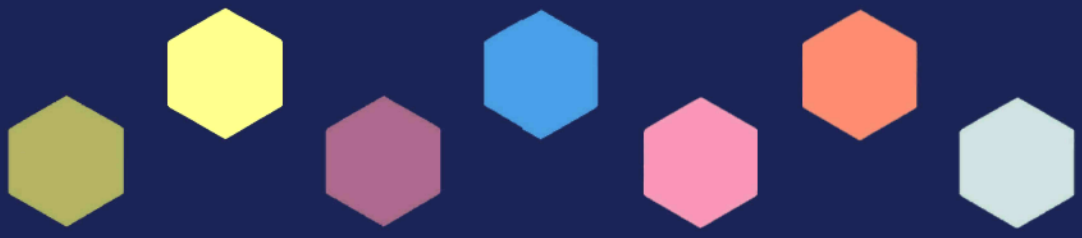
WHO DRUG INFORMATION

VOLUME 13 · NUMBER 1 · 1999

RECOMMENDED INN LIST 41

INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES



WORLD HEALTH ORGANIZATION · GENEVA

General Policy Issues

WHO roundtable with industry

On 21 October 1998, Dr Gro Harlem Brundtland, the newly elected Director-General of WHO, met with key figures of the research-based pharmaceutical industry to explore ways in which access to affordable, innovative and essential drugs can be improved. The roundtable was attended by members of major pharmaceutical companies which included American Home Products, Glaxo Wellcome, Novartis, Pasteur-Mérieux-Connaught and SmithKline Beecham, together with representatives of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The meeting offered an opportunity for both sides to address issues of public health concern and to determine common ground. WHO's goal is to build a constructive dialogue with the private sector, and harness support to improve access to drugs and vaccines for populations in need.

Global partnerships for health

Gro Harlem Brundtland
Director-General
World Health Organization

A roundtable, as we intend to apply the word in WHO, is not a single event but a method of work. It derives from our commitment to meet with broad constituencies involved in public health at the global level and address key issues relevant to the fulfilment of our mandate in combating ill-health and building healthy populations.

I have invited representatives of the research-based pharmaceutical industry to a roundtable because I believe that we have a common aim in health. I am convinced that we can collaborate effectively if we deal with our differences and address them directly and openly as we did in the meeting on the Revised Drug Strategy held earlier in October*. Then, after an initial breakdown in communication, Members States reached a consensus on important issues which are also of concern to the pharmaceutical industry. How did this come about? Because of broader access to information, more time to listen, and a greater commitment to build bridges.

Let me underline where WHO stands: we are committed to national drug policies and the concept of essential drugs and vaccines. The Action Programme on Essential Drugs has been our main instrument in helping governments implement these concepts. When the action programme was established in 1975, very few countries had adopted national drug policies. The developing countries were faced with serious problems of availability, cost, quality, and rational use of drugs. Today, nearly 90 countries have national drug policies in place or in preparation. The WHO Model List of Essential Drugs has been widely adapted by national authorities and three out of every four countries in the world now have an essential drugs list.

WHO plays a key supporting role by helping countries to assess their needs, identify problems and find solutions. WHO sets norms, standards and regulations for implementation by regulatory authorities, while quality assurance of pharmaceuticals is an overriding concern. Nowhere is the responsibility or challenge greater. Of course, operational research is a core function and so is safety monitoring. The two are closely linked. WHO works with partners around the world to monitor the use of drugs — not only to sound the alarm when faced with emergencies and outbreaks but to share the good news when progress has been made against a major disease.

WHO's global vaccination programme has achieved an immunization rate of 80% for all children in the

* Meeting of the ad hoc Working Group on the Revised Drug Strategy convened by WHO from 13 to 16 October 1998. *WHO Drug Information*, **12**(4): 209 (1998).

world. This is a success both from an industry and a public health perspective. However, we need to move on with new vaccine research and development and WHO is actively engaged with the World Bank, UNICEF, leading foundations and industry to pave the way to new breakthroughs in vaccine development and delivery. This kind of joint project has also been established in other areas. For example, the Medicines for Malaria Venture has recently been set up and will be incorporated into the Roll Back Malaria initiative. I hope that WHO and the pharmaceutical industry can work together to strengthen this particular component.

Still much remains to be done. One-third of the world's population lacks access to essential drugs. Those concerned with public health or equity will agree that this is truly unacceptable. Despite the large sums spent on research and development, less than 1% is directed to providing treatment for those diseases that strike developing countries. Frankly, this does not make sense. The price of drugs — especially for the newer products — puts them out of reach in the majority of developing countries. We must work together to ensure development of new drugs for major public health threats. The challenge is there. But we must also create an infrastructure to ensure that drugs for killer diseases like tuberculosis and malaria are provided to those in need.

Emerging diseases, growing drug resistance, global economic instability and uncertainty about the public health impact of new trade agreements are all relevant key issues. WHO will be present in all of these arenas. Health is an integral part of our way of life, how our world evolves, how human resources are nurtured, how trade expands and economies grow, and how environments perish or survive. The pharmaceutical industry has the responsibility for developing, producing and selling pharmaceutical products — drugs and vaccines. WHO has the responsibility for helping countries acquire access to essential drugs. The pharmaceutical industry is in the business of making a profit. But we are in the business of seeing to it that the most vulnerable — who have little or no purchasing power — are allowed equitable access to medicines.

WHO sees great potential in this roundtable as a first step in a serious attempt to build a sustainable mechanism and provide affordable, essential drugs of quality to the needy. We look forward to forging a strong, durable and committed partnership with those having a common purpose in health.

Public health and the pharmaceutical industry

Richard B. Sykes, President, International Federation of Pharmaceutical Manufacturers Associations and Chairman, Glaxo Wellcome, United Kingdom

The research-based pharmaceutical industry and the World Health Organization share a common goal of fighting disease and improving health. With this essential unity of purpose, it seems clear that we should be working closely together wherever it is feasible to do so. I am confident that the discussions which have taken place during this WHO roundtable will be a first step towards a closer partnership based on dialogue and mutual understanding.

We all agree that medicines have made a tremendous contribution to the improvement of health care during the 20th century, and particularly during the 50 years that WHO has existed. Of course, much effort still needs to be concentrated on ensuring that the benefits of modern medicine are made available to all in need. The pharmaceutical industry will play its part in helping to achieve this goal. However, our primary focus is and will continue to be the scientific and technological research needed to produce new medicines to respond to health problems that have so far eluded treatment.

As we go forward into the 21st century, we have every reason to be confident that the medical progress witnessed so far will continue and accelerate. Prospecting for new medicines has entered an era of unprecedented opportunity and offers new insights into areas unimagined until now. Within the industry, much is being done to ensure that we harness this new science and technology and deliver medicines of real value.

The contribution of genetics

Genetics is a vital newcomer to the drug discovery process and helps explain many things that we have observed in practice. The study of genetics offers an entirely new approach by identifying factors that influence an individual's susceptibility to a certain disease. This new knowledge derives from the international human genome project devoted to sequencing the three billion DNA bases in humans.

This tremendous effort will bring about significant improvements in the provision and practice of health care. Intransigent health problems such as

asthma and heart disease, which are increasing at an alarming rate throughout the world, will be understood. Genetic testing will enable individual patients to be targeted for specific treatment to maximize efficacy and minimize side-effects. In other words, drugs can be tailored to people for maximum response.

Effective prevention

In the future, the use of genetics will allow us to screen for susceptibility and we will be able to identify which individuals will develop diseases long before the symptoms appear. This genetic information can then be combined with known conventional risk factors. Although in many cases these benefits can only be provided within a sophisticated medical infrastructure, this new understanding of genetics will prove of great potential value in the fight against diseases of the developing world.

For example, the complete *Mycobacterium tuberculosis* genome sequence has now been published, and the sequence of every potential drug target and antigen is now available. Sequencing of the *Plasmodium falciparum* genome will be of great significance in paving the way for the development of a DNA vaccine against malaria. What, then, needs to be done to ensure that the tremendous potential for the development of new and better medicines is actually realized and that people throughout the world will benefit from them?

The realities of research and development

From an industry perspective, effective protection of intellectual property is essential if billions of dollars are to be invested each year in the research and development of new medicines. Currently used techniques are vastly more efficient and productive than ever before, but the technology that underpins these is very expensive. By contrast, copying and manufacturing medicines are very cheap. Unless companies are assured of intellectual property protection during the limited period conferred by patents, they simply will not be able to find the funds to pay for future research and development. The industry is pleased that progress was made in this regard during the meeting of the ad hoc Working Group on the Revised Drug Strategy convened by WHO from 13 to 16 October 1998*.

There is growing recognition that special measures are needed to encourage research and development for diseases such as malaria and tuberculosis. The involvement of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) in the new WHO Medicines for Malaria Venture demonstrates industry's willingness to find new ways forward. Similarly, legislation has successfully been introduced in the United States to provide incentives to companies developing orphan drugs and the European Union is now setting up a similar system. Regulatory authorities and WHO may wish to explore such an approach for tropical diseases since this would harness the industry's skills and resources for new drug development in an important area.

With regard to the problem of ensuring access to patented medicines, we need to look at ways to encourage companies to offer prices which reflect the economic reality of individual countries. This could be done by offering prices which are lower in developing countries than in more affluent parts of the world. However, if customers in the better-off countries were to import the lower priced medicines, industry would be unable to bear the burden. Parallel trading has understandable attractions for health care providers faced with tight budgets, but its long-term consequences can only be damaging.

Adequate funding is a key precondition for successful public health management and for the continuing supply of new medicines. Equally, there has to be a clear recognition from health care providers that the price paid for medicines will ultimately affect the funds available for further research and development. The pharmaceutical industry cannot be expected to take sole responsibility for ensuring that the least well-off have access to their medicines. This is a vital role for multilateral agencies who must work in close partnership with us. The UNAIDS HIV Drug Access Initiative and the new Medicines for Malaria Venture offer examples of potential opportunities for this kind of partnership.

These are exciting times for the research-based pharmaceutical industry. It is our desire to share our achievements through true partnerships — particularly with WHO — and to ensure that the benefits of modern science and technology are truly available to all peoples of the world.

* See *WHO Drug Information*, **12**(4): 209 (1998).

Personal Perspectives

International harmonization of safety information: a CIOMS initiative

Jens S. Schou
Faculty of Health Sciences
Copenhagen, Denmark and
member of CIOMS Working Group

The Council for International Organizations of Medical Sciences (CIOMS) was constituted in Brussels in 1949 as a nongovernmental organization under an agreement between UNESCO and WHO to facilitate the coordination of the planning and timing of international medical congresses, and with a mandate to collaborate with its two founding organizations and other United Nations agencies. However, it soon became clear that CIOMS also provided an ideal forum for joint projects in the complementary fields of medicine, the social and life sciences, philosophy, ethics and law.

One important project which has developed over the years is a joint CIOMS–WHO programme on the medical, social and economic implications of drug development and use. As an independent organization, CIOMS is well placed to bring together experts from the research-based pharmaceutical industry, national regulatory control agencies and academia to discuss issues of immediate concern.

Many achievements of public health importance have resulted from this joint venture. In particular, attention has been focused on the harmonization of drug safety monitoring and, specifically, terminology. As the use of drugs becomes more globalized, national regulatory agencies demand increasing amounts of foreign and domestic data before they will authorize marketing in their country. This can cause a considerable burden to manufacturers and the time taken to comply with different country procedures holds up the availability of new medicines. The introduction of uniform procedures is thus considered beneficial to regulators, manufacturers and patients alike.

In an effort to address this and similar issues concerning international harmonization, CIOMS working groups on drug safety have been constituted, and are made up of specialist representatives of drug regulatory authorities, academia and the pharmaceutical industry. The system of compact, focused working groups has been very productive, and has also been adopted for use within the International Conference on Harmonization (ICH) process. Furthermore, many of the initiatives proposed by the CIOMS working groups have gone on to be incorporated into ICH guidelines. It is the hope of members of the working groups that their proposals for the international harmonization of drug safety information will be accepted throughout the world.

Model form for suspect adverse reactions

In 1985, an overall plan to improve the monitoring and assessment of adverse drug reactions was mapped out and working group I was set up to study how the international reporting of post-marketing adverse drug reactions could be improved (1). With the collaboration of five regulatory authorities and six pharmaceutical manufacturers, a pilot international reporting system was successfully implemented. As a result, the Model Form for Suspect Adverse Reactions was published in 1987 (2).

International reporting of adverse drug reactions: terminology

Work continued on promoting the application of CIOMS recommendations and the reporting form, and on devising a standard reporting language. Internationally-agreed terms were needed to determine the severity of adverse drug reactions and harmonize postmarketing surveillance reporting. Additionally, many countries required manufacturers to report adverse drug reactions to their regulatory authority. A standardized process of reporting using the model form accompanied by a set of definitions, procedures and methods was devised (3). These methods were tested by seven multinational pharmaceutical companies with 40 affiliated branches in six countries. The rapid collection and transmission of safety information is vital to the safe and proper use of medicines and the project also demonstrated the feasibility and utility of reporting adverse drug reactions occurring anywhere in the world.

Periodic drug safety update summary
In 1989, working group II was established to harmonize reporting of periodic drug safety updates. A safety update provides a review of information accumulated from various sources since the previous report. The usefulness of this project was particularly appropriate, since the USA was the only country at that time to formally require submission of a drug safety update summary prior to filing for a marketing application. In order for safety information to be harmonized, a CIOMS pilot study was carried out to assess the feasibility and utility of a single periodic drug safety update summary containing both foreign and domestic reports (4). After much work and refinement, the final proposal was published in 1992. The periodic safety update report has been extensively implemented, and many of the recommendations proposed by CIOMS have now been incorporated into European Union legislation.

Core data sheet
In order to ensure availability of a central reference manufacturers document, the concept of the core data sheet was pursued by CIOMS. This is a document prepared by the pharmaceutical manufacturer and contains critical information which the manufacturer will include in the labelling or package insert of a medicinal product (5). In devising the Core Data Sheet, the working group took into consideration regulatory requirements of the Summary of Product Characteristics (SPC) of the European Union and the FDA's General Requirements on Content and Format of Labelling for Human Prescription Drugs and Specific Requirements on Content and Format for Human Prescription Drugs.

Core safety information is not meant to be static: the initial information will undergo changes as new knowledge becomes available. The actual moment when new information is to be incorporated into the core data sheet is determined by a "threshold". During discussion of threshold requirements, the CIOMS working group identified a new and important area for future work: how to evaluate the benefit/risk ratio for a marketed medicinal product when a significant new safety signal is identified.

Benefit-risk evaluation report
Discussions were held at great length on this topic and examined the theoretical and practical aspects of reassessment and how a potentially major, new safety signal impacts upon the relationship between benefit and risk, bearing in mind how a standard report should describe this. The working group reviewed a number of case histories to evaluate how major safety concerns had been handled in the past. As a result, the CIOMS Working Group IV report (6) sets out the standard format and content of a benefit-risk evaluation report with details of implementation and a detailed discussion of topics, including decision making, benefit/risk metrics, and the value and limitations of information reporting. A discussion of terminology and a definition of terms are also provided.

A key element to the consistent success of this important long-term venture has been the dedication of working group members and the CIOMS secretariat, and their recognition of the global importance of the task. Another contributing factor has been the focused scope of working group activities and the neutral platform provided by CIOMS.

References:

1. Council for International Organizations of Medical Sciences. Monitoring and assessment of adverse drug effects. CIOMS Working Group Report. CIOMS, Geneva, 1986.

2. Council for International Organizations of Medical Sciences. International reporting of adverse drug reactions. CIOMS Working Group Report. CIOMS, Geneva, 1987.

3. Council for International Organizations of Medical Sciences. International reporting of adverse drug reactions. CIOMS Working Group Report. CIOMS, Geneva, 1990.

4. Council for International Organizations of Medical Sciences. International reporting of periodic drug-safety update summaries. CIOMS Working Group II Report. CIOMS, Geneva, 1992.

5. Council for International Organizations of Medical Sciences. Guidelines for preparing core clinical safety information on drugs. CIOMS Working Group III Report. CIOMS, Geneva, 1995.

6. Council for International Organizations of Medical Sciences. Benefit-risk balance for marketed drugs: evaluating safety signals. CIOMS Working Group IV Report. CIOMS, Geneva, 1998.

Reports on Individual Drugs

Short-course zidovudine in perinatal HIV transmission

In 1994, a reduction of 67.5% in the relative risk of mother-to-child transmission of HIV was demonstrated in newborn infants treated before, during and after birth with zidovudine. (1). Further data from a recent trial in Thailand suggest that an abbreviated regimen of oral zidovudine from 36 weeks of gestation until delivery, with no neonatal component, can reduce the relative risk of transmission by approximately 50% (2). Although the decrease was significant, it was understandably lower than the reduction in the relative risk of perinatal transmission reported in the 1994 study.

The results of a new study undertaken in the USA suggests that more abbreviated zidovudine prophylaxis can reduce the rates of perinatal transmission of HIV even further (3). The timing and response of zidovudine therapy was analysed in 939 HIV exposed infants below 180 days of age. When treatment was begun in the prenatal period, the rate of HIV transmission was 6.1%. However, when zidovudine was begun intrapartum the rate was 10%; begun within the first 48 hours of life 9.3%; and on day 3 of life or later 18.4%. In the absence of zidovudine prophylaxis, the rate of HIV transmission is 26.6.%. These results confirm the efficacy of zidovudine prophylaxis and suggest that reductions in the rates of perinatal transmission of HIV can be achieved even with the use of abbreviated regimens that begin during labour or the first 48 hours of life.

These findings require further confirmation but, even without confirmation, the study offers hope that HIV infection can be prevented after exposure. It also indicates that HIV-infected women who do not receive zidovudine during pregnancy should be identified so that they can receive antiretrovirals during delivery and their infants can begin receiving zidovudine at birth. This study demonstrates that an inexpensive preventive regimen (4) is available for routine use in many parts of the world, including those areas where HIV prevalence is high but resources are severely limited (5).

References

1. Connor, E.M., Sperling, R.S., Gelber, R. et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine*, **331**: 1173–1180 (1994).

2. Centers for Disease Control and Prevention. Administration of zidovudine during late pregnancy to prevent perinatal HIV transmission — Thailand 1996–1998. *Morbidity and Mortality Weekly Report*, **47**: 151–153 (1998).

3. Wade, N.A., Birkhead, G.S., Warren, B.L. et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *New England Journal of Medicine,* **339**: 1409–1414 (1998).

4. McIntosh, K. Short (and shorter) courses of zidovudine. *New England Journal of Medicine*, **339**: 1467–1468 (1998).

5. World Health Organization. Recommendations on the safe and effective use of short-course ZDV for prevention of mother-to-child transmission of HIV. *Weekly Epidemiological Record*, **73**: 313-320 (1998).

Vitamin D supplements in adults

Vitamin D is an essential precursor of 1,25-dihydroxyvitamin D, the steroid hormone necessary not only for bone development and growth in children but maintenance of bone in adults. In particular, vitamin D deficiency is a risk factor for bone loss in osteoporosis and fracture. Correction of an even slightly low concentration of serum 25-hydroxyvitamin D with vitamin D and calcium substantially reduces the risk of osteoporosis fractures and hip fractures (1, 2). The prevalence of hypovitaminosis D in residents of retirement and nursing homes and people over the age of 65 is between 25 and 54%, but can be as high as 79% (3, 4).

