WHO Drug Information

Contents

General Policy Issues
Wider access to HIV drugs now a reality 67
Injectable solid vaccines: a role in future immunization? 68

Reports on Individual Drugs
Antimicrobial therapy in the management of bacterial meningitis 70
Vaccine control of Hib disease 71
WHO requirements for Haemophilus influenzae type b conjugate vaccines 72
Meningococcal vaccines: current status 72
Atovaquone plus proguanil effective in malaria 74
Promising approaches for a serum diagnostic test in Creutzfeldt-Jakob disease 75
Warfarin potentiated by paracetamol 75
Prevention of gastric ulcers caused by nonsteroidal anti-inflammatory drugs 76
Lymphatic filariasis: global elimination in sight 77

Current Topics
Important breakthrough for neurovirulence testing of oral poliovirus vaccine 78
MMR vaccination: update 79
The Erice Declaration 80

Regulatory Matters
Precipitation of carbamazepine suspension and other liquid drugs 81
Medication-associated depression 81
Plasma-derived medicinal products and Creutzfeldt-Jakob disease 81
Troglitazone-induced liver injury 81
Midazolam and paradoxical reactions in children 82
Safety of venlafaxine 82
Bromfenac and liver damage 82
Warning regarding safety of astemizole 82
Dietary supplement contains prescription medicine 83
Fenfluramine and dexfenfluramine: follow-up action 83
Sucralose: a new sweetener approved 83
Sildenafil approved to treat impotence 84
Isotretinoin-associated depression 84
Most frequently reported adverse drug reactions in Finland 84
Fexofenadine approved following terfenadine withdrawal 84
Diphtheria, tetanus and hepatitis B vaccine approved 84
Measles/mumps/rubella vaccine approved 85

Essential Drugs
WHO Model Formulary:
Dermatological drugs (topical)
Antifungal drugs 86
  Benzoic acid + salicylic acid 87
  Miconazole 87
  Selenium sulfide 87
  Methylrosanilinium chloride 88
  Sodium thiosulfate 88
Anti-infective drugs 88
  Potassium permanganate 88
  Neomycin + bacitracin 89
  Silver sulfadiazine 89
Anti-inflammatory and antipruritic drugs 89
  Betamethasone 90
  Calamine lotion 90
  Hydrocortisone 91
Astringents 91
  Aluminium diacetate 91
Drugs affecting skin differentiation and proliferation 91
  Benzoyl peroxide 92
  Coal tar 93
  Dithranol 93
  Fluorouracil 94
  Podophyllum resin 94
  Salicylic acid 94
  Urea 94
Scabicides and pediculicides 94
  Benzyl benzoate 95
  Permethrin 95
Ultraviolet blocking agents 95

.../...
## Recent Publications and Documents

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Travel and Health</td>
<td>97</td>
</tr>
<tr>
<td>Guidance on the clinical investigation of medicinal products for treatment of schizophrenia</td>
<td>97</td>
</tr>
<tr>
<td>Draft guidance for industry: container and closure integrity testing</td>
<td>97</td>
</tr>
<tr>
<td>Regulatory situation of herbal plants</td>
<td>98</td>
</tr>
</tbody>
</table>

## Proposed International Nonproprietary Names: List 79

99
Wider access to HIV drugs now a reality

Under a new UNAIDS initiative aimed at increasing access to HIV drugs in the developing world, pharmaceutical companies have agreed to supply certain medicines at subsidized prices. The UNAIDS HIV Drug Access Initiative is a collaborative effort between the public and private sectors and involves, as a pilot project, four developing countries — Chile, Côte d'Ivoire, Uganda and Viet Nam. The companies that have so far agreed to take part in the initiative are Glaxo Wellcome (United Kingdom), Roche (Switzerland), and Virco (Belgium). Within each country, an advisory board will be established by the Ministry of Health to define HIV drug policy, and a non-profit company will be created to provide the subsidized drugs to distribution outlets and to address business and logistic issues.

Given the broad differences that exist between countries in terms of health systems, economic status and HIV prevalence, it was essential to negotiate individual specific needs with each country. In order to pave the way for implementation of the initiative, criteria for health centre and patient participation, and prescriber treatment guidelines have been issued. Ministries of health involved in the scheme have pledged to strengthen existing programmes and create new sources of funding. The companies in question will make available a range of HIV-related products at subsidized cost, including antiretrovirals for HIV infection, antimicrobials to prevent and treat opportunistic infections, and antibiotics to treat sexually transmitted diseases — which have been shown to increase the risk of HIV transmission (1, 2). Diagnostic kits will also be provided for HIV testing and patient monitoring.

It is currently estimated that more than 20 million people with HIV live in developing countries and the cost of triple therapy, calculated — as an example — at $41 per capita, would largely exceed 25% of the annual gross national product in the majority of countries most affected by the epidemic (3). Multiple barriers block wider access to HIV therapy: lack of health care and management, insufficient laboratory facilities, weak distribution channels, lack of training in administration of HIV therapies, regulatory surveillance and safety monitoring, or insufficient personnel. Each of these components is vital to the provision of care to the millions of people with HIV in the developing world. The scheme aims to select only health care centres that meet set criteria and have well-trained health personnel, laboratory and clinical diagnosis and management, social support and counselling, and drug dispensation amenities.

Notwithstanding these measures, prevention efforts must not be sacrificed since they are recognized as the single, most effective strategy in halting HIV transmission. Governments will therefore be encouraged to continue investing in preventive measures and to improve public education on disease transmission.

This pilot project will provide the information needed to determine if and how potent HIV drugs can be distributed effectively and safely in developing countries. UNAIDS will monitor each of the pilot schemes to determine efficiency and safety, overall health care delivery, the number of people receiving the drugs, and HIV-related morbidity and mortality. A potential exists for the development of viral resistance to the new HIV therapies if they are not properly used, and this will be a major challenge for the initiative.

UNAIDS will also make recommendations for adjustments or expansion of the scheme, and use the evaluation results to help guide other countries in improving their health system infrastructure, setting up evaluation systems and reforming their drug procurement and distribution networks. Above all, UNAIDS is hopeful that the new collaborative approach will make treatment for HIV and AIDS a reality for those people in developing countries who otherwise would have little chance of access to treatment.

References


Injectable solid vaccines: a role in future immunization?

M.T. Aguado, L. Jódar, J. Lloyd & P.H. Lambert, Global Programme for Vaccines and Immunization, World Health Organization

Novel drying technologies combined with recent progress in the development of injection devices are set to transform immunization programmes. The benefits of needle-free parenteral administration of antigens incorporated into inert, temperature-resistant solids will not merely ensure increased efficiency of delivery but will reduce the risks of contamination. This technology will enable vaccines to be distributed without the cold-chain — simplifying logistics and increasing the effectiveness of immunization programmes.

Vaccine stability and sugar glasses

Carbohydrates are widely used to stabilize proteins, but the first hint of the potential of sugars as vaccine stabilizers was originally confirmed in a group of living organisms, the cryptobionts. These organisms have the ability to dry out completely under stressful physicochemical conditions, then regain full metabolic activity when exposed once more to water. The unifying feature among cryptobionts is the presence of the simple disaccharide trehalose in high concentrations. The two glucose moieties are joined through their reducing carbons and the resulting $\alpha$-1,1 glycosidic bond has a very low energy of less than -1kcal/mol. This makes trehalose not only non-reducing but very stable to hydrolysis (1, 2).

A trehalose-based drying and stabilizing technology has already been developed and applied to a number of vaccine antigens prepared as controlled-size powders. For example, in a study carried out with dried measles vaccine, researchers demonstrated that, when stabilized with trehalose, the vaccine suffered no loss of activity after two months at room temperature. By comparison, a marketed freeze-dried measles vaccine lost over 90% of its original titre in the same amount of time (3). In another study, the stability of a trehalose-dried combination of diphtheria, tetanus and acellular pertussis antigens (DTaP) adsorbed to aluminium hydroxide adjuvant was compared with the conventional vaccine. Stored at 60 °C for up to 12 weeks, the trehalose-dried DTaP antigens and adjuvant were shown to be biologically and chemically unaltered. Preclinical investigations have demonstrated the immunogenicity and potency of the trehalose-dried vaccine candidate.

Some man-made analogues which mimic the trehalose stabilizing ability and sometimes improve it have also been developed. These are novel biocompatible sugar glasses which can be surface eroded by phase transitions at slow and controlled rates. Entrapped in glassy matrices, a substance can be automatically released as the erosion front moves through the glass. A number of these glasses are now being developed to produce controlled-release systems with characteristics suitable for a wide range of applications. Technology such as spray drying for microspheres can also be used to stabilize vaccines at temperatures in the order of 45 °C by using sugars other than trehalose with similar stabilizing properties.

At the same time, other methods such as freeze-drying have encountered some operational difficulties. Freeze-dried vaccines are intensely hygroscopic and become unmanageable in low relative humidity. Furthermore, their particle size is at the limit for jet injection which severely hampers their use in powder form for parenteral administration in this way. Finally, aluminium hydroxide, widely used as an adjuvant in currently available vaccines, cannot be freeze-dried since it loses its activity. Meanwhile, experiments have demonstrated that the same adjuvant dried in the presence of trehalose exhibits no significant loss of its gel structure after storage at 60 °C for prolonged periods of time (4).

Despite substantial advances towards the development of sugar-based dried vaccines, research is still needed. Attempts to stabilize certain live viruses such as polioviruses have failed despite extensive work in this area, and many other antigens remain to be tested. Furthermore, safety and immunogenicity studies need to be performed in various animal models. Before new antigens can be tested, comparative assessment studies with known vaccines using different delivery systems — intradermal, subcutaneous and intramuscular — need to be conducted.

Since these vaccines will not require refrigeration, the ever-increasing burden of costs posed by the cold-chain and any new environmental requirements would be substantially alleviated. Production costs can also be reduced by replacing lyophiliza-
tion with ambient drying. The transition from unstable liquid formulations or freeze-dried vaccines to dry powders will also allow the vaccine to be presented in the form and volume in which it is to be administered. Finally, as potential antigens can be incorporated into a stable sugar glass form and there is no interaction with other antigens within the same glass, the development of polyvalent combination vaccines may be limited purely by the volume of the solid to be administered.

Glass-stabilized vaccines can also be fabricated into sharp, water-soluble glass needles. These needles are stable and could be stored in a cheap, disposable and burnable plastic device that would contain no residual sharps. This device would act as a simple gun to thrust the needle painlessly into subcutaneous or intramuscular tissues where it would rapidly dissolve.

Furthermore, instantaneous reconstitution of a single dose of powder vaccine could be attempted during immunization, and in a manner transparent to the person injecting. All the benefits of a dried vaccine would therefore be maintained at the point of use without the logistic and safety problems of multidose reconstitution in the field.

Injection devices
As new drying technologies are rendering possible the use of heat-stable solid vaccines, the need to develop injection devices for their delivery is becoming urgent. Only a small number of companies have so far been willing to face the challenge. Among these, Powderject Pharmaceuticals in the United Kingdom has developed a needleless drug delivery device that can inject into skin tissue large-particle — 20–50 µm diameter — monosized glass powders using a supersonic pulse of helium gas. The supersonic gas dynamics are used to control the acceleration of the jet and hence the depth of particle penetration into the skin. Powderject has demonstrated the suitability of its device for the administration of conventional vaccines in immunization programmes and has carried out feasibility studies (5, 6).

This technology can also be used to deliver DNA (genetic) vaccines on solid carrier particles. The device uses a small burst of helium gas to accelerate DNA-coated particles directly into the outer layers of the skin. A preclinical study carried out in 1997, using the device to deliver dried DNA-coated gold particles encoding for the hepatitis B antigen, showed good antibody and cellular immune response. This needle-free gene delivery technology was assessed in seven healthy volunteers at the University of Maryland’s Center for Vaccine Development (7). The vaccine was well tolerated in all subjects and there were no reports of pain or discomfort due to the method of delivery. An added advantage of these new needle-free injection devices is their ability to deliver vaccines without trauma. In many countries, the pain and distress associated with multiple injections is a growing cause of alarm among parents and, in the long run, can cause reluctance to allow vaccination.

For the 1.2 billion injections associated with immunizations throughout the developing world, it is crucial for devices to be capable of delivering vaccines without any possibility of contamination or cross-infection. There is also a heavy economic toll. In the United States alone, an estimated $1.7 billion is spent every year to treat needlestick injuries from needles possibly infected with hepatitis or HIV. In the last five years, increasing concern for injection safety has led to the introduction of auto-destruct syringes, which has resulted in a 100% increase in syringe costs (8). Above all, vaccine wastage, which today stands at around 50% for conventional systems of delivery, will be largely eliminated.

References


7. Communication to WHO from Dr D. Sarphie, Powderject Technologies Ltd., United Kingdom. 7 May 1998.

Reports on Individual Drugs

Antimicrobial therapy in the management of bacterial meningitis

Integrated Management of Childhood Illness (IMCI) is a joint venture set up by WHO and UNICEF to develop health strategies targeting the major life-threatening illnesses of children. The programme aims to improve knowledge and methods for the prevention and management of childhood diseases.

Bacterial meningitis is an important cause of childhood morbidity and mortality worldwide and case fatality rates in developing countries can reach up to 50%, with many survivors of the disease sustaining neurological sequelae. Haemophilus influenzae type b, Streptococcus pneumoniae and Neisseria meningitidis are the three most common microorganisms implicated in bacterial meningitis in children under five years of age. If a reduction in morbidity and mortality is to be achieved, swift diagnosis and appropriate treatment are essential. However, simple inexpensive diagnostic tests for use in developing countries are not yet widely available and the quality of laboratory facilities for diagnosis and surveillance varies considerably from country to country.

Given this situation and, in particular, the varying approaches to management of the disease, IMCI members recently convened a meeting to consider recommendations on diagnosis, treatment, care, and management of bacterial meningitis in children. Treatment recommendations from the meeting, including precautions to be taken in the event of resistance, are summarized below and preferred regimens are set out in the table on page 71. A report of the meeting is available from WHO.*

The preferred treatment for bacterial meningitis in infants under 3 months of age is injectable cefotaxime/ceftriaxone alone or with injectable ampicillin. If this is not available, ampicillin plus gentamicin may be used. Undiagnosed cases should be treated with ampicillin/penicillin and an aminoglycoside, until bacterial meningitis is confirmed.

In children 3 months of age and above, suspected or confirmed bacterial meningitis may be treated with chloramphenicol and ampicillin or benzylpenicillin if no significant penicillin resistance has been reported in the area. Penicillin-resistant pneumococci are now found with increasing frequency in all parts of the world and systems for resistance monitoring should be set up as a matter of priority wherever these do not exist. If penicillin-resistant pneumococci are common, initial therapy should be with cefotaxime or ceftriaxone.

Where cefalosporin resistance is a problem, ceftriaxone or cefotaxime plus vancomycin or rifampicin may be effective. New drugs such as meropenem, cefpirome or trovafloxacin may also be used, but are very expensive and not commonly available. Oral and injectable quinolones have been used successfully against meningococcal meningitis, but their effect on H. influenzae and S. pneumoniae meningitis has not yet been confirmed.

Confirmed bacterial meningitis in other patients may be treated with oral chloramphenicol 100 mg/kg/day in four equally divided doses. However, chloramphenicol should preferably be given by injection for at least 3–4 days before being administered orally. As a general rule, oral chloramphenicol palmitate is not recommended in neonates or malnourished children because of unreliable absorption and resulting accumulation of the drug to toxic levels. If chloramphenicol is the only drug available to treat malnourished children or neonates, it should be in succinate form and administered by intramuscular or intravenous injection.

Insufficient evidence is available to support recommendations for the routine use of corticosteroids (dexamethasone) in children treated with either penicillin or chloramphenicol. There is limited evidence available to suggest that dexamethasone may be helpful in cases of H. influenzae type b meningitis. If it is to be used, a two-day regimen has proved to be as effective as a four-day regimen, but must be given before antibiotic therapy is initiated.

---

### Antimicrobial treatment options for bacterial meningitis

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Etiology</th>
<th>Antimicrobial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants aged &lt;3 months</td>
<td><em>S. aureus, H. influenzae,</em> N. meningitidis, Salmonella spp.</td>
<td>cefotaxime/ceftriaxone + ampicillin</td>
</tr>
<tr>
<td>infants aged &lt;3 months</td>
<td>group B Streptococcus, E. coli, L. monocytogenes (prevalent in developed countries)</td>
<td>ampicillin + cefotaxime/ceftriaxone</td>
</tr>
<tr>
<td>infants aged &lt;3 months</td>
<td><em>S. pneumoniae, E. coli</em> (prevalent in developing countries)</td>
<td>ampicillin + gentamicin</td>
</tr>
<tr>
<td>children aged &gt;3 months to 18 years</td>
<td><em>H. influenzae, S. pneumoniae,</em> N. meningitidis</td>
<td>*cefotaxime/ceftriaxone OR *ampicillin + chloramphenicol</td>
</tr>
<tr>
<td>children aged &gt;3 months to 18 years</td>
<td>resistant S. pneumoniae</td>
<td>vancomycin + cefotaxime</td>
</tr>
<tr>
<td>Immunodeficient patients</td>
<td>L. monocytogenes, Gram-negative organisms</td>
<td>ampicillin + ceftazidime</td>
</tr>
<tr>
<td>Neurosurgical problems and head trauma</td>
<td><em>S. aureus, Gram-negative organisms, S. pneumoniae</em></td>
<td>vancomycin + third-generation cefalosporin</td>
</tr>
</tbody>
</table>

* Choice dependent on patterns of resistance and allocation of resources.

### Vaccine control of Hib disease

Wherever studies have been performed, *Haemophilus influenzae* type b (Hib) has been shown to be an important cause of childhood meningitis and a major cause of bacterial pneumonia in children. Hib disease is a significant public health concern in both developed and developing countries and is estimated to cause at least 3 million cases of serious disease and hundreds of thousands of deaths annually, mainly in children under 5 years of age. In developed countries, meningitis is the most important manifestation, whereas in developing countries pneumonia is more common. Antibiotics are essential for treatment, but have only a minor role in control, and the emergence of bacterial resistance to some of the most efficient antibiotics underscores the need for preventive measures. Vaccines are the only tool available to prevent the vast majority of Hib disease.

Currently, several Hib conjugate vaccines are available which have demonstrated protective efficacy in early infancy. These are based on Hib polysaccharide conjugated to a protein carrier, but they differ in carrier, method of chemical conjugation and polysaccharide size, giving each vaccine somewhat different immunological properties.

