein cholesterol of -25%, -35%, and +8%, respectively. A total of 256 patients (12%) died in the placebo group, compared with 182 (6%) in the simvastatin group (relative risk 0.70; 95% CI 0.58-0.85, p=0.0003). The estimated relative risk of coronary death in the treated group was even lower (0.58), and other benefits of treatment included a 37% reduction (p=0.00001) in the risk of undergoing myocardial revascularization procedures. The observed reductions in risk, both for mortality and major coronary events, were somewhat less among patients aged over 60, but they remained statistically significant.

Only 19% of the patients studied were female and, among these, the mortality rate was less than half that for the men. This greatly decreased the probability of demonstrating improved survival associated with simvastatin within this group and no such trend was observed. However, the incidence of major coronary events was reduced among each of the sexes to a similar extent.

Only one case of rhabdomyolysis — the most serious adverse effect attributed to inhibitors of HMG-CoA reductase (17-19) — was reported within the context of the trial and this resolved when treatment was withdrawn. No other untoward events were shown to be associated with treatment.

If, as the authors suggest, treatment with lipid lowering agents stabilizes coronary lesions as their lipid core shrinks, this could well reduce the risk of plaque rupture which triggers intramural haemorrhage and intraluminal thrombosis (10, 20-23). Given this hypothesis, long-term treatment with these products may be expected to reduce the risk of major coronary events over many years, although their benefit will be less apparent in older age groups as mortality from other causes increases.

Inevitably, searching questions are already being posed in the wake of this trial (24). It has already been clarified, for instance, that no interactions occurred with other treatments. In particular, long-term use of acetylsalicylic acid, which has an unrelated mechanism of action, was without influence on the response to simvastatin.

Failure to demonstrate increased mortality from non-coronary events reported in a meta-analysis (15) indicates that this effect may not be due to cholesterol-lowering per se, but to non-related effects of specific drugs. It has recently been suggested that fibrates have particularly unfavourable effects in this regard (25). A reworking of the results of the original study offers the most direct and conclusive means of exploring this possibility.

In the light of the Scandinavian study, it is no longer possible to contend that dietary modification alone can provide the same protection as lipid-lowering therapy. All the patients who participated received dietary advice in accordance with the guidelines of the European Atherosclerosis Society. None the less, 28% of the patients who did not receive simvastatin experienced one or more major coronary events during the course of the study.

Clinicians will need to wait a little longer before answers emerge to other fundamental questions. Is one set of encouraging results sufficient to justify a major change in clinical practice? Can it be assumed that all HMG CoA reductase inhibitors known to exert comparable lipid-lowering effects will offer comparable clinical benefit? Is similar clinical benefit likely to be evident in primary prevention studies? Most importantly, how much will such treatment cost? It has already been estimated, on the basis of this study, that the direct drug-cost of preventing one coronary death over a five year period is US$ 125 000 (26). A report on cost-effectiveness and resource use of simvastatin is now under preparation by the Scandinavian group.

References


Angiography: reducing the risk of nephrotoxicity

Intravascular injection of iodinated contrast media is required in many diagnostic and therapeutic procedures. The long-established ionic, high osmolality media are associated with anaphylactoid reactions, cardiovascular instability and, most importantly, with nephrotoxicity which is a frequent cause of hospital-acquired renal insufficiency and a precipitating factor in chronic end-stage renal disease (1-4). The more recently introduced low osmolality agents are undoubtedly safer in this respect (5). However, nephrotoxicity — which is first apparent as a rise in serum creatinine within 48 hours of administration — remains a serious risk among patients with diabetic nephropathy and other pre-existing causes of impaired renal function (6-9). Within one series of 59 such patients who received low osmolality agents for coronary angiography, 9 (or 15%) required dialysis within two weeks (10).

It is probable that this acute renal damage is a consequence of medullary ischaemia resulting from redistribution of blood flow in the cortical region (11) and that it is accentuated by a direct toxic effect on the renal tubular epithelium (12). Saline hydration and induction of diuresis either with the osmotic agent, mannitol (13), or with the sodium reabsorption blocking agent, furosemide (12), are widely employed as prophylactic measures (14). Most of the studies that have been undertaken to explore the effectiveness of these measures have been either uncontrolled (15, 16) or small in scale (17-19) and the results have been inconsistent.

A larger, carefully controlled comparative study has now been reported, in which 78 patients with pre-existing chronic renal insufficiency who were due to undergo cardiac angiography received either 0.45% saline (1 ml/kg/hour) for 12 hours before and 12 hours after the intervention, supplemented in some cases either with mannitol (25 g intravenously infused over 60 minutes) or with furosemide (80 mg intravenously infused over 30 minutes) immediately before angiography (20). The serum creatinine concentration rose by more than 0.5 mg/dl within 24 hours of angiography in a total of 20 patients (3/28 who received saline only; 7/25 who also received mannitol; and 10/25 who also received furosemide). In each treatment group, the rise tended to be somewhat higher among the diabetic patients.

Far from benefiting these patients, diuretic therapy was associated with an increased incidence of renal dysfunction. These results are not implausible. It is feasible that furosemide, by decreasing cortical vascular resistance and thereby shunting blood away from the renal medulla, could exacerbate the intrarenal vascular changes induced by the radiocontrast agent and intensify medullary ischaemia (20).

The possibility remains, however, that other vasoactive drugs, including dopamine and atrial natriuretic peptide, both of which act exclusively on the vasculature of the kidney, could exert a protective effect (18). Indeed, it has already been suggested that the prophylactic potential of these and other vasoactive compounds, including calcium-channel blocking agents and theophylline, should be further explored (12).

Meanwhile, it has been pointed out that no adequate randomized trial of the efficacy of saline prophylaxis alone has been reported (12). The ethical acceptability of undertaking such a study remains subject to discussion (12, 20). Views differ on whether or not the incidence of decreased renal function among patients receiving saline only in the recent randomized trial is lower than that expected among patients who receive no prophylactic therapy.

Pending this information, it is prudent to ensure, when angiography needs to be undertaken on patients with pre-existing renal impairment, that low osmolality contrast agents are preferred and 0.45% saline is administered for some hours before and after the intervention. These steps will reduce the risk of nephrotoxicity, but patients with serious renal impairment — and particularly those with diabetes — remain at high risk during angiography of further deterioration in renal function (12).
References


Home medicines: much promotion but little enlightenment

The invitation to use over-the-counter medicines — which are advertised to the general public — is appealing. In many countries, users also have the assurance that a regulatory body has adjudged them suitable for use in the home. But is the average person sufficiently discriminating when using these preparations?

In developed countries, children seem to receive more of these preparations than other members of the family (1, 2). The published data are sparse and largely outdated, but it seems that many mothers in the USA, and particularly those of higher socioeconomic status, keep a range of seven or more medicines in the home for their children (3, 4). Similar findings generated in the UK some two to three decades ago showed that, even when vitamin preparations are excluded, some two-thirds of children within working class families received a home medicine within any four-week period (5, 6). The same pattern of administration of home medicines to children has recently been confirmed within a national sample of some 8000 preschool-
age children in the United States (7). Over half of all three-year-old children in the sample had received a home medicine within the previous 30 days. Two-thirds of these had received a preparation of paracetamol, and two-thirds had received a proprietary medicine for coughs or colds.

The authors, in commenting on these findings — presumably typical of a winter season in the northern hemisphere — and in reviewing relevant published trials conclude that, in children of this age, proprietary cold medicines have no discernible beneficial effect (8–10). They contrast these findings with a recent report from the American Association of Poison Control Centers (11) indicating that these medicines can represent a hazard in the home: during the early 1980s over-the-counter analgesics, and preparations intended to inhibit the symptoms of coughs, colds and gastrointestinal upset were implicated each year in some 130 000 poisonings and other adverse events involving children under 6 years.

Notably, almost 15% of children who had symptoms of diarrhoea were given antidiarrhoeal agents, notwithstanding warnings in the product literature that their use is contraindicated in children under three years of age (12–14). In contrast, warnings about the association of acetylsalicylic acid with Reye's syndrome (15) appeared to have had an encouraging impact.

These findings leave no doubt that consumers and parents need to be better informed about the use of home medicines. This need is compounded because these products are becoming an ever more important element in health care (16). Within the United States alone, more than $2 billion is spent annually on some 800 products indicated to allay the symptoms of the common cold (16, 17), while more than 100 products are promoted to suppress episodes of diarrhoea (18).

In some countries, associations of manufacturers are beginning to issue practical basic information to the general public on the use of home medicines, but far more professional advice is required from pharmacists at the point of sale. The International Federation of Pharmacists (FIP) has recently adopted a code of good pharmacy practice which defines a role for the pharmacist in community health care. Affiliated national organizations should forcefully promote this aim. Mothers shopping for medicines for their children should not expect to leave the pharmacy without explicit guidance on the how to use the products that they buy with the utmost benefit and safety.

References
Teratogenic risk: need for guidance on management of exposed pregnancies

In 1979, the US Food and Drug Administration introduced a five-point rating scale to indicate the teratogenic risk of new drugs (1):

- A. Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.

- B. No evidence of risk in humans. Either animal findings show no risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative.

- C. Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.

- D. Positive evidence of risk. Investigational or post-marketing data show risk to the fetus. Never the less, potential benefits may outweigh the potential risk.

- X. Contraindicated in pregnancy. Studies in animals or humans, or investigational or post-marketing reports, have shown fetal risk which clearly outweighs any possible benefit to the patient.

These ratings not only provide guidance to doctors needing to prescribe drugs to women during pregnancy, they also influence the management of pregnancies in which exposure to drugs has already occurred (2, 3). Ratings written to discourage non-essential use of drugs during pregnancy have, it seems, disconcerted doctors faced with the necessity of advising a pregnant woman known to have taken prescription drugs in category C or D after conception. Indeed, it has been claimed that such anxiety has led to unnecessary termination of wanted pregnancies (4–6).

This concern has prompted the US Teratology Society to emphasize that the FDA classification offers no indication of whether the teratogenic risks are sufficient to alter the management of an exposed pregnancy (7). It is pointed out that, whereas only some 20 drugs are recognized human teratogens (8), some 140 drugs contained in the 1992 edition of the US Physicians’ Desk Reference (9) carry an FDA rating of D or X, while some two-thirds of all listed drugs are allocated to category B. The conclusion is consequently drawn that the ratings confound interpretation of studies in experimental animals and findings in patients, and that they fail to distinguish between effects that have been demonstrated and those that are only hypothetical.

Given this concern, the Society has recommended that the FDA classification be abandoned (7). Instead, it suggests that specific risks should be described — including possible risks to the fetus resulting from failure to treat the maternal condition; that the available evidence relating to them be summarized and interpreted; and that recommendations be made. It also proposes that specific guidance on the assessment of risk in managing pregnancies in which exposure to a specific product has occurred be available. This guidance, it proposes, should be based on an assessment of risk determined by standard criteria of developmental toxicity (10–12).

References


Regulatory Matters

Reporting adverse effects: new FDA rules

United States of America — The Food and Drug Administration has proposed wide-ranging changes in requirements to be observed by pharmaceutical manufacturers in reporting adverse effects associated with the use of their products. The dual aim is to identify potential hazards of products under development as quickly as possible, and to monitor the safety of marketed products more effectively.

The changes, which are consonant with recommendations developed by the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonization (ICH), were also in part inspired by the recommendations of a task force that reported in 1993 on a clinical study in which severe hepatic and pancreatic damage resulting in 5 deaths was associated with the use of an investigational drug, fialuridine, in the treatment of hepatitis B infection.

Proposals relevant to products undergoing clinical trial:

• before a clinical trial may be started, the sponsor must provide the FDA with a written description of the specific measures that will be taken to monitor the safety of the product in question;

• specific adverse events that need to be reported immediately to the sponsor by the investigators must be discussed and listed in the trial protocol, and the nature and the length of subsequent medical follow-up of subjects who participated in the trial must be described;

• each suspected adverse drug effect must be immediately evaluated by investigators and sponsors to establish as precisely as possible whether it was causally related to administration of the product.

• at the request of the FDA, and in addition to statutory reporting obligations, sponsors may be required to prepare a comprehensive report on information generated in any specific study that bears upon any aspect of the safety of the drug under investigation.

Proposals relevant to currently-marketed products:

• updated safety reports must be filed at six-month intervals throughout the market life of each product;

• sponsors must submit to the FDA comprehensive information on the safety of each product for which they are responsible including any restrictive action that may have been taken ("the core safety data sheet");

• the FDA must be provided with information on the worldwide registration status of every product approved for marketing in the USA, including definitive or pending decisions to withdraw the product on grounds of safety.

The FDA has also published a final rule that extends to biological products reporting requirements currently applicable to other pharmaceutical products. These specify that:

• all serious and unexpected adverse events associated with the use of a product both within and outside the USA — and any significant increase in the frequency of serious but expected adverse events — should be reported to the FDA within 15 working days;

• periodic reports be submitted of all other adverse events associated with the product, together with information on the distribution of the product and its availability.


Clozapine and myocarditis

Australia — One year ago an association between clozapine and myocarditis was postulated on the basis of five case reports notified within the United Kingdom (1). The association has been confirmed by the notification of 5 additional cases in Australia (2). The patients, whose ages ranged from 29 to 37 years, developed symptoms — typically an influenza-like syndrome — within 1–2 weeks of starting treatment. Two of the patients recovered, one died, and the outcome is unknown in the other
two cases. The autopsy report ascribed the cause of death in this one case to "hypersensitivity myocarditis".