A recent study of 152 male and 138 female hospitalized patients with a mean age of 62 years (range 18 to 95 years) had measured low serum 25-hydroxy-vitamin D at 57% (3). In 22%, hypovitaminosis D was severe. Patients hospitalized in March had more hypovitaminosis than those hospitalized in September. The patients in this study were younger than those in many previous studies and

only a minority were housebound or residents of a nursing home. Thus the patients may have been more representative of the general population.

Hypovitaminosis D is associated with conditions such as poor dietary intake, inadequate sun exposure, chronic liver and renal diseases, malabsorption, and therapy with drugs that impair vitamin D activation or accelerate its clearance such as glucocorticoids, phenytoin, carbamazepine and rifampicin.

Increased calcium intake by older people has an important role in prevention of osteoporosis but it is apparent that attention should also be focused on the need for increased intake of vitamin D (4). Vitamin D stimulates calcium absorption, thereby increasing the benefit of supplemental calcium. It also slows bone resorption and increases bone formation.

It is evident that more widespread screening for vitamin D deficiency is required especially in elderly people, and more frequent routine vitamin D supplementation should be considered. An increase in vitamin D intake is likely to have a greater effect on osteoporosis and fractures than many other interventions (4).

References

1. Chapuy, M.C., Arlot, M.E., Duboeuf, F. et al. Vitamin D and calcium to prevent hip fracture in elderly women. *New England Journal of Medicine*, **327**: 1637–1642 (1992).

2. Chapuy, M.C., Arlot, M.E., Delmas, P.D. et al. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *British Medical Journal*, **308**: 1081–1082 (1994).

3. Thomas, M.K., Lloyd-Jones, D.M., Thadhani, R.I. et al. Hypovitaminosis D in medical inpatients. *New England Journal of Medicine*, **338**: 777–783 (1998)

4. Utiger, R.D. The need for more vitamin D. *New England Journal of Medicine*, **338**: 828–829 (1998).

Tacrine and Alzheimer disease

The present ageing of the world's population will lead to an increase in cases of elderly dementia, of which Alzheimer disease is a common form. The possibilities for prevention of Alzheimer are limited by the major determinants — age and genetic makeup — which cannot be modified. As a result, treatment has thus far been directed to the symptomatic relief of the disease.

Although an effective treatment for Alzheimer disease has yet to be marketed, potent acetylcholinesterase inhibitors have been the dominant therapeutic strategy. Tacrine hydrochloride was the first in the generation of cholinesterase inhibitors to be widely marketed for impaired memory and reasoning ability of patients with Alzheimer disease. Several other drugs, such as donepezil, rivastigmine and metrifonate, have a similar mechanism of action.

Using the Cochrane Dementia Group registry of clinical trials, the Dementia Trialists Collaboration Group has now carried out a meta analysis of tacrine in patients with Alzheimer disease (1). The aim was to determine the effects of tacrine on symptoms in terms of cognitive performance, clinical global impression of change, behaviour and functional autonomy. The study analysed 12 randomized, double-blind, placebo controlled trials totalling 1984 patients. All patients enrolled in the trials had been diagnosed as having "probable" Alzheimer disease according to commonly accepted criteria (2). Duration of treatment varied from 3 and 36 weeks.

Cholinesterase inhibition with tacrine appears to reduce deterioration in cognitive performance during the first 3 months of treatment and an increase in the odds of overall clinical improvement. However, as measured by behavioural disturbances, the beneficial effects were of questionable clinical significance and functional autonomy was not significantly affected. Early withdrawal from studies was much higher for patients receiving tacrine compared with placebo and elevated transaminase levels were cited as the main reason for this in the two largest trials.

The benefits of cholinesterase inhibition remain controversial, and long-term trials with clinically relevant end points are required. Only 2 of the 12 trials had assessments beyond 12 weeks and it was therefore not possible to make reliable estimates of the long-term effects of tacrine. Neither was it possible to assess whether beneficial effects are obtained from continuous therapy, how long they endure, or when it is best to withdraw treatment. Efforts should thus continue to define the types of patients and the circumstances in which the newer cholinesterase inhibitors may be beneficial.

References

1. Qizibash, N., Whitehead, A. Higgins, J. et al. Cholinesterase inhibition for Alzheimer disease. *Journal of the American Medical Association*, **280**: 1777–1782 (1998).

2. McKanna, G. Drachman, D. Folstein, M. et al. Clinical diagnosis of Alzheimer disease: report of the NINCDS-ADRDA Working Group. *Neurology*, **4**: 939–944 (1984).

Anti-ulcer drugs may mask early gastric cancer

Dyspepsia, typically presenting as heartburn or gastrointestinal discomfort, is responsible for about 2–5% of patient visits to general health care physicians. In over 50% of cases, no firm diagnosis is possible because symptoms are of an uncertain origin. However, a significant proportion of patients with early gastric cancer experience symptoms typical of dyspepsia.

Following the availability of H_2 receptor antagonists such as cimetidine, famotidine, nizatidine and ranitidine to treat gastric ulcer, it became evident that their use may mask symptoms of cancer and delay diagnosis and appropriate treatment (1). Furthermore, the recently introduced and more powerful proton pump inhibitors such as omeprazole, lansoprazole, and pantoprazole produce significantly more rapid symptom control and healing of benign gastric ulcer.

It would appear that the action of these drugs mask symptoms of gastric cancer to such an extent that endoscopic diagnosis is difficult, thereby altering the prognosis from probable to incurable disease (2–4). In some cases, ulcerated lesions which were visible at an initial gastroscopy are virtually undetectable less than four-weeks later after treatment with a proton pump inhibitor (5). Patients with missed early cancers may alternatively be labelled as having non-ulcer dyspepsia and receive repeated courses of antisecretory drugs which will act to delay diagnosis even further (4, 5).

Antisecretory drugs, including H_2 receptor antagonists, are available in lower doses without prescription. At present, no studies are available to show whether these low-dose drugs are also able to heal the mucosal lesions associated with early gastric cancer.

In conclusion, it is recommended that dyspeptic patients over 45 years of age should undergo endoscopy before any antisecretory ulcer drugs are started (5). Inappropriate use and prescription of anti-ulcer drugs may delay or even prevent diagnosis of early gastric ulcer in two ways. The rapid control of dyspepsia may lead the patient or general practitioner to underestimate the importance of the symptoms and referral for endoscopy will be delayed or even deferred. If the patient should later undergo a gastroscopy, the prior treatment with antisecretory drugs could also mask signs. It remains to be seen whether the increased availability of these drugs over-the-counter and their expanding use for self medication requires reassessment.

References

1. Taylor, R.H., Menzies-Gow, N., Lovell, D. et al. Misleading response of malignant gastric ulcers to cimetidine. *Lancet*, **686**–687 (1978).

2. Wayman. J., Hayes N. Proton pump inhibitors delay the diagnosis of gastric cancer. *British Journal of Surgery*, **84**(Suppl. 1): 62 (1997).

3. Wayman, J., Hayes, N., Griffin, S.M. The response of early gastric cancer to proton-pump inhibitors. *New England Journal of Medicine*, **338**: 1924–1925 (1998).

4. Suvakovic, Z., Bramble, M.G., Jones, R. et al. Improving the detection rate of early gastric cancer requires more than open access gastroscopy: a five year study. *Gut*, **41**: 308–313 (1997).

5. Griffin, S.M., Raimes, S.A. Proton pump inhibitory may mask early gastric cancer. *British Medical Journal*, **317**: 1606–1607 (1998).

Current Topics

WHO develops artesunate for emergency treatment of malaria

*Artesunate Task Force, World Healh Organizaion, Geneva**

Traditionally, the development of new drugs relies heavily on the ability of the pharmaceutical industry to carry out scientific and technological research on behalf of public health. In such a setting, drug development tends to be directed to health problems which give returns on the significant investment of time and money needed to obtain a commercially successful product. The provision of new medicines for diseases endemic in developing countries where a commercial gain is not possible remains a dilemma (1).

A new initiative in public health delivery has recently been launched by WHO with the development of the drug artesunate. The pace of artesunate development has been fast, focused and targeted and the potential beneficiaries are populations at risk of severe malaria. For the reasons described below, WHO has extended its usual drug development process one step further by initiating registration of rectal artesunate for the emergency treatment of malaria in patients.

Although the strategy of artesunate development was orchestrated from within WHO's Special Programme for Research and Training in Tropical Diseases, it relies heavily upon an alliance of scientists, laboratories, industry, regulators and ministries of health to ensure the public health outcome. This change in development strategy has transformed the way in which WHO does business. In essence, each and every player has been rallied to the challenge of reducing the discrepancy between need and availability of an important drug.

Members of the Artesunate Task Force: P. Folb, Professor of Pharmacology, University of Cape Town, South Africa (Chairman), formerly Chairman, Medicines Control Council, South Africa; S. Krishna, St. George's Hospital Medical School, London, United Kingdom; M.E. Molyneux, Wellcome Trust Centre, University of Malawi, Malawi; V. Navaratnam, Director, Dentre for Drug Research, Universiti Sains Malaysia, Malaysia; N. White, Director, Wellcome Trust Foundation, Mahidol University, Bangkok, Thailand; M. Gomes and P.Olliaro, WHO Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva.

The malaria setting

It is estimated that malaria is responsible for up to 500 million episodes of clinical infection annually, killing 2.7 million people with severe and cerebral disease. Existing data indicate that in some African settings, 44% of all mortality in children under the age of 5 is associated with malaria and 82% of these deaths occur at home. The commonest presenting symptoms associated with significant mortality are cerebral malaria, recurrent convulsions, metabolic dysfunction, or symptomatic anaemia (2). In the population most at risk of death — infants and children in Africa — a significant number soon become too ill to take any form of medication orally and they must be referred to hospital for parenteral treatment if they hope to survive.

For those children fortunate enough to reach a hospital, data confirm that the illness progresses rapidly. Children with severe anaemia may present with longer histories of illness, although acute decompensation, manifesting as respiratory distress, often precipitates admission to hospital. The risk of death at hospital is highest within the first 24 hours after admission, and varies from 10–40%. Survival will depend on two factors: the time elapsed between first symptoms and initiation of treatment, and the health facility's ability to manage complications.

It follows that the earlier a patient receives therapeutic concentrations of an effective antimalarial, the lower the risk of mortality. Since the public health need is to provide early, affordable treatment to patients who do not have easy access to hospital, it was urgent for WHO to develop a product to meet these criteria.

The artesunate story

The clinical efficacy of currently marketed antimalarials is generally demonstrated by parasite clearance rates. However, the circumstances of malaria illness are more complicated. Survival will often

depend on early efficacious treatment of a patient too ill to take oral medication. A priority for WHO is therefore to develop an effective, rapidly acting treatment for administration to non per os patients at high risk of mortality and unable to reach hospital quickly.

The drug formulation identified to meet the challenges of this setting is rectal artesunate. This can be administered easily and safely by untrained health workers and is acceptable to young children. WHO's intention is thus to achieve full development and distribution of artesunate in suppository form for emergency treatment of patients during the time needed to reach hospital. Once the patient has reached an equipped health facility, a more precise diagnosis can be made and treatment administered as required.

The development strategy

The Artesunate Task Force was set up in 1996 to operate as a "virtual" pharmaceutical company. It meets twice a year to oversee the development of the registration dossier with its sights firmly on the need to urgently provide national programmes with additional means to control malaria. It is comprised of a core group of 4 members with ad hoc consultation among other experts, regulatory officials and the scientific community. This approach, aside from being flexible, has many advantages:

- A plan of work is created with the ultimate goal of providing national programmes with access to an antimalarial with life-saving qualities.
- World experts in chemotherapy, toxicology, chemistry, regulatory affairs, and pharmacokinetics (nonlinear mixed effects modelling) can be called upon on an expenses-only basis (although many give advice and evaluate material for a symbolic fee).
- The pace of drug development is spurred by an urgent public health need for the product.
- A high level of collaboration can be achieved when parties are engaged in a common aim.
- Research capacity for related public health drug development is established in many areas involving safety monitoring, good clinical practice and laboratory capacity.

Demonstration of benefit

There are several reasons why rectal artesunate was identified for development. A sharp decline in malaria levels following introduction of the artemisinin derivatives in Viet Nam provided evidence of the potential role of these drugs in the control of severe malaria and associated mortality.

Although artesunate is widely regarded as the most efficacious of the artemisinin derivatives, it is not under patent and has not been subject to full registration by a highly-developed regulatory authority. Furthermore, no pharmaceutical company has shown willingness to do this in light of the investment needed to constitute a registration dossier. WHO was thus able to fill the gap in drug development by taking the product to full registration status.

Raw data on the safety of artesunate, which has been collected by investigators working on malaria over the past ten years in South-East Asia has been made available and clinical data has been generated by WHO through studies of hospital-based patients with moderately severe malaria. However, the burden of proof for effectiveness in an emergency situation will fall upon the community trials now beginning in several countries. These trials will be crucial in demonstrating whether early treatment halts severe disease and prevents a fatal outcome. Additionally, they will define the conditions of use and follow-up treatment, and provide a platform for subsequent development of health education programmes.

Regulatory mechanisms

WHO will be the sole applicant for marketing of rectal artesunate for the emergency treatment of severe malaria. Registration dossiers will be submitted in Switzerland, the United Kingdom and the United States of America in late 1999 and registration elsewhere is likely to be made by mutual agreement with the national drug regulatory authority.

The new drug application to be submitted to the FDA will be filed under orphan drug status and within the expedited approval process. Orphan drugs are those drugs that involve a condition or disease affecting less than 200 000 diagnosed cases in the USA and expedited approval is reserved for products addressing serious or life-threatening illnesses. In these circumstances, approval is based on evidence of benefit on a surrogate endpoint pending the outcome of com-

munity based studies designed to provide definitive survival data.

WHO's relationship with regulatory authorities in Europe and the USA has been one of partnership in achieving a public health benefit. Dialogue has taken the form of evaluating an emergency product for life-threatening suspected malaria. The high level of technical input by regulatory authorities and their understanding of the global impact of malaria has been appreciated by the Artesunate Task Force. Above all, the development plan for artesunate has profited from the ability of drug regulatory authorities to look beyond immediate national responsibilities towards the broader goal of global public health.

A direct subsmission by WHO to regulatory authorities for registration of an amtimalarial is unprecedented. In the past, WHO has undertaken focused studies with private-sector partners in various areas of drug development but has not assumed responsibility for the regulatory aspects. It is highly unlikely that a fully registered artesunate product would have been developed if WHO had not responded to the need

Elements of a model strategy

Collaboration is possible wherever parties benefit mutually and share a common aim. The following steps outline how WHO achieved this goal by exploiting its unique international role and expertise in public health.

- A common aim to develop and register a product of public health benefit was identified.
- Collaborative links were established with the pharmaceutical industry, regulatory authorities, scientists, experts, national authorities and community health centres in endemic areas.
- Global expertise was harnessed cost-effectively.
- On behalf of WHO, scientific experts planned, gave advice and executed components of the strategy.
- Industrial partners manufactured a final product in compliance with the highest quality, safety and efficacy requirements.
- A simple and focused path to registration was planned by the application of orphan drug status and accelerated approval.
- Postmarketing surveillance and health education programmes are planned to enable optimal use of the final product by public health agencies such as UNICEF, Roll Back Malaria, and national control programmes.

References

1. Garattini, S. Financial interests constrain drug development. *Science*, **275**: 287 (1997).

2. Newton, C.R., Krishna, S. Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. *Pharmacology and Therapeutics*, **79**(1): 1–53 (1998).

Vitamin A supplementation strategies

Vitamin A deficiency has been identified as a problem of public health importance in over 60 countries worldwide and about 250 million children are estimated to be at risk of this deficiency. Among children under 5 years of age, some 3 million have clinical signs of xerophthalmia.

Reducing vitamin A deficiency requires long-term approaches which include food fortification or increased dietary intake of foods rich in vitamin A. Periodic supplementation is a rapid, low-cost way to ensure that children at risk receive enough vitamin A. The Expanded Programme on Immunization (EPI) is now linking delivery of vitamin A to its routine and supplementary immunization programmes (1).

In the correct dosage, vitamin A is safe and has no negative effect on seroconversion rates for OPV or measles vaccine. Occasionally, side effects such as headache, loss of appetite, vomiting, or a bulging fontanelle in infants may occur the day following vitamin A administration. These symptoms are minor and transitory. Vitamin A supplements should not be given to any pregnant woman or a woman of reproductive age because of the risk of teratogenicity (2).

To avoid multiple dosing, vitamin A supplementation should be recorded on the child's health card. Children aged 6 months and above should ideally receive high-dose supplements at intervals of 4–6 months. If infants under 6 months are not breast-fed, they should receive one 50 000 IU supplement as a preventive measure, and if they show signs of clinical vitamin A deficiency they should receive

Schedule for vitamin A supplementation *(3)*

Target group	Encounter point	Vitamin A dose
All mothers irrespective of mode of infant feeding up to 6 weeks postpartum if no vitamin A supplement received after delivery	BCG, OPVO, DTPI immunization schedule	200 000 IU
Infants 9–11 months	Measles vaccination schedule	100 000 IU
Children 12 months and older		200 000 IU
Children 1–4 years	Booster doses* Special campaigns* Delayed primary immunization	200 000 IU

* *The minimum interval between doses is1 month (exceptionallly the interval my be reduced in the case of clinical vitamin A deficiency: see above).*

treatment of one 50 000 IU dose on 2 successive days. The recommendation for postpartum supplementation for mothers is one 200 000 IU dose to be administered within 6 weeks after delivery, which is usually a period of infertility in breastfeeding mothers (2).

Vitamin A supplementation is the easiest intervention to add to routine EPI schedules or national immunization days and requires a minimum of training and equipment. Good planning is essential for the successful integration of vitamin A supplementation in national immunization events. The following are useful steps to follow when undertaking such an event.

1. Define whether the area or region has a vitamin A deficiency problem. Indications of this may be high infant mortality and high measles case fatality rates.

2. Convince decision-makers of the importance of vitamin A supplementation and engage partners such as WHO, UNICEF, the Red Cross or non-governmental organizations and aid agencies.

3. Inform and educate the public, health care workers and politicians about the advantages of supplementation and the dangers of deficiency.

4. Evaluate success and use this information to improve delivery of vitamin A in subsequent events.

References

1. World Health Organization. Integration of vitamin A supplementation with immunization. *Weekly Epidemiological Record*, **4**: 1–8 (1999).

2. Expanded Programme on Immunization. *EPI Update No. 33*. November 1998.

The microbial threat: Copenhagen recommendations

The implications to human health of the increasing resistance of microorganisms to antimicrobial agents is a major public health problem in Europe. The international spread of microorganisms which has recently been recorded indicates that this can no longer be regarded as a national, but an international problem and requires a common, global solution.

In September 1998, Ministers of Health from European Union countries met at a conference in Copenhagen, Denmark, to address the growing problem of antimicrobial resistance within Europe. Recommendations from the conference were subsequently drafted and transmitted to all Ministers of Health in the European Union. A summary of their conclusions and recommendations follows.

Participants at the conference agreed that there is an established but complex link between the consumption of antimicrobial agents and the preva-

lence of drug resistance. Although the full extent of the problem is as yet unknown, resistance is leading to increased deaths and illness, with consequential health expenditure. Although the pharmaceutical industry is making great efforts to develop new antimicrobials, innovative medicines cannot be expected to solve the immediate problem. It is thus a priority to introduce policies which govern the rational use of the antimicrobials which are available.

