WHO Drug Information

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General Policy Issues

WHO Model List of Essential Drugs celebrates its twentieth anniversary

The year 1997 commemorates the twentieth anniversary of the WHO Model List of Essential Drugs. The Model List will now have been revised nine times, and the tenth list will be published early next year.

In 1977, the first list was published in response to the need by developing countries to rationalize drug selection and now, in 1997, the concept of essential drugs has become widely accepted throughout the world. The need to determine priorities in drug selection has never been greater in view of the diminishing resources available to the health sector, and developing countries in particular. In addition, the escalating expense of many of the newly-marketed drugs will mean that the cost of therapy for many patients will be prohibitive.

The WHO Expert Committee on the Use of Essential Drugs, which is mainly composed of eminent clinical pharmacologists from many different parts of the world, meets every two years and is responsible for reviewing the Model List. The Committee is guided by the following statement, which appears in every report: "Because of the great differences between countries, the preparation of a drug list of uniform, general applicability is not feasible or possible. Therefore, each country has the direct responsibility of evaluating and adapting a list of essential drugs, according to its own policy in the field of health."

Within a few years of publication of the first list, it was recognized that a list alone was insufficient to guide countries on the selection of drugs. The report of the Expert Committee has since been extended to include sections providing guidance for countries wishing to establish national programmes for essential drugs. Information on such issues as quality assurance, drug use in primary health care, post-marketing drug evaluation, nomenclature, research and development, drug information and education has also been included. The Expert Committee meetings thus provide a forum for discussion of many important issues.

Antimicrobial resistance, which is an increasing global problem, is addressed extensively in the reports and the use of "reserve antimicrobials" is recommended. Reserve antimicrobials are those that "... are useful for a wide range of infections but, because of the need to reduce the risk of development of resistance, and because of their relatively high cost, it would be inappropriate to recommend their unrestricted use." The report stresses the need for more systematic and coordinated approaches to the surveillance of antimicrobial resistance. This information must be linked to the development of an essential drug list, since the concept of reserve antimicrobials is of practical relevance only when information is available on the prevailing sensitivities of important bacterial pathogens. Such reserve antimicrobials include ceftazidime, ceftriaxone, vancomycin and artemether.

The section on antivirals is under discussion as a consequence of the rapid development of therapies for use in HIV/AIDS and the problem of their availability in those countries most affected by the disease. Whereas it is not possible to foresee the decision of the Expert Committee concerning their place on the list, the use of these drugs in countries with limited resources will almost certainly merit some serious debate.

The Expert Committee report also acts as a reminder to the pharmaceutical industry for the continued need to improve existing therapies and to develop new drugs for many prevalent diseases that are still without satisfactory or effective therapy, such as tropical diseases. The treatment of onchocerciasis and schistosomiasis was revolutionized by the introduction of ivermectin and praziquantel and, in recognition, the Expert Committee immediately included these drugs in the Model List. This action has encouraged countries to use these drugs in their national control programmes. Similarly, when efflamithine became available for the treatment of African trypanosomiasis, it was placed on the Model List. More recently, tricalbendazole for the treatment of liver flukes has been discussed and will almost certainly be evaluated for inclusion in the list when a product becomes available.
Fixed combinations have been accepted only when the dosage of each ingredient meets the requirements of a defined population group, and the combination has advantage over single compounds in therapeutic effect, safety or compliance. As an example, the combination products rifampicin + isoniazid + pyrazinamide and isoniazid + ethambutol were recently added to the list to improve compliance, reduce prescription errors and also facilitate case management by health care workers. However, it was emphasized that any combination tablets containing rifampicin should show adequate bioavailability.

The actual list is still maintained at less than 300 active ingredients — although the square symbol placed in front of many of the products indicates that other drugs in the same therapeutic class may be substituted. The judicious use of this symbol allows much flexibility for local adaptation. The list covers a wide range of drugs from the very old and inexpensive, such as ether or acetylsalicylic acid, to the latest, but highly-priced, antibacterials or cardiovascular drugs.

It should be made clear that the listing of drugs is intended only to be illustrative and informative. The list does not reflect the medicinal drug needs for any particular country and is not intended as a national formulary. Its primary purpose is to provide a wide selection of drugs which collectively serve to treat prevalent endemic and epidemic diseases. It may serve as an example to be used by donor agencies and governments in selecting their drugs and in making rational decisions on procurement.

The Model List will also be useful for many different organizations wishing to standardize drug supply. No where is this better exemplified than in the case of exceptional conditions such as war, natural catastrophes and other emergency situations, and the Interagency Procurement Working Group has developed an abbreviated list of selected drugs for use during the immediate phase in emergencies. This list covers the drugs needed for displaced populations, with additional drugs for anaesthesia, surgery and key drugs for hospitalized patients. The New Emergency Health Kit comprises a short-list to cover the basic needs of a population of 10 000 for a period of 3 months.