References

Further problems with antiarrhythmic agents

United States of America — The Food and Drug Administration has announced that a multicentre trial of the antiarrhythmic agent, d-sotalol (Bristol-Myers Squibb) involving some 3000 patients with non life-threatening left ventricular dysfunction following myocardial infarction has been suspended prematurely. Interim analysis has shown that 3.9% of patients receiving d-sotalol died during the course of the study compared with only 2% in the placebo group. Other ongoing studies involving investigation of d-sotalol in patients with life-endangering ventricular arrhythmias have been allowed to continue.

d-Sotalol is one of the isomeric components of dl-sotalol, a racemate already approved as an antiarrhythmic agent (Betapace®, Berlex). The FDA has reminded prescribers that dl-sotalol is indicated only for use in life-threatening disturbances of cardiac rhythm and that this restrictive indication should not be relaxed.


Fluoxetine: adverse reaction profile

Australia — Fluoxetine hydrochloride, a selective serotonin uptake inhibitor, was the first launched and remains the widely used of this new class of antidepressant. During the four years that it has been available in Australia the national regulatory authority has received some 400 reports of adverse effects associated with its use (1). Some two-thirds of these reports relate to neurological, psychiatric, gastrointestinal and skin reactions.

Several of these reactions are considered to be of particular clinical importance:

• 27 reports of extrapyramidal signs, associated with restlessness and dyskinesia;

• 11 reports of suicidal ideas or attempts, none of which has resulted in death;

• a comparable number of reports of disorders of endocrine or sexual function including engorged breasts, galactorrhoea, impotence and changes in libido;

• 11 reports of hyponatraemia in elderly patients — an effect associated with other drugs of this class, and which has tentatively been ascribed to inappropriate secretion of antidiuretic hormone;

• potentiation of other drugs, including tricyclic antidepressants, which, like fluoxetine, are metabolized by the cytochrome P450 enzyme system;

• an interaction of uncertain mechanisms resulting in erratic changes in serum concentrations of lithium.

The Committee emphasizes that, notwithstanding press speculation associating fluoxetine with suicidal thoughts and actions, the data so far available have not established that the product presents a greater risk in this connection than any other antidepressant (2, 3).

References

HIV vaccine efficacy trials

Global Programme on AIDS — A consultation convened by the Global Programme on AIDS, which included participants from public health institutions, the scientific sector, the pharmaceutical industry, and community representatives, has concluded that, provided appropriate conditions are met, the need will shortly arise to test candidate HIV vaccines in large-scale efficacy trials (1). Indeed, many different trials may be required to assess the degree and duration of immunity
conferring by different vaccine “concepts” against different HIV subtypes transmitted by different routes. Considerable planning at international level to assure the necessary coordination and collaboration will thus be required.

Such a trial will provide information on the efficacy of the envelope vaccine approach, and could also increase knowledge of the mechanisms of protective immunity in human subjects. Even demonstration of low efficacy would be important, it is argued, if vaccine research is to be effectively guided in exploring alternative and possibly more successful approaches.

Proposed trials will be approved only following satisfactory review, on a case by case basis, of laboratory data, animal protection studies, phase I and II safety and immunogenicity data, and consideration of prevailing HIV-I subtypes in the proposed trial population. The initiative and final decision to undertake any proposed trial will rest with the host country.

Also to be taken into consideration are the potential benefits and risks of undertaking the trial having regard, in particular, to the prevalence of HIV infection within the trial population, and the feasibility of implementing the study and recruiting the required number of subjects.

In all instances the guiding principles should include respect for sovereignty; adherence to ethical precepts; perceived benefits to the community as a whole; true partnership between national and international public health agencies, participating communities, the scientific community and the pharmaceutical sector; and the need for a systematic approach to resolving essential scientific issues.

The Global Programme, it is emphasized, should take the initiative to promote the development of appropriate and affordable vaccines worldwide, and should explore every mechanism to make future vaccines accessible to everyone in need of protection.


Silicone oil for retinal reattachment

United States of America — The Food and Drug Administration has announced the approval of a sterile preparation of silicone oil (Adatomed, Germany) for treating complicated cases of retinal detachment that cannot be corrected by standard surgery. It has been shown to offer the most effective means of repairing detachments resulting from cytomegalovirus retinitis in patients with HIV infection.

Injected under the detachment, the oil holds the retina in place until it reattaches to the inner surface of the eye. Except in patients with HIV infection, it is recommended that the oil be removed within one year.

The FDA has reviewed data received on a total of some 450 patients treated with the oil in various centres in Europe and the United States. Success rates for reattachment in individual centres ranged from 60% to 75%. Normally, vision deteriorates in patients successfully treated for complicated retinal detachment. However, in some 80% of these patients, visual acuity either improved or remained stable.


Vincristine: fatal intrathecal administration

The US Food and Drug Administration has advised WHO that deaths continue to occur outside the USA as a result of intrathecal — instead of intravenous — administration of the antineoplastic agent, vincristine (1). These cases are assumed to result from confusion with a related antineoplastic agent, vinblastine, which can be safely administered intrathecally.

The hazard was identified in the USA in 1991, when the FDA required the packaging of all vials or preloaded syringes containing vincristine to include a light-resistant overwrap stating: “Do not remove covering until the moment of injection. Fatal if given intrathecally. For intravenous use only” (2). From this time, no further cases have been notified within the country.

In 1990, following such an incident in the UK, the Medicines Control Agency introduced a colour coding scheme intended to distinguish between products containing these two agents.

Source: Communication from the US Food and Drug Administration to WHO, 16 November 1994.
Essential Drugs

Symptomatic relief of migraine and headache

Chronic recurrent headache is associated with many disorders, both somatic and psychogenic. An accurate diagnosis must consequently be made before appropriate treatment can be prescribed. Many etiological classifications have been devised, and the one proposed by the International Headache Society is particularly comprehensive.* This account is concerned with symptomatic relief of headache, but not with treatment of the underlying causes.

Migraine

The mechanisms that trigger attacks of migraine remain obscure, but the pain is ascribed to activation of sensory nerve endings in extracranial arteries resulting from transient and intense vasodilatation. The disorder is extremely common. It tends to run in families, and women are affected more often than men. In some communities as many as one in three adults is affected, but the incidence varies widely. Typical attacks may start in childhood, but they usually first occur in early adult life. They decline in frequency after the age of 50 and usually remit completely during pregnancy.

The headaches are recurrent, commonly unilateral and associated with malaise, nausea, vomiting and photophobia. The pain is usually most severe in the temporal and frontal regions. Untreated, attacks last for several hours and sometimes for as long as 3 days. Emotional or physical stress, lack or excess of sleep, missed meals, specific foods, alcohol and menstruation are sometimes cited as precipitating factors, and oral contraceptives may increase the frequency of attacks. "Classic" migraine is preceded or accompanied by visual disturbances, dizziness, tinnitus and, occasionally, hemiparesis. Permanent neurological sequelae, which are rare, have been associated with the use of oral contraceptives. Women patients with migraine are best advised to use other contraceptive measures.

Treatment

Most patients need to lie down in a quiet, darkened room. Drugs used to obtain relief should be taken as early as possible because gastric stasis can impair absorption.

Acetylsalicylic acid or paracetamol is sometimes effective in mild forms of migraine. Metoclopramide can also be useful, both in relieving nausea and restoring gastric motility. When these drugs fail to relieve the headaches, use of other nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen is warranted.

Prescription of the vasoconstrictor compound ergotamine should be considered only when attacks are unresponsive to non-opioid analgesics. Because ergotamine is poorly absorbed when taken orally or sublingually, rectal suppositories may sometimes offer advantage. To be fully effective, the prescribed dose must be taken as early as possible during each attack. When ergotamine is prescribed in the correct dosage, in the absence of contraindications, it is a safe and useful drug; few serious complications have been reported from its use in migraine. Ergotamine should be recognized, however, as a potentially highly toxic substance that can cause acute or chronic poisoning. The recommended dosage should consequently never be exceeded.

Treatment may exacerbate the nausea and vomiting that is characteristic of migraine. Numbness and tingling in fingers and toes and, occasionally, precordial pain are cautionary symptoms of ergotism that signal a need for discontinuation of treatment. Opioids and anti-emetics are sometimes used to treat intractable attacks but their effects need to be better evaluated in controlled studies. Use of barbiturates or codeine is undesirable — and dangerous when administered together with ergotamine in combination products — since this may induce physical dependence and withdrawal headaches.

A recently-developed compound, sumatriptan, described as a 5-hydroxytryptamine1 receptor blocking agent, effectively relieves symptoms in

many patients unresponsive to other treatment when administered either orally or subcutaneously. However, it is extremely expensive. Moreover, some 3–5% of patients experience chest pain sometimes associated with ECG changes suggestive of cardiac ischaemia (1, 2) — but which, it has been suggested, may be related to changes in oesophageal motility (3, 4).

Prevention of attacks
The success of preventive treatment can never be assured, but it is worth a trial in patients who are unresponsive to non-opioid analgesics and ergotamine and who have more than one attack each month.

Among the many drugs that are sometimes effective, beta-adrenoreceptor antagonists are most frequently used. Propranolol and other compounds with a partial agonist effect are generally preferred but in some trials only about half the patients have responded satisfactorily. Pizotifen, a serotonin antagonist, is similarly effective. It is particularly useful when propranolol is contraindicated, but some patients tend to gain weight during treatment.

Amitriptyline and other tricyclic antidepressants have been used less extensively. The therapeutic response takes several weeks to develop, and the incidence of drowsiness, dry mouth, weight gain and blurred vision among treated patients limits their usefulness.

Calcium channel-blocking agents are better tolerated, and useful results have been obtained with the cerebroselective agents, nimodipine and flunarizine.

Methysergide remains the most effective preventive agent, but its use in migraine is no longer justified because of its association with cases of retroperitoneal and pulmonary fibrosis.

Cluster headaches
Cluster headaches — which, like migraine, are of vascular origin — are more common in men than in women. Short-lived attacks of severe, unilateral pain occur in a series of closely spaced attacks, each cluster lasting several weeks followed by symptom-free intervals extending from one month to a year or more. Each episode lasts for 30–40 minutes and typically awakens the patient at night after two or three hours of sleep.

Oral drug therapy is largely ineffective because most attacks cease spontaneously before relief can be anticipated, but oxygen inhaled through an open mask is claimed to be effective.

When the headaches within a cluster occur at regular intervals, lithium carbonate has been used as a preventive measure with some success.

Tension-type headaches
Headaches caused by tension are widely prevalent. They are claimed to occur more frequently among patients who are either depressed or who suffer from migraine. They are often attributed to emotional difficulties, but they can also be indicative of somatic conditions including cervical spondylosis, eye strain or sinus infections. Patients complain of recurrent daily headaches in the suboccipital region which may be episodic or chronic. The pain is typically bilateral, steady, non-throbbing and of moderate intensity. It is not accompanied by nausea, vomiting or other autonomic disturbances.

Analgesics are rarely necessary. Indeed, patients need to be persuaded to decrease their reliance on self-medication and, if possible, to discard such preparations completely. Some patients may be helped by short courses of anxiolytic agents, while tricyclic antidepressants may be of value in others. Correction of abnormalities of posture resulting in sustained muscle contraction is also sometimes helpful.

Cervicogenic headache
These headaches, which are unilateral and typically associated with non-radiating pain in the shoulder or arm of the same side, are of unknown origin. The pain may be provoked by mechanical pressure or by particular movements of the neck, but there is no obvious underlying pathology. Nonsteroidal anti-inflammatory agents are often prescribed, but they are of questionable value.

Cranial arteritis
Cranial (or giant cell) arteritis is an important cause of headache in elderly patients. The condition is assumed to be related to polyarteritis or to polymyalgia rheumatica, and it is characterized by tender thickening of cranial vessels, and particularly of the temporal arteries. Infiltration of the vessel walls by mononuclear cells, plasma cells and giant cells not only gives rise to intense headache, it predisposes to thrombosis and a risk of blindness.
Complete recovery often ensues within several months, but it is important, if serious complications are to be averted, to institute corticosteroid therapy as soon as the diagnosis is confirmed.

Facial pain
Trigeminal neuralgia is characterized by momentary paroxysms of piercing pain along the distribution of the maxillary or mandibular divisions of the trigeminal nerve. These paroxysms may continue for days or weeks, and remissions become shorter and less frequent as the disease progresses. The cause of the condition is unknown, but some cases result from tumours and other lesions which must always be excluded. Carbamazepine in a daily dose of 400–800 mg is commonly effective in suppressing symptoms. Phenytoin, 100 mg three times daily, is also useful and can be given with advantage together with carbamazepine in less responsive cases.

Atypical facial pain is characterized by a unilateral burning sensation. Simple analgesics, tricyclic antidepressants, or carbamazepine offer limited relief in some cases, but treatment is in general unsatisfactory. Opioid analgesics should never be prescribed since there is a high risk of inducing addiction.

Post-herpetic neuralgia is a distressing and persistent complication of herpes zoster infection. When simple analgesics do not provide adequate relief, tricyclic antidepressants are sometimes effective.

References

ERGOTAMINE
tablet 2 mg (as tartrate)
An alkaloid of ergot which causes intense and prolonged vasoconstriction of peripheral arterioles largely by a direct action but also by depressing vasomotor centres and blocking peripheral adrenergic autonomic activity. It also exerts a tonic action on the uterus late in pregnancy. Excessive use is dangerous since it can readily result in obliterative peripheral arterial disease (chronic ergotism).

Ergotamine is slowly and incompletely absorbed from the gastrointestinal tract, particularly in the presence of gastric stasis. The plasma half-life is about two hours but vasoconstriction persists long after the drug is cleared from the plasma. Much is metabolized and excreted via the bile.

Uses
Symptomatic relief of migraine.