The provision of good quality data on resistance patterns which are clinically and epidemiologically relevant is essential if effective interventions are to be implemented. A European surveillance system should be established based on existing national systems to monitor trends in antimicrobial resistance of microorganisms of both human and animal origin and the European Union should coordinate the medical and veterinary sectors and seek the active involvement of all parties.

Rational use of antimicrobial agents

Educational initiatives for both health professionals and the general public are of major importance for improving the use of antimicrobial agents. Antimicrobials for therapeutic use should be prescription-only medicines and as such should not be advertised to the public. Guidelines for the rational use of antimicrobials should be introduced into medical and veterinary practice. Guidelines on good practice in prescribing antimicrobials should be drawn up which set out (i) the conditions under which antimicrobials should be prescribed; and (ii) the importance of patient compliance and how this can be achieved. Laboratories carrying out antimicrobial testing should be strengthened.

The majority of participants at the conference considered that use of antimicrobials as growth promoters was not justified and that safer non-antimicrobial alternatives should be developed, including improved farming practice. It was also considered urgent to conduct a full risk assessment and coordinated research on antimicrobial resistance should be igiven high priority.

Recommendations

- Antimicrobial resistance is a major European and global problem.
- Pharmaceutical companies should be encouraged to develop new antimicrobial agents.
- The European Union and member states should set up a European surveillance system of antimicrobial resistance.
- The European Union and member states should collect data on the supply and consumption of antimicrobial agents.
- The European Union and member states should encourage the adoption of a wide range of measures to promote prudent use of antimicrobial agents.
- The European Union, member states and national research councils should make coordinated research on antimicrobial resistance a high priority.
- A way should be found to review progress of these recommendations and proposals.

Reference: Ministry of Health & Ministry of Food, Agriculture and Fisheries, Denmark. European Union Conference, *The Microbial Threat. "The Copenhagen Recommendation"*. 10 September 1998.

General Information

The *International Pharmacopoeia:* 50 years on

In countries with a robust pharmaceutical market, regulatory control measures ensure that drugs are efficacious, safe and of good quality. However, the extent to which a national health authority is able to provide adequate regulatory control will depend on prevailing conditions, experience and the resources available to it. A prime consideration for WHO is to support national health authorities with reliable expertise, information and technology. One important tool in the overall task of assuring quality is a pharmacopoeia.

A pharmacopoeia is an official, legally binding document which, in the majority of countries, is incorporated into the framework of national health legislation. This means that any pharmaceutical product being manufactured within its boundaries must conform to the nationally adopted pharmacopoeia which will contain quality specifications for the determination of finished drug products, drug substances and excipients. A quality specification describes appropriate tests to confirm the identity and purity, and to determine the strength or content, of an active substance.

The underlying principles of a pharmacopoeia are that pharmaceutical substances and products intended for human use should be manufactured in adequately equipped facilities which are managed by competent professionals and operated by qualified staff. General rules governing pharmaceutical manufacture are contained in good manufacturing practices (GMP). Processes, premises, and installations should also comply with regulations under which the product licence or marketing authorization has been granted and with any binding international standards in the case of those products destined for export.

Pharmaceutical preparations are usually produced on a large scale and are stored while they await transport. During storage, pharmacopoeial testing should be undertaken to verify physical and chemical stability during the claimed shelf-life. Such pharmacopoeial tests will allow for the inevitable variations that occur during production and packaging as well as for subsequent degradation during storage.

The following important principles should be considered when pharmacopoeial standards are used to establish compliance with regulatory requirements:

• the application of a monograph is understood as compliance with **all** general requirements contained therein and testing methods, texts, or notices pertaining to it;

• a product is not of pharmacopoeial quality unless it complies with **all** the stated requirements.

A clear distinction exists between pharmacopoeial standards and release specifications, although both comprise identical or similar tests. Release specifications are applied by the manufacturer of a pharmaceutical product to confirm quality. However, since the manufacturer is also responsible for the quality of the product throughout its shelf-life, tests must also be predictive. Thus, manufacturers' release specifications are generally more exacting than the corresponding pharmacopoeial requirements. As a general rule, quality must be built into a product throughout the manufacturing process and cannot be added at a later stage of production.

The International Pharmacopoeia

The history of the *International Pharmacopoeia* dates back to 1874 when the strengths and composition of drugs and their terminology were documented in the *Unification of the Formulae of Potent Drugs*. In 1929, an agreement drawn up between 19 countries proposed that the League of Nations should collaborate in the task of preparing an "international pharmacopoeia".

In 1948, the First World Health Assembly approved the establishment of an expert committee to support the work of the *International Pharmacopoeia*. Within the same context, the Programme on International Nonproprietary Names (INN) for Pharmaceutical Substances was created in 1950 to create a single nonproprietary name to identify pharmaceutical substances unambiguously on a worldwide basis.

In collaboration with national pharmacopoeia commissions, the first edition of the *International Pharmacopoeia* was prepared by adapting and harmonizing monographs which were already published in major pharmacopoeias, or by the development of new standards. Drug substances were chosen with the needs of developing countries in mind, and with emphasis on treatments for tropical diseases. The first edition of the *International Pharmacopoeia* appeared in English, French and Spanish, and was subsequently translated into German and Japanese. It comprised 422 monographs and 59 appendices, including monographs on pharmaceutical starting materials.

The second edition of the *International Pharmacopoeia* saw the addition of a number of new monographs. Specifications were tested by national pharmacopoeia commissions, national quality control laboratories, pharmaceutical manufacturers and national institutes and 162 pharmaceutical preparations were added, while 114 monographs were deleted. The appendices included a number of new analytical control methods using infrared spectrophotometry, chromatography (column, paper and thin-layer), non-aqueous titration, and radioactivity.

By 1975, a trend was developing among the major pharmacopoeias to include techniques requiring expensive analytical instrumentation of the kind that is not readily available in smaller drug testing laboratories operating on low budgets. In response, it was decided that the *International Pharmacopoeia* should focus on providing information adapted to the needs of developing countries and recommend only simple, classical techniques which would give a reasonable assurance of identity and quality. Henceforth priority was given to monographs for those drugs that are most widely available throughout the world, such as those used in national control programmes or contained in the Model List of Essential Drugs. Information was also provided on drugs likely to contain impurities arising from degradation during storage or difficult to manufacture.

Volume 5 of the third edition is now in the final stages of preparation. It contains additions to the list of monographs for active pharmaceutical substances and a number of important general texts on dissolution tests, nomenclature and specifications for tablets. A section will include the newly developed antimalarial drug substances arteether, artemether, artemisinin, artesunate, and dihydroartemisinin.

Future activities

In the future, work on dissolution tests for predicting the capacity of equivalence testing of groups of drug products will be undertaken. WHO will also continue to provide monographs for starting materials using simple test methodologies. The importance of this activity was emphasized following incidents of contamination of pharmaceutical products with diethylene glycol.

Future activities of the *International Pharmacopoeia* should be regarded in the context of quality control of pharmaceuticals in general. Many countries still do not have their own national pharmacopoeia and depend either totally or in part on the monographs included in the *International Pharmacopoeia*.

It must be emphasized that the trend of advocating expensive methods for drug testing is driven by increasingly large-scale drug manufacture and does not consider the more varied practical needs of lesser developed countries. This renders the major pharmacopoeias less and less adapted for the practice of drug quality control in countries that need drug testing methods for various other reasons, such as on-the-spot identification of counterfeit pharmaceuticals. If the *International Pharmacopoeia* is abandoned, WHO would lose all potential influence in this field.

Artemisinin: guidelines for use

Artemisinin products, including artesunate, artemether, and arteether, were first developed as antimalarials in China. They resolve fever and clear parasites more rapidly than any other known antimalarial agent. Moreover, they are the only group of antimalarial drugs to which resistance of *P. falciparum* has not yet developed and, as such, play an essential role in malaria control. Protection of this product from resistance will depend on controlled, rational use requiring the urgent development and implementation of global and national policies concerning management, availability and prescription.

In order to address these issues, a meeting was held in Geneva from 10–12 June 1998 to review the use of artemisinin products in the light of experience now available from several countries. Participants at the meeting gave advice on policy and drafted guidelines for the selection and correct use of artemisinin products in different epidemiological situations. A summary of the report of the meeting follows. More concise information is available from

the report itself and includes information on recommended regimens and clinical use of artemisinin products as well as priority areas for further research*.

In practice, the process of registration and availability of artemisinin products varies depending on the particular circumstances of each country. Some countries, such as Bangladesh and the Philippines, do not have a problem with multidrug resistant malaria and have not allowed these drugs onto the market. Others, such as Myanmar and Viet Nam, face problems of resistance to antimalarials and consequently allow artemisinin products to be traded by pharmacies and market sellers where populations do not have access to public health services.

Thailand was one of the first countries outside China and Viet Nam to use artemisinin products in the public sector. During the early 1990s, it was facing acute problems of multidrug resistance with failure rates of antimalarials, and particularly mefloquine, reaching over 50% in some areas. In view of the lack of full registration of artemisinin products in any highly-developed country, the Thai authorities allowed probational use of the drug in the public health sector only on the understanding that reinforced postmarketing surveillance would be carried out. All batches of imported artemisinin products were controlled for quality by the Thai Food and Drug Administration.

Faced with an unacceptable level of chloroquine failures, Papua New Guinea has also revised its antimalarial drug policy. A combination of chloroquine plus sulfadoxine/pyrimethamine is the first-line drug of choice with oral artesunate in reserve. Parenteral or rectal artesunate is available for the treatment of severe malaria. In Brazil, dispensing of artemisinin products is restricted to approved public sector hospitals, but only for the treatment of severe malaria.

By contrast, artemisinin products are widely available in Africa despite warnings recommending caution. Injectable artemether and oral artesunate produced by French-based companies have now been registered in 38 countries in Africa. Formulations from China are also circulating.

A weak regulatory system is one of the greatest obstacles to the correct deployment and rational use of antimalarials. Even in countries where regulatory mechanisms are well established, the system is bypassed by illegal activities which lead to the sale of substandard and counterfeit drugs. The WHO Certification Scheme is a useful way of verifying the status of imported products. Alternatively, many countries insist on the provision of a certificate of registration and free sale from the country of origin. However, a free-sale certificate will not give information on the quality and stability of the product under local conditions.

Essential requirements for the rational use of artemisinin products are:

- A drug registration authority which will regulate the import and distribution of drugs and will be able to resist commercial pressure to make drugs freely available.
- Development of a sound national antimalarial drug policy and inclusion in the national essential drugs list.
- Awareness campaigns to prescribers on the rational use of drugs.
- Information, education and communication on appropriate treatment seeking behaviour to the general public.

An assessment of the quality of artemisinin products can be made using several methods, ranging from the relatively cheap thin-layer chromatography (TLC), to the high-performance liquid chromatography (HPLC) with ultraviolet detector allowing accurate quantitation of diluents and breakdown products. The former system may be used at entry ports or for on-the-spot testing, with confirmation from the second method situated, for example, in a national control laboratory when regulatory action needs to be taken. WHO is presently developing *in vitro* dissolution profiles for dosage forms, and quality specifications for the artemisinin products will soon be published in the *International Pharmacopoeia*.

Recommendations

1. Use

- Artemisinin is a safe and effective alternative to quinine for the treatment of **severe malaria**. In ar-

*World Health Organization. *The use of artemisinin and its derivatives as antimalarial drugs*. Report of a joint CTD/DMP/TDR Informal Consultation. Unpublished document WHO/MAL/98.1086.

eas where sensitivity to quinine is reduced, artemisinin is the treatment of choice. In other areas, a change from quinine to artemisinin may not necessarily improve survival, but may be preferred in view of ease of administration and lessened side effects.

- Artemisinin is a potent and effective drug for the treatment of **uncomplicated malaria.** However, use should be limited to patients with multidrug-resistant malaria.

- To improve efficacy of the drug and **delay onset of resistance** artemisinin should always be used in combination with another effective antimalarial. Under certain circumstances, such as a history of adverse reactions to the combination, monotherapy may be indicated. In this case, a 7-day course of treatment is recommended as long as compliance can be assured.

- In areas where mefloquine is the first-line drug of choice, or a change to mefloquine is being considered, a 3-day course of artemisinin in combination with mefloquine is recommended.

- Combination therapy using artemisinin and artemisinin derivatives could slow resistance to each component and is a promising strategy. However, studies have not yet evaluated the tolerability, efficacy, effectiveness and cost benefit of this approach.

- The use of parenteral preparations of artemisinin in patients able to take oral medication is not indicated.

- Artemisinin or its derivatives should not be used for chemoprophylaxis.

2. Registration

- National authorities should develop policies regarding the manufacture, import, distribution, promotion and use of artemisinin products with a view to preventing or delaying the development of resistance. It is important that health care providers, together with those involved in distribution and sale of these products, health organizations and community service agencies should comply with national policy.

- Only artemisinin products manufactured according to good manufacturing practices (GMP) should be used.

- In order to ascertain the regulatory and GMP status of products, the WHO Certification Scheme may be used by governments to provide information on the status of the product in the exporting country.

- Governments lacking expertise may call on the assistance of WHO when developing systems of GMP, quality assurance or testing.

- In order to maintain stability, special attention should be paid to conditions of transport, distribution and storage.

3. Drug susceptability monitoring

- Monitoring is the responsibility of the national control programme and should be conducted in sentinel sites on a regular and sustained basis. Patient response should be monitored to detect changes in susceptibility.

- Wherever artemisinin products are used, post-marketing surveillance should be in place. Although there is now a body of information confirming the safety of standard artemisinin regimens, information is still needed on the long-term effects, particularly among pregnant women and following repeat treatments.

4. Information

- Guidelines on the use of artemisinin products should be made available by national authorities and distributed to all health care providers, distributors and sales outlets. This information may complement the national formulary, prescribing information or guidelines for pharmacists.

- To avoid consumer misuse, it is important to educate the general public on the correct use and need for compliance when taking these products.

- Donor agencies, consumer service organizations and pharmaceutical companies should be discouraged from promoting or importing these drugs outside of official channels.

- Countries facing problems of multidrug resistance should develop mechanisms whereby they may share information and experience with other countries.

In order to achieve implementation of these recommendations, collaboration will be required not only from the public and private health care sectors but the community at large.

Regulatory Matters

Tolcapone and fatal liver injury

European Union — The European Agency for the Evaluation of Medicinal Products (EMEA) has issued a recommendation to suspend the marketing authorization for tolcapone, a catechol-O-methyl transferase (COMT) inhibitor indicated as adjunctive treatment for Parkinson disease. The product was approved by the CPMP in August 1997.

The Manufacturer has reported 9 cases of serious abnormal hepatic function, 2 of which were fatal. Monitoring of liver function did not predict these reactions, and the Agency has also identified a risk of rhabdomyolysis and neuroleptic malignant syndrome. The latter reaction may be associated with abrupt discontinuation of therapy.

The EMEA advises patients taking tolcapone to consult their physician immediately to initiate discontinuation which should be undertaken over 3–6 days under medical supervision.

Reference: Press release from EMEA. CPMP/2457/98: Recommendation for the suspension of the marketing authorization for Tasmar® (tolcapone). 17 November 1998.

United States of America — The Food and Drug Administration and the manufacturer of tolcapone have advised physicians to carefully follow new warnings added to the labelling. The warning calls for liver monitoring tests fortnightly and suggests self-monitoring by patients for signs of liver disease, including jaundice, fatigue and loss of appetite. The warning also states that if a patient fails to show substantial clinical benefit within three weeks of initiating treatment they should be withdrawn from the drug under medical supervision.

Reference: *FDA Talk Paper*, T98–81, November 1998.

Entacapone labelling strengthened

European Union — The European Agency for the Evaluation of Medicines has requested reinforced patient information from the manufacturer of entacapone, a COMT inhibitor which was approved in September 1998 for Parkinson disease (1, 2), that the product must not be used if there is a history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis, and that if the drug is stopped discontinuation should be carried out under medical supervision.

These changes have been made based on the possibility that abrupt discontinuation may be associated with adverse reactions such as those reported with another COMT inhibitor, tolcapone.

The Committee for Proprietary Medicinal Products (CPMP) has concluded that the most recent safety data for entacapone show that the product does not appear to be hepatotoxic. Rare reports of an increase in liver enzymes have been received but these cases involved patients with an underlying disease which could have been the cause.

References

1. Press release from EMEA. CPMP/2178/98. December, 1998.

2. *WHO Drug Information*, **12**(4), 242 (1998).

Rituximab: new recommendations

European Union — The European Agency for Evaluation of Medicinal Products (EMEA) has received reports of severe adverse reactions, including 8 fatal cases of cytokine release syndrome, associated with the monoclonal antibody, rituximab. The product was approved in June 1998 for treatment of patients with stage III and IV follicular lymphoma who are chemoresistant, although 3 of the fatal cases were receiving the medication for a different indication (1).

It is estimated that some 14 000 patients have been treated worldwide. A common feature of the fatal cases was the development of severe reactions during the first infusion. Cytokine release syndrome is characterized by dyspnoea accompanied by bronchospasm or hypoxia.

New recommendations have been provided by the manufacturer in a circular letter, outlining the

changes and emphasizing that rituximab should only be prescribed for its approved indication. Patients with a history of cardiac disease should be monitored closely (2).

References

1. Press Release. Mabthera® (Rituximab): Reports of adverse reactions – new recommendations for use. EMEA/40532/98, 30 November 1998

2. *SCRIP* No. 2393, 4 December 1998.

United States of America — The Food and Drug Administration and the manufacturer of rituximab have informed physicians that, since its approval in November 1997, approximately 70 cases of serious infusion-related events have been reported. A review of reports seems to suggest that patients with a high tumour burden or with a high number of circulating malignant cells may be at higher risk. Such patients should be treated with extreme caution and be closely monitored throughout each infusion. The package insert was revised in September 1998 to include additional information in the warnings section regarding tumour lysis syndrome.

Reference: Communication from FDA Medwatch transmitting letter from Genentech, Inc. and IDEC Pharmaceuticals Corporation. 5 December 1998. http://www.fda.gov/medwatch/safety/1998/rituxa.htm

Montelukast and eosinophilia

United States of America — Montelukast is a selective leukotriene (LTD4) receptor antagonist that was approved by the Food and Drug Administration in February 1998 for the prophylaxis and chronic treatment of asthma in adults and paediatric patients over 6 years of age.

The FDA, in collaboration with the manufacturer, has informed physicians that therapy with montelukast has been associated rarely with systemic eosinophilia, presenting on occasions clinical features of vasculitis consistent with Churg-Strauss syndrome. This adverse reaction has been associated with a reduction in concomitant oral corticosteroid therapy. Physicians should be alert to patients developing eosinophilia, vasculitis rash, worsening of pulmonary symptoms, cardiac complications or neuropathy (1).

Leukotriene antagonists are also marketed in many European countries (2).

Reference:

1. Communication from FDA Medwatch transmitting letter from Merck & Co, Inc. December 1998. http://www.fda.gov/medwatch/safety/1998/singul.htm

2. *WHO Drug Information*, **12**(4): 241 (1998).

Amineptine and dependence

France — In collaboration with the manufacturer, the Medicines Agency has decided to suspend the marketing authorization of amineptine following reports of drug abuse and dependence.