The WHO Model List forms the basis of drugs selected for inclusion in the UNICEF catalogue. UNHCR has its own list which has been adapted from the WHO list, and Médecins sans Frontières have devised data sheets on essential drugs. UNAIDS are discussing the development of their own "action drug list". But, no matter how many lists are adapted, there will remain only one WHO Model List of Essential Drugs that will be evaluated and updated periodically in the light of new needs and developments in the rational treatment of diseases.

The continuing need for rational selection and use of drugs

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The Alma Ata Declaration of 1978 identifies access to essential drugs as one of the eight basic elements of primary health care. Subsequently, the problems surrounding the rational use of drugs were amply addressed at the WHO Conference on the rational use of drugs held in Nairobi in 1985, where experts from governments, industry, and patient and consumer associations were brought together to discuss the issue in all its complexities and to propose means and methods for improving access to knowledge and reliable information. The Conference was instrumental in laying a foundation for development of the WHO Ethical criteria for medicinal drug promotion.

As part of its revised drug strategy, WHO later published its Guidelines for Developing National Drug Policies which have been used by many countries. By 1995, more than 60 countries had either developed, or were in the process of implementing, their own national drug policy.

In Pakistan, a national workshop was sponsored in 1992 by the Ministry of Health to develop a draft national drug policy on legislation for production and promotion of drugs. This also set out to review the drug supply system and strengthen quality assurance and drug information. However, no progress was made on its acceptance until 1995, when the Ministry circulated the draft policy to interested parties for comment. The draft met with strong resistance from the pharmaceutical industry and the document was put into cold storage until 1997, when it was reviewed, amended and finally published. Within the implementation of this policy, drugs continue to be regulated by the Drugs Act of...
1976 which controls the import, export, manufacturing, storage, distribution and sale of drugs. Prices are also determined by the Act.

In 1994, an essential drugs list for Pakistan was compiled and published by the Ministry of Health, and included 419 drugs. It was also planned to publish a national formulary to complement the list, but this has not yet been finalized. The list is used exclusively within Government hospitals and health facilities, but has not yet been adopted by the majority of other health professionals throughout the country who, in great part, are unaware of its existence.

Despite strong opposition, Pakistan was one of the first countries, in 1972, to introduce a Generic Drugs Act. Opponents argued that generic drugs were of poor quality and low efficacy. Unfortunately, the subsequent lack of regulation or control of generics led effectively to the market being flooded by poor quality drugs and the scheme needlessly failed some few years later.

By 1995, 80% of the total drug requirements of the country were being produced by local manufacturers, including multinationals. The raw materials used in their production, however, were imported, as were the remaining 20% of finished products on the market. In 1995, the total number of registered formulations available within the country had reached 14,000, and this had increased to 20,000 by 1997. The average per capita expenditure on medicine in 1994 was $5 per annum. Although the price of essential drugs is controlled, all other products are at the mercy of market forces. This price differential has resulted in the disappearance of many essential drugs, such as digoxin, thyroxin, methotrexate, and phenytoin, through lack of commercial incentive.

The 1976 Drugs Act provides for regulation of promotional activities of the pharmaceutical industry and emphasizes the importance of supplying correct information to the medical profession. In reality, the Act is not implemented rigorously enough, with the result that information provided by the industry is incomplete. For example, the only side-effect mentioned on the data sheet for loperamide is dryness of mouth. There are very few sources of objective information available to the health professional in Pakistan. Although the Ministry of Health issues a Drug Information Bulletin on an irregular basis, it is not circulated. The two most important sources of information are the Network for the Rational Use of Medication and the Prescriber, by UNICEF.

Although the government has recognized that rationalization is essential, it is unable to make headway in the present situation. Basic training in pharmacology and prescribing is sadly lacking for health professionals. The situation within the country is further complicated by the ready availability of all drugs over-the-counter. Although the Drugs Act provides for penalties for selling drugs which normally require a prescription, in reality this law is hardly implemented. In addition, representatives of pharmaceutical companies regularly hand out drug samples, while giving verbal instructions on their use to unqualified storekeepers. In this situation, it is impossible to transmit information on the side-effects or special indications of a medication to the patient.

Even more damaging to any progress is the traditional system, whereby a general practitioner does not charge for a consultation but for the care and medicines which are dispensed. This practice leads to misuse and overuse, since the practitioner is obliged to give the patient an injection, some syrup or a powder in exchange for a fee. Such a system cannot continue if the rational use of drugs is to be realized. An improvement in the situation would also require a change in the patient's attitude through education. In many cases, a patient will place much trust in medicines and will not be satisfied with advice alone. This attitude was clearly reflected after regulatory action was taken to withdraw the paediatric antidiarrhoeal drug, loperamide, from the market. When this drug was no longer available, it was replaced on the chemist's shelves by irrational therapies with similar claims, and adult formulations were adapted for paediatric use.