The vaccine is usually given in infancy in repeated doses, together with diphtheria/tetanus/pertussis (DTP) or other vaccines included in national childhood immunization programmes. A booster dose is recommended in many countries at 12–18 months of age, but may not be necessary in developing countries where most Hib disease occurs before this age. In adults and children over 18 months of age a single dose is sufficient to induce immunity.
All conjugate Hib vaccines are given by the intramuscular route. No serious side-effects have so far been recorded, and no contraindications known, except for hypersensitivity to the vaccine components. The vaccine may safely be administered concurrently with any other vaccine given routinely in national childhood programmes, as well as with pneumococcal and meningococcal vaccines.

Hib vaccines are now used as part of routine childhood vaccination programmes in more than 20 countries, and have been shown to be highly efficacious. Because these vaccines significantly reduce nasopharyngeal carriage, a herd effect is achieved through reduced transmission of the microorganism. In view of their demonstrated safety and efficacy, WHO encourages the introduction of Hib vaccines worldwide and they should be included — as appropriate to national capacity and priority — in routine infant immunization programmes.

Unfortunately, in large areas of Asia, population-based data on the burden of Hib disease are largely missing and, so far, no Asian country has adopted Hib vaccination as part of its routine immunization programme. Issues that need to be addressed before the vaccine is introduced into developing countries are the need to evaluate the effect of combination with other antigens such as locally produced DTP, and other vaccines. Questions of appropriate formulation and presentation of the vaccine preparation will also need clarification.


**WHO requirements for Haemophilus influenzae type b conjugate vaccines**

In 1990, the WHO Expert Committee on Biological Standardization adopted requirements for *Haemophilus* type b (Hib) conjugate vaccines. These include recommendations on the evaluation of immunogenicity in humans and a model certificate to be used in the release of *Haemophilus* type b conjugate vaccines (1).

*Haemophilus* type b conjugate vaccines produced by various manufacturers differ in composition, so that certain control tests must be product-specific. Requirements for Hib vaccines thus take into account the differences in vaccine composition and national control authorities will need to consider the control methods and specifications appropriate as well as the degree of consistency of production achieved before agreeing to approval of such vaccines (1).

Based on new experience gained in the production, control and use of these vaccines, an Informal WHO Consultation on the Standardization and Control of *H. influenzae* type b conjugate vaccines, held in Brussels in April 1997, has reviewed and made proposals for updating the requirements. It was agreed that the mouse immunogenicity assay could be deleted as a routine batch control test, and that efforts should now focus on the physicochemical criteria required for monitoring the consistency of bulk conjugate production (2). As a consequence, a further consultation is planned to elaborate more specific guidance on physicochemical test methods and to present the revised requirements to the WHO Expert Committee on Biological Standardization for consideration.

**References**


**Meningococcal vaccines: current status**

K. Mulholland, Global Programme for Vaccines and Immunization, World Health Organization

Throughout the world, *Neisseria meningitidis* (meningococcus) is an important cause of bacterial meningitis. There are three main types of meningococcus, each defined by their capsular serological characteristics and known as serogroups A, B and C. Each of these serogroups has different epidemiological characteristics: the annual epidemics of meningitis seen in sub-Saharan Africa, for example, are mainly due to serogroup A meningococcus. Serogroup B meningococcal disease also occurs in epidemics but tends to be spread over a long period, sometimes lasting for years. Recently, this type of disease has been reported in northern Europe, Latin America and New Zealand. Serog-
group C meningococcal disease, on the other hand, has a low level of reporting and is more commonly responsible for sporadic cases which occur throughout the world. It has also been a cause of some epidemics in Africa.

Regardless of serogroup, all meningococcal disease tends to present a similar picture. The main clinical manifestations are bacterial meningitis and septicaemia. While all age groups are affected, most episodes occur in children beyond infancy and up to about 15 years of age.

Strategies to prevent meningococcal disease by vaccination vary with the different serotypes. Vaccines against serogroups A and C meningococcal disease based on capsular polysaccharide antigens have been available for many years. However the appropriate use of these vaccines remains controversial. Current WHO policy in sub-Saharan Africa relies on the early detection of epidemics and the prompt use of AC polysaccharide vaccines in the surrounding community to stop them. Since the serious epidemics of 1996 in sub-Saharan Africa, this policy has come under criticism. Some have argued that the meningococcal AC polysaccharide vaccines should be used for prevention of epidemics, either as part of a routine immunization programme or in mass campaigns in the affected areas.

However, many questions remain about the most appropriate use of these vaccines in children. The effectiveness of a policy based on infant immunization has not been demonstrated, with the main outstanding questions being the ability of the vaccine to protect young infants and the duration of protection in all age groups. Furthermore, doubts have been raised about the safety of meningococcal polysaccharide vaccines in infancy. Several studies have shown that meningococcal C vaccine administration in infancy results in hyporesponsiveness in later childhood, and few would argue in favour of routine use of this component in infants at present. Recent data suggest that the same may be true for meningococcal A vaccine. This issue is currently under investigation.

Following the outstanding success of the polysaccharide protein conjugate vaccines against *Haemophilus influenzae* type b, the same approach has been used to develop new vaccines against meningococcal A and C disease. Several products based on this technology are now undergoing phase II evaluation. Conjugate vaccines offer a number of important advantages over polysaccharide vaccines. Although neither the safety nor the efficacy of polysaccharide vaccines in infancy has been quantified, it is likely that the conjugate vaccines will be both safer and more efficacious. Furthermore, the protection afforded by conjugate vaccines should be more long-lasting and may be boosted by subsequent administration of polysaccharide vaccine.

Meningococcal C conjugate vaccines are likely to be used first in Europe where meningococcal C disease is seen as a significant problem. The use of AC conjugate vaccines in sub-Saharan Africa may be delayed because of the issue of cost. However, it is likely that eventual control of meningococcal disease in Africa will rely on the use of these conjugate vaccines. In the meantime, it is important that optimal use is made of the existing polysaccharide vaccines. While there are significant doubts about the use of these vaccines in infancy, other strategies such as routine vaccination of school-age children are being tried and may be useful in the medium term.

Serogroup B meningococcal disease raises special problems for the development of vaccines. The capsular polysaccharide of serogroup B meningococcus is poorly immunogenetic making it an unsuitable vaccine candidate. Of greater concern is the fact that antibodies to this polysaccharide may cross-react with certain antigens found in the central nervous system of infants — raising serious doubts about the safety of vaccines based on the capsular polysaccharide.

During the 1980s, serious epidemics of meningococcal B disease occurred in Scandinavia and Latin America. In response to these epidemics, new vaccines against serogroup B meningococcus were developed in Norway and Cuba. These vaccines used the outer membrane protein of serogroup B meningococcus as an antigen. Preparations were then made in which the polysaccharide was chemically removed from the bacterial preparation which was then modified to present cell-wall protein epitopes in vesicles.

As the serological characteristics of these proteins vary between different strains of meningococcus, serogroup B vaccines prepared to deal with epidemics caused by one strain, such as the strain responsible for the epidemic in Norway during the 1980s, may not be effective in preventing disease caused by other strains. This problem of hetero-
geneity in the antigenic characteristics of serogroup B meningococcus has led investigators to try many different approaches to vaccine development. At present, one of the most promising approaches is one in which class-1 proteins belonging to six or more strains of the organism are presented together in a recombinant semisynthetic vaccine. Another approach being developed relies on the transferrin-binding protein as an epitope. It is not clear what will be the most successful approach to vaccine development, but it is likely that serogroup B meningococcal disease will continue to be a public health problem for many years. Once a suitable vaccine effective against many strains has been developed this may be used routinely in those countries that can afford it. However in those countries that choose not to vaccinate or cannot afford to vaccinate routinely, serogroup B meningococcal epidemics may continue to occur.

WHO is currently assessing the possibility of constructing special tailor-made vaccines for the control of serogroup B meningococcal epidemics. It is conceivable that these vaccines will be different from those that are suitable for routine immunization. Thus, the future may see two different approaches to serogroup B meningococcal vaccination.

Meningococcal meningitis is a horrifying and deadly disease. Many of the cases currently occurring could be prevented by vaccination, and recent developments in the meningococcal vaccine field mean that, in the future, this serious public health problem could be eliminated.

**Atovaquone plus proguanil effective in malaria**

As more information becomes available from clinical trials in Thailand (1), Gabon (2), and Brazil (3), it seems likely that atovaquone, in combination with proguanil, may prove to be effective for the prophylaxis and treatment of falciparum malaria.

Atovaquone, a hydroxynaphthoquinone, inhibits the parasite mitochondrial respiratory chain and pyrimidine synthesis. Earlier clinical trials with atovaquone showed that the drug, as monotherapy, was associated with high rates of recrudescence leading rapidly to development of resistance (1). However, when combined with proguanil, a synergistic effect on the parasites was achieved leading to high cure rates in patients with acute uncomplicated malaria (2).

A new study to assess the efficacy and safety of chemosuppression using atovaquone plus proguanil has been carried out in schoolchildren living in the tropical rainforest of Gabon, hyperendemic for *Plasmodium falciparum* malaria highly resistant to chloroquine (4). All children received initial curative treatment with atovaquone plus proguanil. Thereafter, atovaquone plus proguanil or placebo was randomly assigned to children aged 4–16 years of age once daily for 12 weeks as chemosuppression. At conclusion of the trial period, 25 of 140 children in the placebo group had positive smears, but none in the chemosuppression group. Adverse events were mild in all children throughout chemosuppression and laboratory data did not differ between the groups.

Notwithstanding these results, a high rate of gastrointestinal disturbances was recorded during the initial curative treatment phase. This was considered to be largely attributable to the disease. Nevertheless, a lower rate of adverse effects during the chemosuppression phase may be attributable to exclusion of children who did not tolerate the drug well during the initial curative treatment. During this trial, the combination of atovaquone plus proguanil was shown to be highly efficacious and safe. Simple administration in a single daily dose for 3 days seems to indicate that this is a promising new antimalarial.

At the present time, atovaquone is an expensive drug to produce, and the price would be restrictive for developing countries where malaria is endemic. However, the manufacturer, Glaxo Wellcome plc. has announced its intention to provide this new drug combination through a controlled donation programme to be set up with the Task Force for Child Survival and Development. The twin objectives of this programme are to ensure that the new medication is used only when other products have failed, and that ability to pay should not be a criterion in the decision on whether to treat. A pilot study is expected to be conducted soon in Kenya.

**References**


Promising approaches for a serum diagnostic test in Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease is a transmissible spongiform encephalopathy characterized by rapidly progressing dementia and more than 90% mortality within one year of onset. At present, diagnosis can only be made by examination of human brain tissue and confirmed by biochemical analysis of cerebrospinal fluid identifying neuron-specific enolase, S100 protein, tau protein and 14-3-3 protein.

A group of scientists in Germany have recently developed a test that measures concentrations of brain-specific S100 protein in the serum of patients believed to have Creutzfeldt-Jakob disease. S100 protein increases in serum and cerebrospinal fluid as a result of major and minor head injuries but decreases rapidly — the biological half-life is about 2 hours — as the protein is eliminated by the kidneys. S100 was originally thought to be a marker of brain destruction in acute disease, but now it is thought to be a marker of activated astroglia which are seen at all stages of Creutzfeldt-Jakob disease (2). Consequently, concentrations of S100 do not fall during the course of the disease and can be used as confirmation with a sensitivity of 77.8% and a specificity of 81.1%. Further studies are required to determine whether serial testing of serum S100 protein will enhance diagnostic accuracy.

With regard to new variant Creutzfeldt-Jakob disease which primarily affects patients under 40 years of age, other possibilities for diagnostic tests point to a monoclonal antibody which specifically recognizes the pathological conformer of the prion protein (3). A further avenue for research may be the discovery that, among the various cells in the blood, only the differentiated B lymphocytes play a crucial role in the pathogenesis of the disease (4).

References


Warfarin potentiated by paracetamol

Warfarin is commonly used as an anticoagulant in preventing thromboembolism. However, a major complication of therapy is haemorrhage which can cause severe morbidity and even death. It is therefore vital to assure the safety of oral anticoagulation therapy by careful monitoring of prothrombin time, calculated as international normalized ratio (INR).

Many drugs are known to interact with warfarin, and this may cause dangerously elevated INR and bleeding (1). A number of prescription and nonprescription drugs available over-the-counter are known to complicate warfarin therapy in this way. Patients should be routinely warned to avoid, for example, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs and antimycotics (2, 3). Paracetamol (acetaminophen), a commonly used analgesic and antipyretic, is often taken in place of acetylsalicylic acid and nonsteroidal anti-inflammatories in order to avoid gastric irritation. None the less, only a few case reports have been published regarding paracetamol interaction with warfarin (1).

A recent study of outpatient anticoagulant therapy has demonstrated that use of paracetamol is an under-recognized cause of excess anticoagulation (4). The study involved 93 patients with an INR greater than 6.0 and 196 controls. When paracetamol was taken at a rate of 4 regular strength (325 mg) tablets daily for one week, the odds of having an INR greater than 6.0 were increased tenfold. The risk decreased with lower intakes and levelled off at 6 or fewer tablets per week.
The study clearly demonstrates that clinicians should advise warfarin patients not to take paracetamol. If this cannot be avoided, INR levels should be closely monitored once or twice a week. Many paracetamol-containing products do not yet contain warnings of this potentially dangerous interaction. Manufacturers should revise product information to provide adequate instructions to the user and include this in package inserts of over-the-counter medicines. Physicians and pharmacists, in particular, should be reminded of this serious interaction and should pass on this information to patients.

References

Prevention of gastric ulcers caused by nonsteroidal anti-inflammatory drugs

In certain diseases, long-term daily use of drugs is necessary to alleviate invaliding symptoms and maintain the patient’s ability to live a normal life. Rheumatoid arthritis, osteoarthritis and many other musculoskeletal diseases require daily treatment with a nonsteroidal anti-inflammatory drug (NSAID).

Adverse gastric reactions are a common complication of regular use of NSAIDs and peptic ulcers occur in 20–30% of users (1). In general, the risk of gastropathy and death is 3 to 10 times higher among regular users of NSAIDs than among non-users (2–4). This risk increases in elderly patients who are more likely to be frequent users of NSAIDs.

It is an unwritten rule in good medical practice that adverse reactions should, if possible, be prevented by some means other than using another drug. Upper gastro-intestinal symptoms in those taking NSAIDs would best be managed by reducing the dosage, using antacids, changing the drug, or taking the tablets with sufficient fluid or with meals. The risk of gastric bleeding is increased by steady doses of NSAIDs which should be avoided in patients with an active peptic ulcer. If this is not possible, and the patient has any kind of ulcer or gastric erosion, a histamine H₂-receptor antagonist such as ranitidine, or a proton pump inhibitor such as omeprazole, or the prostaglandin analogue, misoprostol, may give relief (4).

Misoprostol replaces the cytoprotective prostaglandins that NSAIDs deplete from the gastroduodenal mucosa, but is often poorly tolerated because of diarrhoea and abdominal pain (5). An alternative is to protect the gastroduodenal mucosa by suppressing acid secretion, since acid has an important permissive role in NSAID-associated mucosal injury (4). Omeprazole, ranitidine and famotidine have been of value in a number of clinical trials in preventing NSAID-induced gastroduodenal injuries such as erosion, ulcers and bleeding (4).

Misoprostol has also been compared with omeprazole in trials to prevent and heal ulcers or erosions in patients who require continuous NSAID therapy (4). An 8-week treatment with omeprazole, 20 mg or 40 mg daily, or misoprostol, 200 µg four times daily, was successful in more than 70% of cases. The rate of gastric or duodenal ulcer healing was higher with 20 mg omeprazole than with misoprostol, whereas erosions healed faster with misoprostol. Misoprostol caused somewhat more adverse reactions, particularly diarrhoea and abdominal pain, than omeprazole — at 59% and 48% respectively.

Further comparative studies are required before a conclusion can be reached on which therapy is the most successful. However, before prophylaxis with drugs is implemented, it is stressed that alternative non-pharmacotherapeutic measures should be tried.

References


**Lymphatic filariasis: global elimination in sight**

WHO, in collaboration with national health authorities and collaborating agencies, will carry out a worldwide programme to eliminate lymphatic filariasis. Estimated to affect 120 million and place 1.1 billion people at risk, the disease is identified as one of the major causes of individual disability and resulting socioeconomic burden. Since efforts to eliminate the carrier of the disease have failed, the best opportunity for combating lymphatic filariasis is by use of medicines which break the cycle of infections between mosquitoes and humans.

In the largest donation of its kind, SmithKline Beecham will provide the antiparasitic, albendazole, free of charge to national authorities through the WHO elimination campaign. Albendazole has already become standard treatment worldwide to combat intestinal parasites and has proven to be 99% effective against the parasite that causes lymphatic filariasis when administered with either diethylcarbamazine (DEC) or ivermectin. The drug regimen now proposed will require administration of a single dose yearly for 4–5 years to all people in infected areas. It is estimated that it will take approximately 20 years to fully eliminate the disease. At the same time, administration of albendazole will serve to treat parasitic infections such as hookworm.

Merck and Co. has already donated ivermectin for the clinical trials and has shown a willingness to provide this drug for the elimination campaign. This will be of particular importance in Africa where DEC is contraindicated for these populations. Merck has been donating ivermectin to treat river blindness in Africa for the last 11 years.

Thanks to these impressive commitments, countries with insufficient resources will now acquire the best medication available and endemic populations will be alleviated from a debilitating disease.

**References**


Current Topics

Important breakthrough for neurovirulence testing of oral poliovirus vaccine

D.J. Wood

National Institute for Biological Standards and Control

United Kingdom

Oral poliovirus vaccine, a trivalent blend of the attenuated poliovirus strains developed by Sabin, has been used worldwide for more than 30 years to safely and effectively immunize children. The consistent production of safe and efficacious vaccines has demanded a high level of skill from manufacturers in order to avoid the attenuated strains reverting to virulence during production.

Quality control of working seed viruses and vaccine batches is essential to this process (1). One of the key indicators of safety is the neurovirulence test carried out in primates, which was standardized by WHO in 1982 (2). Every monovalent pool must pass the neurovirulence test in order to be included in the final vaccine. Although this test provides an extremely rigorous examination of manufacturing consistency, the need for primates in the test has provided a powerful incentive to find suitable alternatives.

Major advances in our understanding of the biology of polioviruses have now resulted in the development of two new tests with the potential to replace, refine or reduce the use of primates in the current neurovirulence test. One, the TgPVR test, is based on genetically engineered mice that are susceptible to poliovirus, and the other, MAPREC, hinges on a method which measures molecular changes at key locations in the virus genetic code, thereby pinpointing any weakening in the vaccine virus.