Amineptine is an antidepressant which inhibits the reuptake of dopamine and is indicated in major depressive episodes. It has been available in France since 1978, but is also marketed in 66 other countries worldwide, particularly Africa, Asia and South America . After suspension, amineptine will be available through compassionate use in hospitals until June 1999 for addicted patients who need gradual discontinuation.

The risk of dependence with amineptine is well known and the two major complications are significant weight loss and micro- and macrocystic acne. Dependence always results in major withdrawal difficulties, including agitation, mania, confusion and relapse of depression.

Reference: Communication to WHO from the Agence du Médicament, 22 January 1999.

Cosmetic contains pharmaceutical substances

Germany — The Federal Institute for Drugs and Medical Devices has withdrawn a range of skin products, Psorigon®, from the market after formulations were found to contain unlabelled cortisone derivatives and tretinoin. Neither of these substances has been approved for use in cosmetics and are available on prescription only in Germany.

Reference: PIC Rapid Alert, Federal Institute for Drugs and Medical Devices, Berlin, 6 November 1998.

United Kingdom — The Medicines Control Agency is currently analysing samples of Psorigon® for the presence of undeclared corticosteroids. This product is advertised as a treatment for psoriasis and is available through the Internet. The distributor has

agreed to withdraw the product, which is manufactured in Germany and provided through a supplier in Gibraltar.

Reference: Defective Medicines Report Centre, Medicines Control Agency, Communication to WHO.

Sweden — The Medical Products Agency has withdrawn a range of skin products, Psorial®. The products did not have a marketing authorization although they contained the corticosteroids triamcinolone and halcinonide. The products were labelled to treat psoriasis and various types of eczema. Many patients had purchased the products in order to avoid corticosteroid use.

Reference: *Information från Läkemedelsverket,* **9**(7): 3 (1998).

Jurisdiction over cloning technology

United States of America — The Food and Drug Administration has issued a letter to all institutional review boards (IRBs) confirming that the agency has jurisdiction over clinical research involving human cloning technology and informing IRBs of the FDA regulatory process that is required before an investigator can proceed with such a clinical investigation.

Before any research using cloning technology to create a human being can begin, the sponsor of the research is required to submit to FDA an Investigational New Drug (IND) application describing the proposed research plan; obtain authorization from a properly constituted and functioning IRB; and to provide a commitment from the investigators of informed consent from all human subjects involved in the research.

Reference: Letter from FDA communicated through http://www.fda.gov/oc/oha/irbletr.html

Contaminated hydrocortisone

France/Belgium — Following a request by the University Hospital of Kamenge, Burundi, the Agence du Médicament has analysed a 200 mg/20 ml preparation of injectable solution hydrocortisone manufactured in China by Shanghai Sine Pharmaceutical Company and distributed by Exphar, Belgium.

Analysis demonstrated an unacceptably high ethanol content of 52% v/v or 41% m/v. Patients had experienced a burning sensation and been subject to behavioural disturbances on injection of the solution.

Reference: Communication to WHO from the General Pharmaceutical Inspectorate, Belgium enclosing conclusions of analysis from the Agence du Médicament, France. 29 October 1998.

Intravenous immune globulin and acute renal failure

United States of America — The Center for Biologics Evaluation and Research of the Food and Drug Administration has circulated a warning to physicians concerning the potential risk of acute renal failure associated with the intravenous administration of human immunoglobulin products. Since introduction in 1981, the FDA has gathered over 114 reports, including 80 reports from the USA, associated with renal dysfunction or acute renal failure. Of the 17 fatal cases, many were due to serious underlying conditions.

Preliminary evidence suggests that products which also contain sucrose may present a greater risk and renal histopathological examinations have indicated an osmotic injury to the proximal renal tubules.

In order to avoid these reactions the FDA recommends adequate hydration prior to infusion, and particular caution in patients with preexisting renal insufficiency, diabetes, volume depletion, sepsis, concomitant use of nephrotoxic drugs and over 65 years of age.

Reference: Dear Doctor letter from the Center for Biologics Evaluation and Research, November 1998.

Sertindole suspended pending evaluation

United Kingdom — The Committee on Safety of Medicines has informed physicians that the manufacturer of sertindole, an antipsychotic agent indicated for the treatment of schizophrenia, has voluntarily suspended availability of the product because of reports of cardiac arrhythmias and sudden death associated with its use.

Sertindole was approved by the European Union in 1996. It is now suspended pending a full evaluation of risks and benefits in collaboration with the Medicines Control Agency.

Physicians are advised to recall all patients using sertindole and to propose alternative treatment if possible. Discontinuation should be initiated under medical supervision and tapered over a period of two weeks while other antipsychotic treatment is introduced.

Reference: Communication from the Committee on Safety of Medicines, 2 December 1998.

Labelling information for paediatric use

United States of America — The Food and Drug Administration has issued a final rule requiring that applications for new drugs and biological products contain sufficient data and information to support directions for paediatric use. This action came about to ensure adequate medical care for children. Paediatricians often stated that they were required to prescribe drugs to young children that were not labelled for children and for which paediatric dosage forms did not exist.

Most drugs and biologicals have not been adequately tested in the paediatric subpopulation and product labelling frequently fails to provide directions for safe and effective use in children. Manufacturers of certain products already marketed will now be required to provide data and information to support paediatric use. Manufacturers have 20 months to submit the required assessment. The new rule should significantly improve paediatric labelling.

Reference: *Federal Register*, Volume 63(231): 66631–66672 (1998).

Tryptophan prescribing warning

Sweden — The Medical Products Agency has informed physicians that tryptophan is not authorized as a medical product and can be prescribed only in the context of clinical trials as a supplementary medication for sleeping disorders or depression.

The Agency also reminds physicians of an adverse reaction syndrome involving muscle and leg pains, fever, skin rash and eosinophilia that has been reported in association with high doses of tryptophan.

Reference: *Information från Läkemedelsverket,* **9**(7): 5 (1998).

Impurities in dietary tryptophan products

United States of America — The Food and Drug administration has confirmed the presence of impurities in some 5-hydroxy-L-tryptophan (5HTP) products promoted for use as aids for insomnia, depression, obesity and for children with attention deficit disorders.

One of the impurities is known as peak X. Although the significance of peak X is unknown, past experience with these products has shown that eosinophilia-myalgia syndrome is associated with 5HTP and L-tryptophan. It has not yet been resolved whether EMS cases were caused by L-tryptophan or 5HTP, one or more impurities, or other factors. The Centers for Disease Control and Prevention has identified more than 1500 cases of EMS, including at least 38 deaths, associated with the use of L-tryptophan.

Eosinophilia-myalgia syndrome is a serious systemic illness characterized by elevations of certain white blood cells and severe muscle pain. At the present time, the Agency is unaware of any recent illnesses associated with 5HTP products. However, the widespread sale of these products has only recently begun.

Reference: *FDA Talk Paper*, T98–48, 1998.

Chlormezanone withdrawn

Zimbabwe — The Medicines Control Authority has cancelled the marketing authorization for products containing chlormezanone following international regulatory action based on safety evaluations. The drug has been associated with an unacceptable incidence of Stevens-Johnson syndrome.

Reference: *Drug Information Bulletin*, Volume 2(1), 1998.

New home screening test for abuse drugs

United States of America — The Food and Drug Administration has approved a nonprescription test for drugs of abuse that can be performed at home and gives preliminary results in minutes. However, conclusive results can only be provided by a laboratory.

The Quickscreen At-Home Drug Test® comes in two models. One tests for cocaine, marijuana, opiates, amphetamine and phencyclidine and the second for cocaine, marijuana, opiates, amphetamines and metamfetamine. Some drugs can be detected within two hours of use and remain detectable for several days or more. Other drugs have a different timing.

If the initial results are "negative" nothing further needs to be done, but if the results are "inconclusive" the urine sample is placed into a mailer provided with the kit and sent to a designated laboratory for confirmatory testing. The results are available in three days. Numerous factors can affect test results. For example, certain foods and medicines and being in the presence of a heavy marijuana smoker may give a positive result.

Reference: *FDA Talk Paper*, T98-74, October 1998.

High-dose terfenadine withdrawn

European Union — The Commission for Proprietary Medicinal Products (CPMP) has decided to withdraw 120 mg strength terfenadine products from the market because of a higher risk of overdose (1). The labelling for lower dose products has also been changed to reflect age and weight restrictions and to emphasize contraindications.

Terfenadine has been associated with serious, fatal, cardiac adverse reactions when metabolism of the drug is reduced by disease or interaction with other drugs influencing the same metabolizing enzymes (2).

References

1. *The Pharmaceutical Journal*, **261**: 658 (1998).

2. *WHO Drug Information*, **11**: 17, **11**:67 and **11**.68 (1997).

Liquid ecstasy (GHB) trading investigated

United Kingdom — The Medicines Control Agency is investigating the illegal trading and promotion of gamma hydroxybutyrate (GHB), a drug known as "liquid ecstasy". The drug has been promoted for body building, claiming that it stimulates the body's production of growth hormone (1). It has also been used as a sleeping aid and reports have been received of overdosing and abuse and as a recreational drug used with other substances (2). The drug is legally manufactured within the European Union as a general anaesthetic but is not licensed in the United Kingdom.

Overdosing with GHB causes severe intoxication. Cases of poisoning have been reported (57 cases) over a three month period in the USA, as well as in the United Kingdom.

References:

1. Liquid ecstasy trading to be investigated. *British Medical Journal*, **317**: 1035 (1998).

2. Thomas, G. Bonner, S., Gascoigne, A. Coma induced by abuse of gamma-hydroxybutyrate (GBH or liquid ecstasy): a case report. *British Medical Journal*, **314**: 35 (1997).

2. *WHO Drug Information,* **12**(4): 229 (1998).

Metamizole sodium withdrawn

Zimbabwe — The Medicines Control Agency has cancelled the marketing authorization for all pharmaceutical products containing metamizole sodium because of the potential risk of fatal agranulocytosis.

Reference: *Drug Information Bulletin*, Volume 2(1), 1998.

Medication guides

United States of America — The Food and Drug Administration has issued a final rule on requirements for the distribution of patient labelling for selected prescription products used primarily on an outpatient basis. Medication Guides will now be provided with certain products that pose a serious or significant public health concern. They will contain information necessary for the safe and effective use of the medication.

A Medication Guide will be required when: (1) the drug product is one for which the information could help prevent serious adverse effects; (ii) the drug product has serious risks and these risks could affect the patient's decision to use or continue to use the product; and (iii) the drug product is important to health, and compliance with the directions for use is crucial to effectiveness of the treatment.

Reference: *Federal Register*, **63**(230): 66377–664001 (1998).

Streptokinase: severe back pain

Sweden — The Medical Products Agency has received reports of severe acute back pain in six patients treated with streptokinase infusion. The pain occurred when 10–15 ml of streptokinase had been given to patients requiring a further dose.

Reference: *Information från Läkemedelsverket,* **9**(7): 45 (1998).

Sildenafil: revised labelling

United States of America — In collaboration with the manufacturer, the Food and Drug Administration is advising doctors of new warnings and information which have been added to the product labelling for sildenafil (Viagra®).

Over 6 million prescriptions have been written for sildenafil, and adverse events constitute only a small fraction of these. The updated information includes information on cardiovascular events, risk of sexual activity and underlying cardiovascular status, vasodilatory effects and priapism. Several groups of patients were not studied in the clinical trials for sildenafil and these include patients with cardiovascular problems, hypotension or hypertension, and retinitis pigmentosa. Such patients should be prescribed sildenafil with extreme caution.

Reference: *FDA Talk Paper*, T98-83, 1998.

Chlorzoxazone and hepatotoxicity

Chile — The product information and labelling for products containing chlorzoxazone, a muscle relaxant, have been revised to include a warning of severe hepatic damage. This is a rare, but unpredictable occurrence and will depend on the susceptibility of the patient. A physician should be contacted immediately if fever, nausea or vomiting occur.

Reference: *Boletin Informativo sobre Medicamentos*, **15** (1), 1998.

Mislabelling of glucose

Belgium — Two premature infants have died after being administered potassium chloride (KCl) taken from containers labelled "glucose 5% 10-ml sterile solution for injection". The manufacturer and distributor reports that one batch, number 97H21C and 7344C16, is implicated and may be circulating in Belgium Luxembourg, Slovak Republic and Germany. The product may have been exported to other countries.

Reference: EU Rapid Alert, General Pharmaceuticals Inspectorate, Brussels, 20 January 1999.

Internet sale of gamma butyrolactone (GBL)

United States of America — Products containing gamma butyrolactone (GBL) are being sold via the internet, in health food stores, gymnasiums and fitness centres under various brand names such as Blue Nitro, or GH Revitalizer. These products, while labelled as dietary supplements, are unapproved new drugs and have not been approved for marketing.

When taken orally, GBL — which is converted in the body to gamma hydroxybutyrate (GHB) has serious side effects (see page 22). Reported effects include seizures, vomiting, slow heart rate and death. In some cases consumers became unconscious or comatose and several required intubation for respiratory assistance.

Consumers are advised to dispose of any products of this type in their possession and companies are being requested to voluntarily recall such products.

Reference: *FDA Talk Paper*, T99-5, January 1999.

ATC/DDD Classification (temporary)

The following temporary classifications were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 12–14 October 1998 in Geneva. Comments on or objctions to the classification should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, P.O. Box 100, Veivet, 0518 Oslo, Norway (telephone: 0047 22 16 9811, fax: 0047 22 16 9818, e-mail: whocc@nmd.no) before **15 April 1999**. A final list of classifications will be published subsequently in this journal. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC Level	INN/common name	ATC code
New ATC level codes (other than 5th level)		
Selective estrogen receptor modulators		G03XC
COX-2 specific inhibitors		M01AH
New ATC 5th level codes		
	abacavir	J05AF06
	azelastine	S01GX07
	basiliximab	L04AA09
	becaplermin	D03AX06
	betaxolol, combinations	S01ED52
	budipine	N04BX03
	celecoxib	M01AH01
	clobetasol and antibiotics combinations	D07CD01
	dexketoprofen	G04BE30
	finasteride	M01AE17
	fluconazole	D11AX10
	fluocortolone and antibiotics	D01AC15
	flurithromycin	D07CC06
	fomivirsen	J01FA14
	fosphenytoin	S01AD08
	insulin lispro	N03AB05
	insulin lispro	A10AC04
	ioflupane (^{123}I)	A10AD04
	lansoprazole, amoxicillin and metronidazole	V09AB03
	lansoprazole, tetracycline and metronidazole	A02BD03
	levacetylmethadol	A02BD02
	loperamide, combinations	N02AC06
	mannitol	A07DA53
	metoprolol, combination packages	A06AD16
	nonacog alfa	C07AB52
		B02BD09

ATC Level	INN/common name	ATC code
	perindopril and diuretics	C09BA04
	potassium permanganate	D08AX06
	pramocaine	D04AB07
	raloxifene	G03XC01
	rizatriptan	N02CC04
	sertaconazole	D01AC14
	sevelamer	V03AE02
	sodium hypochlorite	D08AX07
	technetium (^{99m}Tc) depreotide	V09IA05
	telmisartan	C09CA07
	temocapril	C09AA14
	tilactase	A09AA04
	tirofiban	B01AC17
	trovafloxacin	J01MA13
	trypsin, combinations	M09AB52
	valsartan and diuretics	C09DA03
	voglibose	A10BF03
	ziprasidone	N05AE04
ATC code changes		
Previous:	ferric ammonium citrate	B03AB10
New:	ferric ammonium citrate	V08CA07
Change of level name		
Previous: Imidazole derivatives		
New: Imidazole and triazole derivatives		*D01AC*
Previous: Drugs for treatment of hyperkalaemia		
New: Drugs for treatment of hyperkalaemia and hyperphosphataemia		V03AE

New DDDs:

INN/common name	DDD	Unit	Route of administration	ATC code
balsalazide	6.75	g	O	A07EC04
clopidogrel	75	mg	O	B01AC04
dexketoprofen	75	mg	O	M01AE17*
dihydroergotamine	1	mg	N	N02CA01
fenofibrate	0.2	g (micronised)	O	C10AB05
finasteride	1	mg	O	D11AX10*
fosphenytoin	0.45	g	P	N03AB05*
mometasone	0.2	mg	N	R01AD09
ondansetron	16	mg	R	A04AA01
orlistat	0.36	g	O	A08AB01

New DDDs (continued):

INN/common name	DDD	Unit	Route of administration	ATC code
pantoprazole	40	mg	P	A02BC02
propiverine	30	mg	O	G04BD06
quetiapine	0.4	g	O	N05AH04
raloxifene	60	mg	O	G03XC01*
riluzole	0.1	g	O	N07XX02
rivastigmine	9	mg	O	N07AA06
rizatriptan	10	mg	O	N02CC04*
temocapril	10	mg	O	CO9AA14*
triamcinolone	0.22	mg	N	R01AD11
trovafloxacin	0.2	g	O,P	J01MA13*
ziprasidone	80	mg	O	N05AE04*

** temporary ATC code*

Change of DDDs:

dalteparin	2.5	TU (antiXa)	P	B01AB04
danaparoid	1.5	TU (antiXa)	P	B01AB09
dexibuprofen	0.8	g	O	M01AE14
dolasetron	0.1	g	P	A04AA04
enoxaparin	2.0	TU (antiXa)	P	B01AB05
fluticasone	0.2	mg	N	R01AD08
nandroparin	2.85	TU (antiXa)	P	B01AB06
parnaparin	3.2	TU (antiXa)	P	B01AB07
reviparin	1.43	TU (antiXa)	P	B01AB08
tinzaparin	3.5	TU (antiXa)	P	B01AB10

Temporary ATC codes and DDDs under evaluation:

INN/common name	ATC code	DDD
follitropin beta	G03GA06	75 U* P
memantine	N06BX21*	
propentofylline	N06BC02*	

ATC/DDD Classification (final)

The following classifications were agreed at a meeting of the WHO International Drug Utilization Working Group which took place on 30 and 31 March 1998 in Oslo.They came into force on **15 November 1998**. All requests for classification should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, P.O. Box 100, Veivet, 0518, Oslo, Norway (telephone: 00 47 22 16 9811, fax: 0047 22 16 9818, e-mail: whocc@nmd.no). The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC Level	*INN/common name*	*ATC code*

New ATC level codes (other than 5th level):

Helicobacter pylori, combinations for eradication of	A02BD
Antipsoriatics, other, for systemic use	D05BX
Gynecologicals, other	G02CX

New ATC 5th level codes:

azidamfenicol	S01A A25
albumin tannate, combinations	A07X A51
balsalazide	A07E C04
benzoyl peroxide, combinations	D10A E51
brimonidine	S01E A05
candesartan	C09C A06
candesartan and diuretics	C09D A06
canrenone	C03D A03
carbamide, combinations	D02A E51
charcoal, medicinal, combinations	A07B A51
cefdinir	J01D A42
cefprozil	J01D A41
cinolazepam	N05C D13
delavirdine	J05A G02
diphtheria-*haemophilus influenzae* B-pertussis-poliomyelitis-tetanus	J07C A06
efavirenz	J05A G03
emedastine	S01G X06
ethambutol, combinations	J04A M03
etilefrine, combinations	C01C A51
ferric oxide dextran complex	B03A C06
ferric proteinsuccinylate	B03A B09
fluocinonide and antibacterials	D07C C05
fumaric acid derivatives, combinations	D05B X51
gadoversetamide	V08C A06