Dosage and administration
Oral or sublingual dosage: 1–2 mg should be taken as early as possible during the attack. Patients vary considerably in their sensitivity to ergotamine. The original dose may thus need to be repeated after an interval of 30 minutes. No more than 4 mg should be taken in any 24-hour period and no more than 12 mg in any one week.

Contraindications
Ergotamine should not be taken by patients with peripheral vascular disorders, coronary artery disease, obliterative vascular disease, severe hypertension, sepsis, or severe hepatic or renal dysfunction.

Use in children under 12 not recommended.

Because of the danger of ergotism, ergotamine should never be used for the prevention of migraine.

It should never be included in combination preparations. Its use together with dependence-generating drugs (including barbiturates and codeine) has induced ergotism.

Use in pregnancy
Ergotamine is contraindicated during pregnancy because of its tonic effect on the uterus, and during lactation, because it enters breast milk and can cause ergotism in the infant.

Precautions
Ergotamine should be prescribed for migraine only when the condition is unresponsive to analgesics.

Any sign of vascular insufficiency, including anginal pain or peripheral paraesthesiae, is a reason for
immediate and permanent withdrawal of ergotamine.

Adverse effects
Many patients cannot accept the malaise, nausea and vomiting sometimes induced by ergotamine. Concurrent administration of an anti-emetic may enable some patients to continue treatment.

Signs of permanent peripheral circulatory insufficiency (chronic ergotism) should never be allowed to develop. Signs of circulatory insufficiency may be preceded by malaise, nausea and headache. Ergotamine should be withdrawn progressively and definitively. If severe arteriospasms occur, a vasodilator such as sodium nitroprusside should be administered.

Drug interactions
The danger of vasoconstriction is potentiated by concomitant use of beta-adrenoreceptor blocking agents.

Overdosage
Acute poisoning can result when the recommended dose is exceeded by two to three fold. It is characterized by vomiting, diarrhoea, severe thirst, paraesthesiae, itching, coldness of extremities, rapid and weak pulse. Confusion, convulsions and coma may supervene. Gastric lavage or emesis may be of value within a few hours of ingestion. Otherwise treatment is symptomatic. Various vasodilator agents, including nitrates and sodium nitroprusside, have been used to relieve ischaemia, but much of the vascular damage is likely to be irreversible.

Anticoagulants and low molecular weight dextran have also been advocated.

Storage
Ergotamine tablets should be stored in tightly closed containers protected from light below 25°C.

ACETYLSALICYLIC ACID

tablet 100–500 mg
suppository 50–150 mg

Acetylsalicylic acid has anti-inflammatory, analgesic, antipyretic and anti-rheumatic activity. In part, these effects result from inhibition of the synthesis of endogenous prostaglandins.

The compound is hydrolysed partly in the gut and partly in the liver, and it is excreted mainly in the urine, both as free salicylic acid and as inactive metabolites. The plasma half-life of salicylic acid is of the order of three hours and is strongly dose-dependent.

Uses
Symptomatic relief of migrainous and tension headaches.

Dosage and administration
Adults: 300–1200 mg at onset of headache or during the prodromal phase, then every 4–6 hours as required to a maximum of 4 g daily.

Treatment should not be continued for more than 5 days except on medical advice.

Administration with food or a full glass of water reduces gastric irritation. This may not be practicable during migrainous attacks which are often associated with nausea and vomiting. Coadministration of metoclopramide which promotes gastric emptying counter these effects. Rectal absorption is slow and incomplete, but suppositories may be of value in patients unable to take oral dosage forms.

Contraindications
Hypersensitivity to acetylsalicylic acid.
Bleeding disorders, anticoagulant therapy, haemorraghic stroke, active peptic ulcer or gastritis.
Chronic renal insufficiency.
Children under 12 years of age.

Precautions
Symptoms of hypersensitivity are more likely to occur in:

• patients with asthma, urticaria or chronic rhinitis; and
• patients who have developed skin rashes or anaphylactic phenomena after exposure to other nonsteroidal anti-inflammatory agents.

A mild haemolytic reaction may occur in patients with glucose-6-phosphate dehydrogenase deficiency.

Young children are particularly susceptible to the dose-related toxic effects of acetylsalicylic acid. They should never receive more than the maximum recommended dose, and stocks of tablets should never be left within their reach.
Reye's syndrome (a rare but often fatal non-infectious encephalopathy and fatty degeneration of the liver) has been reported in children and adolescents with influenza or chickenpox who have received acetylsalicylic acid. The risk is remote, but it is readily avoidable since paracetamol is comparably effective and apparently devoid of this hazard.

To avoid the risk of haemorrhage, acetylsalicylic acid should not be administered within 7 days of an elective surgical operation.

Use in pregnancy
Occasional use of acetylsalicylic acid carries no apparent risk during early pregnancy. However, it should not be taken during the last three months of pregnancy since it has been reported to prolong labour and contribute to maternal and neonatal bleeding.

Adverse effects
Hypersensitivity reactions, which may occasionally be severe, include urticaria, angio-oedema, pruritus, and anaphylactic phenomena.

Gastrointestinal effects, which include dyspepsia, heartburn, epigastric distress and nausea, are common and sometimes severe. Gastrointestinal bleeding can result from acute mucosal erosion or reactivation of peptic ulceration. It is commonly occult but occasionally profuse and even fatal.

Inhibition of platelet aggregation may result in prolongation of bleeding time. Leukopenia, thrombocytopenia, purpura and pancytopenia have rarely been reported.

Drug interactions
The therapeutic actions of anticoagulants may be potentiated.

Conversely, the efficacy of uricosuric agents and spironolactone may be reduced.

Co-administration of acetylsalicylic acid and corticosteroids greatly increases the risk of gastrointestinal bleeding.

Overdosage
Acute ingestion of 20–25 g by an adult, or 4 g by a small child, can be lethal and smaller quantities can cause serious toxicity.

Characteristic early symptoms of overdosage include nausea and vomiting, abdominal pain and tinnitus which may ultimately progress to deafness.

These are followed by flushing, sweating and hyperventilation with respiratory alkalosis. In severe cases metabolic acidosis and coma supervene.

Gastric lavage should be carried out immediately. Failing this, vomiting should be induced. Hyperthermia, dehydration, acidosis and potassium deficiency should be corrected symptomatically.

Whole blood transfusion may be necessary in the event of spontaneous haemorrhage. No advantage is obtained by administering vitamin K supplements.

Forced alkaline diuresis accelerates excretion of salicylate. However, when the serum salicylate concentration is dangerously high or when serious complications develop, such as unresponsive acidosis, impaired urinary output, pulmonary oedema, persistent seizures or coma, haemodialysis may offer the only hope of survival.

Storage
Acetylsalicylic acid tablets should be kept in tightly closed containers. If an odour of acetic acid is perceptible on opening the container, the tablets should be discarded. Suppositories should be stored below 15°C.

PARACETAMOL

tablet 100–500 mg
suppository 100 mg

Paracetamol is a synthetic derivative of p-amino-phenol with analgesic and antipyretic activity but no anti-inflammatory action. Its plasma half-life is about 2 hours. It is extensively metabolized in the liver and subsequently excreted in the urine.

Uses
Symptomatic relief of migraine and headache.

Dosage and administration
Adults: 0.5–1 g at onset of headache or during the prodromal phase then every 4–6 hours to a maximum of 4 g daily.

Children 6–12 years: 20–30 mg/kg at onset of headache or during the prodromal phase then every 4–6 hours as necessary.

Dosage should be reduced in patients with renal failure.

Suppositories are available for patients unable to take the drug orally.
Treatment should not be continued for more than 5 days except on medical advice.

Contraindications
• Hypersensitivity to paracetamol.
• Hepatic insufficiency.

Adverse effects
At doses within the therapeutic range, paracetamol is usually well tolerated.

Hypersensitivity, dermatologic reactions, neutropenia and thrombocytopenic purpura have rarely been reported.

Overdosage
In overdosage, paracetamol is dangerously hepatotoxic: potentially fatal hepatic necrosis can occur after ingestion of as little as a single dose of 10 to 15 g. Signs of mild gastrointestinal irritation are commonly followed 2 days later by anorexia, nausea, malaise, abdominal pain, progressive evidence of liver failure and ultimately hepatic coma.

Gastric lavage should be performed or emesis induced whenever there is a possibility that paracetamol remains in the stomach. When feasible, plasma paracetamol concentrations should be determined to assess the risk of liver failure. This is likely when the plasma concentration is greater than 200 micrograms/ml at 4 hours after ingestion, 100 micrograms/ml at 8 hours, 50 micrograms/ml at 12 hours, 25 micrograms/ml at 16 hours and 6 μg/ml at 24 hours.

Either methionine or acetylcysteine may be used as a specific antidote. To be effective, the antidote must be administered within 16 hours and before signs of hepatic damage become evident. A loading dose of 140 mg/kg administered orally or through a nasogastric tube is supplemented by 70 mg/kg every four hours until the results of liver function tests have returned to normal. If this has not occurred within 3 days, no further improvement can be expected.

Fluid and electrolyte balance must be maintained and ventilation must be assisted when respiration is depressed.

Storage
Paracetamol tablets should be stored in tightly closed containers protected from light, below 25°C. Suppositories should be stored below 15°C.

CARBAMAZEPINE
scored tablets 100 mg, 200 mg

Carbamazepine is an iminostilbene derivative which is used both as an anticonvulsant and in the treatment of trigeminal neuralgia.

It is slowly absorbed from the gastrointestinal tract and peak plasma concentrations may not be attained until several hours after ingestion. The drug is extensively protein bound and is ultimately excreted in the urine as metabolites, including conjugates. The plasma half-life is initially very prolonged but decreases on repeated administration.

Uses
Treatment of acute attacks of trigeminal neuralgia.

Dosage
Initial dose: 100 mg twice daily on the first day increased gradually by 100 mg increments every 12 hours until pain is relieved. The effective daily dose is usually 600–800 mg (or 10–15 mg/kg); it should not exceed 1200 mg. Once pain is relieved treatment should be gradually withdrawn.

Carbamazepine may be used not only to relieve but also to suppress attacks of trigeminal neuralgia. The need for such use must be balanced against the remote risk of serious adverse effects.

Contraindications
• Hypersensitivity to carbamazepine or tricyclic antidepressants.
• Atrioventricular conduction abnormalities.
• Patients taking a monoamine oxidase inhibitor, or who have taken one within the previous 2 weeks.

Precautions
The incidence of dose-related adverse reactions can be reduced by increasing dosage gradually, and carefully adjusting the maintenance dose. Particular care is necessary in patients with severe cardiovascular disease, or with hepatic or renal disorders.

Dermatitis may be the first sign of a severe idiosyncratic reaction and is an indication for withdrawal of treatment.

Treatment should be withdrawn in the very rare event of severe bone-marrow depression. Patients should be advised to stop taking the tablets and to
report to their doctor immediately if they develop sore throat or fever. This advice can be of greater value than routine monitoring of the white cell count during the first months of treatment.

**Use in pregnancy**
Safe use in pregnancy has not been established and epidemiologic data are suggestive of an association between carbamazepine and certain congenital abnormalities. It should not be used for the treatment of trigeminal neuralgia during pregnancy.

**Adverse effects**
Dose-related reactions include gastrointestinal intolerance, dryness of the mouth, drowsiness, dizziness, blurred vision, diplopia and ataxia. Cutaneous eruptions are frequent and, rarely, more serious skin conditions such as Stevens-Johnson syndrome have been reported.

Hypersensitivity reactions are usually mild and reversible but light-sensitive dermatitis has occurred.

Bone-marrow depression and hepatic dysfunction are rare events.

**Drug interactions**
Repeated use of carbamazepine induces hepatic enzymes. It thus promotes its own metabolism and that of other drugs metabolised in the liver, including phenobarbital, phenytoin and oral anticoagulants.

Carbamazepine can reduce the effectiveness of oral contraceptives, particularly if the estrogen content is low. Break-through bleeding is an indication to use another method of contraception or a higher-dose estrogen product.

Concomitant administration of monoamine oxidase inhibitors has resulted in hypertensive crises, severe convulsions and death. At least 2 weeks should elapse between the withdrawal of a monoamine oxidase inhibitor and the start of carbamazepine therapy.

Various drugs inhibit the metabolism of carbamazepine. These include macroclide antibiotics, isoniazid, some calcium antagonists, dextropropoxyphene, viloxazine and possibly cimetidine. This can result in raised plasma levels and consequent neurotoxicity.

**Overdosage**
The first symptoms of overdosage occur within 1-3 hours. Neuromuscular disturbances are prominent. Convulsions, tremor and excitation may develop. Tachycardia and variations in blood pressure are indicative of severe overdosage.

Emesis or gastric lavage are of value within a few hours of ingestion. Treatment is otherwise symptomatic and is directed to the maintenance of the airway, assisted respiration and treatment of shock. Administration of diazepam has been used successfully in the management of carbamazepine-induced convulsions.

**Storage**
Carbamazepine tablets should be kept in a tightly closed container.

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The information in this section is subject to consultation prior to definitive publication in the *Model Prescribing Information* series. Comments, which are invited at this stage, should be referred to:

**Division of Drug Management & Policies**
World Health Organization
1211 Geneva 27, Switzerland
Consultative Document

Guidance for small national drug regulatory authorities

Draft guidelines on import procedures for pharmaceutical products

1. Introductory notes
1.1 Public health considerations demand that pharmaceutical products should not be treated as ordinary commodities. Their manufacture and subsequent handling within the distribution chain, both nationally and internationally, must conform to prescribed standards and be rigorously controlled. These precautions serve to assure the quality of authentic products, and to prevent the infiltration of illicit products into the supply system.