Basic research on the biology of polioviruses has identified the gene for the human cellular receptor for poliovirus and led to development of transgenic (TgPVR) mice that express this receptor. Unlike normal mice, TgPVR mice are susceptible to infection with all three poliovirus serotypes. Applied research has shown that a neurovirulence test in TgPVR mice is possible and offers an alternative to the monkey neurovirulence test. Secondly, identification of mutations in the 5’ non-coding region of the poliovirus genome, especially for the Sabin type-3 strain, that are critical to the attenuated phenotype allowed development of a molecular biological assay for quantification of neurovirulent mutants in vaccine batches. This new assay opens up a new era in vaccine control since consistency of production can be monitored for the first time at molecular level.

Both new methods have recently been reviewed (3) and progress discussed at a meeting organized by WHO. TgPVR mice develop clinical signs and histological changes in the central nervous system similar to those observed in primates. A standard neurovirulence test in TgPVR mice was successfully introduced in nine laboratories and a WHO collaborative study showed that the mouse neurovirulence test demonstrated good correlation with the monkey neurovirulence test for two batches of type-3 oral poliovirus vaccine. Development and validation of a regulatory decision-making model are now under way and are expected to be completed in time to report to the 1998 meeting of the WHO Expert Committee on Biological Standardization. Manufacturers and national control authorities will be encouraged to apply the decision-making procedures, once validated, to vaccine batches previously tested in monkeys. Proposals to use the mouse neurovirulence test as an alternative to the monkey neurovirulence test will then be developed if supported by the results of this collaboration.

The new molecular method, called mutant analysis by PCR and restriction enzyme cleavage (MAPREC), is now well established and is being used by both manufacturers and national control laboratories. The assay quantifies the very small proportion of revertant mutants that may be present in monovalent pools. A WHO collaborative study of candidate virus reference materials for poliovirus type-3 that were designed as validation controls for the assay was recently completed. The results showed that the candidate reference materials were suitable for the intended purpose and moreover confirmed the MAPREC assay as a sensitive, robust and standardized molecular biological assay suitable for use in quality control of poliovirus production. The virus reference materials were
adopted as WHO International Reference Reagents at the 1997 meeting of the WHO Expert Committee on Biological Standardization and supplement the WHO International Standard for MAPREC of poliovirus type-3 established in 1996. A comprehensive data base of poliovirus type-3 MAPREC results from current manufacturers will now be prepared and reviewed. A proposal to revise the WHO Requirements for Oral Poliomyelitis Vaccine will be made if the outcome of this review is favourable.

The MAPREC assay could be used, in conjunction with other tests, to characterize new virus seeds and also as a test of consistency of manufacture of monovalent bulks. As the MAPREC assay for poliovirus type-3 is highly predictive of monkey neurovirulence test results, any batches that failed by MAPREC would not then be tested by an in vivo neurovirulence test. However, as it is possible for the Sabin vaccine strains to revert to virulence at molecular loci other than those tested by MAPREC, it will be necessary to retain an in vivo neurovirulence test for batch release purposes.

Both TgPVR mice and MAPREC are suitable for tests of poliovirus type 1 and 2 oral vaccine, and development of appropriate assays and reference materials is also under way.

References

MMR vaccination: update

Since 1988, the United Kingdom has routinely used the combined measles, mumps, rubella (MMR) vaccine as part of its vaccination programme. However, concerns have surfaced over possible side-effects of the vaccine following the publication of a study which suggested a link with inflammatory bowel disease and autism in children.

Researchers in the study observed a syndrome of colitis and ileal-lymphoid-nodular hyperplasia in children who also demonstrated development disorders, primarily autism. In most cases, they noted that onset of symptoms followed measles, mumps, rubella immunization (1). It should be noted that a first dose of the vaccine, given to about 600,000 children every year in the United Kingdom, mostly in the second year of life, coincides with the age at which autism is often recognized.

It is accepted that no vaccine is perfectly safe. However, vaccine safety concerns gain prominence whenever the incidence of vaccine-preventable disease falls to negligible levels or when the number of adverse events rises as a consequence of high vaccine coverage (2). It is therefore important to examine any reports in perspective. In this respect, adverse drug reaction monitoring and clinical or epidemiological studies are needed. Because of the limitations of any single method, epidemiology, biological plausibility, consistency, strength and specificity of association must also be considered in inferring causation (3, 4).

The authors of the study state that no association between MMR vaccine and the observed syndrome was proven but that virological studies are under way which may help to resolve the issue (1). One separate study has thus far shown the absence of measles-virus genome in inflammatory bowel disease (5). If there is a causal link with measles, mumps, rubella immunization, a rising incidence might be anticipated after the introduction of the vaccine into the United Kingdom in 1988. However, published evidence is inadequate to show this (6). A genetic predisposition to autistic spectrum disorders is suggested by over-representation in boys and a greater concordance rate in monozygotic than dizygotic twins (7). At present, information is lacking and further investigations are needed to examine the syndrome and any possible relation to this vaccine.

An expert scientific seminar, convened by the UK Medical Research Council to review the issue, concluded that there is no link between measles, mumps vaccine or MMR immunization and either Crohn disease or autism. Parents were strongly advised to continue to have their children immunized with MMR vaccine as currently recommended (8).

References


---

### The Erice Declaration

The Erice Declaration on Communicating Drug Safety Information was drawn up at the International Conference on Developing Effective Communication in Pharmacovigilance held in Erice, Italy, in September 1997. The conference was attended by health professionals, researchers, academics, media writers, representatives of the pharmaceutical industry, drug regulators, patients, lawyers, consumers and international health organizations.

Monitoring, evaluating and communicating drug safety are public health activities with profound implications that depend on the integrity and collective responsibility of all parties working together. High scientific, ethical and professional standards should govern these activities. The inherent uncertainty of the risks and benefits of drugs needs to be acknowledged and explained. Decisions and actions that are based on this uncertainty should be taken in the light of scientific and clinical considerations, with due regard for social realities and circumstances.

Flaws in drug safety communication at all levels of society can lead to mistrust, misinformation and misguided actions resulting in harm and the possibility that drug safety data may be hidden, withheld, or ignored.

Fact should be distinguished from speculation and hypothesis, and actions taken should reflect the needs of those affected and the care they require. These actions call for systems and legislation, nationally and internationally, that ensure full and open exchange of information, and effective standards of evaluation. These standards will ensure that risks and benefits can be assessed, explained and acted upon openly and in a spirit that promotes confidence and trust.

The following statements were commonly agreed during the conference at Erice.

1. Drug safety information must serve public health. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.

2. Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and health-care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.

3. All evidence needed to assess and understand risks and benefits must be openly available. Constraints which hinder the possibility to achieve this goal must be recognized and overcome.

4. Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated and made accessible to all. Adequate nonpartisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.

5. A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognized and efficiently dealt with and that information and solutions are effectively communicated.

These ideals are achievable and the participants at the conference committed themselves accordingly. Methods for effective implementation of this declaration were considered at the conference and are contained in the conference report*.

*Conference report available from: The Uppsala Monitoring Centre, S-75320 Uppsala, Sweden. Tel: 46 18 65 60 60. Fax: 46 18 65 60 80.*
Regulatory Matters

Precipitation of carbamazepine suspension and other liquid drugs

United States of America — The Food and Drug Administration has informed doctors of the danger of mixing carbamazepine suspension with liquid medications such as chlorpromazine or thioridazine. This can result in a precipitate described as a rubbery orange mass which may decrease bioavailability of the active drug substances concerned. The testing of suspensions and their mixture is being conducted by Novartis following the case of a patient who reported passing an orange rubbery mass in the stool the day after ingesting carbamazepine immediately followed by chlorpromazine, both in liquid formulation.

A warning letter has been sent to physicians and pharmacists with a request to inform patients about this interaction.


Medication-associated depression

Australia — The Australian Drug Evaluation Committee has received 454 reports of medication-associated depression between 1990 and 1996. In 92% of the reports, a single drug was implicated and, in 36 cases, symptoms recurred on rechallenge. The highest number of reports per prescription were found to be for mefloquine, vigabatrin, dexfenfluramine, ciprofloxacin, pravastatin, simvastatin and gemfibrozil.


Plasma-derived medicinal products and Creutzfeldt-Jakob disease

European Union — The Committee for Proprietary Medicinal Products (CPMP) convened a meeting of international experts to consider recent information on new variant Creutzfeldt-Jakob disease (nv-CJD) and transmissible spongiform encephalopathies (TSEs) which may have implications for plasma-derived blood products.

The group concluded that there is no evidence that sporadic, familiar or iatrogenic Creutzfeldt-Jakob disease (CJD) is transmitted via blood transfusion or plasma-derived medicinal products. Therefore, the CPMP reaffirms its recommendation that recall of plasma-derived products is not justified where a donor is later confirmed as having CJD.

It is now known that nv-CJD has different characteristics to sporadic, familiar and iatrogenic CJD. Knowledge of other TSE agents suggests that transmission of nv-CJD by medicinal products derived from human blood or plasma is very unlikely.

The group further recognized that since a recall involving albumin used as an excipient may cause major supply difficulties for essential products, manufacturers should avoid using, as an excipient, albumin from countries where cases of nv-CJD have been reported.

The group agreed that knowledge of CJD and other human TSE agents, and nv-CJD in particular, is still incomplete. All studies contributing to the further understanding of TSEs, including experimental and epidemiological studies, should therefore be urgently promoted. This means that CJD surveillance should continue, laboratory tests should be developed for clinical diagnosis, blood donations should be screened, and research should continue on the tissue distribution of infectivity in nv-CJD compared with other types of CJD.


Troglitazone-induced liver injury

Japan — The Pharmaceutical and Medical Safety Bureau has published an update on liver dysfunction reports associated with the antidiabetic, troglitazone. Since December 1997, there have been a further 61 cases of serious liver dysfunction, including one death for which the causal relationship with the drug could not be ruled out. The total number of reported cases is now 74, including four deaths (1).
The Bureau has issued emergency safety information for troglitazone, emphasizing that the link with liver function disorder must be explained to the patient before treatment, that patients with liver disorders should not be treated with the drug, administration must be discontinued when liver dysfunction is found, and that liver function tests must be performed at least once a month.

Adverse reaction reports associated with troglitazone in various countries were discussed in the previous number of this journal (2).

References


Midazolam and paradoxical reactions in children

**Australia** — Midazolam is a short-acting benzodiazepine commonly used for sedation or as premedication for anaesthesia. The Australian Drug Evaluation Committee has recently assessed 228 adverse reaction reports associated with midazolam. Paradoxical reactions were reported in 31 cases including agitation (18 cases), aggression (11 cases), abnormal crying (9 cases), hallucination (7 cases) or emotional lability (3 cases).

Twenty of the cases occurred in children younger than 11 years of age. Reactions were described as "confused behaviour, manic, running, falling over, unsteady, screaming, unable to be pacified, extreme agitation, bordering on violent behaviour, kicking, lashing out at parents". The events usually occurred within 30 minutes of taking midazolam. The majority of cases involved oral dosage.

All children recovered within one to two hours, although in two cases the benzodiazepine antagonist, flumazenil, was needed.


Safety of venlafaxine

**Australia** — The Australian Drug Evaluation Committee has analysed adverse drug reaction reports received on venlafaxine, a new antidepressant, during its first year of marketing. Among the 190 reports received, 145 implicated venlafaxine alone as a suspected drug in adverse reactions.

Reports were compared with those concerning selective serotonin reuptake inhibitors (SSRIs). Venlafaxine had a greater association — about twice as high as SSRIs — with nausea, vomiting, anorexia, headache, increased sweating, syncope and hypertension. The difference in adverse drug reaction profile may be due to the fact that venlafaxine differs from SSRIs by also inhibiting the neuronal uptake of noradrenaline.


Bromfenac and liver damage

**United States of America** — The Food and Drug Administration together with Wyeth-Ayerst Laboratories has sent an alert to physicians concerning cases of serious liver damage associated with more than 10 days use of bromfenac as a pain reliever. Bromfenac sodium is a nonsteroidal anti-inflammatory drug that is indicated only for short-term management of acute pain and should not be used for more than 10 days. It is not indicated for chronic conditions such as osteoarthritis or rheumatoid arthritis.

Reports have been received of jaundice, fulminant hepatitis, and liver failure requiring transplantation. These patients had used bromfenac for more than 10 days, and sometimes up to one month. A boxed warning will be added to the labelling drawing attention to the risks.


Warning regarding safety of astemizole

**United States of America** — The Food and Drug Administration has circulated a warning from the manufacturer of the antihistamine, astemizole, concerning new contraindications, warnings, precautions, adverse events, and drug interactions. Astemizole is associated with risks of death due to irregular heart rhythm when taken with some other drugs and when used at higher than the recommended labelled dose. A potentially life-threatening, but rare, anaphylactic reaction is also associated
with the use of astemizole. Safety problems regarding astemizole and terfenadine have been discussed previously in this journal (1).

The new product information states that the drug is contraindicated in patients with severe hepatic impairment, and when coadministered with the antibiotics clarithromycin, troleandomycin or the antihypertensive, mibefradil. The antibiotics erythromycin and josamycin, antifungals ketoconazole, itraconazole and miconazole, and quinine are already contraindicated. These drugs are known to impair astemizole metabolism resulting in QT prolongation, torsades de pointes, cardiac arrest and death.

Additional precautions have now been extended. Co-administration of astemizole is not recommended with the selective serotonin reuptake inhibitors fluoxetine, fluvoxamine, nefazodone, paroxetine or sertraline, HIV protease inhibitors ritonavir, indinavir, saquinavir or nelfinavir and other drugs including the antiasthma medication zileuton. Grapefruit juice is also known to alter the metabolism of astemizole. This new updated information is designed to give physicians, pharmacists, health care providers and consumers the latest findings on risks associated with use of astemizole.

References

Dietary supplement contains prescription medicine

United States of America — The Food and Drug Administration has warned consumers that a Chinese product marketed under the name “Sleeping Buddha” as a dietary supplement to calm insomnia and restlessness, contains a prescription-strength active drug ingredient. The product has been promoted as a herbal alternative to sedatives but the product actually contains estazolam, a prescription-only sedative of the benzodiazepine family. The Agency states that estazolam is known to have serious side effects, including the potential to cause fetal damage if taken during pregnancy. The drug also impairs driving performance and the ability to handle complicated machines, and its effects are potentiated by other sedatives and alcohol.

Reference: FDA Statement, March 10, 1998

Fenfluramine and dexfenfluramine: follow-up action

Australia — The anti-obesity agents fenfluramine and its stereo-isomer dexfenfluramine were withdrawn worldwide in September 1997 following an observed association with valvular heart disease (1, 2). At that time, the Adverse Drug Reactions Advisory Committee had not received any reports of this disorder but, subsequently, 3 reports have been received of cardiac valve disease in association with dexfenfluramine. The authorities suggest that any patient exposed to fenfluramine or dexfenfluramine for any length of time should be examined to determine the presence or absence of cardiopulmonary signs or symptoms. This may be good advice for implementation in other countries.

References

Sucralose: a new sweetener approved

United States of America — The Food and Drug Administration has approved sucralose, a new sweetener, for use in a wide variety of products. Sucralose is a non-nutritive, high-intensity sweetener made from a process that begins with sucrose. It is a free-flowing, water-soluble, white crystalline powder that on average is about 600 times sweeter than sugar.

Sucralose has been approved for use in baked goods, baking mixes, non-alcoholic beverages, chewing gum, coffee and tea products, confections, fats, oils, frozen dairy desserts and mixes, fruit and water ices, gelatins, puddings and fillings, jams, jellies, milk products, processed fruits, fruit juices, sugar substitutes, sweet sauces, toppings and syrups.

The Agency has reviewed data from more than 110 studies in humans and animals designed to identify possible toxic effects including carcinogenic, reproductive and neurological effects. Based on this, sucralose has been approved as a safe substance for human consumption.

Sildenafil approved to treat impotence

United States of America — The Food and Drug Administration has approved the first orally administered drug to treat impotence, a dysfunction that affects millions of men in the USA alone. Unlike previously approved treatments for impotence, sildenafil citrate does not directly cause penile erection, but affects the response to sexual stimulation. The drug enhances the smooth muscle relaxant effects of nitric oxide, a chemical that is normally released in response to sexual stimulation allowing increased blood flow into certain areas of the penis resulting in an erection.

The most common side effects reported in clinical trials were headache, flushing and indigestion. The drug should not be used with organic nitrates such as nitroglycerin patches because the combination may lower blood pressure.


Isotretinoin-associated depression

United States of America — The Food and Drug Administration has advised physicians, pharmacists, health care providers and consumers of new safety information regarding the acne drug, isotretinoin.

Depression, psychosis and suicidal thoughts and actions have been reported among patients taking isotretinoin. Although such problems could already be more common among patient populations likely to be suffering from severe recalcitrant nodular acne, some patients reported that the depression subsided when they stopped taking isotretinoin and symptoms came back when they resumed.


Most frequently reported adverse drug reactions in Finland

Finland — The Drug Information Centre of the National Agency for Medicines has published a list of the most frequently reported adverse drug reactions during 1996–1997.

The greatest number of reports (57) concerned clozapine, a neuroleptic associated with agranulocytosis (14 cases), leukocyte disorders (31 cases), thrombocytopenia, myocarditis, hepatic lesions, neuroleptic malignant syndrome and convulsions.

Fluoxetine, a selective serotonin reuptake inhibitor antidepressant was associated with 29 reports of allergic reactions, leukocytopenia, convulsions, extrapyramidal symptoms, vertigo, tremor, diarrhoea and flatulence. Equally, nitrofurantoin was the subject of 29 reports involving pulmonary infiltrates and fibrosis, eosinophilia, dermatitis and hepatic lesions. Terbinafine, with 25 reports, was associated with various kinds of eczema, including erythema, bullous dermal lesions and photosensitivity, damage to the oral mucosa and taste dysfunction. Eleven cases of agranulocytosis, neutropenia and thrombocytopenia were attributed to mianserin.


Fexofenadine approved following terfenadine withdrawal

United States of America — Terfenadine-containing medicinal products, including the combination with pseudoephedrine, have now been withdrawn from the market in the USA. The safety of terfenadine and subsequent regulatory action have been described in previous issues of this journal (1).

In parallel with this withdrawal, the Food and Drug Administration has approved the fexofenadine/pseudoephedrine combination product for treatment of symptoms of seasonal allergies (2). This product is not recommended for patients with hypertension, diabetes, ischaemic heart disease, increased intraocular pressure, hyperthyroidism, kidney impairment or prostate problems.