ATC Level	INN/common name	ATC code
	heparin	S01X A14
	hexamidine	R01A X07
	hydrocortisone, combinations	R01A D60
	hydroxocobalamin, combinations	B03B A53
	ibopamine	S01F B03
	imiquimod	D06B B10
	immunocyanin	L03A X10
	interferon alfa-2a	L03A B04
	interferon alfa-2b	L03A B05
	interferon alfa-n1	L03A B06
	interferon beta-1a	L03A B07
	interferon beta-1b	L03A B08
	isoprenaline, combinations	R03C B51
	isopropanol	D08A X05
	kanamycin	S01A A24
	ketamine	N01A X14
	levobupivacaine	N01B B10
	levofloxacin	J01M A12
	macrogol, combinations	A06A D65
	melitracen and psycholeptics	N06C A02
	mometasone	R01A D09
	nystatin, combinations	G01A A51
	omeprazole, amoxicillin, and metronidazole	A02B D01
	oprelvekin	L03A C02
	penciclovir	J05A B13
	phenylephrine, combinations	R01B A53
	propanol, combinations	D08A X53
	quetiapine	N05A H04
	ramipril and calcium channel blockers	C09B B05
	reboxetine	N06A X18
	rivastigmine	N07A A06
	salicylic acid	S01B C08
	salmeterol and anti-asthma	R03A K06
	sibutramine	A08A A10
	sildenafil	G04B E03
	tazarotene	D05A X05
	tretinoin, combinations	D10A D51
	triamcinolone	R01A D11
	zaleplon	N05C F03
	combinations	A07B C30
	combinations	S02D A30
Change of ATC code:		
previous:	zolpidem	N05C G01
new:	zolpidem	N05C F02
Deleted ATC level:		
	imidazopyridines	N05CG

Change of level name:

Previous	*New*	*ATC code*
cyclopyrrolones	benzodiazepine-related drugs	N05CF
diazepines and oxazepines	diazepines, oxazepines and thiazepines	N05AH
ferric oxide polymaltose complex	dextriferron	B03AB05
interferon alfa	interferon alfa natural	L03A B01
interferon beta	interferon beta natural	L03A B02

New DDDs:

INN/common name	DDD	Unit	Route of administration	ATC code
brimonidine	0.2	ml		S01E A05*
candesartan	8	mg	O	C09C A06*
cefdinir	0.6	g	O	J01D A42*
cidofovir	25	mg	P	J05A B12
eprosartan	0.6	g	O	C09C A02
follitropin beta	75	IU	P	G03G A06
grepafloxacin	0.4	g	O	J01M A11
irbesartan	0.15	g	O	C09C A04
levofloxacin	0.25	g	O, P	J01M A12*
montelukast	10	mg	O	R03D C03
pilocarpine	15	mg	O	N07A X01
polycarbophil calcium	2.5	g	O	A06A C08
reboxetine	8	mg	O	N06A X18*
saquinavir	1.8	g	O	J05A E01
tolcapone	0.45	g	O	N04B X01
tolterodine	4	mg	O	G04B D07
zolmitriptan	2.5	mg	O	N02C C03

Change of DDDs:

INN/common name	DDD	Unit	Route of administration	ATC code
risperidone	5	mg	O	N05A X08

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: Department of Essential Drugs and Other Medicines (EDM), World Health Organization, 1211 Geneva 27, Switzerland.

Diuretics

Diuretics are employed to increase urinary excretion in the treatment of hypertension and oedema due to congestive heart failure, or chronic renal or hepatic disease. They reduce extracellular fluid volume by decreasing total body sodium chloride content and modify renal handling of other cations, thereby enhancing potassium and magnesium excretion, and decreasing calcium and urate.

Thiazide diuretics, such as hydrochlorthiazide, are moderately potent but are not effective if the glomerular function rate is less than 30 ml/minute. They inhibit sodium and chloride resorption at the beginning of the distal convoluted tubule and act within one to two hours of oral administration. Most have a duration of action from 12–24 hours.

In mild to moderate high blood pressure, thiazides are often used at low dose to produce a maximal or near-maximal blood pressure lowering effect with very little biochemical disturbance. Higher doses do not necessarily increase the hypotensive response but may cause marked changes in plasma potassium, magnesium, uric acid, glucose and lipids. Thiazides are also used in combination with other antihypertensives to reduce higher blood pressure and in the management of oedema due to mild to moderate congestive heart failure. Oedema due to kidney or hepatic diseases may also respond to thiazides, although the oedema secondary to the nephrotic syndrome may require more potent loop diuretics. Paradoxically, thiazides are used in the treatment of diabetes insipidus, by reducing urine volume up to 50%. Another less common use of thiazides is treatment of hypercalciuria in patients with calcium-containing renal calculi.

Thiazides often cause potassium depletion which increases ventricular irritability and may lead to cardiac arrhythmias. The avoidance of potassium depletion is particularly important in patients taking cardiac glycosides, such as digoxin, since hypokalaemia potentiates cardiac toxicity of these drugs.

Loop diuretics, or high-ceiling diuretics, such as furosemide, are highly potent diuretics which rapidly produce an intense dose-dependent diuresis of short duration. They inhibit resorption from the ascending loop of Henle in the renal tubule and are useful, particularly in situations where rapid and effective diuresis is needed such as reduction of acute pulmonary oedema due to left ventricular failure or in hypertensive crises. Loop diuretics are also used to treat oedema in chronic renal insufficiency and nephrotic syndrome. Oral furosemide produces diuresis within 30 minutes to 1 hour of administration, with the maximum diuretic effect in 1–2 hours. The diuretic action lasts for 4–6 hours. Intravenous furosemide produces diuresis within 5 minutes, with the maximum diuretic effect in 20–60 minutes and diuresis is complete within 2 hours. Because loop diuretics are highly potent, overtreatment of oedema with loop diuretics can produce severe dehydration and circulatory collapse. Hypokalaemia and other electrolyte disturbances may also develop. Rapid high dose injection or infusion of furosemide may cause tinnitus and even permanent deafness.

Potassium-sparing diuretics, such as amiloride and spironolactone, are relatively weak diuretics and are usually used in combination with thiazide or loop diuretics. They cause retention of potassium, and amiloride causes a small increase in sodium chloride excretion and mild natriuresis. Amiloride

and spironolactone are often used in combination with thiazides or loop diuretics to conserve potassium in patients at risk from hypokalaemia during the long-term treatment of oedema associated with heart failure or hepatic cirrhosis, including ascites. Spironolactone requires multiple doses over 2–3 days to achieve the maximum diuretic effect. The diuretic activity stops 2–3 days after cessation of treatment. Spironolactone is also used in the treatment of hyperaldosteronism and refractory oedema associated with secondary aldosteronism.

The most dangerous adverse effect of potassium-sparing diuretics, such as amiloride or spironolactone, is hyperkalaemia, which can be life threatening. These diuretics are thus contraindicated in patients with hyperkalaemia or who may develop hyperkalaemia, with renal failure, those receiving other potassium sparing diuretics, and patients taking ACE inhibitors or potassium supplements.

Osmotic diuretics such as mannitol are administered in sufficiently large doses to raise the osmolarity of plasma and renal tubular fluid. With adequate rehydration, mannitol is mainly used to increase urine flow in patients with acute renal failure. Osmotic diuretics are used to reduce or prevent cerebral oedema, to reduce raised intraocular pressure or to treat dialysis disequilibrium syndrome. Mannitol is also used to control intraocular pressure during acute attacks of glaucoma, and is particularly useful in reducing intraocular pressure before or after eye surgery.

AMILORIDE

Tablet: 5 mg (hydrochloride)

Uses: Oedema associated with heart failure and hepatic cirrhosis (with or without ascites). Also used in combination with thiazide or loop diuretics to conserve potassium.

Dosage: 10 mg daily adjusted according to response (maximum 20 mg).

Used in combination with thiazides or loop diuretics to treat congestive heart failure and hypertension: Initial oral dose, 5 mg daily. Increase to 10 mg if necessary.

Used in combination with thiazides or loop diuretics to treat hepatic cirrhosis with ascites: Initial oral dose, 5 mg daily.

Contraindications: Hyperkalaemia, renal failure.

Precautions: Pregnancy, breastfeeding, in elderly, diabetes mellitus. Monitor serum electrolytes, in particular potassium.

Adverse effects: Nausea, vomiting, abdominal pain, diarrhoea, constipation, and anorexia. Headache, dizziness and minor psychiatric or visual changes. Skin rashes, pruritus, muscle cramps, orthostatic hypotension. Hyperkalaemia (elevated potassium) and hyponatraemia (decreased sodium). Signs of hyperkalaemia include irregular heartbeat, confusion, nervousness, numbness or tingling in hands, feet or lips, shortness of breath or difficult breathing, unusual tiredness or weakness, and weakness or heaviness of legs. Signs of hyponatraemia include drowsiness, dry mouth, increased thirst and lack of energy.

Drug interactions: Other potassium-sparing diuretics, patients taking potassium supplements or patients taking ACE inhibitors increases risk of hyperkalaemia.

FUROSEMIDE

Tablet: 40 mg
Injection: 10 mg/ml in 2-ml ampoule

Uses: Oedema due to congestive heart failure or renal or hepatic disease.

Dosage:
Oral
Adults: Initial oral dose of 40 mg daily on rising: Maintenance dose of 20 mg daily or 40 mg on alternate days. Resistant cases may need 80 mg daily.

Children: 1–3 mg/kg daily.

Intramuscular injection or slow intravenous injection
Reserved for emergency use only. Do not exceed injection rate of 4 mg/minute.

Adults: 20–50 mg; can be increased in 20 mg increments every 2 hours.

Children: 0.5–1.5 mg/kg up to 20 mg daily.

By intravenous infusion for oedema: If the effective single dose is more than 50 mg, consider using a slow intravenous infusion. Do not exceed infusion rate of 4 mg/minute.

Treatment of oliguria: In patients where glomerular filtration rate is less than 20 ml/minute:
• dilute furosemide 250 mg in 250 ml of infusion fluid. Infuse over 1 hour.

• if no response to first infusion, dilute furosemide 500 mg in appropriate amount of infusion fluid, depending on hydration state of patient. Infusion over 2 hours.

• If no response to second infusion, dilute furosemide 1000 mg (1 gram) in appropriate amount of infusion fluid, depending on hydration state of patient. Infusion over 4 hours.

• If no response to third infusion, patient probably requires dialysis

Contraindications: Severe hyperkalaemia, hyponatraemia, renal failure with anuria and precomatose states associated with liver cirrhosis.

Precautions: Monitor serum electrolytes, especially potassium, calcium, chloride and bicarbonate before beginning furosemide therapy and regularly during therapy.Reduce dosage in elderly. In diabetics or suspected diabetics, monitor urine glucose and blood glucose.

Adverse effects: Hyponatraemia, hypokalaemia and hypomagnesaemia. Hypochloraemic alkalosis, increased calcium excretion, hypovolaemia and hypotension. Nausea, gastrointestinal disturbances, hyperuricaemia and gout are reported less commonly. Hyperglycaemia: but less often than with thiazide diuretics. Temporary increase in plasma cholesterol and triglyceride concentration. Rashes, photosensitivity, bone marrow depression, pancreatitis, tinnitus and deafness are reported rarely. Tinnitus and deafness may be experienced with large parenteral doses and rapid administration of furosemide, and in patients with renal impairment or in patients taking other ototoxic drugs.

HYDROCHLOROTHIAZIDE

Tablet: 25 mg, 50 mg

Uses: Oedema, mild to moderate hypertension.

Dosage: *Hypertension*: 12.5–25 mg daily.

Adults with oedema: Initial oral dose to be taken on rising of 25 mg daily. If necessary, increase to 50 mg daily.

Elderly: Initial oral dose of 12.5 mg daily.

Adults with severe oedema or toxaemia of pregnancy: 100 mg oral daily or intermittently, at intervals of up to 4 days.

Adults with nephrotic diabetes insipidus: initial oral dose of 100 mg daily

Contraindications: Severe kidney or severe liver impairment. Refractory hypokalaemia, hyponatraemia, hypercalcaemia, symptomatic hyperuricaemia, Addison's Disease, porphyria.

Precautions: In elderly, pregnancy, breastfeeding, renal or hepatic impairment. May reduce potassium levels and aggravates diabetes and gout. May exacerbate systemic lupus erythematosus.

Adverse effects: Hypokalaemia and hypomagnesaemia are the most important adverse effects. Other common adverse effects include lethargy, drowsiness, hyperglycaemia, hyperuricaemia, gout, gastrointestinal adverse effects (anorexia, nausea, vomiting, constipation and diarrhoea), hyponatraemia, hypercalcaemia, hypochloraemic alkalosis, rashes and photosensitivity. Rare adverse effects include impotence, blood disorders (including neutropenia and thrombocytopenia), pancreatitis, hepatitis, intrahepatic cholestasis, hypersensitivity reactions and acute renal failure.

Drug interactions: Digitalis and digitalis glycosides (digoxin, digitoxin) will increase the risk of toxicity if hypokalaemia occurs.

MANNITOL

Injectable solution: 10% and 20%

Uses: To treat raised intracranial pressure, intracranial oedema, intraocular pressure and oedema in glaucoma, or for administration in preparation for intraocular surgery.

Dosage:
Adults: Use slow infusion rate (not rapid?

Cerebral oedema (other indications?
Adults: 1.5–2.0 g/kg as 20% solution administered over 30–60 minutes. (as injection?
Children: Dose of 0.25–2.0 g/kg.

Contraindications: Pulmonary congestion, pulmonary oedema, intracranial bleeding except during craniotomy, severe congestive heart failure, severe dehydration and metabolic oedema with abnormal capillary fragility. Patients with renal failure unless a test dose has produced diuresis. Hyperkalaemia, hypokalaemia or hypovolaemia.

Precautions: Extravasation. Never add mannitol to whole blood for transfusion. Never give mannitol using the same set through which blood is being infused. Monitor renal function, fluid balance and electrolytes. Solutions containing more than 15% mannitol may crystallize during storage. Redissolve crystals by warming before use. Do not use solution if all crystals do not completely dissolve. All intravenous administration sets should have a filter.

Adverse effects: Extravasation may cause oedema, skin necrosis, inflammation and thrombophlebitis. Fluid and electrolyte imbalance, including circulatory overload and acidosis. Expansion of extracellular volume can cause pulmonary oedema, particularly in patients with diminished cardiac reserve. Intravenous infusions have been reported to cause nausea, vomiting, headache, dizziness, chills fever, tachycardia, chest pain, blurred vision, urticaria, hypotension, hypertension and allergic reactions.

SPIRONOLACTONE

Tablet: 25 mg

Uses: Refractory oedema in patients with congestive heart failure, nephrotic syndrome, hepatic cirrhosis (with or without ascites) and in ascites associated with malignancy. Diagnosis and treatment of primary hyperaldosteronism.

Dosage:
Oedema
Adults: 100 mg daily, which may be increased in resistant cases to 400 mg daily.

Children: 3 mg/kg in divided doses.
Primary hyperaldosteronism:
Diagnosis (do you mean prophylaxis?) 400 mg daily in 4 divided doses, for 3–5 weeks.
Treatment: 100–400 mg daily.

Contraindications: Hyperkalaemia, hyponatraemia. Severe renal impairment, diabetes with renal impairment. Addison's disease.

Precautions: Monitor serum electrolytes and blood urea nitrogen periodically during therapy especially in the elderly and in patients with decrease in renal or hepatic function, diabetes mellitus, or patients at risk of hyperkalaemia.

Adverse effects: Gynaecomastia, impotence, menstrual irregularities, gastrointestinal disturbances, including cramps and diarrhoea, skin rashes, hyponatraemia, dehydration, headaches, drowsiness, ataxia, mental confusion, fever, and hepatoxicity. Transient increase in blood urea nitrogen. Reversible hyperchloraemia metabolic acidosis. Severe hyperkalaemia in patients with impaired renal function or in patients receiving supplemental potassium.

Drug interactions: ACE inhibitors combined with spironolactone may produce hyperkalaemia. Other interactions will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

Anti-allergics and drugs used in anaphylaxis

Although there are three types of histamine receptors H_1, H_2 and H_3 it is the H_1 receptor antagonists which are generally referred to as antihistamines. These are responsible for a histamine-induced increase in capillary permeability and sensory nerve stimulation, thus inhibiting the wheal, pruritus, sneezing and mucous secretion responses that are characteristic of allergy. H_1 receptor antagonists thus relieve the symptoms of allergic reactions, such as urticaria, angioedema, allergic rhinitis, and allergic conjunctivitis. They are also used to treat drug allergies, food allergies and insect stings and some of the symptoms of anaphylaxis. Antihistamines also control the pruritus in skin disorders, such as eczema. However, they are ineffective in the treatment of acute asthmatic attacks.

Drowsiness and sedation are particular disadvantages of the early antihistamines and the patient should be warned against driving or operating any type of machinery. Other central nervous depressants, including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and neuroleptics may enhance the sedative effects of antihistamines. Since they interfere with skin tests for allergy, therapy should be stopped at least one week before conducting a skin test. Rashes and

photosensitivity reactions, palpitations and arrhythmias have also been reported.

Chlorphenamine is considered the prototype for antihistamine H_1 antagonists. This class includes drugs with less sedative action than the traditional antihistamines or with different therapeutic potencies. In practice, all antihistamines are equally effective in relieving the symptoms of allergic reactions and differ mainly in the intensity of sedative and anticholinergic effects. Selection of drugs in this class should thus be based on the intended therapeutic uses, the adverse reaction profile and the cost.

Corticosteroids, such as dexamethasone, hydrocortisone, or prednisolone suppress or prevent almost all symptoms of inflammation associated with allergy. The route of administration should depend on the particular type of allergic condition. For example, in the case of a mild allergic skin reaction, the best therapy may be to apply a glucocorticoid ointment or cream. If the skin reaction does not respond to topical corticosteroid therapy, it may be necessary to give corticosteroids orally. Allergic diseases of limited duration and with mild reactions, such as urticaria or allergic rhinitis, usually require no treatment. If, on the other hand, symptoms become persistent, antihistamines constitute the mainstay of treatment.

Corticosteroids should be considered as supplements to primary therapy and used to reduce inflammation. Oral corticosteroids may be required for a few days in an acute attack of urticaria. Oral corticosteroids are also used to relieve severe exacerbations in chronic urticaria, but long-term use of oral corticosteroids should be avoided. Corticosteroids may be used topically to reduce inflammation in allergic rhinitis but should not be used orally or parenterally for this condition.

The adverse effects of corticosteroids include inhibition of growth in children, disturbances of the electrolyte balance leading to oedema and hypertension and to potassium loss, production of osteoporosis and spontaneous fractures, skin thinning, increased susceptibility to infection, mental disturbances and diabetes.

Allergic emergencies

Anaphylactic shock is a medical emergency that can result in cardiovascular collapse and death. It requires prompt treatment of possible laryngeal oedema, bronchospasm or hypotension. Atopic individuals are particularly susceptible. Insect bites and certain foods including eggs, fish, peanuts and nuts are also a risk for sensitized persons. Drugs particularly associated with anaphylaxis include blood products, vaccines, antibiotics (especially penicillins), iron injections, heparin and neuromuscular blocking agents. Acetylsalicylic acid and other NSAIDs, may cause bronchoconstriction in leukotreine-sensitive patients. In the case of drug allergy, anaphylaxis is more likely to occur after parenteral administration. Resuscitation facilities should always be available if injection of a drug is associated with a certain risk.