1.2 In 1994, the World Health Assembly endorsed the WHO Guiding Principles for Small National Drug Regulatory Authorities in resolution 47.17 (1). These principles set out a regulatory basis, attuned to resources available within a small national regulatory authority, to assure the quality, safety and efficacy of pharmaceutical products distributed under its aegis.

1.3 The Guiding Principles emphasize the need for effective use of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce (2). This scheme constitutes a formal agreement between participating Member States to provide information on any product under consideration for exportation, notably on its registration status in the country of export and whether or not the manufacturer complies with WHO's standards of good manufacturing practices (GMP).

1.4 To be fully effective, the WHO Certification Scheme needs to be complemented by administrative and other safeguards aimed to ensure that consignments of imported products conform in all particulars with the relevant import licence and that they remain securely within the distribution chain. Storage and transit facilities must be proof against tampering and adverse climatic conditions, and relevant controls must be applied at every stage of transportation.

1.5 Pharmaceutical products containing substances controlled under the international conventions have long been subjected to rigorous border controls. Some of these controls, and particularly those directed to preventing diversion and illicit interchange of products during transit, could be applied to other pharmaceutical products.

2. Objectives and scope
2.1 The following guidelines have been developed in consultation with national drug regulatory authorities, the pharmaceutical industry, the Customs Cooperation Council, and the United Nations Drug Control Programme.

2.2 The guidelines are directed to all parties involved with the importation of pharmaceutical products, including national drug regulatory authorities, competent trade ministries, customs authorities, port authorities, and importing agents or agencies.

2.3 They are intended to promote efficiency in applying relevant regulations, and to simplify checking and handling of consignments of pharmaceutical products in international transit. Inter alia, they provide a basis for collaboration between the various interested parties.

2.4 They are applicable to any pharmaceutical product destined for use within the country of import, and they are intended to be adapted to prevailing national conditions and legal requirements.

3. Legal responsibilities
3.1 Importation of pharmaceutical products should be effected in conformity with regulations promulgated under the national drugs act or other statute and enforced by the national drug regulatory authority. National guidelines providing recommendations on the implementation of these regulations should be drawn up by the national drug regulatory authority in collaboration with the customs authority and other interested agencies or organizations.
3.2 All transactions relating to importation of consignments of pharmaceutical products should be conducted either through the governmental drug procurement agency or through independent wholesale dealers specifically designated and licensed by the national drug regulatory authority for this purpose.

3.3 Importation of all consignments of pharmaceutical products should be channelled through one or more customs posts specifically designated for this purpose.

3.4 All formalities undertaken at the port of entry should be coordinated by the customs authorities which should request the services of an official pharmaceutical inspector as occasion demands. When justified by the workload, a pharmaceutical inspector should be stationed full-time at one or more of the designated ports of entry.

3.5 The customs authority should have discretionary powers to request technical advice and opinion from other appropriately qualified persons, should this be warranted by particular circumstances.

4. The legal basis of control
4.1 Subject to the exemptions outlined in paragraph 4.4 below, only pharmaceutical products proven by appropriate documentation to be duly licensed for marketing within the importing country should be cleared for importation.

4.2 The national drug regulatory authority should compile comprehensive and frequently updated lists of licensed products and authorized importing agents. Notification of any product licences withdrawn on grounds of safety should be rapidly and prominently featured. All lists should be accessible — preferably through a computerized system — to designated customs posts, authorized importing agents or agencies and all drug wholesalers.

4.3 Efficient and confidential channels for communicating information on counterfeit products and other illicit activities should be established between all interested official bodies.

4.4 In countries where no formal system of product licensing has been implemented, importation of products is most effectively controlled by issuance of permits authorizing importation of specific consignments (in the name of the national drug regulatory authority) to the authorized importing agency or agent.

Additional measures that may be invoked in this circumstance include:

- provision by the national drug regulatory authority to the customs authorities, and to the importing agency and agents, of official listings of pharmaceutical products that are either permitted and/or prohibited for importation;

- provision by the importing agent or agency to the customs authority of certified information generated through the WHO Certification Scheme to establish the registration status of the product in the country of export.

4.5 The national drug regulatory authority should reserve to itself discretionary powers to waive product licensing requirements in respect of consignments of pharmaceutical products imported in response to emergency situations and, exceptionally, in response to requests from clinicians for limited supplies of an unlicensed product needed for the treatment of a specific named patient.

5. Documentation
As a prerequisite to customs clearance, the importing agency or agent should be required to furnish the customs authority with the following documentation in respect of each consignment:

5.1 Certified copies of documents issued by the national drug regulatory authority in the importing country, attesting that:

- the importer is duly licensed to undertake the transaction; and

- the product is duly licensed for marketing in the importing country.

5.2 A batch certificate issued by the manufacturer, consonant with the requirements of the WHO Certification Scheme, which documents the results of the final analytical control of the batch(es) constituting the consignment.

5.3 A relevant invoice or bill and, when applicable, an authorization for release of foreign currency granted by the competent national authority in the country of import.

5.4 Any other documentation required by national legislation for customs clearance.

6. Implementation of controls
6.1 A visual and physical examination should be undertaken routinely by the customs authorities, if possible in collaboration with an inspector of the national drug regulatory authority. The size of the consignment should be checked against invoices, and particular attention should be accorded to the nature and condition of packaging and labelling.

6.2 Arrangements should be made with the inspectorate of the national drug regulatory authority to undertake routine sampling and subsequent analysis of exceptionally large and/or valuable consignments, and any other consignment that has apparently deteriorated, or that is damaged or of doubtful authenticity. Materials and reagents needed to undertake simple analytical tests should be provided at the port of entry.

6.3 When samples are taken for analysis to a government or accredited drug quality control laboratory, the consignment should be placed in quarantine. During this procedure, and throughout the time that the consignment is held in customs, particular care must be taken to ensure that packages do not come into contact with potential contaminants.

6.4 A consignment suspected of being counterfeit should be placed in quarantine pending analysis of samples and forensic investigation.

6.4.1 The manufacturer of the authentic product, and/or the owner of the trademark, and the consignee should be advised immediately of such action.

6.4.2 National regulations should define the responsibilities of the interested parties and the precise procedures to be followed. In particular, the provisions should identify the agency responsible for coordinating the investigation and bringing prosecutions.

6.4.3 Counterfeit or other products which have been imported in contravention of the law must be forfeited and destroyed, or otherwise dealt with, in accordance with legal procedures.

6.4.4 The relevant authorities must be indemnified against any consequential legal actions and proceedings.

6.4.5 National drug regulatory authorities are urged to notify other national authorities of confirmed cases of counterfeit pharmaceutical products through the Division of Drug Management and Policies of the World Health Organization.

7. Procedures applicable to pharmaceutical starting materials
7.1 Each imported consignment of a pharmaceutical starting material should be accompanied by a warranty (or batch certificate) prepared by the manufacturer as recommended within the Proposed Guidelines on the WHO Certification Scheme.

7.2 In accordance with good manufacturing practices (3), formal responsibility for the analytical control of starting materials is vested in the manufacturer of the finished pharmaceutical product. Consequently, few countries have implemented formal licensing requirements for starting materials.

7.3 Exceptionally, some national authorities now exercise documentary and, in some cases, analytical control of starting materials as a prerequisite to customs clearance.

7.4 To meet this need, a certifying authority may agree, on a discretionary and voluntary basis, and at the request of a manufacturer, to undertake an inspection of a manufacturer of active ingredients to satisfy specific requirements of a requesting authority. Alternatively, pending the development of specific guidelines for active pharmaceutical ingredients, the certifying authority may be able to attest that the manufacturer is an established supplier of the substance in question to manufacturers of finished dosage forms licensed for marketing under its jurisdiction.

8. Storage facilities
8.1 Many pharmaceuticals, and particularly biological products, including vaccines and sera, tend to degrade on storage and some require to be maintained within a cold chain. All customs posts designated to handle consignments of pharmaceutical products should consequently be provided with secure storage facilities including refrigerated areas. If no pharmaceutical inspector is employed on site, these facilities should be inspected periodically by the national drug regulatory authority to ensure that all equipment is maintained in good working order.

8.2 The importing agency or agent should alert customs in advance of the anticipated arrival of consignments in order that they may be transferred
from the international carrier to the designated storage facility with the minimum of delay and, in appropriate cases, in order to maintain the cold chain.

8.3 Consignments of pharmaceutical products and pharmaceutical starting materials should be accorded high priority for clearance through customs.

8.4 When several different consignments await clearance, the customs authorities should be guided by the drug inspector as to which should be accorded priority.

9. Training requirements
9.1 Performance in implementing the guidelines should be reviewed by the drug regulatory authority on an open-ended basis and, if necessary, improved in the light of on-site monitoring and evaluation. Workshops designed to facilitate efficient implementation of the guidelines and to foster collaborative approaches between the various responsible parties should be organized, as circumstances demand, in collaboration with the customs authority and other agencies involved.

References


The information in this section is subject to consultation prior to definitive publication. Comments, which are invited at this stage, should be referred to:

Division of Drug Management & Policies
World Health Organization
1211 Geneva 27, Switzerland
Drug resistance: fast gathering clouds

Two years ago, a task force set up by the Institute of Medicine in the United States issued a report that should have sensitized officialdom and politicians everywhere to the grave global threat once again posed by microbial infection (1). In developed countries, protective immunization and curative antibiotics have largely disposed of the acute viral and bacterial infections that, in previous generations, struck down children and young adults without warning and in such numbers that the average expectation of life remained less than fifty years. However, there is no guarantee that current degrees of protection can be maintained. The microorganisms are fighting a counter-offensive, and at present they are winning the battle.

This warning has now been reiterated by the British Parliamentary Office of Science and Technology, and the message loses none of its impact in restatement (2). Concern is centred understandably on the progressively worsening problem of multi-drug resistant pulmonary tuberculosis. But there is evidence that this may soon be outpaced by resurgence of other infective diseases.

In Britain, it is estimated, nearly two-thirds of all hospital acquired staphylococcal infections are now resistant to first-line antibiotics. Similarly, the prevalence of penicillin-resistant strains of *Streptococcus pneumoniae* has increased sixfold in five years and resistance to erythromycin has quadrupled. In other places, including Alaska, Chile and South Africa, the situation appears to be worse. There is profound concern that, when these drugs fail, patients with bacterial meningitis, in particular, are exposed to considerable risk (3).

Typhoid fever provides another compelling illustration. Resistant strains of *Salmonella typhi* have become 20 times more prevalent in the UK over the past decade. A quarter of all cases reported within the country are now resistant to chloramphenicol and other widely-used alternative antibiotics.

Ultimately, it may be inevitable that common pathogens will learn to live with the antibiotics intended to destroy them, but there can be no doubt that the pace at which resistance is now developing is accelerated by inappropriate and profligate use of antibiotics. British doctors, it is estimated, are more conservative in this respect than many of their colleagues in other countries. None the less, the tendency for doctors to prescribe these vital drugs for trivial conditions is inexorable. It is reported that the number of prescriptions for antibiotics issued in England rose to 70 million in 1991. Every doctor clearly shares a common responsibility to constrain their prescribing of these drugs if the life-saving properties are to be conserved.

References


International Nonproprietary Names for Pharmaceutical Substances (INN)

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

Lists of Proposed (1-65) and Recommended (1-31) International Nonproprietary Names can be found in Cumulative List No. 8, 1992. The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques les dénominations ci-dessous sont mises à l'étude par l'Organisation mondiale de la Santé en tant que dénominations communes internationales proposées. L'inclusion d'une dénomination dans les listes de DCI proposées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1-65) et recommandées (1-31) dans la Liste récapitulative No. 8, 1992. Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

De conformidad con lo que dispone el párrafo 3 del "Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas", se comunica por el presente anuncio que las denominaciones detalladas en las páginas siguientes están sometidas a estudio por la Organización Mundial de la Salud como Denominaciones Comunes Internacionales Propuestas. La inclusión de una denominación en las listas de las DCI Propuestas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1-65) y Recomendadas (1-31) se encuentran reunidas en Cumulative List No. 8, 1992. Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deban incluirse en las listas recapitulativas de DCI.
### Proposed International Nonproprietary Names: List 72

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for List 72 Proposed INN not later than 30 June 1995.

### Dénominations communes internationales proposées: Liste 72

Des observations ou des objections formelles à l'égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l'Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans *WHO Drug Information*, c'est à dire pour la Liste 72 de DCI Proposées le 30 juin 1995 au plus tard.

### Denominaciones Comunes Internacionales Propuestas: Lista 72

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en *WHO Drug Information*, es decir, para la Lista 72 de DCI Propuestas el 30 de junio de 1995 a más tardar.