If the situation is to improve, rational drug use needs to be emphasized, and widespread support of the essential drugs concept is fundamental.
Current Topics

Prevention of mother-to-child transmission of HIV in developing countries

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The search for treatment to prevent or reduce the risk of mother-to-child transmission of HIV has been heightened as a result of increased knowledge of the underlying mechanism of action (1). The results of recent successful trials of antiretroviral therapy administered during pregnancy and delivery has brought hope of a possible reduction in perinatal transmission to a level of less than two per cent.

Mother-to-child transmission of HIV has been estimated to occur prenatally (2, 3), at the time of delivery (4, 5) or through breast-feeding (6). The exact contribution of each of these routes to overall transmission has not been exactly quantified, but it appears that the greatest proportion of infection occurs at the time of delivery. Knowledge of the likely timing of transmission is very important for determining treatment schedules, as are other concomitant factors such as mode of delivery, length of time of rupture of membranes, and the practice of breast-feeding. The risk of transmission is higher for women with clinical, immunological or virological markers of advanced HIV infection, and a high viral load has been identified as a key factor in transmission, especially during primary HIV infection (7).

Current interventions

Many of the interventions now being studied are based on the understanding that a substantial proportion of HIV transmission occurs at the time of labour and delivery and during breast-feeding. Proposals to reduce the risk of transmission at this stage include elective caesarean section, disinfection of the birth canal, vitamin A prophylaxis, antiretroviral therapy, formula feeding and passive or active immunization.

A reduction in mother-to-child transmission of HIV with treatment using zidovudine (ZDV) was demonstrated in the ACTG076 study (8). This constituted a major breakthrough and the results of the study have opened new areas for research and treatment. The study evaluated the effect of treating the mother with zidovudine during pregnancy and delivery, and the infant during the first 6 weeks of life. In this randomized placebo-controlled study carried out in a non breast-feeding population, treatment with zidovudine achieved a 67.5% reduction in transmission risk and demonstrated a decrease in viral load and inhibition of viral replication in the infant. The drug was well tolerated in both the mothers and infants, and follow-up from this trial and monitoring of the zidovudine pregnancy register do not, as yet, provide any evidence of teratogenicity or short-term adverse effects. None the less, long-term follow-up is still required to provide information on the potential mutagenicity and carcinogenicity of nucleoside analogues, the effect they may have on tissues with high mitochondrial content, and possible effects on the reproductive system.

Current regimens

The treatment regimen used during the above-mentioned study was zidovudine 100 mg 5 times daily during pregnancy and delivery, or placebo. Treatment was begun between 14–34 weeks gestation and patients also received intravenous zidovudine, or placebo, during labour. Infants received oral zidovudine 2 mg/kg or placebo for six weeks after birth, and those infants treated with zidovudine tolerated the drug well: the only adverse effect reported being transient anaemia.

As a result of the study, an international meeting convened by WHO has recommended that simpler and less-costly drug regimens be explored. These should be affordable, feasible and sustainable, particularly in settings with scant resources. Such regimens could include such products as nevirapine, a non-nucleoside reverse transcriptase inhibitor which has potent antiretroviral activity. However, it is associated with the rapid development of drug resistance and this may reduce its application to use during labour and delivery only.
Other studies of short-course zidovudine treatment are under way in developing countries and these may provide more information on the exact role that prenatal, intrapartum and postnatal transmission via breast-feeding play in transmission. The efficacy of short-course antiretrovirals in preventing transmission in developing country populations will also be assessed.

**Resistance**

Women having received extensive prior zidovudine therapy may harbour viral strains with reduced susceptibility. These resistant strains may be transmitted from mother to fetus, although the frequency with which such transmission occurs is unknown at present. Resistant virus appears to emerge more quickly in late-stage disease and, in one study following 12 months of therapy, viral isolates from 89% of patients and 31% from early-stage disease patients were shown to be resistant (9).

The capability of zidovudine to reduce HIV transmission may be decreased for mothers in whom zidovudine-resistant strains predominate, but this assumption is not yet supported by data. In the developing world, few women will have had prior access to antiretroviral therapy before becoming pregnant. Therefore, resistance may be less of a problem than in the United States of America or Europe.

Concerns about the potential long-term adverse effects in women include the development of zidovudine-resistant virus when zidovudine is used for more than one pregnancy, and the potential effect such resistance could have on disease progression. Although the results of some studies have demonstrated an association between emergence of zidovudine resistance and total duration of zidovudine exposure, none of the study designs have specifically addressed the effect of intermittent therapy on the development of resistance.

**Implementation**

Effective implementation of a regimen in overburdened midwifery or obstetrical units with little resources (10) will depend on the number of women willing to be tested for HIV and prepared to return for results and follow-up. Equally, compliance with depend on how easy the regimen is to follow, which would imply the use of oral dosage forms, taken during the day, with minimum adverse effects. It is very important that the health worker and the patient clearly understand the reasons for the regimen and the benefits of maintaining the course of treatment.