First-line treatment includes administering epinephrine, keeping the airway open (assisted respiration may be necessary) and restoring blood pressure. Epinephrine should immediately be given by deep intramuscular or subcutaneous injection to produce vasoconstriction and bronchodilation and injections should be repeated every ten minutes until blood pressure and pulse have stabilized. If there is complete cardiovascular shock, epinephrine must be given by slow intravenous injection.

Further treatment of anaphylaxis often includes intravenous corticosteroids such as hydrocortisone, intravenous antihistamines, such as chlorphenamine, and may include intravenous fluids, oxygen, an intravenous vasopressor agent, such as dopamine, intravenous aminophylline, and an injected or nebulized bronchodilator, such as salbutamol. Chlorphenamine is a useful adjunctive treatment given after epinephrine injection and continued for 24 to 48 hours to reduce the severity and duration of symptoms and to prevent relapse. An intravenous corticosteroid such as hydrocortisone has an onset of action that is delayed several hours, but should be given to help prevent later deterioration in severely affected patients.

Steps in anaphylactic shock management

1. Epinephrine:

- 0.1 ml/10 kg (strength 1:1000, 1 mg/ml) by deep intramuscular injection; the dose can be repeated 10-30 minutes later.

- If the patient is in shock:
  Adult:s 1–3 ml (strength 1:10 000, 0.1 mg/ml) by slow intravenous infusion.
  Children: 0.1–0.5 ml (strength 1:10 000, 0.1 mg/ml) by slow intravenous infusion.

2.Vital functions: maintain an open airway; give oxygen by mask.

3. Corticosteroids–hydrocortisone

Adult: 250–500 mg intravenously

Child: 10 mg/kg intravenously.

4. Intravenous fluids: start infusion with sodium chloride (500–1000 ml during the first hour).

5. If the patient has asthma-like symptoms, give aminophylline: 5 mg/kg by slow intravenous injection.

6. Antihistamine orally.

CHLORPHENAMINE

Tablet: 4 mg (hydrogen maleate)
Injection: 10 mg (hydrogen maleate) in 1-ml ampoule

Uses: Symptomatic relief of allergy, hay fever, allergic rhinitis and conjunctivitis, urticaria, insect stings, pruritus of allergic origin and angioedema. Adjunct in the emergency treatment of anaphylactic shock or in the emergency treatment of severe angioedema.

Dosage:
Adults: 4 mg every 4–6 hours, maximum 24 mg daily.

Emergencies: by subcutaneous or intramuscular injection or slow intravenous injection:

Adults: 5–20 mg, repeated if required (max 40 mg in 24 hours).

Children: 1–2 years: 1 mg twice daily. 2–5 years: 1 mg every 4–6 hours (max 6 mg daily). 6–12 years: 2 mg every 4–6 hours (max 12 mg daily).

Contraindications: Patients with prostate enlargement since chlorphenamine may cause urinary retention. Patients with ileus or pyloric stenosis. Glaucoma. Children under one year.

Precautions: Use with caution in patients with epilepsy, hepatic disease and severe cardiovascular disorders. Ability to drive or operate machinery may be impaired.

Adverse effects: Drowsiness, hypotension, headache, palpitations, psychomotor impairment, urinary retention, dry mouth, blurred vision and gastrointestinal disturbances. Other adverse effects include rash and photosensitivity reactions, sweating and tremor. Injections may be irritant and may cause paradoxical central nervous system stimulation and hypotension.

Drug Interactions: Effects of alcohol and other CNS depressants may be additive. Other drug interactions will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

DEXAMETHASONE

Tablet: 0.5 mg, 4 mg
Injection: 4 mg dexamethasone phosphate (as disodium) in 1-ml ampoule

Uses: Adjunct in the emergency treatment of anaphylaxis. Short-term suppression of inflammation in allergic disorders.

Dosage:
Orally: usual range 0.5–10 mg daily.

By intramuscular injection or slow intravenous injection or infusion:
Adults: 0.5–20 mg daily.
Children: 200–500 micrograms/kg daily.

Contraindications, precautions and adverse effects: Because rare instances of anaphylactoid reactions such as bronchospasm have occurred in patients receiving parenteral corticosteroid treatment, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to drugs.

EPINEPHRINE (ADRENALINE)

Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule

Uses: Severe anaphylactic reaction or severe angioedema.

Dosage:
Caution: Different dilutions of epinephrine solution are used for different routes of administration. Use 1:1000 epinephrine solution for intramuscular or subcutaneous injection.

Anaphylaxis

Age	volume of epinephrine 1: 1 000 (1 mg/ml solution)
under 1 year	0.05 ml
1 year	0.1 ml
2 years	0.2 ml
3–4 years	0.3 ml
5 years	0.4 ml
6–12 years	0.5 ml
Adult	0.5–1.0 ml

Repeat the dose every 10 minutes as necessary, according to blood pressure and pulse, until improvement occurs.

Use 1:10 000 epinephrine solution for slow intravenous injection.

This route should be reserved for severely ill patients when there is doubt about the adequacy of circulation and absorption from the intramuscular site.

Adults: 500 µg (0.5 mg), i.e., 5 ml of a dilute 1:10 000 epinephrine injection solution given at an injection rate of 100 µg (1 ml of a dilute 1:10 000 epinephrine injection solution)/minute, stopping once a response is obtained.

Children: 10 micrograms/kg (0.1 ml/kg of a dilute 1:10 000 epinephrine injection solution) given over several minutes.

Contraindications: Hyperthyroidism, hypertension, diabetes mellitus, ischaemic heart disease, hypertension and closed angle glaucoma. Chronic bronchial asthma and substantial emphysema. Elderly patients.

Adverse effects: Tachycardia and arrhythmias, hypertension, tremor, anxiety, sweating, nausea, vomiting, weakness, dizziness and pulmonary oedema have all been reported. Headache is common.

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

HYDROCORTISONE

Powder for injection, 100 mg (as sodium succinate) in vial

Uses: Adjunct in the emergency treatment of anaphylaxis.

Dosage: Anaphylactic emergency: *By slow intravenous injection*: Adult: 100+300 mg three to four times in 24 hours as required. Children: < 1 year 25 mg, 1-5 years 50 mg, 6-12 years 100 mg.

Contraindications, precautions and adverse effects: Because rare instances of anaphylactoid reactions such as bronchospasm have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to drugs.

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

PREDNISOLONE

Tablet, 5 mg

Uses: Short-term suppression of inflammation in allergic disorders.

Dosage: Initial dose up to 10–20 mg daily. Severe allergy may require up to 60 mg daily. The maintenance dose is 2.5–15 mg daily. Higher doses may be necessary.

Contraindications

Adverse effects

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

Recent Publications and Documents

The New Emergency Health Kit 98

The provision of health care is difficult and demanding in the aftermath of large scale emergencies and disasters. In collaboration with a large number of international agencies, WHO has developed the Emergency Health Kit. The Kit is available from a number of major pharmaceutical suppliers and the newly-revised publication explains how to use the standardized packages of essential drugs, supplies and equipment. Development of the Kit was based on priority health needs and is designed to expedite the provision of supplies, in particular by emergency relief agencies.

A complete emergency health kit contains two separate sets of drugs and supplies. The main set is intended for use by health workers located in remote areas or operating under isolated conditions, and the supplementary kit contains drugs, renewable supplies and equipment needed by doctors working in first level health facilities.

The concept of an emergency health kit has been developed over years of study and field testing. Information has been drawn from epidemiological data, population profiles and specific disease patterns following emergencies. A description of the contents of the health kit, treatment guidelines and checklists for suppliers and prescribers is also included as part of the publication. Useful annexes have been integrated into the book including the *Model Guideline for the International Provision of Controlled Medicines for Emergency Medical Care*, and *Guidelines for Drug Donations*.

The New Emergency Health Kit 98. WHO/DAP/98.10. Available from: World Health Organization, Geneva, Switzerland. Price Sw.Fr. 8.-

Tuberculosis and air travel

In recent years, several episodes of potential transmission of tuberculosis infection during air travel have been reported. Although the risk of transmission during air travel has been documented, it seems to be relatively low. Nonetheless, within the next decade, it is expected that more than two billion passengers per year will travel by scheduled air traffic. Because airlines, passengers, physicians and health authorities need to know the risk of tuberculosis transmission and how to take proper measures, WHO has issued guidelines endorsed by the Aerospace Medical Association and the Airline Medical Directors Association.

The guidelines were produced in collaboration with international health experts, civil aviation authorities and airline company representatives. The guidelines give recommendations for collaboration between physicians, health authorities and airline companies. Advice is given on prevention and management of infectious passengers, contact tracing, conducting investigations, reducing the risk of exposure, and improving air quality and ventilation.

Tuberculosis and Air Travel: Guidelines for Prevention and Control. WHO/TB/98.258. Available from: World Health Organization, Geneva, Switzerland.

Effects of antimicrobials used in food-producing animals

The US Food and Drug Administration has recently issued *A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals*. This is the second step in the Agency's efforts to develop policies to deal with the problem of antimicrobial resistance. The FDA is particularly concerned that significant human antimicrobial therapies are not lost as a result of the overuse of antimicrobials in food-producing animals.

As a first step, the Agency has produced the draft guidance document *Evaluation of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals*. This document set out two criteria for evaluation (i) the quantity of antimicrobial drug resistant enteric bacteria formed in the animal's intestinal tract following exposure to the antimicrobial; and (ii) any changes in the number of enteric bacteria in the animals intestinal tract that

cause human illness (pathogenic load). Its aim is also to address the risk of increased human infections as a result of disturbance of the normal intestinal microbial ecosystem causing an increase in pathogens in the animal.

A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals. Available from the Food and Drug Administration. http://www.fda.gov./cvm/fda/infores/vmac/ANTIM18.htm

Quality control methods for medicinal plant material

Because of their increasing use worldwide, more and more attention is being paid to the quality of plant materials used in over-the-counter preparations, home remedies or as raw materials for pharmaceutical preparations.

This book has been prepared in response to the need for international harmonization in quality control testing of medicinal plant materials. It contains descriptions of recommended test methods for identity, purity and content, together with a detailed list of the reagents and solutions necessary to carry these out. The purpose of the tests is twofold, to fulfil the needs of quality control laboratories and to provide a basis for the development of national standards.

The book will be useful for national drug regulatory authorities, the pharmaceutical industry and pharmacists working with medicinal plant materials.

Quality control methods for medicinal plant materials. Available from: World Health Organization, Geneva, Switzerland. E-mail: publications@who.int. Price Sw.Fr. 35.- (Price in developing countries: Sw.Fr. 24.50).

Basic Tests for Drugs

Basic tests represent one of the many elements of quality assurance for pharmaceutical products. The basic test series has been developed by WHO to provide a simple method to confirm the identity of a substance or indicate whether gross degradation has occurred. The tests described in the latest manual, *Basic Tests for Drugs: Pharmaceutical Substances, Medicinal Plant Materials and Dosage Forms*, are meant to complement the previously published *Basic Tests for Pharmaceutical Substances* and *Basic Tests for Pharmaceutical Dosage Forms*.

The book describes test procedures for 23 pharmaceutical substances and 58 pharmaceutical dosage forms, including basic tests for confirming the identity of 4 commonly used medicinal plant materials. A description of other tests is made, including thin-layer chromatography and volumetric or spectrophotometric analysis which can be useful in screening. The book concludes with a cumulative index of test procedures contained in this and the previous two related publications.

Basic Tests for Drugs: Pharmaceutical Substances, Medicinal Plant Materials and Dosage Forms. Available from: World Health Organization, Geneva, Switzerland. E-mail: publications@who.int. Price Sw.Fr. 26.- (Price in developing countries: Sw.Fr. 18.20).

Information data base for dietary supplements

Currently, the term dietary supplement is used for a wide array of products available in health food stores, pharmacies or by mail order which contain vitamins, minerals, nutrients and herbals as well as ingredients and extracts of animal and plant origin. Given the growing problems surrounding the terminology used to describe the ingredients of dietary supplements, the National Institutes of Health has launched a database for access via the internet to provide scientific information on supplements. The site will assist health experts and the public to determine the status of substances with reference to published scientific literature and will provide definitions on what a dietary supplement is considered to be.

National Institutes of Health Office of Dietary Supplements. Available on: http://odp.od.nih.gov/ods

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 41

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.
Lists of Proposed (1–73) and Recommended (1–35) International Nonproprietary Names can be found in *Cumulative List No. 9, 1996.*

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMENDÉES (DCI Rec): Liste 41

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9)] les dénominations ci-dessous sont choisises par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées 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.*

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 41

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, **60**, 3 (Resolución EB15.R7); 1969, **173**, 10 (Resolución EB43.R9)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas 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.*

An ongoing review is under way of the long-standing objections to proposed International Nonproprietary Names (INN). As a result, objections have been withdrawn to the following names which are now included in this list of recommended INNs:

aspartic acid, amiprilose, dinaline, flumoxonide, mebeverine, megestrol, miroprofen, piridicillin, teclozan, thiram

Les objections formulées de longue date contre des Dénominations communes internationales (DCI) proposées sont examinées. Des objections ont été retirées à la suite de cet examen et les noms suivants sont donc inclus dans cette liste des DCI recommandées:

acide aspartique, amiprilose, dinaline, flumoxonide, mébévérine, mégestrol, miroprofène, piridicilline, téclozan, thirame

Se ha emprendido un examen de las objeciones que se vienen formulando desde hace tiempo a las denominaciones comunes internacionales (DCI) propuestas. Como resultado, se han retirado las objeciones a las denominaciones siguientes, que ahora están incluidas en la presente lista de DCI recomendadas:

ácido aspártico, amiprilosa, dinalina, flumoxónida, mebeverina, megestrol, miroprofeno, piridicilina, teclozán, tiramo

Latin, English, French, Spanish: *Recommended INN*	*Chemical name or description; Molecular formula; Graphic formula*
DCI Recommandée	*Nom chimique ou description; Formule brute; Formule développée*
DCI Recomendada	*Nombre químico o descripción; Fórmula empírica; Fórmula desarrollada*

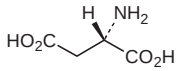
acidum asparticum

aspartic acid — L-aspartic acid

acide aspartique — acide (2*S*)-2-aminobutanedioïque

ácido aspártico — ácido L-aspártico

$C_4H_7NO_4$



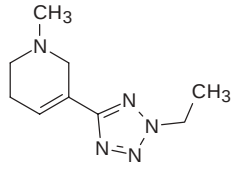
alvamelinum

alvameline — 3-(2-ethyl-2*H*-tetrazol-5-yl)-1,2,5,6-tetrahydro-1-methylpyridine

alvaméline — 3-(2-éthyl-2*H*-tétrazol-5-yl)-1-méthyl-1,2,5,6-tétrahydropyridine

alvamelina — 3-(2-etil-2*H*-tetrazol-5-il)-1,2,5,6-tetrahidro-1-metilpiridina

$C_9H_{15}N_5$



amediplasum

amediplase — 173-L-serine-174-L-tyrosine-175-L-glutamine-173-275-plasminogen activator (human tissue-type reduced), fusion protein with urokinase (human urine β-chain reduced)

amédiplase — [173-L-sérine-174-L-tyrosine-175-L-glutamine]173-275-activateur du plasminogène (type tissulaire humain réduit)-159-411-urokinase (chaîne β urinaire humaine réduite)

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)

SYQGNSDCYF GNGSAYRGTH SLTESGASCL PWNSMILIGK
VYTAQNPSAQ ALGLGKHNYC RNPDGDAKPW CHVLKNRRLT
WEYCDVPSCS TCGLRQYSQP QFRIIGGEFT TIENQPWFAA
IYRRHRGGSV TYVCGGSLIS PCWVISATHC FIDYPKKEDY
IVYLGRSRLN SNTQGEMKFE VENLILHKDY SADTLAHHND
IALLKIRSKE GRCAQPSRTI QTICLPSMYN DPQFGTSCEI
TGFGKENSTD YLYPEQLKMT VVKLISHREC QQPHYYGSEV
TTKMLCAADP QWKTDSCQGD SGGPLVCSLQ GRMTLTGIVS
WGRGCALKDK PGVYTRVSHF LPWIRSHTKE ENGLAL

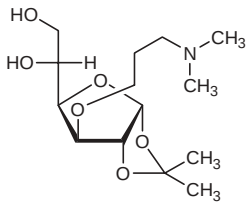
amiprilosum

amiprilose — 3-*O*-[3-(dimethylamino)propyl]-1,2-*O*-isopropylidene-α-D-glucofuranose

amiprilose — 3-*O*-[3-(diméthylamino)propyl]-1,2-*O*-(1-méthyléthylidène)-α-D-glucofuranose

amiprilosa — 3-*O*-[3-(dimetilamino)propil]-1,2-*O*-isopropilideno-α-D-glucofuranosa

$C_{14}H_{27}NO_6$



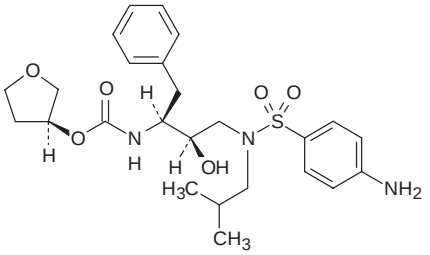
amprenavirum

amprenavir — (3*S*)-tetrahydro-3-furyl [(*S*)-α-[(1*R*)-1-hydroxy-2-(*N*[1]-isobutylsulfanilamido)ethyl]phenethyl]carbamate

amprénavir — [(1*S*,2*R*)-3-[[(4-aminophényl)sulfonyl](2-méthylpropyl)amino]-1-benzyl-2-hydroxypropyl]carbamate de (3*S*)-tétrahydrofuran-3-yle

amprenavir — [(*S*)-α-[(1*R*)-1-hidroxi-2-(*N*[1]-isobutilsulfanilamido)etil]fenetil]carbamato de (3*S*)-tetrahidro-3-furil

$C_{25}H_{35}N_3O_6S$



anatumomabum mafenatoxum

anatumomab mafenatox — immunoglobulin G 1, anti-(human tumor-associated glycoprotein 72) (human-mouse clone pMB125 Fab fragment γ1-chain) fusion protein with enterotoxin A (227-alanine) (*Staphylococcus aureus*) complex with mouse clone pMB125 κ-chain)

anatumomab mafénatox — immunoglobuline G1 (chaîne γ1 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 κ de l'anticorps monoclonal de souris clone pMB125

anatumomab mafenatox — inmunoglobulina G 1 (cadena γ1 del anticuerpo monoclonal quimérico hombre-ratón pMB125 dirigido contra la glicoproteina 72 asociada a tumor humano) proteina de fusión con enterotoxina A de *Staphylococcus aureus* (227-alanina) con el clón de pMB125 cadena κ del anticuerpo

ancestimum

ancestim — *N*-L-methionyl-1-165-hematopoietic cell growth factor KL (human clone V19.8:hSCF162), dimer

ancestim — dimère du *N*-L-méthionyl-1-165-facteur de croissance KL de cellules hématopoïétiques (clone humain V19.8:hSCF162)

ancestim — *N*-L-metionil-1-165-factor de crecimiento celular hematopoietico KL (clon humano V19.8:hSCF162), dímero