References

Diphtheria, tetanus and hepatitis B vaccine approved

European Union — The European commission has issued a marketing authorization valid throughout the European Union for a combined trivalent vaccine containing previously authorized vaccines. The approved indication is for active immunization...
against hepatitis B, caused by all known subtypes, and diphtheria and tetanus. It is for use in infants as a primary or booster vaccination.

In clinical studies, the trivalent vaccine elicited an immune response comparable to that observed following simultaneous administration of the existing bivalent vaccine containing diphtheria and tetanus toxoid and recombinant hepatitis B vaccine.

The most frequent undesirable effects observed in the first three days after injections were local reaction such as pain, redness, induration and nodules, and systemic reactions such as transient hyperthermia, irritability, drowsiness, unusual crying, vomiting and diarrhoea.


---

**Measles/mumps/rubella vaccine approved**

A new MMR (measles/mumps/rubella) vaccine, Priorix®, made by SmithKline Beecham has been approved in three European countries, Belgium, Germany and the United Kingdom. It is claimed to have the same immunogenicity but better local tolerability than the other available MMR vaccine in general use, Pasteur Merieux/MSD's MMR II.

In studies involving more than 4000 patients in whom local reactions were investigated, these were reduced by about half with Priorix®. Clinical use of the vaccine will now demonstrate if these preliminary findings can be confirmed.

**Reference:** Scrip, March 20, 1998
Essential Drugs

WHO Model Formulary

As described in previous issues of this journal, work is now under way on the WHO Model Formulary, and draft texts will be published regularly to obtain comments on the material proposed for publication. Observations concerning the following sections should be addressed to: Drug Selection and Information (DSI), Division of Drug Management & Policies, World Health Organization, 1211 Geneva 27, Switzerland.

Dermatological drugs (topical)
Antifungal drugs

Dermatophyte infections
Benzoic acid and methylrosanilinium chloride (gentian violet) solution are inexpensive and effective fungistatic compounds for the treatment of ringworm, which is caused by dermatophytes. Minor skin lesions due to ringworm can also be cleared with repeated applications of a mixture of benzoic acid and salicylic acid ointment. This combines the fungistatic action of benzoic acid with the keratolytic action of salicylic acid.

However, the most effective topical treatment for dermatophyte infections is creams and powders containing an imidazole. Topical application of miconazole is effective for long-established lesions, but is more expensive than benzoic acid and salicylic acid ointment. Extensive and generalized infections of the skin and hair should be treated systematically for several weeks with oral griseofulvin. Ketoconazole is also an effective systemic fungicide but close monitoring of liver function is required throughout treatment. Information on systemic antifungals will appear in section 6 of the WHO Model Formulary.

Scalp ringworm (tinea capitis) typically appears as a patch of scaling alopecia, or a swollen inflammatory area (tinea kerion). Mild forms often remit spontaneously at puberty. Inflamed lesions should be treated systematically with oral griseofulvin. Topical application of miconazole may accelerate healing of scaly lesions.

Lesions of ringworm on the body (tinea corporis) can also be cleared with a benzoic acid and salicylic acid ointment, or an imidazole cream, such as miconazole. In resistant cases, a 4-week course of oral griseofulvin is required.

Foot ringworm (tinea pedis or Athlete’s foot), is usually treated topically. A mixture of benzoic acid and salicylic acid ointment should be applied twice daily to all infected areas and all toe clefts for at least 4 weeks. Systemic oral therapy may be required if the foot is extensively infected. Chronic tinea pedis commonly recurs and may be treated with miconazole cream.

Severe weeping lesions respond to frequent soaking in solutions of 0.5% aqueous methylrosanilinium chloride or 1:10 000 potassium permanganate, and systemic antifungals may be needed as treatment.

Trichophyton rubrum and T. mentagrophytes cause nail infections (onychomycosis). Infections of the fingernails may require 6 months of treatment with oral griseofulvin before responding and infections of the toenails may require 12 months of this treatment. Approximately 60% of nail infections either do not respond or relapse after treatment with oral griseofulvin.

Ringworm of the groin (tinea cruris) is usually limited to the skin of the inner thigh in contact with the scrotum. Flexural eczema, often superinfected with candida or bacteria, occurs in the same site. The latter is frequently treated with antifungal/ corticosteroid preparations. However, ringworm must not be treated with a corticosteroid, which will worsen the condition. An imidazole cream such as miconazole, applied daily for 2 weeks, is usually effective. Lesions unresponsive to topical preparations can usually be cleared with a 4-week course of oral griseofulvin.
Candidiasis
Candida can infect the oral cavity, the vagina or the skin. Cutaneous lesions tend to occur in patients with diabetes and other chronic debilitating conditions, including hypoparathyroidism and various congenital disorders of the immune system. The most severe infections of candida are now seen in patients with AIDS.

Cutaneous candidiasis usually responds to miconazole cream as a twice daily application. Chronic candida paronychia, which can result ultimately in nail dystrophy, is more difficult to cure. Treatment of this condition should be based on determination of the underlying cause and its reduction or elimination. The patient must keep hands and the folds of the nail dry. Daily treatment for several months with topical application of an imidazole cream may be required. This should be allowed to penetrate the cleft between the nail plate and the swollen skin around the nail.

Pityriasis (tinea) versicolor
Pityriasis versicolor is caused by a commensal yeast. Application of sodium thiosulfate twice daily for 4 weeks should be started promptly. This is usually curative although areas of depigmentation remain after completion of successful treatment. Relapses can be frequent, however, probably because much of the infected area may appear normal and be left untreated. Better results have been reported with topical applications of miconazole or selenium sulfide.

BENZOIC ACID + SALICYLIC ACID
Ointment or cream: 6% benzoic acid + 3% salicylic acid
Uses: Mild superficial infections, particularly tinea pedis and tinea corporis and, occasionally, tinea capitis.
Dosage: The ointment or cream should be applied twice daily until the infected skin is shed. This may take several weeks.
Precaution: Avoid contact with the eyes.
Adverse effects: Occasionally, a localized, mild inflammatory response occurs.

MICONAZOLE
Ointment or cream: 2% (nitrate)
Uses: Topical treatment of superficial fungal infections of the skin caused by both dermatophytes and yeasts, and of secondary infections caused by Gram-positive cocci. Specific indications include ringworm, intertrigo, diaper dermatitis, mycotic paronychia, fungal infection of the outer ear and pityriasis versicolor.
Dosage: Apply twice daily to affected skin lesions which have been cleaned and dried, and for at least 10 days after the condition has cleared.
Contraindications: Severe liver impairment.
Precautions: Discontinue if irritation or sensitization occurs, and avoid contact with the eyes. There is no information to date indicating that miconazole is absorbed through the skin.
Adverse effects: Occasional irritation and burning.

SELENIUM SULFIDE
Lotion: 2.5%
Detergent-based suspension: 2.5%
Uses: The lotion is used to treat pityriasis versicolor and the detergent-based suspension to treat seborrheic dermatitis.
Dosage:
Pityriasis versicolor: Apply the undiluted lotion with a small amount of water to the entire affected area and rinse off after 10 minutes. Treatment should be repeated after 3 and 6 days.
Seborrheic dermatitis: Massage 5–10 ml of suspension into the wet scalp and leave for 2–3 minutes before rinsing thoroughly. Repeat twice weekly for 2 weeks. Thereafter, once weekly for 2 weeks. Then use only when needed.
Contraindications: Age under 2 years.
Precautions: Do not apply to damaged skin because of the risk of systemic toxicity and discontinue if cutaneous sensitization occurs. Avoid contact with eyes. Do not apply selenium sulfide preparations to the hair within 48 hours of applying any type of hair colouring or permanent waving preparations.
Adverse effects: Skin irritation. If applied to damaged skin, systemic toxicity can occur and cause tremors, weakness, lethargy, pain in the lower abdomen and occasional vomiting. These symptoms usually resolve within 10 days of discontinuing treatment. May also discolor hair or cause hair loss.

METHYLROSANILINUM CHLORIDE (GENTIAN VIOLET)
Aqueous solution: 0.5%
Tincture: 0.5%

Uses: Superficial dermatophyte infections, seborrhoeic dermatitis, superficial bacterial pyodermas, cutaneous, mucocutaneous and vaginal candidiasis.

Dosage: Topical application 2 or 3 times daily produces significant clearing of lesions within a few days.

Contraindications: Excoriated or ulcerated cutaneous lesions which may permit significant systemic absorption.

Precautions: If sensitization occurs, withdraw the drug. Temporary staining of the skin and permanent staining of cloth and fabric may occur.

Adverse effects: Occasionally, severe irritation may necessitate discontinuation of treatment.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

SODIUM THIOSULFATE
Lotion: 25%
Solution: 25%

Uses: Pityriasis versicolor.

Dosage: Clean and dry affected areas thoroughly. Apply twice daily in a thin film to the affected areas. Symptoms of active infection usually disappear quickly but treatment should be continued for several weeks.

Precautions: Discontinue treatment if irritation or sensitization occurs. Avoid contact with the eyes.

Anti-infective drugs

Staphylococcal infections of the skin such as impetigo, ecthyma, folliculitis and furunculi, and streptococcal infections such as cellulitis and erysipelas, are very common where the climate is hot and humid, where standards of hygiene are compromised, and in immunodeficient patients.

In all skin infections, the most important part of treatment is cleansing of the skin and thorough drying. Washing with soap and water will often help prevent infection.

Light localized superficial infections can often be treated effectively with an application of antiseptic solution such as gentian violet, brilliant green or chlorhexidine. Superficial crusted sores should be gently washed with soap and water or a weak solution of aluminium diacetate or a 0.01% solution of potassium permanganate. Infected burns should be treated with silver sulfadiazine, which is bactericidal against both Gram-positive and Gram-negative organisms.

A topical antibiotic ointment containing 2% mupirocin, which is active against Gram-positive bacteria, is of value, particularly in impetigo. To prevent the development of resistance, mupirocin cream should not be used for more than 10 days. Topical preparations containing neomycin and bacitracin are also widely used but these carry a risk of skin sensitization particularly with continued or repeated use.

Topical use of preparations containing antimicrobials which are widely used systemically should be avoided. These include penicillin, sulfonamides, streptomycin and gentamicin. They should be reserved for the systemic treatment of infections, because of the possibility of inducing sensitivity and favouring the emergence of resistant organisms. Only widespread superficial or deep-seated infections associated with fever require treatment with a systemic antibiotic. Whenever possible, the choice of an antimicrobial should be based on the results of sensitivity tests.

POTASSIUM PERMANGANATE
Aqueous solution: 1:10 000 (0.01% solution)

Potassium permanganate is sometimes supplied as an aqueous stock solution of 1 in 1000 (0.1%). This must be diluted before use.
**Uses:** As an antiseptic agent used in wet dressings to assist healing of suppurating superficial wounds, tropical ulcers, tinea pedis, pemphigus and eczematosus skin lesions caused by impetigo.

**Dosage:**

**Suppurating superficial wounds and tropical ulcers**
Use the 1:10 000 (0.01%) solution in wet dressings. Change the dressing 2 or 3 times daily. Tropical ulcers also require treatment for 2–4 weeks with procaine benzylpenicillin.

**Tinea pedis**
Soak severe weeping lesions with the 1:10 000 (0.01%) solution every 8 hours.

**Pemphigus**
Soak compresses in 1:10 000 (0.01%) solution. Apply every 4 hours.

**Impetigo**
Superficial crusts should be gently separated with a 1:10 000 (0.01%) solution.

**Precautions:** Never cover the affected area with plastic or rubber occlusive dressings.

**Adverse effects:** Skin irritation. Skin and clothing will be coloured brown.

**SILVER SULFADIAZINE**

**Cream: 1%, in 500-g container**

**Uses:** As an adjunct in the prevention and treatment of infection in second and third degree burns.

**Dosage:** Apply the cream liberally with a sterile spatula or with a sterile gloved hand using an aseptic technique. Apply to cleaned and debrided burns once or twice daily and more frequently if volume of exudate is large. Burns should be covered with cream at all times and treatment should be continued if there is a possibility of infection, or until healing is complete.

**Contraindications:** Late pregnancy, breast-feeding mothers and neonates. Blood dyscrasias. Patients with glucose-6-phosphate-dehydrogenase deficiency may develop haemolytic anaemia.

**Precautions:** Use with caution in patients with renal or hepatic impairment.

**Adverse effects:** Occasionally, allergic reactions include rashes, burning and itching. Argyria and sulfonamide-induced systemic toxicity, such as blood disorders due to large area application or prolonged use, also occur. Transient leukopenia has been reported.

**Anti-inflammatory and antipruritic drugs**

**Eczematous diseases**

**Contact dermatitis**
Contact dermatitis can cause allergy or skin irritation. Removal of the substance provoking the reaction is the first step in treating this condition. Mild cases of contact dermatitis can be treated with topical hydrocortisone, which suppresses inflammation.

A short course of oral prednisolone or a topical corticosteroid, such as betamethasone valerate, should be considered for more severe cases and for suppression of severe acute reactions associated with blistering, exudation and oedema. Soaking in clean water or mild saline solution is recommended in the acute stages of severe dermatitis.

**Pruritus**
Pruritus, or itching, is a common symptom of many skin diseases. However, contact with certain sub-
stances, conditions that dry the skin, stress, and extremes of temperature may also be a cause. Thus, an important part of treatment is to eliminate or minimize the reason for the irritation.

Corticosteroids, such as hydrocortisone or betamethasone applied topically, can give relief. Soothing baths, or the application of calamine lotion or an emollient cream may also be helpful. Systemic antihistamines, such as oral chlorphenamine, may relieve generalized pruritus.

**Atopic dermatitis**

Also known as eczema, atopic dermatitis is a common skin disorder which mainly occurs in infants and children. Patients are bothered by constant intense itching, with areas of red skin.

Pruritus may be partially relieved by applying astringent aluminium diacetate lotion to exudative lesions, and emollients to lichenified plaques. Topical hydrocortisone should be applied regularly to treat even mild areas of involvement. The use of betamethasone should be considered in the treatment of persistent localized dermatitis in adults. Topical antihistamines are often not effective and should be avoided because of the risk of sensitization. However, oral antihistamine can be given at night to calm pruritus and facilitate sleep. Non-sedating histamines can be given during the day, and may provide symptomatic relief. Information on oral antihistamines will appear in Section 3 of the WHO Model Formulary.

A secondary infection, often involving *Staphylococcus aureus*, can be responsible for exacerbation of the disease. In this case, an oral antibiotic such as erythromycin can be given for 7–10 days, or a topical antibiotic such as mupirocin ointment can be applied to the skin.

**Seborrhoeic dermatitis**

Use of special shampoos and exposure to ultraviolet light reduce inflammation and scaling. Treatment shampoo should be massaged into the scalp and left on for at least 5 minutes. Such preparations may contain keratolytics, such as tar derivatives, or imidazole compounds, such as miconazole. Selenium sulfide, which has antifungal and keratolytic properties, is widely used in many proprietary shampoos. A shampoo containing the two antifungal agents, sulfur and salicylic acid, is also available. Topical applications of corticosteroids and/or imidazoles, such as ketoconazole or miconazole, can be effective.

---

**BETAMETHASONE**

*Ointment or cream: 0.1% (as valerate)*

**Uses:** Contact dermatitis, atopic dermatitis, seborrheic dermatitis, lichen planus, psoriasis and intractable pruritus.

**Dosage:**

*For adults and children over 2 years of age:* Apply a small quantity of cream or ointment thinly to the affected area once or twice daily until improvement occurs, and then apply less frequently.

**Contraindications:** Skin infections or broken skin.

**Precautions:** Adverse systemic corticosteroid effects (adrenal suppression) may occur if betamethasone is used on a large area of the body or for a long time, with an occlusive dressing or on broken skin. Potent corticosteroids such as betamethasone should not be used on the face for more than 7 days.

Secondary infection may occur during treatment, particularly if occlusive dressings are used. If this happens, stop corticosteroid treatment immediately and give an appropriate antimicrobial.

**Adverse effects:** Exacerbation of untreated infections, local atrophic changes particularly on the face and in skin-folds characterized by thinning of the dermis, depigmentation, dilatation of superficial blood vessels and formation of striae due to prolonged use. Hypercorticalism and suppression of the hypothalamic-pituitary-adrenal axis may occur with prolonged or widespread use.

**CALAMINE LOTION**

*Lotion (BP 15% calamine, USP 8% calamine)*

**Uses:** Symptomatic topical treatment of mild pruritus and insect stings.

**Dosage:** Shake well before using. Apply liberally to affected skin 3–4 times daily.

**Precautions:** Avoid contact with the eyes and mucous membranes.

**Adverse effects:** May rarely cause sensitization.
HYDROCORTISONE
Ointment or cream: 1% (acetate)

Uses: Topical treatment of contact dermatitis, atopic dermatitis, lichen planus, intractable pruritus, and phototoxic reactions, including polymorphic light eruptions and actinic prurigo; short-term treatment of psoriasis of the face, scalp, palms and soles of the feet.

Dosage: A thin film should be applied to the affected area 1–4 times daily. When a favourable response occurs, reduce the frequency of application to the minimum necessary to maintain control and avoid relapse. Treatment should be stopped as soon as all lesions have resolved.

The cream is suitable for most dermatooses and the ointment is often used for dry, scaly lesions. Occlusive dressings should only be used for severe or resistant lesions.

Contraindications: Bacterial, fungal or viral infections at the intended site of application. Age under 2 years.

Precautions: The use of occlusive dressings increases the penetration of hydrocortisone into keratinized lesions. Use occlusive dressings only at night and for no longer than two nights. Occlusive dressings should never be used on weeping lesions.

If secondary infection occurs, stop hydrocortisone and give an appropriate antimicrobial.

Adverse effects: Exacerbation of untreated infections. Prolonged use can induce local atrophic changes, particularly on the face and in skin folds, characterized by thinning of the dermis, depigmentation, dilatation of superficial blood vessels and formation of striae. Hypercorticalism and suppression of the hypothalamic-pituitary-adrenal axis are possible with prolonged use or widespread use on large areas of the body. However, local atrophic changes are much less common with hydrocortisone than with some more potent corticosteroids.

Astringents
Aluminium diacetate is a topical astringent which is used as an antiseptic for various skin conditions. It precipitates proteins and does not penetrate even broken or damaged skin. It is used to treat suppurating superficial wounds and tropical ulcers and the skin lesions produced by pemphigus and impetigo.

ALUMINIUM DIACETATE
Stock solution: 13% for dilution

Uses: As an antiseptic in wet dressings to assist healing of suppurating superficial wounds, tropical ulcers and eczematous skin lesions. Treatment of tropical ulcers and impetigo and to aid the removal of adherent crusts.