Ethical concerns have been raised at the practice of stopping antiretroviral therapy after delivery. In fact, the primary role of zidovudine is to reduce the viral load at the moment when mother-to-child transmission is most likely to take place. Monotherapy has been demonstrated to effectively reduce transmission, but it has no role in the long-term management of HIV infection. In settings where access to antiretrovirals is not possible, the cost of continuing zidovudine in combination with other treatments for the duration of the mother's life may be prohibitive. None the less, it is of vital importance that governments, health ministries, pharmaceutical companies and international agencies should make every possible effort to provide treatment to those in need. At the same time, research should continue on other biological compounds.

Results from studies designed to prevent mother-to-child transmission suggest different strategies for the prevention of transmission. The completion of trials with antiretroviral agents — possibly in combination with hyperimmune immunoglobulin, vitamin A, caesarian section, or vaginal lavage — will not only help to understand the efficacy of each of these interventions, but will also provide insight into the timing and the risk factors involved in transmission. Short-course antiretroviral therapy and less costly drug regimens, if effective, should be implemented for use in developing countries.

Results from studies on the role of antiretrovirals during the intrapartum period should be analysed in an attempt to make regimens like this available to the many women who do not have antenatal care. In those areas where women have access to antenatal care but deliver elsewhere, antepartum interventions may be more applicable. Postnatal transmission may be minimized by the use of antiretrovirals during this period in both the mother and infant. Further investigation is also needed into combination therapy and the new classes of more potent antiretrovirals, including protease inhibitors and non-nucleoside reverse transcriptase inhibitors and their role in mother-to-child transmission of HIV.

The ACTG076 study demonstrated that the antiretroviral, zidovudine, significantly reduced mother-to-child transmission of HIV. The mechanism of protection may be due to reduction of maternal viral load or an inhibition of viral replication in the fetus. The challenge now facing researchers and public health specialists is to find an antiretroviral regimen that is not only effective and safe, but short, simple
and affordable for global use. The evolution of current therapies has been and continues to be fast and practitioners caring for HIV infected persons must remain abreast of any new developments. Implementation of such new interventions should not place undue pressure on the already overburdened health systems of developing countries.

References


Improving the compliance of antimalarials

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Although a large proportion of people can harbour malaria parasites without any signs of infection, symptomatic disease must be treated early and effectively in order to prevent its rapid, and sometimes fatal, evolution. However, the weapons for effective treatment and prevention of death from malaria have been successively eroded through parasite resistance to drugs. A major cause of this resistance has been identified as a lack of patient compliance with the recommended full treatment regimen.

The majority of the currently-used antimalarials need to be taken more than once a day and for longer than one day in order to achieve total elimination of all parasites from the body. For most patients, once the initial symptoms have disappeared, there is little incentive to take the full regimen — particularly if the drug or drug combination has an unpleasant taste or side effects. Compliance with a full course of antimalarial treatment is therefore rarely achieved.

For the individual patient, poor compliance with a full regimen undermines therapeutic efficacy and will result in recrudescent malaria, but the effect of poor compliance on the population at large is far more devastating. Partial therapy will permit parasites exposed to low concentrations of a drug to survive and acquire resistance to larger concentrations. Widespread use and underdosing in the presence of parasitaemia, either through poor compliance, poor drug quality or reinfection in the presence of an antimalarial with a long half-life, is an important element in precipitating rises in the rates of parasite resistance to drugs, and increasing the subsequent acute case-load and mortality from malaria. Efforts to ensure drug quality and proper use in malaria-endemic areas, particularly in populations who have high re-infection rates and a large parasite load, are crucial in protecting long-term effectiveness.

Devising strategies

Poor compliance with antimalarials can be a result of complex regimens, poor prescribing practices,
poor instructions, either verbal or written, poor packaging, inadequate package inserts and prescriber advice on the importance of full compliance and information on side effects. Every day, millions of antimalarials are prescribed and sold to persons seeking care for themselves or their children at hospitals, health centres, pharmacies or stores, or directly from community health care providers and traditional healers. Self-medication from private purchase of drugs dominates. Business transactions involving medicines for malaria often relate to compounds and formulations, such as injectables, which are not necessary and may be dangerous. Poor quality products which do not comply with the labelled claim, and even counterfeit medicines, are increasingly manufactured and sold undetected.

Improvements in approaches to achieve a better use of drugs are therefore essential in assuring the long-term effectiveness of drugs, and reducing case fatality from the complications arising from poor drug use. The UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR) has set up a Task Force on Improved Use of Antimalarials which began operations in 1993. Its aim is to identify and test solutions for rationalizing and improving the home and community-based treatment of malaria using existing antimalarials. The focus of the work began in 6 countries of South-East Asia chosen for their high rates of multidrug resistance, and was subsequently extended to Africa, which claims the highest mortality from the disease. Treatment regimens varied from 5-day (8 tablet) combinations of artesunate and mefloquine to 7–day (49 tablet) regimens of quinine + tetracycline.