$C_{1662}H_{2650}N_{422}O_{512}S_{18}$

M
EGICRNRVTN NVKDVTKLVA NLPKDYMITL KYVPGMDVLP
SHCWISEMVV QLSDSLTDLL DKFSNISEGL SNYSIIDKLV
NIVDDLVECV KENSSKDLKK SFKSPEPRLF TPEEFFRIFN
RSIDAFKDFV VASETSDCVV SSTLSPEKDS RVSVTKPFML
PPVAA
2

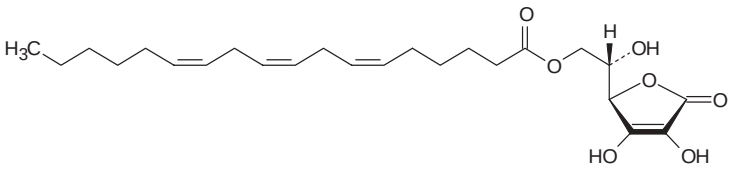
ascorbylum gamolenas

ascorbyl gamolenate — L-ascorbic acid 6-[(6*Z*,9*Z*,12*Z*)-6,9,12-octadecatrienoate]

ascorbyl gamolénate — (6*Z*,9*Z*,12*Z*)-octadéca-6,9,12-triénoate de (2*S*)-2-[(2*R*)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl]-2-hydroxyéthyle

gamolenato de ascorbilo — 6-[(6*Z*,9*Z*,12*Z*)-6,9,12-octadecatrienoato] de ácido L-ascórbico

$C_{24}H_{36}O_7$



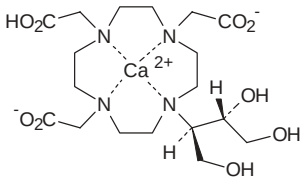
calcobutrolum

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

calcobutrol — hydrogéno 2,2',2''-[10-[(1*RS*,2*SR*)-2,3-dihydroxy-1-(hydroxyméthyl)propyl]-1,4,7,10-tétraazacyclododécane-1,4,7-triyl]triacétate de calcium

calcobutról — 10-[(1*RS*,2*SR*)-2,3-dihidroxi-1-(hidroximetil)propil]-1,4,7,10-tetraazaciclododecano-1,4,7-triacetato de hidrógeno y calcio

$C_{18}H_{32}CaN_4O_9$



and enantiomer
et énantiomère
y enantiómero

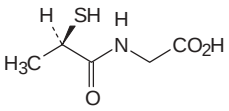
dextioproninum

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

dextiopronine — acide [[(2*R*)-2-sulfanylpropanoyl]amino]acétique

dextiopronina — *N*-[(*R*)-2-mercaptopropionil]glicina

$C_5H_9NO_3S$



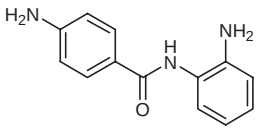
dinalinum

dinaline 2',4-diaminobenzanilide

dinaline 4-amino-*N*-(2-aminophényl)benzamide

dinalina 2',4-diaminobenzanilida

$C_{13}H_{13}N_3O$



edodekinum alfa

edodekin alfa interleukin 12 (human)

édodékine alfa interleukine 12 humaine

edodekina alfa interleuquina 12 (humana)

IWELKKDVYV VELDWYPDAP GEMVVLTCDT PEEDGITWTL
DQSSEVLGSG KTLTIQVKEF GDAGQYTCHK GGEVLSHSLL
LLHKKEDGIW STDILKDQKE PKNKTFLRCE AKNYSGRFTC
WWLTTISTDL TFSVKSSRGS SDPQGVTCGA ATLSAERVRG
DNKEYEYSVE CQEDSACPAA EESLPIEVMV DAVHKLKYEN
YTSSFFIRDI IKPDPPKNLQ LKPLKNSRQV EVSWEYPDTW
STPHSYFSLT FCVQVQGKSK REKKDRVFTD KTSATVICRK
NASISVRAQD RYYSSSWSEW ASVPCS

RNLPVATPDP GMFPCLHHSQ NLLRAVSNML QKARQTLEFY
PCTSEEIDHE DITKDKTSTV EACLPLELTK NESCLNSRET
SFITNGSCLA SRKTSFMMAL CLSSIYEDLK MYQVEFKTMN
AKLLMDPKRQ IFLDQNMLAV IDELMQALNF NSETVPQKSS
LEEPDFYKTK IKLCILLHAF RIRAVTIDRV TSYLNAS

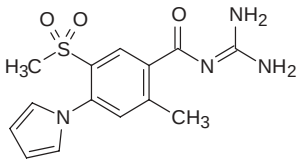
eniporidum

eniporide *N*-(diaminomethylene)-5-(methylsulfonyl)-4-pyrrol-1-yl-*o*-toluamide

éniporide *N*-(diaminométhylène)-2-méthyl-5-(méthylsulfonyl)-4-(1*H*-pyrrol-1-yl)benzamide

eniporida *N*-(diaminometileno)-5-(metilsulfonil)-4-pirrol-1-il-*o*-toluamida

$C_{14}H_{16}N_4O_3S$



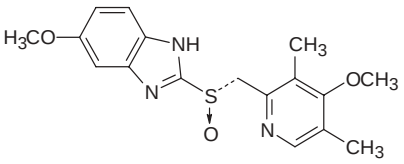
esomeprazolum

esomeprazole — 5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]=sulfinyl]benzimidazole

ésoméprazole — 5-méthoxy-2-[(*S*)-[(4-méthoxy-3,5-diméthylpyridin-2-yl)méthyl]sulfinyl]-1*H*-benzimidazole

esomeprazol — 5-metoxi-2-[(*S*)-[(4-metoxi-3,5-dimetil-2-piridil)metil]sulfinil]benzimidazol

$C_{17}H_{19}N_3O_3S$



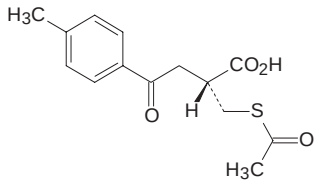
esonarimodum

esonarimod — (±)-3-mercapto-2-(*p*-methylphenacyl)propionic acid acetate

ésonarimod — acide (2*RS*)-2-[(acétylsulfanyl)méthyl]-4-(4-méthylphényl)-4-oxobutanoïque

esonarimod — acetato del ácido (±)-3-mercapto-2-(*p*-metilfenacil)propiónico

$C_{14}H_{16}O_4S$



and enantiomer
et énantiomère
y enantiómero

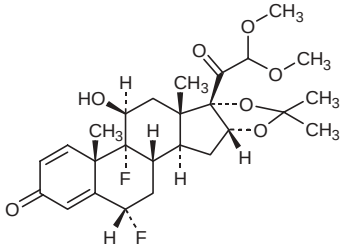
flumoxonidum

flumoxonide — 6α,9-difluoro-11β,16α,17-trihydroxy-3,20-dioxopregna-1,4-dien-21-al 21-(dimethyl acetal) cyclic 16,17-acetal with acetone

flumoxonide — 6α,9-difluoro-11β-hydroxy-21,21-diméthoxy-16α,17-*O*-(1-méthyléthylidène)prégna-1,4-diène-3,20-dione

flumoxónida — 6α,9-difluoro-11β,16α,17-trihidroxi-3,20-dioxopregna-1,4-dien-21-al 21-(dimetil acetal) cíclico 16,17-acetal con acetona

$C_{26}H_{34}F_2O_7$



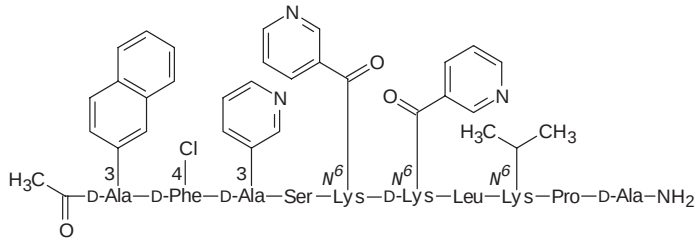
iturelixum

iturelix — [*N*-acétyl-3-(naphtalén-2-yl)-D-alanyl]-*p*-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-N^6-nicotinoyl-L-lysyl-N^6-nicotinoyl-D-lysyl-L-leucyl-N^6-isopropyl-L-lysyl-L-prolyl-D-alaninamide

iturélix — [*N*-acétyl-3-(naphtalén-2-yl)]-D-alanyl]-(4-chloro-D-phénylalanyl)-[3-(pyridin-3-yl)-D-alanyl]-L-séryl-[N^6-(pyridin-3-ylcarbonyl)-L-lysyl]-[N^6-(pyridin-3-ylcarbonyl)-D-lysyl]-L-leucyl-[N^6-(1-méthyléthyl)-L-lysyl]-L-prolyl-D-alaninamide

iturelix — *N*-acetil-3-(2-naftil)-D-alanil-*p*-cloro-D-fenilalanil-3-(3-piridil)-D-alanil-L-seril-N^6-nicotinoil-L-lisil-N^6-nicotinoil-D-lisil-L-leucil-N^6-isopropil-L-lisil-L-prolil-D-alaninamida

$C_{82}H_{108}ClN_{17}O_{14}$



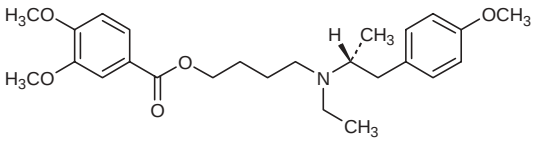
mebeverinum

mebeverine — 4-[ethyl(*p*-methoxy-α-methylphenethyl)amino]butyl 3,4-dimethoxybenzoate

mébévérine — 3,4-diméthoxybenzoate de 4-[éthyl[(1*RS*)-2-(4-méthoxyphényl)-1-méthyléthyl]amino]butyle

mebeverina — 3,4-dimetoxibenzoato de 4-[etil(*p*-metoxi-α-metilfenetil)amino]butilo

$C_{25}H_{35}NO_5$



and enantiomer
et énantiomère
y enantiómero

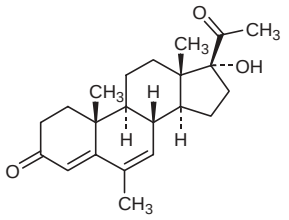
megestrolum

megestrol — 17-hydroxy-6-methylpregna-4,6-diene-3,20-dione

mégestrol — 17-hydroxy-6-méthylprégna-4,6-diène-3,20-dione

megestrol — 17-hidroxi-6-metil-4,6-pregnadieno-3,20-diona

$C_{22}H_{30}O_3$



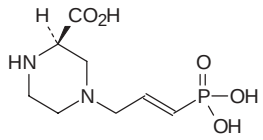
midafotelum

midafotel — (-)-(*R*)-4-[(*E*)-3-phosphonoallyl]-2-piperazinecarboxylic acid

midafotel — (-)-acide (2*R*)-4-[(2*E*)-3-phosphonoprop-2-ényl]pipérazine-2-carboxylique

midafotel — ácido (-)-(*R*)-4-[(*E*)-3-fosfonoalil]-2-piperazincarboxílico

$C_8H_{15}N_2O_5P$



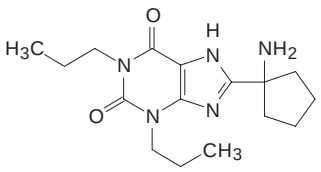
midaxifyllinum

midaxifylline — 8-(1-aminocyclopentyl)-1,3-dipropylxanthine

midaxifylline — 8-(1-aminocyclopentyl)-1,3-dipropyl-3,7-dihydro-1*H*-purine-2,6-dione

midaxifilina — 8-(1-aminociclopentil)-1,3-dipropilxantina

$C_{16}H_{25}N_5O_2$



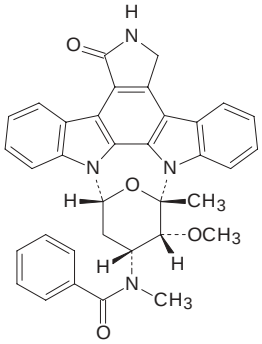
midostaurinum

midostaurin — *N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3',2',1'-*lm*]pyrrolo[3,4-*j*]=[1,7]benzodiazonin-11-yl]-*N*-methylbenzamide

midostaurine — *N*-[(9*S*,10*R*,11*R*,13*R*)-10-méthoxy-9-méthyl-1-oxo-2,3,10,11,12,13-hexahydro-9,13-époxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3',2',1'-*lm*]pyrrolo[3,4-*j*]=[1,7]benzodiazonin-11-yl]-*N*-méthylbenzamide

midostaurina — *N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahidro-10-metoxi-9-metil-1-oxo-9,13-epoxi-1*H*,9*H*-diindolo[1,2,3-*gh*:3',2',1'-*lm*]pirrolo[3,4-*j*]=[1,7]benzodiazonin-11-il]-*N*-metilbenzamida

$C_{35}H_{30}N_4O_4$



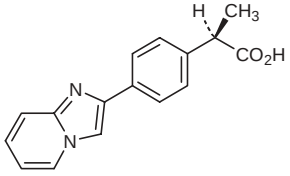
miroprofenum

miroprofen — *p*-imidazo[1,2-*a*]pyridin-2-ylhydratropic acid

miroprofène — acide (2*RS*)-2-[4-(imidazo[1,2-*a*]pyridin-2-yl)phényl]propanoïque

miroprofeno — ácido *p*-imidazo[1,2-*a*]piridin-2-ilhidratrópico

$C_{16}H_{14}N_2O_2$



and enantiomer
et énantiomère
y enantiómero

morolimumabum

morolimumab — human monoclonal IgG1 antibody against human Rhesus-D antigen

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

morolimumab — inmunoglobulina G 1 (anticuerpo monoclonal humano dirigido contra el antígeno Rhesus-D humano)

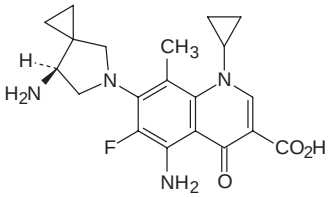
natalizumabum

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

olamufloxacinum

olamufloxacin	(-)-5-amino-7-[(*S*)-7-amino-5-azaspiro[2.4]hept-5-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-4-oxo-3-quinolinecarboxylic acid
olamufloxacine	(-)-acide 5-amino-7-[(7*S*)-7-amino-5-azaspiro[2.4]hept-5-yl]-1-cyclopropyl-6-fluoro-8-méthyl-4-oxo-1,4-dihydroquinoléine-3-carboxylique
olamufloxacina	ácido (-)-5-amino-7-[(*S*)-7-amino-5-azaspiro[2.4]hept-5-il]-1-ciclopropil-6-fluoro-1,4-dihidro-8-metil-4-oxo-3-quinolinacarboxílico

$C_{20}H_{23}FN_4O_3$



palivizumabum

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
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
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

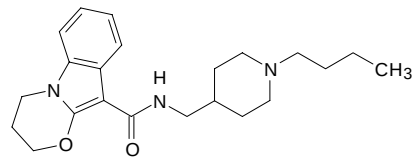
piboserodum

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

piboserod — *N*-[(1-butylpipéridin-4-yl)méthyl]-3,4-dihydro-2*H*-[1,3]oxazino[3,2-*a*]indole-10-carboxamide

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

$C_{22}H_{31}N_3O_2$



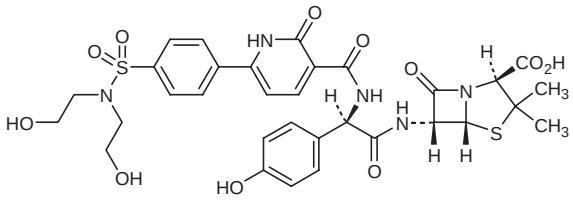
piridicillinum

piridicillin — (2*S*,5*R*,6*R*)-6-[(*R*)-2-[6-[*p*-[bis(2-hydroxyethyl)sulfamoyl]phenyl]-1,2-dihydro-2-oxonicotinamido]-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

piridicilline — acide (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-[[[6-[4-[bis(2-hydroxyéthyl)sulfamoyl]phényl]-2-oxo-1,2-dihydropyridin-3-yl]carbonyl]amino]-2-(4-hydroxyphényl)acétyl]=amino]-3,3-diméthyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylique

piridicilina — ácido (2*S*,5*R*,6*R*)-6-[(*R*)-2-[6-[*p*-[bis(2-hidroxietil)sulfamoil]fenil]-1,2-dihidro-2-oxonicotinamido]-2-(*p*-hidroxifenil)acetamido]-3,3-dimetil-7-oxo-4-tia-1-azabiciclo[3.2.0]heptano-2-carboxílico

$C_{32}H_{35}N_5O_{11}S_2$



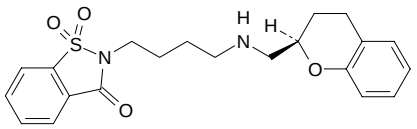
repinotanum

repinotan — (-)-2-[4-[[(*R*)-2-chromanylmethyl]amino]butyl]-1,2-benzisothiazolin-3-one 1,1-dioxide

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

repinotán — (-)-2-[4-[[(*R*)-2-cromanilmetil]amino]butil]-1,2-benzisotiazolin-3-ona 1,1-dióxido

$C_{21}H_{24}N_2O_4S$



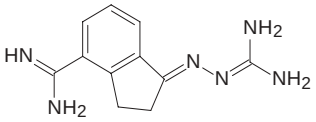
sardomozidum

sardomozide — urea azine with 1-oxo-4-indancarboxamidine

sardomozide — [(4-carbamimidoyl-2,3-dihydro-1*H*-indén-1-ylidène)amino]guanidine

sardomozida — azina de la urea con 1-oxo-4-indancarboxamidina

$C_{11}H_{14}N_6$



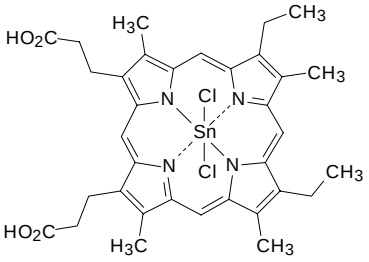
stannsoporfinum

stannsoporfin — 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-)

stannsoporfine — dihydrogéno (*OC*-6-13)-dichloro[7,12-diéthyl-3,8,13,17-tétraméthyl=porphyrine-2,18-dipropanoato(4-)-N^{21},N^{22},N^{23},N^{24}]stannate(2-)

estannsoporfina — (*OC*-6-13)-dicloro[7,12-dietil-3,8,13,17-tetrametilporpirina-2,18-dipropionato(4-)-N^{21},N^{22},N^{23},N^{24}]estannato(2-) de dihidrógeno

$C_{34}H_{36}Cl_2N_4O_4Sn$



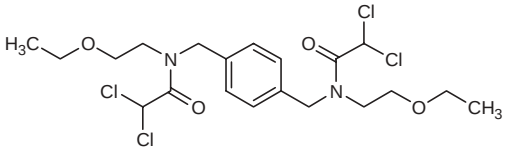
teclozanum

teclozan — *N*,*N*′-(*p*-phenylenedimethylene)bis[2,2-dichloro-*N*-(2-ethoxyethyl)acetamide]

téclozan — *N*,*N*′-[1,4-phénylènebis(méthylène)]bis[2,2-dichloro-*N*-(2-éthoxyéthyl)acétamide]

teclozán — *N*,*N*′-(*p*-fenilenodimetileno)bis[2,2-dicloro-*N*-(2-etoxietil)acetamida]