Dosage:
Suppurating superficial wounds and tropical ulcers
Dilute 1 ml of stock solution in 20 ml water to produce a 0.65% solution. Soak dressings in this solution and apply for 30 minutes to 2 hours each day. Change dressings every 5–15 minutes. Tropical ulcers also require treatment with injections of procaine benzylpenicillin for 2–4 weeks.

Pemphigus
Dilute 10 ml of stock solution in 26 ml water to produce a 5% solution. Soak the dressings in this solution and apply every 4 hours.

Impetigo
Apply dressings soaked in a 0.65% solution until it is possible to gently separate superficial crusts.

Contraindications: Never use plastic or rubber occlusive dressings.

Adverse effects: No adverse effects have been reported.

Drugs affecting skin differentiation and proliferation

Acne vulgaris
Typically, acne first appears during early puberty when androgenic stimulation triggers excessive production of sebum. Since scarring of the skin resulting from severe nodular acne causes major distress, acne should always be treated as soon as possible. Exposure to substances suspected of causing or aggravating the condition should be avoided.

Mild cases usually respond satisfactorily to topical therapy alone. Oral antibiotics are commonly used
in moderate to severe cases, while oral estrogens, antiandrogens or retinoids should be reserved for severe, unresponsive cases.

Systemic treatment must be sustained for several months before a response can be anticipated. During this time, topical preparations should be applied to the affected areas to prevent the development of new lesions. Information on the systemic treatment of acne will appear in Section 6 and Section 18 of the WHO Model Formulary.

Benzoyl peroxide is a mild keratolytic drug with bacteriostatic activity against *Propionibacterium acnes*. Treatment is usually begun with a 2.5–5% preparation applied topically every day. Begin treatment with benzoyl peroxide lotion at the lowest possible strength and increase as the patient develops tolerance to the initial irritant reaction.

Preparations containing sulfur, which is bactericidal and promotes desquamation, are often used. Sulfur may be combined with salicylic acid, which is a keratolytic agent.

**BENZOYL PEROXIDE**

*Cream or lotion: 5%*

**Uses:** Mild to moderate acne vulgaris and as an adjunct to oral therapy in more severe forms.

**Dosage:** Apply to clean skin on alternate days.

**Contraindications:** Inflamed or broken skin.

**Precautions:** Avoid contact with eyes and mucous membranes. Do not apply an occlusive dressing over the application area since benzoyl peroxide is a potent contact sensitizer.

**Adverse effects:** Initial irritation commonly occurs and subsides with continued use. Rarely, contact sensitivity occurs and sometimes even one application can cause severe irritation and reaction. Bleaches clothes, hair and skin.

**Psoriasis**

Psoriasis, which affects people of all ages in all countries, is one of the most common chronic dermatoses in industrialized countries. Considerable local variations in its prevalence have been attributed to genetic, climatic, nutritional and ecological factors. Various biological events may trigger psoriasis, such as streptococcal or viral infection, an emotional crisis, or pregnancy. Psoriasis vulgaris is the most common form of the condition. Guttate psoriasis, commonly seen in children, is often caused by a streptococcal infection. Patients may require antimicrobial treatment, whereafter the lesions may disappear following resolution of the infection. The condition is also known to resolve spontaneously. No treatment is known to assure remission, although sunlight often clears lesions.

Dithranol restores the normal rate of epidermal cell proliferation and keratinization, and localized psoriasis vulgaris can frequently be cleared by daily applications of dithranol ointment for a period of 2 to 4 weeks. A short contact method in which each application is carefully washed off with soap and water within 10–30 minutes after application causes little, if any, irritation or staining of normal skin. This method is particularly useful for outpatient management. There is a risk of severe conjunctivitis if dithranol accidentally enters the eye. Dithranol should only be administered under medical supervision.

Crude coal tar is also effective in the treatment of psoriasis. Some preparations additionally contain salicylic acid as a keratolyte. Good results are often obtained when daily applications or baths are combined with exposure to ultraviolet light or sunlight.

Emollients containing low concentrations of salicylic acid (1–2%) are a useful adjunct to treatment, particularly where there is thick scaling. A cream containing 10% urea, which has moisturizing, keratolytic and antimitotic properties, may prove more effective than an emollient. Topical corticosteroids, such as hydrocortisone or betamethasone, are widely used in mild or moderate psoriasis. However, when extensive areas of the body are involved or when there is erythrodermic psoriasis, they can induce systemic adrenal suppression. Rebound often occurs after stopping treatment, and this may result in a more unstable form of psoriasis.

**Actinic keratoses**

The lesions of actinic keratosis are distributed primarily over sun-exposed areas. Horny growths, which are often covered by light brown scales, are usually asymptomatic but they can be disfiguring. They respond to light cautery and cryosurgery or topical application of fluorouracil over a three-week period. Simple emollients may be satisfactory for people with many lesions.
Warts
Warts (verrucae) are caused by the human papilloma virus and may regress spontaneously within months or years of their first appearance. However, particularly in immunosuppressed patients, they may spread and be difficult to cure. Many common, plane and plantar warts can reasonably be left untreated, but painful or unsightly lesions generally respond to application of paints or lotions containing salicylic acid. Where available, liquid nitrogen applied with a cotton-tip or a spray is highly effective. It should be noted, however, that freezing the skin can produce temporary or permanent depigmentation, and liquid nitrogen should be used with caution. This is particularly true when used on patients with dark skin.

Anogenital warts (condylomata acuminata), which are usually transmitted by sexual contact, should always be treated, even though they frequently recur, since they increase the risk of cervico-uterine cancer. Podophyllum resin, a potent cytotoxic agent, may be applied to small lesions. The risk of extensive local necrosis and of systemic toxicity excludes the use of podophyllum resin on larger lesions. It should not be used in pregnant women due to the risk of teratogenicity and other fetal abnormalities. When available, podophyllotoxin is a less toxic alternative. When podophyllum resin is contraindicated or ineffective, surgical removal, electrocautery, cryosurgery and laser therapy are possible options. Topical application of fluorouracil has been reported to be of value in resistant cases but treatment is expensive and efficacy is still under investigation.

COAL TAR
Solution: 5%

Uses: To treat chronic psoriasis, either applied alone or in combination with exposure to ultraviolet (UVB) light.

Dosage: Treatment is usually initiated with a 1% solution. Apply directly to psoriasis lesions and massage gently. A cotton or gauze pad can also be used to apply the solution. The frequency of application can range from 1 to 4 times daily. If necessary, the strength of the solution can be increased every few days according to response and tolerance. The strong odour, staining and irritant properties are reduced when refined products are used.

Coal tar bath
The patient should soak for 10–20 minutes in a bath full of tepid water to which 100 ml of 5% coal tar solution has been added and thoroughly mixed. The frequency of bathing can range from once daily to once every three days on at least 10 occasions. The baths are often used in alternance with ultraviolet (UVB) rays but at least 24 hours should elapse between exposure and treatment with coal tar. Carefully regulate the amount of UVB light to avoid seriously burning the skin.

Contraindications: Inflamed, broken or infected skin.

Precautions: Coal tar preparations produce photosensitivity reactions. After an application, the patient must protect the skin from exposure to sun for at least 24 hours and possibly 72 hours. Patients should wear protective clothing and use sunscreen or sunblocking agents if necessary. Concurrent use of coal tar preparations and other photosensitizing medications may enhance sensitization.

Adverse effects: Skin irritation, allergic sensitization, photosensitivity reactions, skin and hair discoloration.

DITHRANOL
Ointment: 0.1% – 2%

Uses: Topical management of moderately severe psoriasis.

Dosage: Treatment should be administered under medical supervision.

Treatment is usually begun with the 0.1% ointment. Leave the ointment on the skin for 30 minutes. Gradually extend the application time and strength of ointment: increases are usually made at 3–7 day intervals.

It is not usually necessary to increase the strength beyond 0.5%. However, in non-responsive cases, it may be necessary to increase to 2%.

Contraindications: Not to be used on the face, acute eruptions, or excessively inflamed areas.

Precautions: Dithranol is a powerful irritant. Reduce the frequency of application or discontinue if the initial treatment produces soreness or if the lesion spreads.

Concurrent use of dithranol and other photosensitizing medications may enhance photosensitizing effects. Skin, hair and fabrics can be stained.
Adverse effects: Conjunctivitis may occur after contact with the eyes. Skin irritation and excessive erythema may occur, particularly on normal skin adjacent to the area treated.

**FLUOROURACIL**  
**Ointment:** 5%

**Uses:** Multiple actinic keratoses. Genital warts unresponsive to podophyllum resin.

**Dosage:** The ointment should be applied thinly to the affected area once or twice daily. Continue treatment until there is a marked inflammatory response. The usual duration of treatment is 3–4 weeks or longer. Healing may not occur until 2 months after completion of treatment.

**Contraindications:** Haemorrhagic ulcerated tissue.

**Precautions:** Do not apply with a metal instrument. If the area does not respond to fluorouracil therapy, take a biopsy to confirm the diagnosis. Avoid mucous membranes and eyes. Since UV light intensifies the inflammatory reaction, avoid exposure to sunlight. Possible photosensitivity reactions may occur during therapy and for 1–2 months thereafter.

**Adverse reactions:** Local inflammatory reactions include irritation, swelling, scaling, burning, pain, erosions, scarring and hyperpigmentation.

**PODOPHYLLUM RESIN**  
**Solution:** 10–25%

**Uses:** Topical treatment of warts and genital warts.

**Dosage:** A 10% solution should be applied to the affected area. Care must be taken to avoid contact with normal tissue. The solution should be thoroughly rinsed off after 1–4 hours. Applications may be repeated once or twice weekly, but no more than four times in all.

**Contraindications:** Should not be used on large areas of skin, or on cervical, urethral, rectal or oral warts.

**Precautions:** Medical supervision is necessary because it is locally corrosive and potentially toxic and should not be in contact with friable, bleeding lesions.

**ADVERSE EFFECTS:** Systemic effects resulting from cutaneous absorption include nausea, vomiting, abdominal pain and diarrhoea. Transient leukopenia and thrombocytopenia (bone-marrow depression) may occur. Neurotoxicity resulting in visual and auditory hallucinations, delusions, disorientation, confusion and delirium may occur following excessive application.

**SALICYLIC ACID**  
**Topical solution:** 5%  
**Ointment:** 1–6%

**Uses:** Topical treatment of hyperkeratotic conditions.

**Dosage:** Initially 1% ointment is applied daily. The concentration is progressively increased to a maximum of 6%, and applications are continued until a satisfactory remission is obtained.

**Contraindications:** Broken or inflamed skin. Age under 2 years.

**Adverse effects:** Rarely, allergic contact dermatitis is reported. Systemic salicylism may occur, especially when large areas are treated — particularly in children.

**UREA**  
**Ointment or cream:** 10%

**Uses:** As a hydrating agent to treat dry, scaling and itching skin. Promotes hydration of keratin.

**Dosage:** The cream or ointment should be applied to the affected skin 1–3 times daily. Better moisturizing effects are obtained if applied to damp skin.

**Precautions:** Avoid application on face or broken skin. Avoid contact with eyes.

**Adverse effects:** Transient stinging and local irritation.

**Scabicides and pediculicides**

**Scabies**  
Scabies is caused by a mite that burrows into the skin and is transmitted from person to person. The entire household must therefore be treated at the
same time. Benzyl benzoate, used as a 25% lotion, is an inexpensive scabicide. It must be applied to all skin surfaces, from the scalp to the soles of the feet, while taking care to protect the eyes. Benzyl benzoate should not be used on children because of irritation.

A 5% solution of permethrin is less irritant and more effective than benzyl benzoate, but more expensive. Young infants can be treated with a cream containing 6–10% precipitated sulfur applied once daily for one week.

**Pediculosis**

Pediculosis of the head, body and pubic hair is caused by different species of louse which are usually transmitted from person to person, particularly in poor hygienic conditions. The clothing, towelling and bedding of infected persons are also contaminated. Pediculosis pubis is transmitted by sexual contact, skin-to-skin contact or by sharing a bed or linen with an infested individual.

Public health control will depend on education and improving domestic and institutional accommodation. Infected individuals must be treated promptly and followed up to detect recurrences. Contacts should also be treated at the same time. Head lice are readily treated with topical applications of permethrin. All combs and brushes should be soaked in a pediculicide disinfectant for at least 2 hours or washed in scalding soapy water for at least 10 minutes. Do NOT share combs, brushes, linen or clothes.

Body lice are effectively treated with powdered preparations. Protect the face, nose and mouth when using powders. Clothes should be dusted at the same time and washed in boiling water if possible.

**BENZYL BENZOATE**

*Lotion: 25%*

**Uses:** Scabies and pediculosis of the scalp, body and pubis.

**Dosage:**

- **Scabies**
  A 25% lotion applied once daily on two consecutive days is usually sufficient.

- **Pediculosis**
  The lotion should be applied to the affected area and left for 24 hours before being rinsed off. One or two repeated applications may be required thereafter at weekly intervals.

**Contraindications:** Acutely inflamed or broken skin.

**Adverse effects:** Irritation of the skin with a burning or stinging sensation commonly occurs.

**PERMETHRIN**

*Cream: 5%*

*Lotion: 1%*

**Uses:** Scabies, pediculosis of the scalp, body and pubis.

**Dosage:**

- **Scabies**
  Massage the cream into the skin from the head to the soles of the feet. In general, 30 g is sufficient for an average adult. The cream should be left in place for at least 8 hours before being removed by thorough washing. One application is usually curative.

- **Head lice**
  Wash the hair and dry. Immediately massage the lotion into the hair and scalp until wet. Leave on for 10 minutes and rinse. Dry thoroughly. One application is usually curative.

- **Body and pubic lice**
  Leave on affected area for 10 minutes before removing.

**Contraindications:** Known hypersensitivity to permethrin, pyrethrins or any synthetic pyrethroid.

**Precautions:** May exacerbate pruritus, oedema and erythema.

**Adverse effects:** Mild and transient burning and stinging sensations may follow application in cases of severe infestation.

**Ultraviolet blocking agents**

Exposure of skin to sunlight is beneficial in moderation since ultraviolet light is vital for the synthesis of vitamin D. Excessive exposure is hazardous, however, particularly in light-skinned persons who tan poorly, and in patients with pathological or drug-induced photosensitivity. Photodamage is first evident as acute sunburn and, in the longer term, as premature ageing of the skin. Excessive expo-
sure to sunlight also predisposes to the development of malignant and premalignant skin lesions including actinic keratosis, squamous cell carcinoma, basal cell carcinoma and malignant melanoma.

Ideally the best protection is to reduce exposure and thereby avoid sunburn either by the use of protective clothing or, when this is not practicable, by regular use of sunscreen products with a sun protection factor (SPF) of at least 15.

The major categories of chemical sunscreens include cinnamates, which are UVB absorbers, and dibenzoylmethanes, which are UVA absorbers. Physical sunscreens, such as titanium dioxide, are opaque and reflect ultraviolet light. Many sunscreen products combine sunscreens from different groups in order to widen the range of protection. A broad-spectrum topical sun protection product which protects from both UVA and UVB contains 3% octyl methoxycinnamate (synonym is 2-ethylhexyl-p-methoxycinnamate), 2% avobenzone (synonym is butylmethoxydibenzoylmethane), and 2% titanium dioxide, formulated in an arylate polymer or an oily base.
Recent Publications and Documents

International travel and health

The 1998 revised edition of *International travel and health: vaccination requirements and health advice* has now been issued and contains vital information on medical and personal health precautions needed for international travellers. The guide contains a country-by-country listing of vaccination requirements.

In view of the deteriorating malaria situation, relevant information is included for prophylaxis and treatment, including a recommended chemoprophylactic regimen for each malarious area. A section on multidrug-resistant malaria is also included.

Other sections of the guide provide information on health hazards commonly encountered in different parts of the world, such as risks posed by contaminated food and water, or diseases spread by insect bites.


Guidance on the clinical investigation of medicinal products for treatment of schizophrenia

The Committee for Proprietary Medicinal Products (CPMP) of the European Union has approved a guidance document for the evaluation of drugs in the treatment of schizophrenia which comes into force in August 1998.

Although the guideline focuses mainly on antipsychotic products developed specifically for schizophrenia, comments are also made on related psychotic syndromes. In the past, products that demonstrated efficacy in schizophrenia were generally called neuroleptics. However, these products have also traditionally been used to treat psychotic symptoms such as those manifested in delusion disorder or substance-related disorder.

Antipsychotic agents have generally been used in three ways: in the acute phase to treat positive symptomatology, as maintenance therapy to control symptoms, and as long-term prophylactic treatment to prevent relapses or recurrence.

Initially, the effect of antipsychotic agents on positive symptoms in schizophrenic patients was attributed to the anti-dopamine effect of these compounds. Recently, so-called atypical antipsychotic agents have been developed which have shown, in vitro, more affinity for serotonergic receptors, though they also have an affinity for dopamine receptors.

The guideline also covers investigations concerning use of placebo, potential negative symptoms, methods to assess efficacy, selection of patients, strategy, and safety aspects.


Draft guidance for industry: container and closure integrity testing

The Food and Drug Administration has announced the availability of draft guidance for industry: *Container and closure integrity testing in lieu of sterility testing as a component of the stability protocol for sterile products.*

All sterile products are required to have adequate container and closure integrity and to remain free from contamination throughout the entire shelf-life. The guidance proposes methods that reliably confirm the integrity of the container and closure system in the final product.

It is intended to offer alternative methods for sterility testing to confirm the integrity of container and closure systems for sterile biological products, human and veterinary drugs, and medical devices. The guidance applies only to the replacement of the
sterility test with an appropriate container and closure integrity test in the stability protocol. It is not offered as a replacement for the sterility test in product release.


Regulatory situation of herbal plants

In many parts of the world, many people rely on medicinal plants and herbal medicines to deal with their health problems, and public interest in natural therapies is increasing everywhere. Real benefits can be gained by the use of herbal medicines but most still need to be studied scientifically.

The evaluation of the safety and efficacy of these products is an important challenge and WHO has begun to document experience from countries around the world on the registration, regulation and national requirements for herbal medicines. Thus far, 52 countries have provided information, which is set out in a document produced by WHO's Traditional Medicine Unit. The document will be updated as more contributions become available.

Achieving self sufficiency in blood and blood products

In Europe, self sufficiency in blood production has again become an important concern. The Finnish Red Cross Blood Transfusion Service encourages other European Union countries to rely on unpaid blood donors and dismantle import barriers on blood products.