Within the 6 countries of South-East Asia, the national malaria control programmes decided that, in view of the common borders and continual movement of populations from one country to another through malaria endemic areas, a consistent and joint policy was required in the whole region to optimize the use of existing antimalarials. Motivation was high, since the last resort in the malaria armamentarium — the qinghaosu derivatives — were already on public sale in some countries for the treatment of uncomplicated malaria.

The work began by identifying the major causes of poor drug use in each country. These varied considerably and included poor prescribing practices by the medical and health professionals, sale of single-dose or inappropriate drugs, inadequate packaging or lack of information in the packaging inserts, and poor drug quality. Each country embarked on an intervention programme to improve drug use — the objective was either to improve compliance with multidose antimalarials or to develop mechanisms to improve surveillance and detection of seriously substandard drugs.

**Major observations**
The results of these interventions are now published as a special 1997 Supplement to the *Bulletin of the World Health Organization*. They include:

- the introduction of a subsidized system for providing combination drugs for treatment of uncomplicated malaria;
- an unsubsidized package of drug combination treatment, with dose compartments for each day’s treatment;
- community-based health education interventions focusing on full compliance;
- the introduction of a new dose-specific blister packaging system for chloroquine/ primaquine treatment for vivax malaria;
- development of a methodology for the measurement of compliance with short-course drugs through the use of a pharmacological marker; and
- quantification of the variation in drug quality of the artemisinin derivatives sold for the treatment of malaria.

User-friendly packaging of drugs by dose worked best. In the countries in which the interventions were implemented — China and Myanmar — a total of 800 patients with confirmed blood smears were randomly assigned to the new packaging group or provided with the same treatment as usual, for example, all the tablets together in a folded paper. The packaging concentrated on two simple but important elements, the dose to be taken at each time point — whether this was more than one tablet of a single drug or a drug combination, and simple non-medical information. Emphasis was placed on the patient taking all the tablets, even if there were no apparent symptoms. A separate leaflet provided the usual pharmaceutical information. When providing packaging by dose and provision of non-medical information, the technology concentrated
on what would be most practical for the patient to do, and to know. Each patient was followed up at home, both in the control and the intervention groups, and compliance with the full regimen was measured in body fluid. In China, packaging achieved 97.1% compliance in the blister-pack group, compared to 88.1% in the control group (p < 0.05) for a 3-day treatment of chloroquine, and 97.1% compliance in the blister-pack group compared with 73.1% in the control group (p<0.05) for an 8-day treatment of primaquine. In Myanmar, measured compliance was 99.3% at full cost (Fisher Exact, p=0.01). When patients were asked why they preferred the new packaging, they indicated that they were less likely to lose tablets, and the tablets did not disintegrate during the wet season, which is when malaria transmission mainly occurs.

In community-based health education interventions, the focus was on increasing the proportion of patients with malaria who bought a full regimen of 7–day quinine + tetracycline, increasing the proportion of patients who took the full regimen (once bought), and reducing the use of non-essential or dangerous drugs. Exposure to an awareness campaign through video and posters increased purchase of the full course by 18%. For those who bought a full regimen of quinine + tetracycline, there was a 58% improvement in the proportion of persons who took the full regimen and a 53% reduction in the use of inappropriate or dangerous drugs.

Subsidies for drug combinations were not successful. This is potentially because the subsidy involved the redemption of a voucher at a specific location. Only 3% of over 800 patients redeemed the voucher.

In Africa, where death from *Plasmodium falciparum* malaria is a risk in children under 5 years of age, shopkeepers were trained to advise and sell a full regimen for treatment of uncomplicated malaria, and to refer children requiring specialist care to a health professional. Results show that following training, shopkeepers took their role in health seriously enough to provide better information to parents of sick children and a greater number of children were given the full regimen by their mothers. Other interventions in Africa on appropriate verbal and written advice and the use of paediatric formulations have also given promising results.

Since quantitative information on adherence to prescribed oral drug regimens was considered important, the studies also tested the validity of an adherence marker in the same preparation as the treatment under scrutiny. In collaboration with the University of Leeds Pharmacology Unit, which is specialized in the use of markers to measure compliance, drug defaulting with tablets prescribed to be taken once, twice or three times daily was evaluated. Work was first carried out in an Asian reference population and then applied to field studies. Results indicate that it is possible to detect the total doses taken of the prescribed regimen and a saliva test is now under development.

Regarding drug quality, serious questions were raised on the ability of countries to monitor the situation. Antimalarials, including chloroquine, quinine, or sulfadoxine-pyrimethamine, randomly collected from malaria endemic areas in three provinces all revealed an unacceptably low content of active ingredient.