<table>
<thead>
<tr>
<th>Proposed INN (Latin, English, French, Spanish)</th>
<th>Chemical name or description: Action and use: Molecular formula</th>
<th>Chemical Abstracts Service (CAS) registry number: Graphic formula</th>
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</tr>
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<td>[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]phosphonic acid antiviral</td>
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<tr>
<td>adefovir</td>
<td>acide [[2-(6-amino-9H-purin-9-yl)éthoxy]méthyl]phosphonique antiviral</td>
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</tr>
</tbody>
</table>
adefovir
ácido [[2-(6-amino-9H-purín-9-il)etoxi]metil] fosfónico antiviral
C₉H₁₂N₅O₄P 106941-25-7

afelimomabum
afelimomab
immunoglobulin G 3 (mouse monoclonal LU54107 Fab’ fragment γ-chain anti-human tumor necrosis factor α), disulfide with mouse monoclonal LU54107 κ-chain, dimer
immunomodulator

afélimomab
immunoglobuline G 3 (chaîne γ du fragment Fab’ de l’anticorps monoclonal de souris LU54107 anti-factor de nécrose tumorale α humain), dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris LU54107
immunomodulateur

afélimomab
immunoglobulina G 3 (cadena γ del fragmento Fab’ del anticuerpo monoclonal de ratón LU54107 anti-factor de necrosis tumoral α humano), dimero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón LU54107
immunomodulador

156227-98-4

alniditanum
alniditan
2-[[3-[[R]-2-chromanylmethyl]amino]propyl]amino]-1,4,5,6-tetrahydropyrimidine
antimigraine, serotonin receptor agonist

alniditan
N-[[2(R)-3,4-dihydro-2H-chromën-2-yl]méthyl]-N’-(1,4,5,6-tétrahydropyrimidín-2-yl)propan-1,3-diyldiamine
antimigraineux, agoniste de la sérotonine

alniditan
2-[[3-[[R]-2-cromanilmetil]amino]propil]amino]-1,4,5,6-tetrahidropirimidina
antimigráneo, agonista de los receptores de la serotonina

C₁₇H₂₅NaO 152317-89-0
anakinra

$N^2$-L-methionylinterleukin 1 receptor antagonist (human isoform x reduced)
immunomodulator, interleukin-1 receptor antagonist

anakinra

$N^2$-L-méthionylantagoniste du récepteur de l'interleukine-1 (isoforme x humaine réduite)
immunomodulateur, antagoniste du récepteur de l'interleukine-1

anakinra

$N^2$-L-metionil antagonista del receptor de interleukina 1 (isoforma x reducida, humana)
immunomodulador, antagonista del receptor de la interleukina-1

$\text{C}_{759}\text{H}_{1186}\text{N}_{208}\text{O}_{232}\text{S}_{10}$ 143090-92-0

anastrozol

anastrozole

$\alpha,\alpha,\alpha',\alpha'-\text{tetramethyl-5-}[1\text{H}-1,2,4\text{-triazol-1-ylmethyl}-m\text{-benzenediacetonitrile}
antieoplastic

anastrozole

$2,2'\text{-diméthyl-2',2'-[5-}'[1\text{H}-1,2,4\text{-triazol-1-yl}]{\text{méthyl}}\text{benzène-1,3-diyl]}=$
dipropanenitrile

anastrozol

$\alpha,\alpha,\alpha',\alpha'-\text{tetrametil-5-}[1\text{H}-1,2,4\text{-triazol-1-imetil}-m\text{-bencendiacetonitrilo}
antieoplasico

$\text{C}_{17}\text{H}_{19}\text{N}_{5}$ 120511-73-1

aptiganel

aptiganel

1-(m-etilfenil)-1 -méthyl-3-(1 -naphtil)guanidine
NMDA receptor antagonist

aptiganel

1-(3-éthylphényl)-1-méthyl-3-(naphtalén-1-yi)guanidine
antagoniste des récepteurs du NMDA

aptiganel

1-(m-etilfenil)-1-metil-3-(1-naftil)guanidina
antagonista de los receptores de NMDA

$\text{C}_{30}\text{H}_{29}\text{N}_{3}$ 137159-92-3
atexakinum alfa
1-(1-L-alanyl-L-proline) interleukin 6 (human clone HGF15 protein moiety reduced), cyclic (44→50), (73→83)-bis(disulfide)
immunomodulator

atexakine alfa
(44→50), (73→83)-bis(disulfure cyclique) de la [1-(1-L-alanyl-L-proline)]=
interleukine 6 (partie proteique reduite de la substance issue du clone human HGF15)
immunomodulateur

atexakina alfa
1-(1-L-alanil-L-prolina) interleukina 6 (fraccion proteica reducida del clon humano HGF15), bis(disulturo)ciclico (44→50), (73→83)
immunomodulador

C917H1483N255O288S9 143631-61-2

atibepronum
7-[(5-isopropyl-1,3,4-thiadiazol-2-yl)methoxy]-3,4-dimethylcoumarin
antidepressant

atibéprone
3,4-dimétilyl-7-[(5-(1-méthylethyl)-1,3,4-thiadiazol-2-yl)méthoxy]-2H-
chromén-2-one
antidépresseur

atibeprona
7-[(5-isopropil-1,3,4-thiadiazol-2-il)metoxi]-3,4-dimetilcumarina
antidepresivo

C17H18N2O3S 153420-96-3

azimilidum
1-[[5-(p-chloropheny)]fururylidene]amino]-3-[4-(4-methyl-1-
piperazinyl)butyl]hydantoin
antiarrhythmic

azimilide
1-[[5-(4-chlorophényl)furan-2-yl]méthyle]amino]-3-[4-(4-méthylpipérazin-
1-yl)butyl]imidazolidine-2,4-dione
antiarythmique

azimiliida
1-[[5-(p-clorofenil)furfuriliden]amino]-3-[4-(4-metil-1-piperazinil)butil]=
hidantoina
antiarrítmico

C23H28ClN5O3 149906-53-2
basifunginum
basifungin
\[ N\{[2R,3R]-2-hydroxy-3-methylvaleryl\}-N-methyl-L-valyl-L-phenylalanyl-\]
\[ N-methyl-L-phenylalanyl-L-prolyl-L-alloisoleucyl-N-methyl-L-valyl-L-leucyl-\]
\[ 3-hydroxy-N-methyl-L-valine \alpha_1\]-lactone \]
antifungal

basifungine
\[ \alpha_1\]-lactone de la \[ N\{[2R,3R]-2-hydroxy-3-méthylpentanoyl\}-N-méthyl-L-valyl\]-\]
\[ L-phenylalanyl-N(N-méthyl-L-phenylalanyl)L-prolyl-L-alloisoleucyl-(N-méthyl-L-\]
\[ valyl)L-leucyl-(3-hydroxy-N-méthyl-L-valine) \]
antifongique

basifungina
\[ N\{[2R,3R]-2-hidroxi-3-metilvaleril\}-N-metil-L-valil-L-fenilalanil-N-metil-\]
\[ L-fenilalanil-L-profil-L-alloisoleucil-N-metil-L-valili-L-leucil-3-hidroxi-N-metil-\]
\[ L-valina \alpha_1-lactona \]
antifúngico

C_{60}H_{92}N_{8}O_{11} 127785-64-2

bervastatinum
bervastatin
ethyl (±)-(3R*,5S*,6E)-7-[4-(p-fluorophenyl)spiro[2H-1-benzopyran-2,1'-cyclopentan]-3-yl]-3,5-dihydroxy-6-heptenoate
antihyperlipidaemic, HMG-CoA reductase inhibitor

bervastatine
(±)-(6E)-(3RS,5SR)-7-[4-(4-fluorophényl)spiro[2H-chromène-2,1'-cyclopentane]-3-yl]-3,5-dihydroxyhept-6-énoate d'éthyle
hypolipémiant, inhibiteur de la HMG-CoA réductase

bervastatina
(±)-(3R*,5S*,6E)-7-[4-(p-fluorofenil)espiro[2H-1-benzopiran-2,1'-ciclopentan]-3-i]-3,5-dihidroxi-6-heptenoato de etilo
antihiperlipémico, inhibidor de la reductase de la HMG-CoA

C_{28}H_{31}FO_{5} 132017-01-7
**betalizofiranum**

**betalizofiran**  
Scleroglucan or poly(→3(O-β-D-glucopyranosyl-(1→3))-O-β-D-glucopyranosyl-(1→6))-O-β-D-glucopyranosyl-(1→3)-O-β-D-glucopyranosyl-(1→) produced by Sclerotium rolfsii; relative molecular mass is about 5.10^6

**laxative**

---

**scleroglucan or poly(→3(O-β-D-glucopyranosyl-(1→3))-O-β-D-glucopyranosyl-(1→6))-O-β-D-glucopyranosyl-(1→3)-O-β-D-glucopyranosyl-(1→) produced by Sclerotium rolfsii; la masse moléculaire relative est voisine de 5.10^6 laxatif**

---

**escleroglucano o poli(→3(O-β-D-glucopiranosil-(1→3))-O-β-D-glucopiranosil-(1→6))-O-β-D-glucopiranosil-(1→3)-O-β-D-glucopiranosil-(1→) producido por Sclerotium rolfsii; la masa molecular relativa es aproximadamente de 5.10^6 laxante**

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**bivalirudinum**

**bivalirudin**  

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**Bivalirudina**

**Bivalirudine**  
C<sub>98</sub>H<sub>138</sub>N<sub>24</sub>O<sub>33</sub>  
128270-60-0

**H-D-Phe-Pro-Arg-Pro-Gly-Gly-Gly-Asn-Gly-**  
**Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-OH**
capecitabín
capecitabine
1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinecarbamic acid
antineoplastic

capécitabine
acide [1-(5-désoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidine-4yl]carbamide
antinéoplasique

capécitabina
ácido 1-(5-desoxi-β-D-ribofuranosil)-5-fluoro-1,2-dihidro-2-oxo-4-pirimidincarbámico
antineoplásico

\[ \text{C}_{10}\text{H}_{12}\text{FN}_{3}\text{O}_{6} \]
158798-73-3

\[
\text{\includegraphics[width=0.3\textwidth]{capecitabine_structure.png}}
\]

cartasteinum
cartasteine
(S)-3-[N-{(R)-2-mercaptopropionyl}glycyl]-4-thiazolidinecarboxylic acid
mucolytic

cartastéine
acide (4S)-3-[2-[(2R)-2-mercaptopropanoyl]amino]acétyl]thiazolidine-4-carboxylique
mucolytique

cartastaína
ácido (S)-3-[N-{(R)-2-mercaptocaptopionil}glicil]-4-thiázolidinecarboxílico
mucolítico

\[ \text{C}_{9}\text{H}_{14}\text{N}_{2}\text{O}_{4}\text{S}_{2} \]
149079-51-6

\[
\text{\includegraphics[width=0.3\textwidth]{cartasteine_structure.png}}
\]

cidofovirum
cidofovir
[[[S]-2-(4-amino-2-oxo-1(2H)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]-phosphonic acid
antiviral

cidofovir
acide [[[(1 S)-2-(4-amino-2-oxopyrimidin-1(2H)-yl)-1-(hydroxyméthyl)éthoxy]méthyl]phosphonique
antiviral

\[
\text{\includegraphics[width=0.3\textwidth]{cidofovir_structure.png}}
\]
cidofovir
ácido [[(S)-2-(4-amino-2-oxo-1(2H)-pirimidinil)-1-(hidroximetil)etoximetil]-fosfónico
antiviral
\(\text{CaH}_{14}\text{N}_{2}\text{O}_{6}\text{P}\) 113852-37-2

**cromoglicas lisetilum**
cromoglicate lisetil
diethyl 5,5'-[(2-hydroxytrimetileno)dioxi]bis[4-oxo-4H-1-benzopyran-2-carboxilate], ester with L-lysine
antiallergic, antiasthmatic

**cromoglicate lisétil**
antiallergique, antiasthmatique

**cromoglicato lisétil**
5,5'-[(2-hidroxitrimetileno)dioxi]bis[4-oxo-4H-1-benzopirano-2-carboxilato] de dietilo, éster con L-lisina
antialérgico, antiasmático
\(\text{C}_{33}\text{H}_{36}\text{N}_{2}\text{O}_{12}\) 110816-79-0

**ébalzotanum**
**ébalzotan**
(R)-N-isopropyl-3-(isopropilpropilamino)-5-chromancarboxamide
serotonin receptor agonist

ébalzotan
(3R)-N-(1-éthylméthyl)-3-[(1-éthylméthyl)propilamino]-3,4-dihydro-2H-chromène-5-carboxamide
agoniste de la sérotonine

ébalzotan
(R)-N-isopropil-3-(isopropilpropilamino)-5-cromancarboxamida
agonista de los receptores de la serotonina
elisartanum

elisartan (±)-1-hydroxyethyl 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, ethyl carbonate (ester)
angiotensin II receptor antagonist

élisartan 2-butyl-4-chloro-1-[4-[2-(1H-tétrazol-5-yl)phényl]benzyl]-1H-imidazol-5-carboxylate de (RS)-1-{(éthoxy carbonyl)oxy}éthyle
antagoniste du récepteur de l'angiotensine II

elisartan (±)-2-butil-4-cloro-1-[p-(o-1H-tetrazol-5-ilfenil)bencil]imidazol-5-carboxilato, etil carbonato de 1-hidroxietilo (éster)
antagonista del receptor de angiotensina II

epoetinum epsilonum

epoetin epsilon 1-165-erythropoietin (human clone λHEPOFL13 protein moiety), glycoform ε antianemic

époéline epsilon 1-165-érythropoïétine (partie protéique du clone humain λHEPOFL13), forme glycosylée ε antianémique

epoetina epsilon 1-165-eritropoietina (fracción proteica del clon humano λHEPOFL13), forma glicosilada ε antianémico

epoetinum epsilonum

epoetin epsilon 1-165-erythropoietin (human clone λHEPOFL13 protein moiety), glycoform ε antianemic

époéline epsilon 1-165-érythropoïétine (partie protéique du clone humain λHEPOFL13), forme glycosylée ε antianémique

epoetina epsilon 1-165-eritropoietina (fracción proteica del clon humano λHEPOFL13), forma glicosilada ε antianémico

C_{19}H_{30}N_{2}O_{2} 149494-37-1

C_{27}H_{29}ClIN_{6}O_{5} 158682-68-9

C_{80}H_{130}N_{22}O_{240}S_{5} 154725-65-2

(for non-glycosylated protein)

(for la protéine non glycosylée)

(fracción proteica no glicosilada)
Eptacogum alfa (activatum)

Eptacog alfa (activated)

Blood-coagulation factor VII (human clone \( \lambda \)HVII2463 protein moiety)