Testing for alanine aminotransferase is considered obsolete since the start of testing for hepatitis C but yet some countries require all donations to be screened for alanine aminotransferase. Cost of plasmapheresis is high because many authorities have set standards and criteria for plasmapheresis which far exceed the European regulations. The Finnish Red Cross suggests that member states should accept European standards, remove barriers to receiving blood from other states and should ensure that their blood donors are unpaid volunteers which assures the integrity of the product.


International Nonproprietary Names (INN) to be used within the European Union

European Union — In 1983, a Council Directive established that International Nonproprietary Names (INNs) recommended by the World Health Organization will be used, where such names exist, throughout the European Union. The change was to be a legal requirement from a date to be announced, which has now been fixed as December 1998.

A 5-year transition period has been accorded when a risk to health from possible confusion has been identified. During this time, both the INN and the national approved name will appear on the labelling.

It is expected that the Directive will start to be implemented by May/June 1998 since the change-over must be completed by December 1998.

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 (1–73) and Recommended (1–35) International Nonproprietary Names can be found in Cumulative List No. 9, 1996. 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 de 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 (1–73) et recommandées (1–35) dans la Liste récapitulative No. 9, 1996. 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 figurent 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 (1–73) y Recomendadas (1–35) se encuentran reunidas en Cumulative List No. 9, 1996. 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 deben incluirse en las listas recapitulativas de DCI.
Proposed International Nonproprietary Names: List 79
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 79 Proposed INN not later than 30 November 1998.

### Dénominations communes internationales proposées: Liste 79
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 79 de DCI Proposées le 30 novembre 1998 au plus tard.

### Denominaciones Comunes Internacionales Propuestas: Lista 79
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 79 de DCI Propuestas el 30 de noviembre de 1998 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>
</tr>
</thead>
<tbody>
<tr>
<td>alvamelinum (alvameline, alvaméline, alvamelina)</td>
<td>3-(2-ethyl-2H-tetrazol-5-yl)-1,2,5,6-tetrahydro-1-methylpyridine nootropic agent</td>
<td>C9H15N5 120241-31-8</td>
</tr>
</tbody>
</table>

![Diagram of the molecular structure of alvamelinum](image)
amediplasum

amediplase

fibrinolytic

amédiplase

fibrinolytique

amediplasa

173-L-serina-174-L-tirosina-175-L-glutamina-173-275-activador del plasminógeno (tipo tisular humano reducido), proteína de fusión con urokinasa (orina humana cadena β reducida)
fibrinolítico

151912-11-7

SYQGNSDCYF GNGSAYRGTH SLTESGASCL PWNSMILIGK
VYTAQNPASAQ ALGLSKHNYC RNPDOAASKW CHVLKNRRLT
WEYCDVPSCS TCGLRQYSQP QFRIIGGEFT TIEQPWFAA
IYRRHRGSVS TYVCGGSLIS PCWVISATHC FIDYPPKEDY
IVYLGRSRLN SNTQGEMKPE VENLILHDKY SADTLAHNND
IALLKIRSKE GRCAQPSRTI QTICLPQSMN DPQFGTSCIE
TGPGKSENDN YLYPEQLKMT VVKLISHREC QQPHYGSRV
TTEMLCAADP QWKTDSQGQD SQGELVCSLQ GRMTLTGIVS
WGRGSCALKDK PGYVTRVSHF LPWIRSHTKE ENGLAL

amprenavirum

amprenavir

(3S)-tetrahydro-3-furyl [(S)-α-{(1R)-1-hydroxy-2-(N'-isobutylsulfanilamido)ethyl]phenethyl]carbamate
antiviral

amprénavir

[(1S,2R)-3-[(4-aminophényl)sulfonyl][2-méthyl(propyl)amino]-1-benzyl-2-hydroxypropyl]carbamate de (3S)-tétrahydrofuran-3-yl
antiviral

amprenavir

[(S)-α-{(1R)-1-hidroxi-2-(N'-isobutilsulfanilamido)etil]fenetil]carbamato de (3S)-tetrahidro-3-furil
antiviral
anatumomab mafenatoxum
\[ \text{immunoglobulin} \, G \, 1, \text{anti-(human tumor-associated glycoprotein 72) (human-mouse clone pMB125 Fab fragment } \gamma 1\text{-chain) fusion protein with enterotoxin A (227-alanine) (Staphylococcus aureus) complex with mouse clone pMB125 } \kappa \text{-chain) immunomodulator} \]

anatumomab mafenatox
immunoglobuline G1 (chaîne } \gamma 1\text{ du fragment Fab de l'anticorps monoclonal de souris humanisé, clone pMB125, dirigé contre la glycoprotéine 72 humaine associée aux tumeurs)-[227-alanine]entérotoxine A (Staphylococcus aureus), complexée à la chaîne } \kappa\text{ de l'anticorps monoclonal de souris clone pMB125 immunomodulateur}

anatumomab mafénatox
immunoglobulina G1 (cadena } \gamma 1\text{ del anticuerpo monoclonal químérico hombre-ratón pMB125 dirigido contra la glicoproteína 72 asociada a tumor humano) proteína de fusión con enterotoxina A de Staphylococcus aureus (227-alanina) con el clon de pMB125 cadena } \kappa\text{ del anticuerpo immunomodulador}

ancestimum
\[ \text{N-L-methionyl-1-165-hematopoietic cell growth factor KL (human clone V19.8hSCF162), dimer } \text{antianémico} \]

ancestim
dímère du N-L-méthionyl-1-165-facteur de croissance KL de cellules hématopoïétiques (clone humain V19.8hSCF162) antianémique

ancestim
\[ \text{N-L-metionil-1-165-factor de crecimiento celular hematopoético KL (clon humano V19.8hSCF162), dímero } \text{antianémico} \]
ascorbyl gamolenas
ascorbyl gamolenate
L-ascorbic acid, 6-{(6Z,9Z,12Z)-6,9,12-octadecatrienoate]
diabetic antineuropathic agent

ascorbyl gamolenate
(6Z,9Z,12Z)-octadeça-6,9,12-triénoate de (2S)-2-[(2R)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl]-2-hydroxyéthyle
gent de traitement de la neuropathie diabétique

gamolenato de ascorbilo
6-{(6Z,9Z,12Z)-6,9,12-octadecatrienoato] de ácido L-ascórbico
gent para el tratamiento de la neuropatía diabética

C₁₆H₁₅NO₄S₁₈ 163545-26-4

calcobutrolum
calcobutrol
calcium hydrogen 10-[(1RS,2SR)-2,3-dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate
pharmaceutical aid

calcobutrol
hydrogéno 2,2',2"-[10-[(1RS,2SR)-2,3-dihydroxy-1-(hydroxyméthyl)propyl]-1,4,7,10-tétrazaazacyclododécane-1,4,7-triyl]triacétate de calcium
auxiliaire pharmaceutique

calcobutról
10-[(1RS,2SR)-2,3-dihidroxi-1-(hidroximetil)propil]-1,4,7,10-tetraazaciclododecano-1,4,7-triacetato de hidrógeno y calcio
excipiente
Proposed INN: List 79


**defoslimodum**

2-deoxy-6-O-[2-deoxy-2-[(R)-3-hydroxytetradecanamido]-β-D-glucopyranosyl]-2-[(R)-3-hydroxytetradecanamido]-α-D-glucopyranose 1,6'-bis(dihydrogen phosphate) 2'(3')-laurate

*immunomodulator*

**dextioproninum**

*N*-[*(R)*]-2-mercaptopropionyl]glycine

*anti-inflammatory agent*

104
edodekinum alfa
interleukin 12 (human)
immunomodulator

édodékin alfa
interleukine 12 humaine
immunomodulateur

edodekina alfa
interleuquina 12 (humana)
immunomodulador

eniporidum
N-(diaminomethyene)-5-(methylsulfonyl)-4-pyrrol-1-yl-o-toluamide
Na⁺/H⁺ antiport inhibitor

éniporide
N-(diaminométhylène)-2-méthyl-5-(méthylsulfonyl)-4-(1H-pyrrol-1-yl)benzamide
inhibiteur de l'échange Na⁺/H⁺

eniporida
N-(diaminometileno)-5-(metilsulfonil)-4-pirrol-1-il-o-toluamida
inhibidor del transporte activo Na⁺/H⁺
esomeprazolum
esomeprazole 5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]benzimidazole
antisucre agent
ésoméprazole 5-méthoxy-2-[(S)-[(4-méthoxy-3,5-diméthylpyridin-2-yl)méthyl]sulfényle]-1H-benzimidazole
antisucreux
esomeprazol 5-metoxi-2-[(S)-[(4-metoxi-3,5-dimetil-2-piridil)metil]sulfinitl]benzimidazol
antisucleroso
C_{14}H_{16}N_{4}O_{3}S

esonarimodum
esonarimod (±)-3-mercapto-2-(p-methylfenacil)propiónico acid acetate
immunomodulator
ésonarimod acide (2RS)-2-[(acétylsulfanyl)méthyl]-4-(4-méthylphényl)-4-oxobutanoïque
immunomodulateur
esonarimod acetato del ácido (±)-3-mercapto-2-(p-metilenacil)propiónico
immunomodulador
C_{14}H_{16}O_{4}S  101973-77-7

and enantiomer et énantiomère
y enantiómero
fondaparinum natricum

fondaparin sodium

methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-β-O-
glucopyranuronosyl-(1→4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-α-D-
glucopyranosyl-(1→4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-6-O-
sulfo-2-(sulfoamino)-α-β-O-glucopyranoside, decasodium salt

antithrombotic

fondapanne sodique

O-6-O-sulfo-2-(sulfoamino)-2-desoxy-α-β-O-glucopyranuronosyl-(1→4)-O-β-O-
glucopyranuronosyl-(1→4)-O-3,6-di-O-sulfo-2-(sulfoamino)-2-desoxy-α-O-
glucopyranosyl-(1→4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1→4)-6-O-sulfo-2-
(sulfoamino)-2-desoxy-α-β-O-glucopyranoside de méthyle décasodium

antithrombotique

fondaparina sódica

sal decasódica del O-2-desoxi-6-O-sulfo-2-(sulfoamino)-α-β-O-glucopiranosi-
(1→4)-O-β-O-glucopiranuronosil-(1→4)-O-2-desoxi-3,6-di-O-sulfo-2-
(sulfoamino)-α-β-O-glucopiranosil-(1→4)-O-2-O-sulfo-α-L-idopiranuronosil-(1→4)-
2-desoxi-6-O-sulfo-2-(sulfoamino)-α-β-O-glucopiranosido de metilo

antitrombótico

C₃₁H₄₃N₃Na₁₀O₄₉S₈

114870-03-0

iturelixum

iturelix

\[N\text{-}acétyl\text{-}3\text{-}(naphthalén\text{-}2\text{-}yl)\text{-}o\text{-}alanyli(\text{4\text{-}chloro\text{-}o\text{-}phénylalanyli}(3\text{-}pyridyl)\text{-}o\text{-}alanyliL\text{-}séryl\text{-}N\text{\textsuperscript{6}}\text{-}nicotinoil\text{-}L\text{-}lysyl\text{-}N\text{\textsuperscript{6}}\text{-}nicotinoil\text{-}D\text{-}lysyl\text{-}L\text{-}leucyl\text{-}N\text{\textsuperscript{6}}\text{-}isopropyl\text{-}L\text{-}lysyl\text{-}\text{D\text{-}alaninamida}\]

luteinizing hormone-releasing hormone (LHRH) antagonist

iturelix

\[N\text{-}acétyl\text{-}3\text{-}(naphthalén\text{-}2\text{-}yl)\text{-}o\text{-}alanyli(4\text{-}chloro\text{-}o\text{-}phénylalanyli}(3\text{-}pyridin-
3\text{-}yli(o\text{-}alanyliL\text{-}séryl\text{-}M\text{\textsuperscript{6}}\text{-}pyridin\text{-}3\text{-}ylcarbonobil\text{-}L\text{-}lysyl\text{-}M\text{\textsuperscript{6}}\text{-}pyridin-
3\text{-}ylcarbonobil\text{-}o\text{-}lysyl\text{-}L\text{-}lysyl\text{-}(3\text{-}méthyléthyl)\text{-}L\text{-}lysyl\text{-}L\text{-}prolyl\text{-}o\text{-}alaninamida}\]

antagoniste de l'hormone de libération de la lutéostimuline

iturelix

\[N\text{-}acétyl\text{-}3\text{-}(2\text{-}naftil)\text{-}o\text{-}alani(o\text{-}cloro(o\text{-}fenilalanil)\text{-}(3\text{-}pirdil)\text{-}o\text{-}alani\text{-}L\text{-}seril\text{-}M\text{\textsuperscript{6}}-
nicotinoil\text{-}L\text{-}lisil\text{-}M\text{\textsuperscript{6}}\text{-}nicotinoil\text{-}L\text{-}lisil\text{-}L\text{-}leucil\text{-}M\text{\textsuperscript{6}}\text{-}isopropil\text{-}L\text{-}lisil\text{-}L\text{-}proy-
o\text{-}alaninamida\]

antagonista de la hormona de liberación de hormona luteinizante
Proposed INN: List 79


C82H108ClN17O14  112568-12-4

\[
\begin{align*}
\text{midafotelum} & \quad \text{midafotel} \\
& \quad (\cdash)(R)-4\{[(E)-3\text{-phosphonooalyl}]-2\text{-piperazinocarboxylic acid} \\
& \quad \text{NMDA receptor antagonist}
\end{align*}
\]

\[
\begin{align*}
\text{midafotel} & \quad \text{(-)-acic(2)}(R)-4\{[2(E)-3\text{-phosfonoprop-2-ën}]\text{pipérazine-2-carboxylique} \\
& \quad \text{antagoniste des récepteurs du NMDA}
\end{align*}
\]

\[
\begin{align*}
\text{midafotel} & \quad \text{ácido (-)-(R)-4-[(2E)-3-fosfonoalil]-2-piperazincarboxilico} \\
& \quad \text{antagonista de los receptores de NMDA}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifyllinum} & \quad \text{midaxifylline} \\
& \quad 8-(1\text{-aminocyclopentyl})-1,3\text{-dipropixanthine} \\
& \quad \text{adenosine receptor antagonist}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifylline} & \quad 8-(1\text{-aminocyclopentyl})-1,3\text{-dipropylo}-3,7\text{-dihydro-1H-purine-2,6-dione} \\
& \quad \text{antagoniste de récepteur adenosine}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifilina} & \quad 8-(1\text{-aminociclopentil})-1,3\text{-dipropixantina} \\
& \quad \text{antagonista del receptor adenosina}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifyllinum} & \quad \text{midaxifylline} \\
& \quad 8-(1\text{-aminocyclopentyl})-1,3\text{-dipropixanthine} \\
& \quad \text{adenosine receptor antagonist}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifylline} & \quad 8-(1\text{-aminocyclopentyl})-1,3\text{-dipropylo}-3,7\text{-dihydro-1H-purine-2,6-dione} \\
& \quad \text{antagoniste de récepteur adenosine}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifilina} & \quad 8-(1\text{-aminociclopentil})-1,3\text{-dipropixantina} \\
& \quad \text{antagonista del receptor adenosina}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifyllinum} & \quad \text{midaxifylline} \\
& \quad 8-(1\text{-aminocyclopentyl})-1,3\text{-dipropixanthine} \\
& \quad \text{adenosine receptor antagonist}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifylline} & \quad 8-(1\text{-aminocyclopentyl})-1,3\text{-dipropylo}-3,7\text{-dihydro-1H-purine-2,6-dione} \\
& \quad \text{antagoniste de récepteur adenosine}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifilina} & \quad 8-(1\text{-aminociclopentil})-1,3\text{-dipropixantina} \\
& \quad \text{antagonista del receptor adenosina}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifyllinum} & \quad \text{midaxifylline} \\
& \quad 8-(1\text{-aminocyclopentyl})-1,3\text{-dipropixanthine} \\
& \quad \text{adenosine receptor antagonist}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifylline} & \quad 8-(1\text{-aminocyclopentyl})-1,3\text{-dipropylo}-3,7\text{-dihydro-1H-purine-2,6-dione} \\
& \quad \text{antagoniste de récepteur adenosine}
\end{align*}
\]

\[
\begin{align*}
\text{midaxifilina} & \quad 8-(1\text{-aminociclopentil})-1,3\text{-dipropixantina} \\
& \quad \text{antagonista del receptor adenosina}
\end{align*}
\]
midostaurinum
midostaurin

N-[(9S,10R,11R,13R)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo[1,2,3-g:h;3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazocin-11-yl]-N-methylbenzamide

antineoplastic

midostaurine

N-[(9S,10R,11R,13R)-10-methoxy-9-methyl-1-oxo-2,3,10,11,12,13-hexahydro-9,13-epoxy-1H,9H-diindolo[1,2,3-g:h;3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazocin-11-yl]-N-methylbenzamide

antineoplasique

midostaurina

N-[(9S,10R,11R,13R)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo[1,2,3-g:h;3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazocin-11-yl]-N-methylbenzamide

antineoplásico

C_{35}H_{30}N_{4}O_{4}

120685-11-2

morolimumabum
morolimumab

human monoclonal IgG1 antibody against human Rhesus-D antigen

immunomodulator

morolimumab

immunoglobuline G 1 (anticorps monoclonal humain dirigé contre l'antigène Rhésus-D humain)

immunomodulateur

morolimumab

immunoglobulina G 1 (anticuerpo monoclonal humano dirigido contra el antígeno Rhesus-D humano)

immunomodulador

202833-07-6
natalizumab

*immunoglobulin G 4 (human-mouse monoclonal AN100226 4-chain anti-human integrin 4), disulfide with human-mouse monoclonal AN100226 light chain, dimer
*immunomodulator

natalizumab

*immunoglobuline G 4 (chaîne γ de l'anticorps monoclonal de souris humanisé AN100226 dirigé contre l'intégrine 4 humaine), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris humanisé AN100226
*immunomodulateur

natalizumab

*immunoglobulina G 4 (cadena γ del anticuerpo monoclonal humanizado de ratón AN100226 dirigido contra la integrina 4 humana), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de ratón AN100226
*immunomodulador

189261-10-7

olamufloxacinum

*acide 5-amino-7-[(S)-7-amino-5-azaspiro[2.4]hept-5-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-méthyl-4-oxo-3-quinolinecarboxylique
*antibactérien