$C_{20}H_{28}Cl_4N_2O_4$



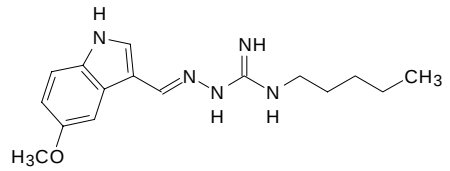
tegaserodum

tegaserod — 1-[[(5-methoxyindol-3-yl)methylene]amino]-3-pentylguanidine

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

tegaserod — 1-[[(5-metoxiindol-3-il)metilen]amino]-3-pentilguanidina

$C_{16}H_{23}N_5O$



tenecteplasum

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

ténectéplase — [103-L-asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanine]activateur du plasminogène (type tissulaire humain)

tenecteplasa — 103-L-asparagina-117-L-glutamina-296-L-alanina-297-L-alanina-298-L-alanina-299-L-alanina-activador del plasminógeno (de tipo tisular humano)

$C_{2558}H_{3872}N_{738}O_{781}S_{40}$

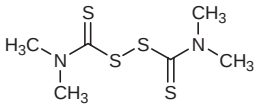
thiramum

thiram — bis(dimethylthiocarbamoyl)disulfide

thirame — bis(diméthylthiocarbamoyl)disulfane

tiramo — disulfuro de bis-(dimetiltiocarbamoilo)

$C_6H_{12}N_2S_4$



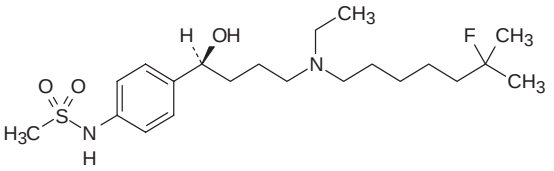
trecetilidum

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

trécétilide (-)-*N*-[4-[(1*S*)-4-[éthyl(6-fluoro-6-méthylheptyl)amino]-1-hydroxybutyl]phényl]méthanesulfonamide

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

$C_{21}H_{37}FN_2O_3S$



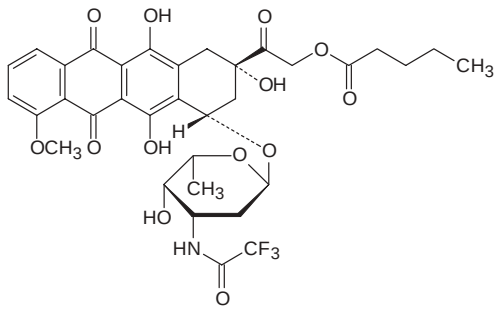
valrubicinum

valrubicin (8*S*,10*S*)-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl]oxy]-5,12-naphthacenedione 8^2-valerate

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

valrubicina 8^2-valerato de (8*S*,10*S*)-8-glicoloil-7,8,9,10-tetrahidro-6,8,11-trihidroxi-1-metoxi-10-[[2,3,6-tridesoxi-3-(2,2,2-trifluoroacetamido)-α-L-*lixo*-hexopiranosil]oxi]-5,12-naftacenodiona

$C_{34}H_{36}F_3NO_{13}$



AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Recommended International Nonproprietary Names (Rec. INN): List 8
(WHO Chronicle, Vol. 22, No. 10, 1968)

p. 466 **hypromellosum**

hypromellose — *replace the chemical name by the following:*
a mixed methyl and 2-hydroxypropyl ether of cellulose

Dénominations communes internationales recommendées (DCI Rec.): Liste 8
(Chronique OMS, Vol. 22, No. 10, 1968)

p. 521 **hypromellosum**

hypromellose — *remplacer le nom chimique par le suivant:*
mélange d'éthers méthyliques et 2-hydroxypropyliques de cellulose

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 8
(Crónica de la OMS, Vol. 22, No. 10, 1968)

p. 513 **hypromellosum**

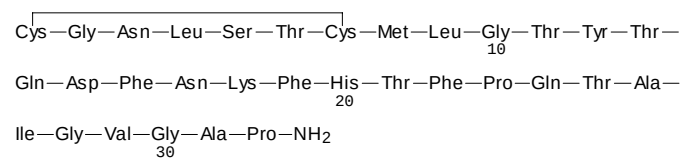
hipromelosa — *sustitúyase el nombre quimico por el siguiente:*
mezcla de éteres metílicos y 2-hidroxipropílicos de celulosa

Recommended International Nonproprietary Names (Rec. INN): List 14
(WHO Chronicle, Vol. 28, No. 10, 1974)

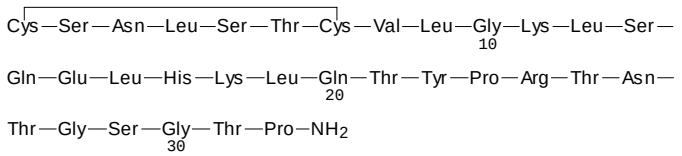
p. 2 **calcitoninum**

calcitonin — *replace the description by the following:*
a polypeptide hormone that lowers the calcium concentration
(the species specificity should be indicated in brackets behind the name)
e.g.

calcitonin (human)
$C_{151}H_{226}N_{40}O_{45}S_3$



calcitonin (salmon)
$C_{145}H_{240}N_{44}O_{48}S_2$



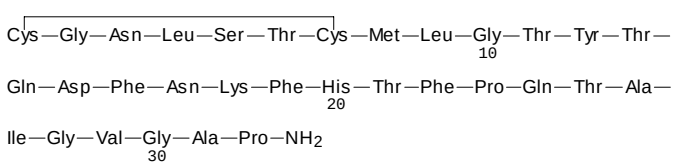
Dénominations communes internationales recommendées (DCI Rec.): Liste 14
(Chronique OMS, Vol. 28, No. 10, 1974)

p. 2 **calcitoninum**

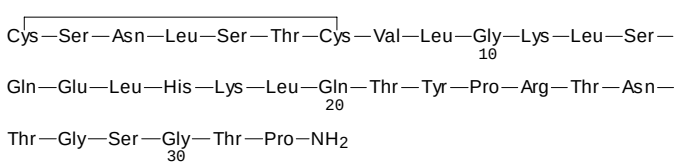
calcitonine

remplacer la description par la suivante:
hormone polypeptidique qui abaisse le taux de calcium
(la spécifité de l'espèce doit être indiquée entre parenthèses derrière la dénomination), ex.:

calcitonine (humaine)
$C_{151}H_{226}N_{40}O_{45}S_3$



calcitonine (saumon)
$C_{145}H_{240}N_{44}O_{48}S_2$



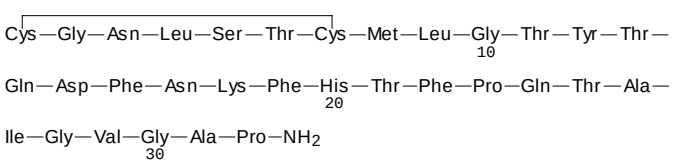
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 14
(Crónica de la OMS, Vol. 28, No. 10, 1974)

p. 3 **calcitoninum**

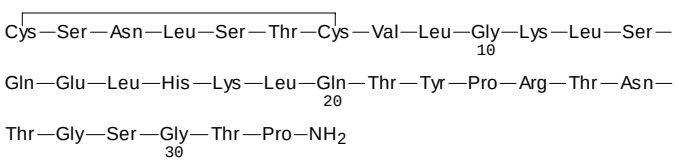
calcitonina

sustitúyase la descripción por la siguiente:
hormona polipeptídica que disminuye la concentración del calcio
(la especifidad de especie debe estar indicada entre paréntesis después de la denominación) p. ej.

calcitonina (humana)
$C_{151}H_{226}N_{40}O_{45}S_3$



calcitonina (salmón)
$C_{145}H_{240}N_{44}O_{48}S_2$



Recommended International Nonproprietary Names (Rec. INN): List 33
(WHO Drug Information, Vol. 7, No. 3, 1993)

p. 1 **altumomabum**

altumomab	*replace the description by the following:* immunoglobulin G1, anti-(human carcinoembryonic antigen) (mouse monoclonal ZCE025 γ1-chain), disulfide with mouse monoclonal ZCE025 light chain, dimer

p. 7 **satumomabum**

satumomab	*replace the description by the following:* immunoglobulin G1, anti-(human tumor-associated glycoprotein 72) (mouse monoclonal B72.3 light chain), disulfide with mouse monoclonal B72.3 light chain, dimer

Dénominations communes internationales recommendées (DCI Rec.): Liste 33
(Informations Pharmaceutiques OMS, *Vol. 7, No. 3, 1993)*

p. 1 **altumomabum**

altumomab	*remplacer la description par la suivante:* immunoglobuline G1, anti-(antigène associé aux carcinomes embryonnaires humains) (chaîne γ1 de l'anticorps monoclonal de souris ZCE025), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris ZCE025

p. 8 **satumomabum**

satumomab	*remplacer la description par la suivante:* immunoglobuline G1, anti-(glycoprotéine 72 humaine associée aux tumeurs) (chaîne légère de l'anticorps monoclonal de souris B72.3), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris B72.3

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 33
(Información Farmacéutica OMS, *Vol. 7, No. 3, 1993)*

p. 1 **altumomabum**

altumomab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-(antígeno carcinoembrionario humano) (cadena γ1 del anticuerpo monoclonal de ratón ZCE025), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón ZCE025

p. 7 **satumomabum**

satumomab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-(glicoproteína 72 humana asociada al tumor) (cadena ligera del anticuerpo monoclonal de ratón B72.3), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón B72.3

Recommended International Nonproprietary Names (Rec. INN): List 34
Dénominations communes internationales recommendées (DCI Rec.): Liste 34
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 34
(WHO Drug Information, Vol. 8, No. 3, 1994)

p. 2 **abciximabum**

abciximab	*replace the description by the following:* immunoglobulin G1, anti-(human integrin αIIbβ3) Fab fragment (human-mouse monoclonal c7E3 clone p7E3V_Hh$C_{\gamma1}$ γ1-chain), disulfide with human-mouse monoclonal c7E3 clone p7E3V_κhC_κ κ-chain
abciximab	*remplacer la description par la suivante:* immunoglobuline G1, anti-(intégrine αIIbβ3 humaine) fragment Fab (chaîne γ1 de l'anticorps monoclonal chimérique homme-souris c7E3 clone p7E3V_Hh$C_{\gamma1}$), disulfure avec la chaîne κ de l'anticorps monoclonal chimérique homme-souris c7E3 clone p7E3V_κhC_κ
abciximab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-(integrina αIIbβ3 humana) fragmento Fab (cadena γ1 del anticuerpo monoclonal hombre-ratón c7E3 clon p7E3V_Hh$C_{\gamma1}$), disulfuro con la cadena κ del anticuerpo monoclonal hombre-ratón c7E3 clon p7E3V_κhC_κ

p. 5 **capromabum**

capromab	*replace the description by the following:* immunoglobulin G1, anti-(human prostatic carcinoma cell) (mouse monoclonal 7E11-C5.3 γ1–chain), disulfide with mouse monoclonal 7E11-C5.3 light chain, dimer
capromab	*remplacer la description par la suivante:* immunoglobuline G1, anti-(cellules du carcinome prostatique humain) (chaîne γ1 de l'anticorps monoclonal de souris 7E11-C5.3), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris 7E11-C5.3
capromab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-(células de carcinoma prostático humano) (cadena γ1 del anticuerpo monoclonal de ratón 7E11-C5.3), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón 7E11-C5.3

p. 8 **detumomabum**

detumomab	*replace the description by the following:* immunoglobulin G1, anti-(human B lymphoma cell) (mouse monoclonal SPECIFID heavy chain), disulfide with mouse monoclonal SPECIFID light chain, dimer
détumomab	*remplacer la description par la suivante:* immunoglobuline G1, anti-(cellules de lymphome B humain) (chaîne lourde de l'anticorps monoclonal de souris SPECIFID), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris SPECIFID
detumomab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-(células de linfoma B humano) (cadena pesada del anticuerpo monoclonal de ratón SPECIFID), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón SPECIFID

p. 8 **edobacomabum**

edobacomab	*replace the description by the following:* immunoglobulin M, anti-(endotoxin) (mouse monoclonal XMMEN-0E5 μ-chain), disulfide with mouse monoclonal XMMEN-0E5 light chain, pentameric dimer
édobacomab	*remplacer la description par la suivante:* immunoglobuline M, anti-(endotoxine) (chaîne m de l'anticorps monoclonal souris XMMEN-0E5), dimère pentamérique du disulfure avec la chaîne légère de l'anticorps monoclonal de souris XMMEN-0E5
edobacomab	*sustitúyase la descripción por la siguiente:* inmunoglobulina M, anti-(endotoxina) (cadena μ del anticuerpo monoclonal de ratón XMMEN-0E5), dímero pentamérico del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón XMMEN-0E5

p. 9 **enlimomabum**

enlimomab	*replace the description by the following:* immunoglobulin G2a, anti-(human CD54 (antigen)) (mouse monoclonal BI-RR-1 γ2a–chain), disulfide with mouse monoclonal BI-RR-1 light chain, dimer
enlimomab	*remplacer la description par la suivante:* immunoglobuline G2a, anti-(antigène CD54 humain) (chaîne γ2a de l'anticorps monoclonal de souris BI-RR-1), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris BI-RR-1
enlimomab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G2a, anti-((antígeno) CD54 humano) (cadena γ2a del anticuerpo monoclonal de ratón BI-RR-1), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón BI-RR-1

p. 21 **votumumabum**

votumumab	*replace the description by the following:* immunoglobulin G3, anti-(human carcinoma-associated antigen) (human monoclonal 88BV59 γ3–chain), disulfide with human monoclonal 88BV59 κ-chain, dimer
votumumab	*remplacer la description par la suivante:* immunoglobuline G3, anti-(antigène associé aux carcinomes humains) (chaîne γ3 de l'anticorps monoclonal humain 88BV59), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal humain 88BV59
votumumab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G3, anti-(antígeno asociado a los carcinomas humanos) (cadena γ3 del anticuerpo monoclonal humano 88BV59), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humano 88BV59

p. 22 **zolimomabum aritoxum**

zolimomab aritox	*replace the description by the following:* immunoglobulin G1, anti-(human CD5 (antigen) heavy chain) (mouse monoclonal H65-RTA γ1–chain), disulfide with mouse monoclonal H65-RTA light chain, dimer, disulfide with ricin (castor bean A-chain)
zolimomab aritox	*remplacer la description par la suivante:* immunoglobuline G1, anti-(chaîne lourde de l'antigène CD5 humain) (chaîne γ1 de l'anticorps monoclonal de souris H65-RTA), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris H65-RTA, disulfure avec la chaîne A de la ricine
zolimomab aritox	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-(cadena pesada del antígeno humano CD5) (cadena γ1 del anticuerpo monoclonal de ratón H65-RTA), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón H65-RTA, disulfuro con ricina (cadena A de la judía de ricino)

Recommended International Nonproprietary Names (Rec. INN): List 35
Dénominations communes internationales recommendées (DCI Rec.): Liste 35
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 35
(WHO Drug Information, Vol. 9, No. 3, 1995)

p. 3 **afelimomabum**

afelimomab	*replace the description by the following:* immunoglobulin G3, anti-(human tumor necrosis factor α) F(ab')2 fragment (mouse monoclonal LU54107 γ3-chain), disulfide with mouse monoclonal LU54107 κ-chain, dimer
afélimomab	*remplacer la description par la suivante:* immunoglobuline G3, anti-(facteur de nécrose tumorale α humain) fragment F(ab')2 (chaîne γ3 de l'anticorps monoclonal de souris LU54107), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris LU54107
afelimomab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G3, anti-(factor de necrosis tumoral α humano) fragmento F(ab')2 (cadena γ3 del anticuerpo monoclonal de ratón LU54107), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón LU54107

p. 13 **inolimomabum**

inolimomab	*replace the description by the following:* immunoglobulin G1, anti-(human interleukin 2 receptor α-chain) (mouse monoclonal B-B10 γ1-chain), disulfide with mouse monoclonal B-B10 κ-chain, dimer
inolimomab	*remplacer la description par la suivante:* immunoglobuline G1, anti-(chaîne α du récepteur de l'interleukine 2 humain) (chaîne γ1 de l'anticorps monoclonal de souris B-B10), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris B-B10
inolimomab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-(cadena α del receptor de interleukina 2 humano) (cadena γ1 del anticuerpo monoclonal de ratón B-B10), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón B-B10

p. 18 **nacolomabum tafenatoxum**

nacolomab tafenatox	*replace the description by the following:* immunoglobulin G1, anti-(human colorectal tumor antigen C242) Fab fragment (mouse monoclonal r-C242Fab-SEA clone pkP941 γ1-chain) fusion protein with enterotoxin A (*Staphylococcus aureus*), disulfide with mouse monoclonal r-C242Fab-SEA clone pkP941 κ-chain
nacolomab tafénatox	*remplacer la description par la suivante:* protéine de fusion entre l'immunoglobuline G1, anti-(antigène C242 associé aux tumeurs colorectales humaines) fragment Fab (chaîne γ1 de l'anticorps monoclonal de souris r-C242Fab-SEA clone pkP941) et l'entérotoxine A (*Staphylococcus aureus*), disulfure avec la chaîne κ de l'anticorps monoclonal de souris r-C242Fab-SEA clone pkP941
nacolomab tafenatox	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-(antígeno C242 de tumor colorrectal humano) fragmento Fab (cadena γ1 del anticuerpo monoclonal de ratón r-C242Fab-SEA clon pkP941) proteína de fusión con la enterotoxina A (*Staphylococcus aureus*), disulfuro con la cadena κ del anticuerpo monoclonal de ratón r-C242Fab-SEA clon pkP941

p. 22 **priliximabum**

priliximab	*replace the description by the following:* immunoglobulin G1, anti-(human CD4 (antigen)) (human-mouse monoclonal cm-T412 γ1-chain), disulfide with human-mouse monoclonal cm-T412 κ-chain, dimer
priliximab	*remplacer la description par la suivante:* immunoglobuline G1, anti-(antigène CD4 humain) (chaîne γ1 de l'anticorps monoclonal chimérique homme-souris cm-T412), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal chimérique homme-souris cm-T412
priliximab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-((antígeno) CD4 humano) (cadena γ1 del anticuerpo monoclonal hombre-ratón cm-T412), dímero del disulfuro con la cadena κ del anticuerpo monoclonal hombre-ratón cm-T412

p. 23 **regavirumabum**

regavirumab	*replace the description by the following:* immunoglobulin G1, anti-(human herpesvirus 5 glycoprotein B) (human monoclonal γ1-chain), disulfide with human monoclonal κ-chain, dimer
régavirumab	*remplacer la description par la suivante:* immunoglobuline G1, anti-(glycoprotéine B du virus de l'herpès 5 humain) (chaîne γ1 de l'anticorps monoclonal humain), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal humain
regavirumab	*sustitúyase la descripción por la siguiente:* inmunoglobulina G1, anti-(glicoproteina B del virus del herpes 5 humano) (cadena γ1 del anticuerpo monoclonal humano), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humano

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

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

Les textes de la *Procédure à suivre en vue du choix de dénominations communes internationales recommandées pour les substances pharmaceutiques* et des *Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques* seront publiés seulement dans les numéros impaires des listes des DCIs proposées.

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