**Difficulties in adherence to therapy**

Traditionally, chloroquine tablets for adults are usually purchased at a lower cost than the paediatric tablet formulation. When used for children, the adult tablet needs to be broken into two or four pieces and this may cause the tablet to decompose and accentuates the bitter taste. These segments of tablets are commonly wrapped together in newspaper, or any other available paper, and may be exposed to dirt, heat and light or other factors which may interfere with the stability of the product. Additionally, it is often not possible to find paediatric formulations of second-line multidose drugs in many malaria endemic areas.

The importance of tablet size and shape, or whether sugar-coated or polymer coated, has not been investigated. Yet these are important factors in caretaker or child acceptance of the medication and reaction to therapy, and children are a primary target group in Africa. For adult adherence to multidose therapy, appropriate packaging which protects the integrity of each tablet, including non-medical package inserts, and public awareness of the need for ingesting a full regimen are important factors in protecting therapeutic efficacy and the long-term effectiveness of drugs in use.

**Implications for the future**

The drug development costs associated with a single drug for malaria have been quoted as high
as US$ 300 million for each innovative new drug registered and it can take over 10 years from the point at which a lead has been identified up to full development, registration and marketing.

Much effort is expended by the pharmaceutical industry on basic research and pre-registration development of new candidate products. Given the importance of formulation, taste, size, packaging, package inserts, advice to the patient, and acceptance of side effects, it is surprising that only a small amount of market research is carried out to ensure long-term safety and compliance of antimalarials compared to the marketing of, say, beer. Yet these aspects of drug development have such an important impact on the risk of death from malaria and on the tendency to drug resistance. Moreover, it is vital to emphasize implementation of good manufacturing practice (GMP) and vigorous quality assurance in production of antimalarials in order to avoid distribution and use of substandard products and subsequent risk of resistance.

Thailand was one of the first countries to introduce sulfadoxine/pyrimethamine in 1973, and found that high levels of drug resistance to this compound were attained within 10 years. The treatment efficacy of the triple combination of mefloquine/sulfadoxine/pyrimethamine introduced in 1985 lasted for 5 years only and, today, artesunate plus mefloquine is given as first-line treatment for uncomplicated malaria in highly drug-resistant malaria areas. Malaria control programmes in most countries are worried about future prospects, particularly in African countries, where malaria is associated with high mortality.

Fenfluramine and dexfenfluramine recalled worldwide

Fenfluramine and dexfenfluramine have been marketed as anorectics (anti-obesity drugs) for more than 30 years in a number of industrialized countries. Fenfluramine was approved in the United States of America in 1973, however, the stereoisomer of fenfluramine, dexfenfluramine, was approved only in April 1996 (1) following a second hearing of the US Food and Drug Administration's Advisory Committee which voted by a margin of one in its favour. The Committee's concerns were centred principally on reports that fenfluramine and dexfenfluramine damage brain serotonin neurons in animals, and on studies linking use of both drugs with the development of primary pulmonary hypertension in humans (2, 3).

Later during 1996, the Committee for Proprietary Medicinal Products (CPMP) within the European Union issued restrictions on the use of all centrally-acting anorectic drugs (including fenfluramine, dexfenfluramine, amfepramone, clobenzorex, phenmetrazine, fenbutrazate, mazindol, mfenorex, norpseudoephedrine, phentermine, phenidimetrazine and propylhexedrine) because of the risk of severe, often fatal, primary pulmonary hypertension (3).

Evidently spurred by the response to awareness campaigns on the need for weight-loss within the USA, physicians began prescribing fenfluramine or dexfenfluramine, sometimes in combination with another anorectic, phentermine, and often for extended periods of time (1). This combined use — referred to as "fen-phen" and "dexfen-phen" — was not approved or recommended by the FDA, and no studies are available to demonstrate either the effectiveness or safety of these combinations (1). It has been estimated that the total number of prescriptions issued during 1996 in the USA for "fen-phen" exceeded 18 million (4).

Now, fenfluramine and dexfenfluramine have been recalled following increased reports that their use contributes to heart-valve defects and abnormal echocardiograms when taken alone or in combination with phentermine (1, 4–6).

Valvular heart disease

The first 24 cases of valvular heart disease were reported in July 1997 (7) by scientists at the Mayo Clinic, who subsequently published a comprehensive evaluation of these cases (4). All involved women, with a mean age of 44 years, treated with a combination of fenfluramine-phentermine, and with no previous history of cardiac disease. Patients presented with cardiovascular symptoms such as dyspnoea, oedema, congestive heart failure, palpitations, chest pain and heart murmur. Echocardiography demonstrated unusual valvular morphology and regurgitation in all patients between one and 60 months after initiation of therapy. Both right and left-sided valves were involved and 8 women also had newly-documented primary pulmonary hypertension.