C₂₀H₂₃FN₄O₃

167887-97-0

110
palivizumab

*palivizumab*

**WHO Drug Information, Vol. 12, No. 2, 1998**

**Proposed INN: List 79**

**palivizumab**

**palivizumab**

**palivizumab**

**palivizumab**

**immunoglobulin G 1 (human-mouse monoclonal MEDI-493 γ1-chain anti-
respiratory syncytial virus protein F), disulfide with human-mouse monoclonal
MEDI-493 κ-chain, dimer**

**immunomodulator**

**palivizumab**

**palivizumab**

**palivizumab**

**immunoglobuline G 1 (chaîne γ1 de l’anticorps monoclonal de souris humanisé
MEDI-493 dirigé contre la protéine F du virus syncytial respiratoire), dimère du
disulfure avec la chaîne κ de l’anticorps monoclonal de souris humanisé MEDI-
493**

**immunomodulateur**

**palivizumab**

**palivizumab**

**palivizumab**

**inmunoglobulina G 1 (cadena γ1 del anticuerpo monoclonal humanizado de
ratón MEDI-493 dirigido contra la proteína F del virus respiratorio sincitial),
dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de
ratón MEDI-493**

**inmunomodulador**

**188039-54-5**

**piboserodum**

**piboserod**

**pibosérod**

**piboserod**

**N-[(1-butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-
carboxamide**

**serotonin receptor antagonist**

**N-[(1-butylpiperidin-4-yl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-
carboxamide**

**antagoniste de la sérotonine**

**N-[(1-butil-4-piperidil)metil]-3,4-dihidro-2H-[1,3]oxazino[3,2-a]indol-10-
carboxamida**

**antagonista de los receptores de la serotonina**

**C_{22}H_{31}N_{3}O_{2}**

**152811-62-6**

**repinotanum**

**repinotan**

**répinotan**

**repinotán**

**(-)-2-[4-[[R]-2-chromanyl(methyl)amino]butyl]-1,2-benzothiazolin-3-one**

**1,1-dioxide**

**serotonin receptor agonist**

**(-)-2-[4-[[[2R]-3,4-dihydro-2H-chromén-2-yl]méthyl]amino]butyl]-
1,2-benzothiazol-3(2H)-one 1,1-dioxyde**

**agoniste de la sérotonine**

**(-)-2-[4-[[R]-2-cromanilmetil]amino]butil]-1,2-benzisotiazolin-3-onna**

**1,1-dixoído**

**agonista de los receptores de la serotonina**
**sardomozidum**

*urea azine with 1-oxo-4-indancarboxamidine*
*antineoplastic*

C_{21}H_{24}N_{2}O_{4}S 144980-29-0

**stannsoporfinum**

*dihydrogen (OC-6-13)-dichloro[7,12-diethyl-3,8,13,17-tetramethylporphyrin-2,18-dipropionato(4-)-N^{21},N^{22},N^{23},N^{24}]stannate(2-)*
inhibitor de la bilirubine

C_{34}H_{36}Cl_{2}N_{4}O_{4}Sn 106344-20-1
**Tegaserodum**

**Tegaserod**

1-[[5-methoxyindol-3-yl]methylene]amino]-3-pentylguanidine

*serotonin receptor antagonist*

**Tégaséro**

*N*-[[(5-méthoxy-1H-indol-3-yl)méthylène]amino]-*N*'-pentylguanidine

*antagoniste de la sérotonine*

**Tegaserod**

1-[[5-metoxiindol-3-il)meten]amino]-3-pentilguanidina

*antagonista de los receptores de la serotonina*

\[C_{16}H_{23}N_{5}O\]

145158-71-0

**Tenecteplasum**

**Tenecteplase**

103-L-asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanineplasminogen activator (human tissue-type)

*antithrombotic*

**Ténecléplase**


*antithrombotique*

**Tenecteplasa**


*antitrombótico*

\[C_{2558}H_{3872}N_{738}O_{781}S_{40}\]

191588-94-0

**Trecetilidum**

**Trecetilide**

(-)-4'-(S)-4-[ethyl(6-fluoro-6-methylheptyl]amino]-1-hydroxybutyl]methanesulfonanilide

*antiarrhythmic*

**Trécétilide**

(-)–*N*-4'-(1S)-4-[étyle(6-fluoro-6-méthylheptyl]amino]-1-hydroxybutyl]phényl]méthanesulfonamide

*antiarythmique*

**Trecetilida**

(-)-4'-[(S)-4-[(6-fluoro-6-metilheptil]amino]-1-hidroxibutil]metanosulfonanilida

*antiarrítmico*

\[C_{21}H_{37}FN_{2}O_{3}S\]

180918-68-7
valrubcinum

valrubcin

(8S,10S)-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[[2,2,2-trifluoroacetamido]-\(\alpha\)-L-\(\beta\)-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione 8\(^2\)-valerate

antineoplastic

valrubcine

pentanoate de 2-oxo-2-[(2S,4S)-2,5,12-trihydroxy-7-méthoxy-6,11-dioxo-4-[[3-[(trifluoroacétyl)amino]-2,3,6-tridésoxy-\(\alpha\)-L-\(\beta\)-lyxo-hexopyranosyl]oxy]-1,2,3,4,6,11-hexahydrotétracén-2-yl]éthyle

antinéoplasique

valrubcina

8\(^2\)-valerato de (8S,10S)-6-glicoloil-7,8,9,10-tetrahidro-6,8,11-trihidroxi-1-metoxy-10-[[2,3,6-tridesoxi-3-[[2,2,2-trifluoroacetamido]-\(\alpha\)-L-\(\beta\)-lyxo-hexopiranosil]oxi]-5,12-naftacenodiona

antineoplásico

C\(_{34}\)H\(_{36}\)F\(_3\)NO\(_{13}\) 56124-62-0
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Proposed International Nonproprietary Names (Prop. INN): List 10
(WHO Chronicle, Vol. 14, No. 6, 1960)

- Chlorprothixenum replace the chemical name and the graphic formula by the following:
  \((Z)-3-(2\text{-chloro-9H-thioxanthen-9-ylidene})-N,N,\text{dimethylpropan-1-amine}\)
- Chlorprothixène remplacer le nom chimique et la formule développée par:
  \((Z)-3-(2\text{-chloro-9H-thioxanthén-9-ylidène})-N,N,\text{diméthylpropan-1-amine}\)
- Chlorprothixeno sustituyanse el nombre químico y la fórmula empírica por:
  \((Z)-3-(2\text{-cloro-9H-tioxanten-9-ilideno})-N,N,\text{dimetilpropan-1-amina}\)

Dénominations communes internationales proposées (DCI Prop.): Liste 13
(Chronique OMS, Vol. 17, No. 10, 1963)

- Galantaminum replace the chemical name and the graphic formula by the following:
  \((4a,5,6r,8aS)-4a,5,9,10,11,12\text{-hexahydro}-3\text{-méthoxy}-11\text{-méthyl-6H-benzofuro}
  [3a,3,2-ef][2] \text{benzazépine-6-ol}\)
- Galantamine remplacer le nom chimique par le suivant:
  \((4a,5,6r,8aS)-4a,5,9,10,11,12\text{-hexahydro}-3\text{-méthoxy}-11\text{-méthyl-6H-benzofuro}
  [3a,3,2-ef][2] \text{benzazépine-6-ol}\)
- Galantamina sustituyase el nombre químico por el siguiente:
  \((4a,5,6r,8aS)-4a,5,9,10,11,12\text{-hexahidro}-3\text{-metoxi}-11\text{-metil-6H-benzofuro}
  [3a,3,2-ef][2] \text{benzazepina-6-ol}\)
Proposed International Nonproprietary Names (Prop. INN): List 65

p. 15 \textit{galantaminum}  
galantamine \textit{replace the chemical name by the following:}  
\begin{align*}
& (4a,6R,8aS)-4a,5,9,10,11,12\text{-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef]}[2] \text{ benzazepin-6-ol}
\end{align*}

\textbf{Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 76}  
(\textit{WHO Drug Information, Vol. 10, No. 4, 1996})

p. 212 \textit{suprimase} \textit{insértase}  
\textit{omiloxetino} \textit{omiloxetina}

Proposed International Nonproprietary Names (Prop. INN): List 78  
Dénominations communes internationales proposées (DCI Prop.): Liste 78  
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 78  
(\textit{WHO Drug Information, Vol. 11, No. 4, 1997})

p. 268 \textit{bepotastinum}  
bepotastine \textit{replace the chemical name by the following:}  
\begin{align*}
& (+)-4-\left[\left(\mathcal{S}\right)-p\text{-chloro-\alpha\text{-2-pyridylbenzyl}\right]\text{oxy}\right]-1\text{-piperidinebutyric acid}
\end{align*}

\textit{bepotastina} \textit{sustituyase el nombre químico por el siguiente:}  
\begin{align*}
& \text{ácido (+)-4-}\left[\left(\mathcal{S}\right)-p\text{-cloro-\alpha\text{-2-piridilbenzil}\right]\text{oxi}\right]-1\text{-piperidinobutírico}
\end{align*}

p. 269 \textit{biricodarum}  
biricodar \textit{replace the CAS registry number by the following:}  
\begin{align*}
& \text{remplacer le numéro dans le registre du CAS par le suivant:}
\end{align*}

\textit{biricodar} \textit{sustituyase el número del registro del CAS por el siguiente:}  
159997-94-1

p. 274 \textit{fandofoxacinum}  
fandofoxacin \textit{replace the CAS registry number by the following:}  
\begin{align*}
& \text{remplacer le numéro dans le registre du CAS par le suivant:}
\end{align*}

fandofoxacine \textit{sustituyase el número del registro del CAS por el siguiente:}  
164150-99-6

p. 274 \textit{fasoracetatum}  
fasoracetam \textit{add the following molecular formula and CAS registry number:}  
\begin{align*}
& \text{insérer la formule brute et le numéro dans le registre du CAS suivants:}
\end{align*}

fasoracétam \textit{insértense la fórmula empírica y el número del registro del CAS:}  
\begin{align*}
& \text{C}_{10}\text{H}_{16}\text{N}_{2}\text{O}_{2} \quad 110958-19-5
\end{align*}
p. 275 fulvestrantum
fulvestrant
fulvestrant
fulvestrant

add the following CAS registry number:

insérer le numéro dans le registre du CAS suivant:

insértese el número del registro del CAS siguiente:

129453-61-9

p. 278 lotrafibanum
lotrafiban
lotrafiban
lotrafibán

replace the molecular formula by the following

remplacer la formule brute par la suivante:

sustituyase la fórmula empírica por la siguiente:

C_{23}H_{32}N_4O_4

p. 280 moxlubantum
moxilubant
moxilubant
moxilubant

replace the CAS registry number by the following:

remplacer le numéro dans le registre du CAS par le suivant:

sustituyase el número del registro del CAS por el siguiente:

146978-48-5
Annex 1

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

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

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

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

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

A. Such notice shall be given by publication in the Chronicle of the World Health Organization1 and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

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

B. Such notice shall:

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

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

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

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

A. Such objection shall:

   (i) identify the person objecting;

---


1 The title of this publication was changed to WHO Chronicle in January 1959. From 1987 onwards lists of INNs are published in WHO Drug Information
(ii) state his interest in the name;

(iii) set forth the reasons for his objection to the name proposed.

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

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

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:

A. request that it be recognized as the nonproprietary name for the substance; and

B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or trade-name.

Annex 2

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

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

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

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

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

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

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

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

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

* In its twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic "stem" indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed.
7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

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

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.\(^1\) Where a stem is shown without any hyphens it may be used anywhere in the name.

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>anti-inflammatory agents of the ibufenac group</td>
</tr>
<tr>
<td>-actidum</td>
<td>synthetic polypeptides with a corticotropin-like action</td>
</tr>
<tr>
<td>-adolum</td>
<td>analgetics</td>
</tr>
<tr>
<td>-adol</td>
<td>analgetics</td>
</tr>
<tr>
<td>-astum</td>
<td>antiasthmatic, antiallergic substances not acting primarily as antihistaminics</td>
</tr>
<tr>
<td>-astinum</td>
<td>antihistaminics</td>
</tr>
<tr>
<td>-azepamum</td>
<td>diazepam derivatives</td>
</tr>
<tr>
<td>-bactamum</td>
<td>β-lactamase inhibitors</td>
</tr>
<tr>
<td>bol</td>
<td>steroids, anabolic</td>
</tr>
<tr>
<td>-buzonum</td>
<td>anti-inflammatory analgesics, phenylbutazone derivatives</td>
</tr>
<tr>
<td>-cain-</td>
<td>antifibrillant substances with local anaesthetic activity</td>
</tr>
<tr>
<td>-cainum</td>
<td>local anaesthetics</td>
</tr>
<tr>
<td>-cef-</td>
<td>antibiotics, ceftalosporanic acid derivatives</td>
</tr>
<tr>
<td>-cilinum</td>
<td>antibiotics, derivatives of β-lactamacyllic acid</td>
</tr>
<tr>
<td>-conazolum</td>
<td>systemic antifungal agents, miconazole derivatives</td>
</tr>
<tr>
<td>cort</td>
<td>corticosteroids, except prednisolone derivatives</td>
</tr>
<tr>
<td>-dipinum</td>
<td>calcium channel blockers, nifedipine derivatives</td>
</tr>
<tr>
<td>-fibratum</td>
<td>clofibrate derivatives</td>
</tr>
<tr>
<td>gest</td>
<td>steroids, progestogens</td>
</tr>
<tr>
<td>-glu-</td>
<td>sulfonamide hypoglycaemics</td>
</tr>
<tr>
<td>-io-</td>
<td>iodine-containing contrast media</td>
</tr>
<tr>
<td>-ium</td>
<td>quaternary ammonium compounds</td>
</tr>
<tr>
<td>-metacinum</td>
<td>anti-inflammatory substances, indometacin derivatives</td>
</tr>
<tr>
<td>-mycinum</td>
<td>antibiotics, produced by <em>Streptomyces</em> strains</td>
</tr>
<tr>
<td>-nidazolum</td>
<td>antiprotozoal substances, metronidazole derivatives</td>
</tr>
<tr>
<td>-olol</td>
<td>β-adrenoreceptor antagonists</td>
</tr>
<tr>
<td>-oxacinum</td>
<td>antibacterial agents, nalidixic acid derivatives</td>
</tr>
<tr>
<td>-pridum</td>
<td>sulpiride derivatives</td>
</tr>
<tr>
<td>-pril(at)um</td>
<td>angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>-profenum</td>
<td>anti-inflammatory substances, ibuprofen derivatives</td>
</tr>
<tr>
<td>prost</td>
<td>prostaglandins</td>
</tr>
<tr>
<td>-relinum</td>
<td>hypophyseal hormone release-stimulating peptides</td>
</tr>
<tr>
<td>-terolum</td>
<td>bronchodilators, phentyleamine derivatives</td>
</tr>
<tr>
<td>-tidinum</td>
<td>histamine H(_2) receptor antagonists</td>
</tr>
<tr>
<td>-trexatum</td>
<td>folic acid antagonists</td>
</tr>
<tr>
<td>-verinum</td>
<td>spasmolytics with a papaverine-like action</td>
</tr>
<tr>
<td>vin-</td>
<td>vinca alkaloids</td>
</tr>
<tr>
<td>-vin-</td>
<td>vinca alkaloids</td>
</tr>
</tbody>
</table>

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

PROCEDURE À SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDÉES POUR LES SUBSTANCES PHARMACEUTIQUES

L'Organisation mondiale de la Santé observe la procédure exposée ci-dessous pour l'attribution de dénominations communes internationales recommandées pour les substances pharmaceutiques, conformément à la résolution WHA3.11 de l'Assemblée mondiale de la Santé:

1. Les propositions de dénominations communes internationales recommandées sont soumises à l'Organisation mondiale de la Santé sur la formule prévue à cet effet.

2. Ces propositions sont soumises par le Directeur général de l'Organisation mondiale de la Santé aux experts désignés à cette fin parmi les personnalités inscrites au Tableau d'experts de la Pharmacopée internationale et des Préparations pharmaceutiques; elles sont examinées par les experts conformément aux "Directives générales pour la formation des dénominations communes internationales", reproduites ci-après. La dénomination acceptée est la dénomination employée par la personne qui découvre ou qui, la première, fabrique et lance sur le marché une substance pharmaceutique, à moins que des raisons majeures n'obligent à s'écarter de cette règle.

3. Après l'examen prévu à l'article 2, le Directeur général de l'Organisation mondiale de la Santé notifie qu'un projet de dénomination commune internationale est à l'étude

A. Cette notification est faite par une insertion dans la Chronique de l'Organisation mondiale de la Santé et par l'envoi d'une lettre aux Etats Membres et aux commissions nationales de pharmacopée ou autres organismes désignés par les Etats Membres.

   (i) Notification peut également être faite à toute personne portant à la dénomination mise à l'étude un intérêt notoire.

B. Cette notification contient les indications suivantes.

   (i) dénomination mise à l'étude;
   (ii) nom de l'auteur de la proposition tendant à attribuer une dénomination à la substance, si cette personne le demande;
   (iii) définition de la substance dont la dénomination est mise à l'étude;
   (iv) délai pendant lequel seront reçus les observations et les objections à l'égard de cette dénomination; nom et adresse de la personne habilitée à recevoir ces observations et objections;
   (v) mention des pouvoirs en vertu desquels agit l'Organisation mondiale de la Santé et référence au présent règlement.

C. En envoyant cette notification, le Directeur général de l'Organisation mondiale de la Santé demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l'étude par l'Organisation mondiale de la Santé

4. Des observations sur la dénomination proposée peuvent être adressées à l'Organisation mondiale de la Santé par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans la Chronique de l'Organisation mondiale de la Santé (voir l'article 3).


1 Depuis janvier 1959, cette publication porte le titre de Chronique OMS. A partir de 1987, les listes des DCIs sont publiées dans les Informations pharmaceutiques OMS
5 Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans la Chronique de l'Organisation mondiale de la Santé (voir l'article 3).

A. Cette objection doit s'accompagner des indications suivantes:
   i) nom de l'auteur de l'objection;
   ii) intérêt qu'il porte à la dénomination en cause;
   iii) raisons motivant l'objection contre la dénomination proposée

6. Lorsqu'une objection formelle est formulée en vertu de l'article 5, l'Organisation mondiale de la Santé peut soit soumettre la dénomination proposée à un nouvel examen, soit intervenir pour tenter d'obtenir le retrait de l'objection. Sans préjudice de l'examen par elle d'une ou de plusieurs appellations de remplacement, l'Organisation mondiale de la Santé n'adopte pas d'appellation comme dénomination commune internationale recommandée tant qu'une objection formelle présentée conformément à l'article 5 n'est pas levée.