Eptacog alfa (active)

Facteur VII de coagulation sanguine (partie protéique de la substance issue du clone humain \( \lambda \)HVII2463)

Eptacog alfa (activado)

Factor de coagulación VII (fracción proteica del clon humano \( \lambda \)HVII2463)

\[
\text{C}_{262}\text{H}_{4056}\text{N}_{728}\text{O}_{812}\text{S}_{36} 102786-52-7
\]

Ersentilidum

Ersentilide


Antiarrhythmic

Ersentilide

\[
\text{N}=[\{(S)-2-hydroxy-3-[[2-\{1H-imidazol-1-yl\}phenoxy]ethyl]amino]propyl\}oxygenyl]methylsulfonamide
\]

Antiarrhythmic

Ersentilida

4'-[(2S)-2-hidroxi-3-[[2-(p-imidazol-1-ilfenoxi)etil]amino]propoxi]=metansulfonanilida

Antiarrítmico

\[
\text{C}_{21}\text{H}_{26}\text{N}_{4}\text{O}_{5}\text{S} 125279-79-0
\]

Examorelinum

Examorelin

L-histidyl-2-methyl-o-tryptophyl-L-alanyl-L-tryptophyl-D-phenylalanyl-L-lysaminamide

Growth hormone release stimulating peptide

Examoréline

L-histidyl-{2-(méthyl-o-tryptophyl)}-L-alanyl-L-tryptophyl-D-phénylalanyl-L-lysaminamide

Peptide stimulant la libération de l’hormone de croissance

Examorelina

L-histidil-2-metil-o-triptofill-L-alanii-L-triptofill-D-fenilalanil-L-lisinamida

Peptide estimulante de la liberación de la hormona del crecimiento

\[
\text{C}_{47}\text{H}_{58}\text{N}_{12}\text{O}_{6} 140703-51-1
\]

\[
\text{CH}_3
\]

\[
\text{H} - \text{His} - \text{D-Trp} - \text{Ala} - \text{Trp} - \text{D-Pho} - \text{Lys} - \text{NH}_2
\]
**fampridinum**

4-aminopyridine

potassium channel blocker

**fampridine**

pyridin-4-ylamine

antagoniste potassique

**fampridina**

4-aminopirdina

antagonista del potasio

C₉H₆N₂      504-24-5

![Fampridine Structure](image)

**fenleutonum**

(±)-1-\{(1R,S)-3-[3-(4-fluorophenoxo)phenyl]-1-methyl-2-propynyl\}-1-hydroxyurea

leukotriene synthesis inhibitor

(±)-1-\{(1R)-3-[3-(4-fluorophenoxo)phenyl]-1-methylprop-2-ynyl\}-1-hydroxyuree

inhibiteur de la synthèse des leucotriènes

(±)-1-[3-[m-(p-fluorofenoxi)fenil]-1-metil-2-propinil]-1-hidroxiurea

inhibidor de la síntesis de leucotrienos

C₁₇H₁₅FN₂O₃      141579-54-6

![Fenleuton Structure](image)

**fodipirum**

N,N'-ethylenebis[N-[3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl]methyl]glycine 5,5'-bis(dihydrogenphosphate)

diagnostic agent

N,N'-éthane-1,2-diylbis[N-[3-hydroxy-2-méthyl-5-[(phosphonoxy)méthyl]pyridin-4-ylméthyl]glycine]

produit à usage diagnostique

N,N'-etilenbis[N-[3-hidroxi-5-(hidroximetil)-2-metil-4-piridil]=metil]glicina 5,5'-bis(dihidrógenofosfato)

agente de diagnóstico
frazafibanum (3S,5S)-5-[[4'-amidino-4-biphenylyloxy]methyl]-2-oxo-3-pyrrolidineacetic acid fibrinogen receptor antagonist

frazafiban acide 2-[(3S,5S)-5-[[4'-amidino-4-biphenyl]oxy)methy]-2-oxopyrroldin-3-y]acétique antagoniste du récepteur du fibrinogène

frazafiban ácido (3S,5S)-5-[[4'-amidino-4-bifenil]oxi]metil]-2-oxo-3-pirrolidinacético antagonista del receptor del fibrinógeno

C$_{20}$H$_{21}$N$_3$O$_4$ 148396-36-5

Galdansetronum (+)-(3R)-2,3-dihydro-9-methyl-3-{(5-methylimidazol-4-yl)methyl}carbazol-4(1H)-one serotonin receptor antagonist

Galdansétron (+)-(3R)-9-méthyl-3-{(5-méthyl-1H-imidazol-4-yl)méthyl]-1,2,3,9-tétrahydro-4H-carbazol-4-one antagoniste de la sérotonine

Galdansetron (+)-(3R)-2,3-dihidro-9-metil-3-{(5-metilimidazol-4-ill)metil]carbazol-4(1H)-ona antagonista de los receptores de la serotonina

C$_{18}$H$_{19}$N$_3$O 116684-92-5
goralatidum

goralatide

1-\(N^2-[N-(N\text{-acetyl}-L\text{-seryl})-L\text{-}\alpha\text{-aspartyl}]\text{-L-lysyl}]\text{-L-proline}

immunomodulator

goralatide

(N\text{-acetyl}-L\text{-seryl})-L\text{-}\alpha\text{-aspartyl}-L\text{-lysyl}-L\text{-proline}

immunomodulateur

goralatida

1-\(N^2-[N-(N\text{-acetil}-L\text{-seril})-L\text{-}\alpha\text{-aspartil}]\text{-L-lisil}]\text{-L-prolina}

inmunomodulador

\(C_{20}H_{33}N_{5}O_{9}\) 120081-14-3

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{O} \\
\text{N} \\
\text{H} \end{array}
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{H} \end{array}
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{N} \end{array}
\begin{array}{c}
\text{C} = \text{O} \\
\text{H} \\
\text{N} \end{array}
\begin{array}{c}
\text{H} \\
\text{N} \end{array}
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{CO}_2\text{H} \\
\text{NH}_2
\end{array}
\]

imiglucerasum

imiglucerase

495-L-histidineglucosylceramidase (human placenta isoenzyme protein moiety)

enzyme

imiglucérase

[495-L-histidine]glucosylcéramidase (partie protéique d'isoenzyme de placenta humain)

enzyme

imiglucerasa

495-L-histidinaglucosilceramidasa (isoenzima de placenta humana, fracción proteica)

enzima

\(C_{25}H_{38}N_{7}O_{11}S_{1}\) 154248-97-2

inogatranum

inogatran

\(N\text{-}[1(R)-2\text{-cyclohexyl}-1\text{-}[[(2S)-2\text{-}[[3\text{-guanidinopropyl}]\text{carbamoyl}]\text{piperidino}]=\text{carbonyl}]\text{ethyl}]\text{glycine}\)

thrombin inhibitor

inogatran

acide 2-[[1(R)-1-(cyclohexylméthyl)-2-[[2(S)-2-[[3\text{-guanidinopropyl}]\text{amino}]=\text{carbonyl}]\text{pipéridin}-1-yl]-2-oxéthyl]\text{amino}]\text{acétique}

inhibiteur de la thrombine

inogatran

\(N\text{-}[1(R)-2\text{-ciclohexil}-1\text{-}[[(2S)-2\text{-}[[3\text{-guanid¡nopropil}]\text{carba¡moyl}]\text{piperidino}]=\text{carbonyl}]\text{etil}]\text{glicina}\)

inhibidor de la trombina
insulinum lisprum
insulin lispro
28β-L-lysine-29β-L-prolineinsulin (human)
antidiabetic

insuline lispro
[28β-L-lysine-29β-L-proline]insuline humaine
antidiabétique

insulina lispro
28β-L-lisina-29β-L-prolineinsulina (humana)
antidiabético

C25H38N6O4 155415-08-0

lamifibanum
lamifiban
[[1-[[N-(p-amidinobenzoyl)-L-tyrosyl]-4-piperidyl]oxy]acetic acid
fibrinogen receptor antagonist

lamifiban
acide 2-[[1-[[2S]-2-[[4-amidinobenzoyl]amino]-3-(4-hydroxyphényl)-
propanoyl]pipéridin-4-yl]oxy]acétique
antagoniste du récepteur du fibrinogène

lamifiban
àcido[1-[[N-(p-amidinobenzoll)-L-tirosil]-4-piperidil]oxi] acético
antagonista del receptor del fibrinógeno

C24H28N4O6 144412-49-7
lanperisone
(-)-(R)-2-methyl-3-(1-pyrrolidinyl)-4'-(trifluoromethyl)propiophenone
central muscle relaxant

lanpérisonone
(-)-(2R)-2-méthyl-3-(pyrrolidin-1-yl)-1-[4-(trifluorométhyl)phényl]propan-1-one
myorelaxant central

lanperisona
(-)-(R)-2-metil-3-(1-pirrolidinil)-4'-(trifluorometil)propofenona
miorelajante central

C_{15}H_{18}F_{3}NO
116267-14-0

lanprostonum
lanproston
(Z)-7-[(1R,2R,3R,5S)-2-[(E)-2-[[m-chlorophenoxy]methyl]-1,3-dioxolan-2-y]vinyl]-3,5-dihydroxycyclopentyl]-5-heptenoic acid
luteotropic agent (vet.)

lanprostone
agent lutéotrope (vet.)

lanproston
ácido (2)-7-[(1R,2R,3R,5S)-2-[(1E)-2-[[m-clorofenoxi]metil]-1,3-dioxolan-2-il]vinil]-3,5-dihidroxiciclopentil]-5-heptenoico
luteotrópico (vet.)

C_{24}H_{31}ClO_{7}

lenerceptum
lenercept
1-182-tumor necrosis factor receptor (human reduced), (182→104')-protein with 104-330-immunoglobulin G 1 (human clone pTJ5 Cγ 1 reduced)
tumor necrosis factor antagonist

lénérercept
1-182-récepteur du facteur de nécrose tumorale (humain réduit),
(182→104')-protéine avec la 104-330-immunoglobuline G 1 (clone humain pTJ5 Cγ 1 réduit)
antagoniste du facteur de nécrose tumorale

lenercept
1-182-receptor del factor de necrosis tumoral (humano reducido),
(182→104')-proteina con la 104-330-inmunoglobulina G 1 (clon humano pTJ5 Cγ 1 reducido)
antagonista del factor de necrosis tumoral

C_{193}H_{317}O_{58}N_{32}C_{52}S_{12} 156679-34-4
levosemotiadil

(-)-(S)-2-[[5-methoxy-2-[3-methyl[2-[3,4-(methylenedioxy)phenoxy]ethyl]-amino]propoxy]phenoxy]-4-methyl-2H-1,4-benzothiazin-3(4H)-one
antiarrhythmic

lévosémotiadil

(-)-(2S)-2-[[3-[[2-(1,3-benzodioxol-5-yloxy)ethyl]methylamino]propyl]oxy]-5-méthoxyphényl]-4-méthyl-2H-1,4-benzothiazin-3(4H)-one
antiarythmique

levosemotiadil

antiarrítmico

C_{29}H_{32}N_{2}O_{6}S
116476-16-5

lirequinilum

lirequinil

(3S)-1-[(10-chloro-6,7-dihydro-4-oxo-3-phenyl-4H-benzo[a]quinolizin-1-yl)=carbonyl]-3-ethoxypyrrolidine
hypnotic

liréquinil

(3S)-1-[(10-chloro-4-oxo-3-phényl-6,7-dihydro-4H-benzo[a]quinolizin-1-yl)=carbonyl]-3-éthoxyypyrrolidine
hypnotique

lirequinto

(3S)-1-[(10-dixoro-6,7-dihidro-4-oxo-3-fenil-4H-benzo[a]quinolizin-1-il)=carbonyil]-3-etoxiipirrolidina
hipnótico

C_{26}H_{25}ClN_{2}O_{3}
143943-73-1
lisofyllinum
lisofylline
1-[(R)-5-hydroxyhexyl]theobromine
non-steroidal anti-inflammatory

lisofylline
1-[(5R)-5-hydroxyhexyl]-3,7-dimethyl-3,7-dihydro-1H-purin-2,6-dione
anti-inflammatoire non-steroidal

lisofilina
1-[(R)-5-hidroxihexil]teobromina
antiinflamatorio no esteroide

C_{13}H_{20}N_{4}O_{3} 100324-81-0

lobucavirum
lobucavir
9-[(1R,2R,3S)-2,3-bis(hydroxymethyl)cyclobuty]guanine
antiviral

lobucavir
2-amino-9-[(1R,2R,3S)-2,3-bis(hydroxymethyl)cyclobutyl]-1,9-dihydro-6H-purin-6-one
antiviral

lobucavir
9-[(1R,2R,3S)-2,3-bis(hidroximetil)ciclobutil]guanina
antiviral

C_{11}H_{15}N_{5}O_{3} 127759-89-1

mangafodipirum
mangafodipir
hexahydrogen (OC-6-13)-[[N,N'-ethylenebis[3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl[methyl]glycine] 5,5'bis(phosphato)](8-)]manganate(6-)
diagnostic agent

mangafodipir
(OC-6-13)-hexahydrogéno[[N,N'-éthane-1,2-diybis[3-hydroxy-2-méthyl-5-[(phosphonoxy)méthyl]pyridin-4-yl]méthyl]glicinato(8-)]manganate(6-)
produit à usage diagnostique

mangafodipir
hexanhidrogeno (OC-6-13)-[N,N'-etilenbis[3-hidroxil-5-(hidroximetil)-2-metil-4-piridil]glicina] 5,5'-bis(fosfato)(8-)manganato(6-)
agente de diagnóstico
**mapinastinum**