During the same month, the FDA received 28 additional reports (5). Of these, two were reports of valvular disease with fenfluramine alone, four with dexfenfluramine alone, and two of dexfenfluramine with phentermine. Cardiac surgical interventions have thus far been required in 5 patients. Upon intervention, the heart valves had a glistening white appearance and histopathological inspection showed plaque-type encasement of the leaflets and chordal structures with valve architecture intact. These findings were identical with symptoms of malignant carcinoid syndrome (8) or similar to those reported after exposure to serotonin-like drugs such as ergotamine and methysergide (9).

As of 15 September 1997, the FDA has received over 100 reports of heart-valve disease associated mainly with use of fenfluramine-phentermine. Moreover, of 291 asymptomatic patients who have received the combination therapy and who were screened by echocardiogram, almost 30% showed abnormal valve function, primarily aortic regurgitation (1).

The mechanism involved

Fenfluramine is a sympathomimetic amine and its anorectic action is mediated through activation of serotonergic pathways in the brain. Fenfluramine promotes the rapid release of serotonin, inhibits re-uptake and may have receptor-agonist activity — thus making serotonin more susceptible to metabolism and breakdown. In animal studies,
fenfluramine and dexfenfluramine have been shown to damage brain serotonin neurons, but it is not known if such damage occurs in humans (2).

Patients with malignant carcinoid syndrome have high levels of circulating serotonin. Associated cardiac disease is expressed as fibroplasia of the valvular endocardium. The mechanism of valve injury in carcinoid syndrome has not been determined but is most likely to be serotonin-mediated because such patients have higher circulating levels of serotonin than do their counterparts without cardiac involvement (10). Ergotamine-induced and carcinoid valve disease are microscopically identical, with fibrotic endocardial changes. Phentermine is known to interfere with the pulmonary clearance of serotonin, which has been postulated to explain its association with primary pulmonary hypertension (4).

Based on these findings, the combination of fenfluramine and phentermine seems to potentiate the effect or concentration of circulating serotonin and result in valvular injury similar to that seen in patients with carcinoid syndrome or those who have taken ergotamine. Unfortunately, serotonin levels were not measured in the affected patients.

Lessons for the future
It is evident that fenfluramine and dexfenfluramine are no longer of use as anorectic medications. But it is surprising that, after having been used for decades, severe adverse reactions to these substances have not come to light before. It must be stated that valvular disease is not known to be associated with drug use and, unless patients develop symptoms, screening for this kind of side-effect would not be carried out as part of the requirements of a clinical trial. The clinical documentation supporting the new drug application for dexfenfluramine covered 500 patients with a one year follow-up. Within the FDA, no cases of valvular heart disease were received (1) because the frequency of clinical symptoms is too low to be detected in these limited clinical trials. As more reports become available, not only in the USA but potentially in other countries, it will become easier to determine if phentermine, amfepramone, norpseudoephedrine or the other centrally-acting anorectics have a different safety profile to fenfluramine or dexfenfluramine.

This incident has once again clearly demonstrated that the supporting data for marketing approval is often insufficient to determine the safety profile of a drug and stresses the vital importance of rigorous post-marketing surveillance. It also shows that even well-established drugs which have been on the market for some time can have hidden adverse reactions which are rare and difficult to discover until increased use or interaction with other drugs brings them to light. This can then lead to the withdrawal of a commonly-used drug, with inevitable fear and confusion among patients.

References

Reduction in use of antimicrobials decreases resistance
Resistance to antimicrobials is a worldwide public health problem which is responsible for a growing number of infections becoming untreatable in both
hospital and community settings (1–5). A major cause of the current crisis has been identified as the uncontrolled and inappropriate use of antibiotics in industrialized and developing countries alike (5).

Antibiotic resistance can develop by various mechanisms (3, 6, 7). One such mechanism is the inherent flexibility which bacteria possess to enable them, sooner or later, to evolve genes that render them resistant to antimicrobials (3). By destroying susceptible microbes, an antimicrobial provides selective pressure that will favour overgrowth of bacteria expressing resistance. Extensive and continuous use of antimicrobials will thus encourage the multiplication and spread of resistant strains.

As early as 1955 (1), it was demonstrated that whereas in 1946 about 90% of S. aureus isolates in hospitals were susceptible to penicillin, 75% of isolates had become resistant by 1952. Although the association of intense antimicrobial use with specific drug resistance has been demonstrated in a hospital setting (7–10), there is less evidence to show that the same is true in outpatient use (2, 11). Although it is important to know whether a reduction in use of antibiotics would similarly reflect a decrease in resistance, lack of reliable drug consumption data, or long-term surveillance on antimicrobial resistance within a community setting have, until now, made such evaluations difficult (12).