7. Lorsqu'il n'est formulé aucune objection en vertu de l'article 5 ou que toutes les objections présentées ont été levées, le Directeur général de l'Organisation mondiale de la Santé fait une notification conformément aux dispositions de la sous-section A de l'article 3, en indiquant que la dénomination a été choisie par l'Organisation mondiale de la Santé en tant que dénomination commune internationale recommandée.

8. En communiquant aux Etats Membres, conformément à l'article 7, une dénomination commune internationale recommandée, le Directeur général de l'Organisation mondiale de la Santé:
   A. demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée, et
   B. demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur cette dénomination, notamment en interdisant le dépôt de cette dénomination comme marque ou appellation commerciale.

Annexe 2

DIRECTIVES GENERALES POUR LA FORMATION DE DENOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES*

1. Les dénominations communes internationales (DCI) devront se distinguer les unes des autres par leur consonance et leur orthographe. Elles ne devront pas être d'une longueur excessive, ni prêter à confusion avec des appellations déjà couramment employées.

2. La DCI de chaque substance devra, si possible, indiquer sa parenté pharmacologique. Les dénominations sus-ceptibles d'évoquer pour les malades des considérations anatomiques, physiologiques, pathologiques ou thérapeutiques devront être évitées dans la mesure du possible.

Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants

* Dans son vingtième rapport (Série de Rapports techniques de l'OMS, No. 581, 1975), le Comité OMS d'experts des Dénominations communes pour les Substances pharmaceutiques a examiné les directives générales pour la formation des dénominations communes internationales et la procédure à suivre en vue de leur choix, compte tenu de l'évolution du secteur pharmaceutique au cours des dernières années. La modification la plus importante a été l'extension aux substances de synthèse de la pratique normalement suivie pour désigner les substances tirées ou dérivées de produits naturels. Cette pratique consiste à employer des syllabes communes ou groupes de syllabes communes (segments clés) qui sont caractéristiques et indiquent une propriété commune aux membres du groupe des substances pour lequel ces segments clés ont été retenus. Les raisons et les conséquences de cette modification ont fait l'objet de discussions approfondies.
3. Lorsqu’on formera la DCI de la première substance d’un nouveau groupe pharmacologique, on tiendra compte de la possibilité de former ultérieurement d’autres DCI appropriées pour les substances apparentées du même groupe.

4. Pour former des DCI des acides, on utilisera de préférence un seul mot. Leurs sels devront être désignés par un terme qui ne modifie pas le nom de l’acide d’origine; par exemple “oxacilline” et “oxacilline sodique”, “ibufénac” et “ibufénac sodique”.

5. Les DCI pour les substances utilisées sous forme de sels devront en général s’appliquer à la base active (ou à l’acide actif). Les dénominations pour différents sels ou esters d’une même substance active ne différeront que par le nom de l’acide inactif (ou de la base inactive).

En ce qui concerne les substances à base d’ammonium quaternaire, la dénomination s’appliquera de façon appropriée au cation et à l’anion en tenant compte des éléments distincts d’une substance quaternaire. On évitera de choisir une désignation évoquant un sel aminé.

6. On évitera d’ajouter une lettre ou un chiffre isolé; en outre, on renoncera de préférence à l’emploi d’un trait d’union.

7. Pour simplifier la traduction et la prononciation des DCI, la lettre “f” sera utilisée à la place de “ph”, “t” à la place de “th”, “e” à la place de “ae” ou “oe” et “f” à la place de “y”; l’usage des lettres “h” et “k” sera aussi évité.

8. On retiendra de préférence, pour autant qu’elles respectent les principes énoncés ici, les dénominations proposées par les personnes qui ont découvert ou qui, les premières, ont fabriqué et lancé sur le marché les préparations pharmaceutiques considérées, ou les dénominations déjà officiellement adoptées par un pays.

9. La parenté entre substances d’un même groupe (voir Directive générale 2) sera si possible indiquée dans les DCI par l’emploi de segments clés communs. La liste ci-après contient des exemples de segments clés pour des groupes de substances, surtout pour des groupes récents. Il y a beaucoup d’autres segments clés en utilisation active. ¹ Les segments clés indiqués sans trait d’union pourront être insérés n’importe où dans une dénomination.

<table>
<thead>
<tr>
<th>Latin</th>
<th>Français</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-ac substances anti-inflammatoires du groupe de l’ibufénac</td>
</tr>
<tr>
<td>-actidum</td>
<td>-actide polypeptides synthétiques agissant comme la corticotropine</td>
</tr>
<tr>
<td>-adalum</td>
<td>-adol analogiques</td>
</tr>
<tr>
<td>-adol-</td>
<td>-adol-</td>
</tr>
<tr>
<td>-astum</td>
<td>-ast antiasthmatiques, allergiques n’agissant pas principalement en tant qu’antihistaminiques</td>
</tr>
<tr>
<td>-astinum</td>
<td>-astine antihistaminiques</td>
</tr>
<tr>
<td>-azepamum</td>
<td>-azépam substances du groupe du diazépam</td>
</tr>
<tr>
<td>-bactamum</td>
<td>-bactame inhibiteurs de β-lactamasases</td>
</tr>
<tr>
<td>bol</td>
<td>bol stéroïdes anabolisants</td>
</tr>
<tr>
<td>-buzonum</td>
<td>-buzone analogiques anti-inflammatoires du groupe de la phénylbutazone</td>
</tr>
<tr>
<td>-cain-</td>
<td>-cain substances antifibrillantes à action anesthésique locale</td>
</tr>
<tr>
<td>-cainum</td>
<td>-caine anesthésiques locaux</td>
</tr>
<tr>
<td>-cef-</td>
<td>-céf antibiotiques, dérivés de l’acide céphalosporanique</td>
</tr>
<tr>
<td>-cillium</td>
<td>-ciline antibiotiques, dérivés de l’acide 6-aminopénicillanique</td>
</tr>
<tr>
<td>-conazolum</td>
<td>-conazole agents antifongiques systémiques du groupe du miconazole</td>
</tr>
<tr>
<td>cort</td>
<td>cort corticostéroïdes, autres que les dérivés de la prednisolone</td>
</tr>
<tr>
<td>-dipinum</td>
<td>-dipine inhibiteurs du calcium du groupe de la nifépine</td>
</tr>
<tr>
<td>-fibratum</td>
<td>-fibrate substances du groupe du clofibrate</td>
</tr>
<tr>
<td>gest</td>
<td>gest stéroïdes progestogènes</td>
</tr>
<tr>
<td>-gl-</td>
<td>-gi- sullamides hypoglycémiants</td>
</tr>
<tr>
<td>io-</td>
<td>io- produits de contraste iodés</td>
</tr>
<tr>
<td>-ium</td>
<td>-ium ammoniums quaternaires</td>
</tr>
<tr>
<td>-metacinum</td>
<td>-métacine substances anti-inflammatoires du groupe de l’indométacine</td>
</tr>
</tbody>
</table>

¹ Une liste plus complète de segments clés est contenue dans le document de travail Pharm S/Nom.15 qui est régulièrement mis à jour et qui peut être demandé auprès de l’Unité pharmaceutique, OMS, Genève.
Anexo 1

PROCEDIMIENTO DE SELECCION DE DENOMINACIONES COMUNES INTERNACIONALES RECOMENDADAS PARA LAS SUSTANCIAS FARMACEUTICAS

La Organización Mundial de la Salud seguirá el procedimiento que se expone a continuación para la selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11 de la Asamblea Mundial de la Salud:

1. Las propuestas de denominaciones comunes internacionales recomendadas se presentarán a la Organización Mundial de la Salud en los formularios que se proporcionen a estos efectos.

2. Estas propuestas serán sometidas por el Director General de la Organización Mundial de la Salud a los Miembros del Cuadro de Expertos de la Farmacopea Internacional y las Preparaciones Farmacéuticas encargados de su estudio, para que las examinen de conformidad con los "Principios Generales de Orientación para formar Denominaciones Comunes Internacionales para Sustancias Farmacéuticas", anexos a este Procedimiento. A menos que haya poderosas razones en contra, la denominación aceptada será la empleada por la persona que haya descubierto, fabricado o puesto a la venta por primera vez una sustancia farmacéutica.

3. Una vez terminado el estudio a que se refiere el artículo 2, el Director General de la Organización Mundial de la Salud notificará que está en estudio un proyecto de denominación internacional.

A. Esta notificación se hará mediante una publicación en la Crónica de la Organización Mundial de la Salud y el envío de una carta a los Estados Miembros y a las comisiones nacionales de las farmacopeas u otros organismos designados por los Estados Miembros.

(i) La notificación puede enviarse también a las personas que tengan un interés especial en una denominación objeto de estudio.

---

1 Denominada Crónica de la OMS desde enero de 1955. A partir de 1967, las listas de DCI se publican en Información Farmacéutica OMS.
B. En estas notificaciones se incluyen los siguientes datos:

(i) denominación sometida a estudio;

(ii) nombre de la persona que ha presentado la propuesta de denominación de la sustancia si lo pide esta persona;

(iii) definición de la sustancia cuya denominación está en estudio;

(iv) plazo fijado para recibir observaciones y objeciones, así como nombre y dirección de la persona a quien deban dirigirse, y

(v) mención de los poderes conferidos para el caso a la Organización Mundial de la Salud y referencia al presente procedimiento

C. Al enviar esta notificación, el Director General de la Organización Mundial de la Salud solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación propuesta, durante el período en que la Organización Mundial de la Salud tenga en estudio esta denominación.

4. Toda persona puede formular a la Organización Mundial de la Salud observaciones sobre la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la Crónica de la Organización Mundial de la Salud, conforme a lo dispuesto en el artículo 3.

5. Toda persona interesada puede presentar una objeción formal contra la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la Crónica de la Organización Mundial de la Salud, conforme a lo dispuesto en el artículo 3.

A. Esta objeción deberá acompañarse de los siguientes datos:

i) nombre de la persona que formula la objeción,

ii) causas que motivan su interés por la denominación, y

iii) causas que motivan su objeción a la denominación propuesta.

6. Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la Organización Mundial de la Salud puede someter a nuevo estudio la denominación propuesta, o bien utilizar sus buenos oficios para lograr que se retire la objeción. Sin perjuicio de que la Organización Mundial de la Salud estudie una o varias denominaciones en sustitución de la primitiva, ninguna denominación podrá ser seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada en tanto que exista una objeción formal, presentada como previene el artículo 5, que no haya sido retirada.

7. Cuando no se haya formulado ninguna objeción en la forma prevista en el artículo 5, o cuando todas las objeciones presentadas hayan sido retiradas, el Director de la Organización Mundial de la Salud notificará, conforme a lo dispuesto en el párrafo A del artículo 3, que la denominación ha sido seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada.

8. Al comunicar a los Estados Miembros una denominación común internacional conforme a lo previsto en el artículo 7, el Director General de la Organización Mundial de la Salud:

A. solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate, y

B. solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación, incluso la prohibición de registrarla como marca de fábrica o como nombre comercial.
Anexo 2

PRINCIPIOS GENERALES DE ORIENTACIÓN PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACEUTICAS*

1. Las Denominaciones Comunes Internacionales (DCI) deberán diferenciarse tanto fonéticamente como ortográficamente. No deberán ser incomodamente largas, ni dar lugar a confusión con denominaciones de uso común.

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse los nombres que puedan inducir fácilmente en el paciente sugestiones anatómicas, fisiológicas, patológicas o terapéuticas.

Estos principios primarios deberán ser tenidos en cuenta al aplicar los siguientes principios secundarios:

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de formar DCI convenientes para las sustancias emparentadas que vengan a incrementar el nuevo grupo.

4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre de ácido; p. ej., "oxacilina" y "oxacilina sódica", "ibufenaco" e "ibufenaco sódico".

5. Las DCI para las sustancias que se usan en forma de sal, deberán en general aplicarse a la base activa o, respectivamente, al ácido activo. Las denominaciones para diferentes sales o ésteres de la misma sustancia activa solamente deberán diferir en el nombre de ácido o de la base inactivas.

En los compuestos de amonio cuaternario, el catión y el anión deberán denominarse adecuadamente por separado, como componentes independientes de una sustancia cuaternaria y no como sales de una amina.

6. Deberá evitarse el empleo de una letra o un número aislados; también es indeseable el empleo de guiones.

7. Para facilitar la traducción y la pronunciación se emplearán de preferencia las letras "f" en lugar de "ph", "t" en lugar de "th", "e" en lugar de "ae" u "oe" e "i" en lugar de "y"; se deberá evitar el empleo de las letras "h" y "k".

8. Siempre que las denominaciones que se sugieran estén de acuerdo con estos principios, recibirán una consideración preferente las denominaciones propuestas por la persona que haya descubierto la sustancia, o la que primeramente fabrique o ponga a la venta la sustancia farmacéutica, así como las denominaciones oficialmente adoptadas en cualquier país.

9. En las DCI, la relación de grupo o parentesco (véanse los Principios Generales de Orientación, apartado 2) se indicará en lo posible utilizando una partícula común. En la lista siguiente se dan algunos ejemplos de estas partículas en relación con diversos grupos de sustancias, en particular los de nuevo cuño. Hay otras muchas partículas comunes en uso. Cuando la partícula no lleva ningún guión, cabe utilizarla en cualquier parte de la denominación.

* En su 20° Informe (OMS, Sede de Informes Técnicos, No. 581, 1975) el Comité de Expertos de la OMS en Denominaciones Comunes para Sustancias Farmacéuticas examina los principios generales de orientación para formar denominaciones comunes internacionales (DCI) y el procedimiento de selección de las mismas, teniendo en cuenta las novedades registradas en los últimos años en materia de preparaciones farmacéuticas. Entre las modificaciones, la más importante ha sido la extensión a las sustancias químicas sintéticas de la práctica reservada anteriormente para designar sustancias originarias o derivadas de productos naturales. Esta práctica consiste en emplear una partícula característica que indique una propiedad común a los miembros de un determinado grupo de sustancias. En el informe se examinan a fondo las razones de esta modificación y sus consecuencias.

1 El documento de trabajo Pharm S/Norm S, que se pone al día regularmente, contiene una lista más extensa de partículas comunes. Las personas que deseen recibirlo deberán solicitar su envío al Servicio de Preparaciones Farmacéuticas, OMS, Ginebra (Suiza).
<table>
<thead>
<tr>
<th>Latin</th>
<th>Español</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-aco antinflamatorios del grupo del ibufenaco</td>
</tr>
<tr>
<td>-actidum</td>
<td>-actida polipéptidos sintéticos de acción semejante a la corticotropina</td>
</tr>
<tr>
<td>-adol</td>
<td>-adol analgésicos</td>
</tr>
<tr>
<td>-adol</td>
<td>-adol analgésicos</td>
</tr>
<tr>
<td>-astum</td>
<td>-ast antiinflamatorios y antialérgicos que no actúan principalmente como antihistamínicos</td>
</tr>
<tr>
<td>-astinum</td>
<td>-astina antihistamínicos</td>
</tr>
<tr>
<td>-azepamum</td>
<td>-azepam sustancias del grupo del diazepam</td>
</tr>
<tr>
<td>-bactamum</td>
<td>-bactam inhibidores de β-lactamasas</td>
</tr>
<tr>
<td>bol</td>
<td>bol esteroides anabólicos</td>
</tr>
<tr>
<td>-buzonum</td>
<td>-buzona analgésicos antiinflamatorios del grupo de la fenilbutazona</td>
</tr>
<tr>
<td>-cain-</td>
<td>-cain- antifibrilantes con actividad anestésica local</td>
</tr>
<tr>
<td>-cainum</td>
<td>-caina anestésicos locales</td>
</tr>
<tr>
<td>cef-</td>
<td>cef- antibióticos derivados del ácido cefalosporánico</td>
</tr>
<tr>
<td>-conazolum</td>
<td>-conazol antifúngicos sistémicos del grupo del miconazol</td>
</tr>
<tr>
<td>cort</td>
<td>cort corticosteroides, excepto los del grupo de la prednisolona</td>
</tr>
<tr>
<td>-dipinum</td>
<td>-dipino antagonistas del calcio del grupo del nifedipino</td>
</tr>
<tr>
<td>-fibratum</td>
<td>-fibrato sustancias del grupo del clofibrato</td>
</tr>
<tr>
<td>gest</td>
<td>gest esteroides progestágenos</td>
</tr>
<tr>
<td>gli-</td>
<td>gli- sulfonamidas hipoglucemiantes</td>
</tr>
<tr>
<td>io-</td>
<td>io- medios de contraste que contienen yodo</td>
</tr>
<tr>
<td>-ium</td>
<td>-io compuestos de amonio cuaternario</td>
</tr>
<tr>
<td>-metacinum</td>
<td>-metacina antinflamatorios del grupo de la indometacina</td>
</tr>
<tr>
<td>-mycinum</td>
<td>-micina antibióticos, producidos por cepas de Streptomyces</td>
</tr>
<tr>
<td>-nidazolum</td>
<td>-nidazol antiprototozarios del grupo del metronidazol</td>
</tr>
<tr>
<td>-ololum</td>
<td>-olol bloqueadores β-adrenérgicos</td>
</tr>
<tr>
<td>-oxacinum</td>
<td>-oxacino antibacterianos del grupo del ácido nalidíxico</td>
</tr>
<tr>
<td>-pridum</td>
<td>-prida sustancias del grupo de la sulpirida</td>
</tr>
<tr>
<td>-pril(at)um</td>
<td>-pril(at) inhibidores de la enzima transformadora de la angiotensina</td>
</tr>
<tr>
<td>-profenum</td>
<td>-profero antinflamatorios del grupo del ibuprofeno</td>
</tr>
<tr>
<td>prost</td>
<td>prost prostaglandinas</td>
</tr>
<tr>
<td>-relinum</td>
<td>-reлина péptidos estimulantes de la liberación de hormonas hipofisarias</td>
</tr>
<tr>
<td>-terolum</td>
<td>-terol broncodilatadores derivados de la fenetilamina</td>
</tr>
<tr>
<td>-tidinum</td>
<td>-tidina antagonistas del receptor H₂ de la histamina</td>
</tr>
<tr>
<td>-trexatum</td>
<td>-trexato antagonistas del ácido fólico</td>
</tr>
<tr>
<td>-verinum</td>
<td>-verina espasmolíticos de acción semejante a la de la papaverina</td>
</tr>
<tr>
<td>vin-</td>
<td>vin- alcaloides de la vinca</td>
</tr>
<tr>
<td>-vin-</td>
<td>-vin-</td>
</tr>
</tbody>
</table>