1-(2-ethoxyethyl)-2-[[4-(4-pyrazol-1-ylbutyl)-1-piperazinyl]methyl]-1H-benzimidazole

*antihistaminic, antiallergic*

**mapinastine**

1-(2-éthoxyéthyl)-2-[[4-[4-(1H-pyrazol-1-yl)butyl]piperazin-1-yl]methyl]-1H-benzimidazole

*antihistaminique, antiallergique*

**mapinastina**

1-(2-etoxietil)-2-[[4-(4-pirazol-1-ilbutil)-1-piperazinil]metil]bencirimidazol

*antihistamínico, antialérgico*

---

**marsidominum**

3-(cis-2,6-dimethylpiperidino)sydnone imine

*antianginal*

**marsidomine**

3-(cis-2,6-diméthylpiperidin-1-yl)sydnone imine

*antiangoreux*

**marsidomina**

3-(cis-2,6-dimetilpiperidino)sidnnone imina

*antianginoso*
mazapertinum  mazapertine  1-[α-4-(α-isopropoxyphenyl)-1-piperazinyl]-m-toluoylpiperidine antipsychotic, dopamin D2 receptor antagonist

mazapertine  1-[3-[4-[2-(1-méthyléthoxy)phenyl]piperazin-1-yl]méthyl]benzoylpipéridine psychotrope, antagoniste du récepteur D2 de la dopamine

mazapertina  1-[α-4-(α-isopropoxifenil)-1-piperazinil]-m-toluoilipiperidina antipsicótico, antagonista del receptor D2 de la dopamina

C_{26}H_{35}N_{3}O_{2}  134208-17-6

mibefradilum  mibefradil  (1S,2S)-2-[2-[[3-(2-benzimidazolyl)propyl]méthylamino]éthyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl méthoxyacetate calcium channel blocker

mibéfradil  2-méthoxyacétate de (1S,2S)-2-[2-[[3-[(1 H-benzimidazol-2-yl)propyl]méthyl-amino]éthyl]-6-fluoro-1-(1-méthyléthyl)-1,2,3,4-tétrahydronaphtalén-2-yile antagonista calcique

mibefradil  (1S,2S)-2-[2-[[3-(2-bencimidazolil)propil]metilamino]etil]-6-fluoro-1,2,3,4-tetrahidro-1-isopril-2-naftil metoxiacetato antagonista del calcio

C_{29}H_{38}FN_{3}O_{3}  116644-53-2

mirisetronum  mirisetron  1-cyclohexyl-1,4-dihydro-4-oxo-N-1αH,5αH-tropan-3α-yl-3-quinoline=carboxamide anxiolytic

mirisétron  1-cyclohexyl-N-[(1R,3r,5S)-8-méthyl-8-azabicyclo[3.2.1]oct-3-yl]4-oxo-1,4-dihydroquinoléine 3-carboxamide anxiolytique

mirisatron  1-ciclohexil-1,4-dihidro-4-oxo-N-1oxH,5uH-tropan-3oxH-3-quinolina=carboxamida ansiolítico
mabenakinum
mabenakin
71-L-serine interleukin 1β (human clone pIL-1-14 reduced)
immunomodulator

mobénakine
[71-L-serina] interleukine 1β (clone humain pIL-1-14, réduite)
immunomodulateur

mobenakina
71-L-serinainterleuquina 1β (clon humano pIL-1-14 reducido)
inmunomodulador

C_{24}H_{31}N_{3}O_{2} 135905-89-4

moroctocogum alfa
moroctocog alfa
(1-742)-(1637-1648)-blood-coagulation factor VIII (human reduced) complex
with 1649-2332-blood-coagulation factor VIII (human reduced)
blood-coagulation factor

moroctocog alfa
complexe du (1-742)-(1637-1648)-facteur VIII de coagulation sanguine
(human réduit) avec le 1649-2332-facteur VIII de coagulation sanguine
(human réduit)
facteur de coagulation sanguine

moroctocog alfa
(1-742)-(1637-1648)-factor de coagulación VIII (humano reducido) complejo
con 1649-2332-factor de coagulación VIII (humano reducido)
factor de coagulación sanguínea

C_{719}H_{1219}N_{201}O_{238}S_{7} 124146-64-1

muplestimum
muplestim
interleukin 3 (human protein moiety reduced)
immunomodulator

muplestim
interleukine 3 (partie protéique humaine réduite)
immunomodulateur

muplestim
interleukina 3 (fracción proteica reducida humana)
inmunomodulador

C_{670}H_{1076}N_{186}O_{199}S_{5} 113315-09-6
napsagatranum
napsagatran
N\[N\^[((3S)-1-amidino-3-piperidyl)methyl]-N\^[2-(2-naphthylsulfonyl)-L-asparaginyl]-N-cyclopropylglycine
thrombin inhibitor

napsagatran
inhibiteur de la thrombine

napsagatran
N\[N\^[((3S)-1-amidino-3-piperidyl]méthyl]-N\^[2-(2-naftilsulfonil)-L-asparraginyl]-N-ciclopropilglicina
inhibidor de la trombina

C<sub>20</sub>H<sub>34</sub>N<sub>6</sub>O<sub>6</sub>S  154397-77-0

netivudinum
netivudine
1-β-α-arabinofuranosyl-5-(1-propynyl)uracil
antiviral

nétique
1-(β-α-arabinofuranosyl)-5-(prop-1-ynyl)pyrimidine-2,4(1H,3H)-dione
antiviral

netivudina
1-β-α-arabinofuranosil-5-(1-propinil)uracilo
antiviral
C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub> 84558-93-0

nicanartinum
nicanartine
2,6-di-tert-butyl-4-[3-(3-pyridylmethoxy)propyl]phenol
antihyperlipidaemic

nicanartine
2,6-bis(1,1-diméthyléthyl)-4-[3-[pyridin-3-yl]méthoxy]propyl]phénol
hypolipémiante
nicaritina
2,6-di-tert-butil-4-[3-(3-piridilmetoxi)propil]fenol
antihiperlipémico
C_{23}H_{33}NO_{2} 150443-71-3

nicotredolum
nicotredole
N-(2-indol-3-ylethyl)nicotinamide
non-steroidal anti-inflammatory (vet.)

nicotrédoile
N-[2-(1H-indol-3-yl)éthyl]pyridine-3-carboxamida
anti-inflammatoire non-stéroïdien (vét.)

nicotredol
N-(2-indol-3-iletil)nicotinamida
antiinflamatorio no esteroideo (vet.)
C_{15}H_{15}N_{3}O 29876-14-0

ocinaplonum
ocinaplon
2-pyridyl 7-(4-pyridyl)pyrazolo[1,5-a]pyrimidin-3-yi ketone
anxiolytic

ocinaplane
(2-pyridin-2-yi)7-(pyridin-4-yi)pyrazolo[1,5-a]pyrimidin-3-yi)méthanone
anxiolytique

ocinaplon
2-piridil 7-(4-piridil)pirazolo[1,5-a]pirimidin-3-il cetona
ansiolitico
C_{17}H_{11}N_{5}O 96604-21-6

olopatadinum
olopatadine
11-[(2)-3-(dimethylamino)propyldinea]-6,11-dihydrodiben[b,e]oxepin-2-acetic acid
antiallergic
olopatadine  acide 2-[11-[(12)-3-(diméthylamino)propylidène]-6,11-dihydrodibenzo- [b,e]oxépin-2-yl]acétique  antiallergique

olopatadina  ácido 11-[(Z)-3-(dimetilamino)propiilen]-6,11-dihidrodibenzo[b,e]oxepin-2- acético  antialérgico

\[ C_{21}H_{23}NO_3 \]  113806-05-6

ontazolastum  ontazolast  2-[[S]-2-cyclohexyl-1-(2-pyrindyl)ethyl]amino]-5-methylbenzoxazole  antialérgico

ontazolast  [(1S)-2-cyclohexyl-1-(pyridin-2-yl)éthyl][5-méthylbenzoxazol-2-yl]amine  antialérgico

ontazolast  2-[[S]-2-ciclohexil-1-(2-piridil)etil]amino]-5-metilbenzoxazol  antiasmático

\[ C_{21}H_{25}N_3O \]  147432-77-7

orientiparacinum  orientiparcin  a mixture of orienticine A and orienticine D, orienticine A (major component):
\(-\)(3S,5R,7R,22R,23S,26S,36R,38aR)-22-[(3-amino-2,3,6-trideoxy-3-C- methyl-\(\alpha\)-L-arabino-hexopyranosyl)oxy]-44-[[2-O-(3-amino-2,3,6-trideoxy-3-C-methyl-\(\alpha\)-L-arabino-hexopyranosyl)beta-C-glucopyranosyl]oxy]-3-(carbamoylmethyl)-19-chloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,26,30,32-tetrahydroxy-6-[[2\(\alpha\)]-4-methyl-2-(methylamino)valeramido-2,5,24,38,39-pentaaxo-22H-11:18,21-dietheno- 23,36-(iminomethano)-13,16,31,35-dimetheno-1H,16H-[1,6,9]oxadiazacyclohexadecino[4,5-m][10,2,16]benzoaxadiza-cyclotetracosine-26-carboxylic acid

250
orientiparcine

mélangé d’orienticine A et d’orienticine D,
orienticine A (constituant principal):
acide (3S,6R,7R,22R,23S,26S,36R,38aR)-22-[(3-amino-3-C-méthyl-2,3,6-tridésoxy-α-L-arabino-hexopyranosyl)oxy]-44-[[2-O-(3-amino-2,3,6-tridésoxy-3-C-méthyl-α-L-arabino-hexopyranosyl)-β-D-glucopyranosyl]oxy]-3-(carbamoylethyl)-19-chloro-7,28,30,32-tétrahydroxy-6-[[2-[(diméthylamino)-4-méthylvaléryl]amino]-2,5,24,38,39-pentaétho-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tétrahydroxy-8,11:18,21-diéthéno-23,36-(iminométhano)-13,16:31,35-diméthéno-1H,13H-1,6,9oxadiazacyclohexadécino-[4,5-m]-[10,2,16]benzoazidaciocyclotétracosine-26-carboxylic acid antibactérien (vet.)

orientiparcine

mezcla de orienticina A y de orienticina D,
orienticina A (constituyente principal):
ácido (3S,6R,7R,22R,23S,26S,36R,38aR)-22-[(3-amino-3-C-metil-2,3,6-tridésoxy-α-L-arabino-hexopiranoso)xi]-44-[[2-O-(3-amino-3-C-metil-2,3,6-tridésoxy-α-L-arabino-hexopiranoso)xi]-β-D-glucopiranoso)xi]-3-(carbamoilmetil)-19-cloro-7,28,30,32-tetráhidro3-6-[[2-(dimetilamino)-4-metilpentanoil]amino]-2,5,24,38,39-pentaox-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahidro-8,11:18,21-diéthéno-23,36-(imino)metilano)-22H-13,16:31,35-dimetilano-1H,13H-1,6,9oxadiazacyclohexadécino[4,5-m]-[10,2,16]benzoazidaciocyclotetracoseno-26-carboxílico antibacteriano (vet.)

orientiparcine

orienticine D (minor component):
**Proposed INN: List 72**

**WHO Drug Information, Vol. 8, No. 4, 1994**

- **A:** $C_{72}H_{89}ClIN_{10}O_{26}$
  - 111073-20-2
- **D:** $C_{72}H_{81}ClIN_{10}O_{26}$
  - 112848-46-1
  - 159445-63-3

![Chemical Structure](image)

**orienticine A:** $R = H$

**orienticine D:** $R = CH_3$

**pegorgoteinum**

- **pegorgotein**
  - superoxide dismutase, reaction product with succinic anhydride, esters with polyethylene glycol monomethyl ether enzyme

**pégorgotéine**

- esters du produit de réaction de l’anhydride succinique sur la superoxyde dismutase et de monoéther méthylque de polyéthylèneglycol enzyme

**pegorgotein**

- esteres del producto de reacción del anhídrido succínico con la superoxido dismutasa y del monoéter metílico del poliálterenglicol enzima

155773-57-2

![Chemical Structure](image)

$m = 116 \text{ to } 137; n = 9 \text{ to } 13; \text{ Enz = superoxide dismutase}

m = 116 \text{ a } 137; n = 9 \text{ a } 13; \text{ Enz = superoxide dismutase}

m = 116 \text{ a } 137; n = 9 \text{ a } 13; \text{ Enz = superoxide dismutase}
premafloxacinum
premafloxacin
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-\{(3R)-3-\{(1S)-1-(methylamino)ethyl\}-1-pyrrolidinyloxy\}-4-oxo-3-quinolinacarboxylic acid
antibacterial (vet.)

prémefloxacine
acide 1-cyclopropyl-6-fluoro-8-méthoxy-7-\{(3R)-3-\{(1S)-1-(methylamino)éthyl\}pyrrolidin-1-yloxy\}-4-oxo-1,4-dihydroquincléine-3-carboxylique
antibactérien (vét.)

premafloxacino
ácido 1-ciclopropil-6-fluoro-1,4-dihidro-8-metoxi-7-\{(3R)-3-\{(1S)-1-(metilamino)etil\}pirrolidili\}xyloxy\}-4-oxo-3-quinolincarboxílico
antibacteriano (vet.)

\[
\text{C}_{21}\text{H}_{26}\text{FN}_{3}\text{O}_{4}
\]
143383-65-7

priliximabum
priliximab
immunoglobulin G1 (human-mouse monoclonal cm-T412 anti-human antigen CD 4), disulfide with human-mouse monoclonal cm-T412 κ-chain, dimer
immunomodulator

priliximab
immunoglobuline G1 (anticorps monoclonal homme-souris cm-T412 anti-antigène CD 4 humain), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal homme-souris cm-T412
immunomodulateur

priliximab
immunoglobulina G 1 (anticuerpo monoclonal hombre-ratón cm-T412 anti-antígeno CD 4 humano), dímero del disulfuro con la cadena κ del anticuerpo monoclonal hombre-ratón cm-T412
immunomodulador

147191-91-1

prulifloxacinum
prulifloxacin
\((\pm)-7\{4\{[(Z)-2,3-dihydroxy-2-butenyl]-1-piperazinyl\}-6-fluoro-1-methyl-4-oxo-1H,4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid, cyclic carbonate\)
antibacterial

prulifloxacine
acide \((\pm)-6\text{-}fluoro\text{-}1\text{-}méthyl\text{-}7\{4\{5\text{-}méthyl\text{-}2\text{-}oxo\text{-}1,3\text{-}dioxol-4\text{-}yl\}méthyl\}piperazin-1-yl\}-4\text{-}oxo\text{-}4\text{-}H\{1,3\}thiazeto[3,2\text{-}a]quinoléine-3\text{-}carboxylique\)
antibactérien

prulifloxacino
ácido \((\pm)-7\{4\{(Z)-2,3\text{-}dihidroxi\text{-}2\text{-}butenil}\}-1\text{-}piperazinil\}-6\text{-}fluoro\text{-}1\text{-}metil\text{-}4\text{-}oxo\text{-}1\text{-}H,4\text{-}H\{1,3\}\text{thiazeto[3,2\text{-}a]quinolina-3\text{-}carboxilico, carbonato cíclico}\)
antibacteriano
quiflaponum

3-(tert-butylthio)-1-(p-chlorobenzyl)-α,α-dimethyl-5-(2-quinolylmethoxy)-indole-2-propionic acid
5-lipoxygenase-activating protein (FLAP) inhibitor

rofleponidum

6α,9-difluoro-11β,16α,17,21-tetrahydroxypregn-4-ene-3,20-dione, cyclic (R)-16,17-acetal with butyraldehyde
glucocorticosteroid

rofleponum

6α,9-difluoro-11β,16α,17,21-tetrahydroxypregn-4-ene-3,20-dione, cyclic (R)-16,17-acetal with butyraldehyde
glucocorticosteroid
Samixogrelum

samixogrel

(\(E\))-6-[(p-[2-(p-chlorobenzenesulfonamido)ethyl]phenyl]-6-(3-pyridyl)-5-hexanoic acid

platelet aggregation inhibitor

Sanfetrinemum

sanfetrinem

\((1S,5S,8aS,8bR)-1,2,5,6,7,8,8a,8b\)-octahydro-1-[(\(R\))-1-hydroxyethyl]-5-methoxy-2-oxoazeto[2,1-a]isoindole-4-carboxylic acid

antibiotic

sanfétrinem

acide \((1S,5S,8aS,8bR)-1,2,5,6,7,8,8a,8b\)-octahydroazéto[2,1-a]iso-indole-4-carboxylique

antibiotique

sanfetrinem

ácido \((1S,5S,8aS,8bR)-1,2,5,6,7,8,8a,8b\)-octahidroazeto[2,1-a]isoindol-4-carboxilico

antibiótico
**Saprisartanum**

**Saprisartan**
1-[[3-bromo-2-o-(1,1,1-trifluoromethanesulfonamido)phenyl]-5-benzofuranylmethyl]-4-cyclopropyl-2-ethylimidazole-5-carboxamide 
angiotensin II receptor antagonist

**Saprisartan**
antagoniste du récepteur de l'angiotensine II

**Saprisartan**
1-[[3-bromo-2-o-(1,1,1-trifluorometansulfonamido)fenil]-5-benzofuranil]metil]-4-ciclopropil-2-etilimidazol-5-carboxamida 
antagonista del receptor de angiotensina II

* **C₁₄H₁₉N₀₅**  156769-21-0

**Seprilosum**

**Seprilose**
3-O-heptyl-1,2-O-isopropylidene-α-o-glucofuranose 
antiinflammatory

**Séprilose**
3-O-heptyl-1,2-O-(1-méthyléthylidène)-α-o-glucofuranose 
antiinflammatory

**Seprilosa**
3-O-heptil-1,2-O-isopropiliden-α-o-glucofuranosa 
antirreumático

* **C₁₆H₃₀O₆**  133692-55-4
setipafantum
setipafant

diplatelet-activating factor antagonist

sétipafant

6-(2-chlorophényl)-N-(4-méthoxyphényl)-1-méthyl-7,10-dihydro-4H-pyrido=
[4',3':4,5]thiéno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazépine-9(8H)-carboxamide
antagoniste du facteur activant les plaquettes

setipafant

triazolo[4,3-a][1,4]diazepina-9(8H)-carboxi-p-anisida
antagonista del factor activador de las plaquetas

\[ C_{26}H_{23}ClN_{6}O_{2} \quad 132418-35-0 \]


tagorizinum
tagorizine

(E)-N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-6-methyl-3-pyridine-
acrylamide
antiallergic

ntagorizine

(2E)-N-[4-[4-(diphénylméthyl)pipérizin-1-yl]butyl]-3-(6-méthylpyridin-
3-yl)prop-2-énamidine
antiallergique

ntagorizina

(E)-N-[4-[4-(difenilmetil)-1-piperazinil]butil]-6-metil-3-piridinacrilamida
antialérgico

\[ C_{30}H_{36}N_{4}O \quad 118420-47-6 \]


talsaclidinum
talsaclidine

(3R)-3-(2-propynloxy)quinuclidine
muscarn M1 receptor agonist

talsaclidine

(3R)-3-(prop-2-ynloxy)-1-azabicyclo[2.2.2]octane
agoniste des récepteurs muscariniques M1
talsaclidina
(3R)-3-(2-propiloxi)quinuclidina
agonista de los receptores muscarinicos M;
C₁₀H₁₅NO
147025-53-4

tasosartanum
tasosartan
5,8-dihydro-2,4-dimethyl-8-[o-(1H-tetrazol-5-ylphenyl)benzyl]pyrido-
[2,3-d]pyrimidin-7(6H)-one
angiotensin II receptor antagonist

C₂₃H₂₁NO
145733-36-3

tazarotenum
tazarotene
ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate
keratolytic

tazarotène
6-[2-(4,4-diméthyl-3,4-dihydro-2H-1-benzothien-6-yl)éthynyl]pyridine-3-
carboxylate d'éthyle
keratolytique

tazaroteno
6-[(4,4-dimetiltiocroman-6-il)etinil]nicotinato de etilo
queratolítico
C₂₁H₂₁NO₂S
118292-40-3
toborinum
toborinone
\((\pm)-6-[2\text{-hydroxy}-3\text{-}(\text{veratrylamino})\text{propoxy}]\text{carbostyril}\)
cardiac stimulant

\begin{align*}
\text{C}_{21}\text{H}_{24}\text{N}_{2}\text{O}_{5} & \quad 143343-83-3 \\
\end{align*}

vedaprofenum
vedaprofen
\((\pm)-4\text{-cyclohexyl}\text{-}\alpha\text{-methyl-1-naphthaleneacetic acid}\)
non-steroidal anti-inflammatory

\begin{align*}
\text{C}_{19}\text{H}_{22}\text{O}_{2} & \quad 71109-09-6 \\
\end{align*}

zaleplonum
zaleplon
3\'-\(3\text{-cyanopyrazolo}[1,5-a]\text{pyrimidin-7-yl}\)-N-ethylacetanilide
sedative, hypnotic

\begin{align*}
\text{C}_{19}\text{H}_{22}\text{O}_{2} & \quad \text{N-[3-(3-cyanopyrazolo}[1,5-a]\text{pyrimidin-7-y]phenyl]-N-ethylacetamidine} \\
\end{align*}

sedative, hypnotic
zanamivirum
zanamivir
5-acetamido-2,6-anhydro-3,4,5-trideoxy-4-guanidino-\(\alpha\)-glycer-\(\beta\)-galacto-non-2-enonic acid
antiviral

zanamivir
acide \((4S,5R,6R)\)-5-(acétylamino)-4-guanidino-\(6\)\{-\(1R,2R\}\}-1,2,3-trihydroxypropyl\}-5,6-dihydro-4\(H\)pyran-2-carboxylique
antiviral

zanamivir
ácido 5-acetamido-2,6-anhidro-3,4,5-tridesoxi-4-guanidino-\(\alpha\)-glicero-\(\beta\)-galacto-non-2-enónico
antiviral

\(\mathrm{C_{12}H_{20}N_{4}O_{7}}\)
139110-80-8

ziprasidonum
ziprasidone
5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-2-indolione
antipsychotic

ziprasidone
5-[2-[4-(1,2-benzisothiazol-3-yl)pipérazin-1-yléthyl]-6-chloro-1,3-dihydro-2\(H\)-indol-2-one
psicotrópico

ziprasidona
5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinil]etil]-6-cloro-2-indoliona
antipsicótico

\(\mathrm{C_{21}H_{21}ClN_{4}O_{5}}\)
146939-27-7
AMENDMENTS TO PREVIOUS LISTS

Proposed International Nonproprietary Names (Prop. INN): List 64
(WHO Drug Information, Vol. 4, No. 4, 1990)

p. 14 liarozolum replace the CAS registry number by the following:
liarozole 145858-51-1

Proposed International Nonproprietary Names (Prop. INN): List 69

p. 4 delete insert
fropenemum faropenemum
fropenem faropenem

Proposed International Nonproprietary Names (Prop. INN): List 71
Dénominations communes internationales proposées (DCI Prop.): Liste 71
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 71
(WHO Drug Information, Vol. 8, No. 2, 1994)

p. 6 candesartanum replace the molecular formula and CAS registry number by the following:
candesartan remplacer la formule brute et le numéro dans le registre de CAS par:
candésartan reemplacense la fórmula empírica y el número de registro del CAS por:
C_{24}H_{20}N_{6}O_{3} 139481-59-7

p.16 monteplasum add the CAS registry number by the following:
monteplase insérer le numéro dans le registre du CAS suivant:
montéplase insértese el número del registro del CAS por el siguiente:
156616-23-8

Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

The text of the Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances and General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances will be reproduced in uneven numbers of proposed INN lists only.

Les textes de la Procédure à suivre en vue de choix de dénominations communes internationales recommandées pour les substances pharmaceutiques et des Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques ont été publiés avec la liste 71 des DCI proposées et seront, à nouveau, publiés avec la prochaine liste.

El texto de los Procedimientos de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas y de los Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas aparece solamente en los números impares de las listas de DCI propuestas.
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES

Dénominations communes internationales proposées (DCI Prop.): Liste 64
(Informations pharmaceutiques OMS, Vol. 4, No. 4, 1990)

p. 15 liarozolum
     liarozole

remplacer le numéro dans le registre de CAS par:

     145858-51-1

Dénominations communes internationales proposées (DCI Prop.): Liste 69
(Informations pharmaceutiques OMS, Vol. 7, No. 2, 1993)

p. 4 supprimer
  fropenemum
  fropénum

insérer
  faropenemum
  faropenem

Pour toutes les modifications des Dénominations communes internationales proposées (DCI Prop.): Liste 71
voyez page 35 sous AMENDMENTS TO PREVIOUS LISTS.

MODIFICACIONES A LAS LISTAS ANTERIORES

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Liste 64
(Información Farmacéutica, OMS, Vol. 4, No. 4, 1990)

p. 14 liarozolum
     liarozole

sustituyase el número de registro del CAS por:

     145858-51-1

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Liste 69

p. 4 suprimase
  fropenemum
  fropénum

insértase
  faropenemum
  faropenem

Para cualquier modificación de las Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Liste 71
vease página 35, AMENDMENTS TO PREVIOUS LISTS.
## SELECTED WHO PUBLICATIONS OF RELATED INTEREST

<table>
<thead>
<tr>
<th>Publication</th>
<th>Price* (Sw. fr.)</th>
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<tbody>
<tr>
<td><strong>The use of essential drugs</strong></td>
<td>10.–</td>
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<tr>
<td>Fifth report of the WHO Expert Committee</td>
<td></td>
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<tr>
<td>WHO Technical Report Series, No. 825</td>
<td></td>
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<tr>
<td>1992 (75 pages)</td>
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<td><strong>WHO model prescribing information:</strong> drugs used in anaesthesia**</td>
<td>11.–</td>
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<tr>
<td>1989 (53 pages)</td>
<td></td>
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<tr>
<td><strong>WHO model prescribing information:</strong> drugs used in parasitic diseases**</td>
<td>21.–</td>
</tr>
<tr>
<td>1990 (128 pages)</td>
<td></td>
</tr>
<tr>
<td><strong>WHO model prescribing information:</strong> drugs used in mycobacterial diseases**</td>
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<td>1991 (40 pages)</td>
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<tr>
<td><strong>The International Pharmacopoeia, third edition</strong></td>
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<td>Volume 1: general methods of analysis. 1979 (223 pages)</td>
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<td><strong>Basic tests for pharmaceutical substances</strong></td>
<td>34.–</td>
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<tr>
<td>1986 (vi + 204 pages)</td>
<td></td>
</tr>
<tr>
<td><strong>Basic tests for pharmaceutical dosage forms</strong></td>
<td>24.–</td>
</tr>
<tr>
<td>1991 (v + 129 pages)</td>
<td></td>
</tr>
<tr>
<td><strong>International Nonproprietary Names (INN) for Pharmaceutical Substances, Cumulative List No. 8</strong></td>
<td>140.–</td>
</tr>
<tr>
<td>1992 (xlvi + 692 pages)</td>
<td></td>
</tr>
</tbody>
</table>

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

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