A nationwide study carried out in Finland has now documented the impact of outpatient use of antimicrobials and has demonstrated that controlled use will result in a decrease in antimicrobial resistance (13). Calculated as defined daily doses (DDDs) per 1000 inhabitants, use of erythromycin nearly tripled between 1979 and 1988. Parallel to this was a rapid and substantial increase in resistance to erythromycin in group A isolates from blood cultures from 4 to 24%, in throat swabs from 7 to 20% and in isolates from pus from 11 to 31% (14). This finding was particularly alarming because few alternative oral antibiotics are available for treatment of group A streptococcal infections.

In response, a national campaign was launched to change outpatient antibiotic therapy. Guidelines were issued which called for a reduction in the use of macrolide antibiotics for respiratory and skin infections in outpatients (13) and physicians were instructed on the use of alternative drugs. The problem of antibiotic resistance received wide publicity, and specialists in infectious diseases and microbiology agreed to revise antibiotic policy. National and local meetings were held to sensitize both general practitioners and members of the pharmaceutical industry to the Guidelines and, in particular, the need for care in promotional practices (13). As a result of the action, consumption of macrolide antibiotics fell from 2.40 DDDs per 1000 inhabitants in 1991 to 1.38 DDDs in 1992 and remained at this low level until 1996. The change in consumption led to a steady decrease, from 16.5% to 8.6%, in the frequency of erythromycin resistance among group A streptococcal isolates.

Although these studies provide evidence that an increase in outpatient use of macrolide antibiotics brings about an increase in resistance, the situation can also be brought under control as a result of effective policies leading to a change in national prescribing practices of antimicrobials.

References
Inhaled corticosteroids and the risk of cataract

The use of systemic corticosteroids is an established risk factor for the development of cataracts (1) but this has not been demonstrated in the case of inhaled corticosteroids, such as beclometasone or budesonide, because they have a weak systemic effect. As clinical information on long-term use accumulates, it has become increasingly evident that both systemic and inhaled corticosteroids can suppress the hypothalamic-pituitary-adrenal axis and may even cause osteoporosis (2–4). The first report of a possible association between aerosolized beclometasone and cataract was published in 1980, although other studies did not find any evidence to suggest such a link (5, 6).

Because almost all asthma patients in the above studies also used systemic corticosteroids, it has been impossible to extrapolate the effect of inhaled corticosteroids. However, a community-based study of cataracts in older adults has recently been published that includes a substantial number of users of inhaled corticosteroids who have never used systemic corticosteroids (6). Information was collected by questionnaire from 3654 people between 49 and 97 years of age and the presence and severity of cortical, nuclear and posterior subcapsular cataracts was determined from photographs. Data on corticosteroid use were missing for 341 subjects but were available for 3313, and some 11% of subjects had used inhaled corticosteroids. These had a higher prevalence of nuclear and posterior subcapsular cataracts, and higher cumulative lifetime doses of beclometasone were also associated with a higher risk of posterior subcapsular cataracts. The highest prevalence of 27%, was found in subjects whose lifetime beclometasone dose was over 2000 mg (6).

Before reaching any final conclusions, these preliminary findings need to be confirmed in different groups. A prospective study to examine whether use of inhaled corticosteroids precedes the onset of cataract should be set up, as should a paediatric trial to complement the study in adults. It has already been suggested that regular direct ophthalmoscopical examination of the lens is warranted in children because they are more likely to receive long-term inhaled corticosteroids (5).

References


General Information

Transmissible spongiform encephalopathies and medical products

Cases of a previously unreported form of Creutzfeldt-Jakob disease have recently been reported in the United Kingdom (1) and, while no scientific evidence of a link was established immediately, the possibility of an association with exposure to the agent that causes bovine spongiform encephalopathy (BSE) was advanced. The general public reacted with deep concern, and there has been a major loss of confidence in meat products and a disruption of trade in cattle and bovine products in and from the United Kingdom and other countries in which BSE has been reported. These events raise many urgent questions about the safety of animal-derived products and by-products entering the food chain and, in particular, their use in the production of medicinal products and medical devices.

Bovine spongiform encephalopathy

BSE was first reported in cattle in the United Kingdom in 1986 and was made notifiable in June 1988. Shortly afterwards a statutory ban on the feeding of ruminant-derived protein back to ruminants was introduced. By the end of 1996, over 168 000 confirmed cases of BSE had been reported in the United Kingdom. Relatively small numbers of cases have also been reported in native-born cattle in Switzerland, the Republic of Ireland, France, Portugal and the Netherlands. Current evidence suggests that BSE originated from the use of feed supplements containing meat and bone meal contaminated by a TSE agent.

The nature of the agent

The nature of the causative agent of transmissible spongiform encephalopathies (TSEs), which includes BSE, Creutzfeldt-Jakob disease (CJD), new variant Creutzfeldt-Jakob disease (vCJD) and Scrapie in sheep, remains the subject of much debate. Many scientists believe the agent is composed entirely of a self replicating isoform of a normal cellular membrane protein — the protein-only, or prion, hypothesis. Others believe the agent is viral-like and contains nucleic acid. The identification of multiple strains of agent, with characteristic incubation periods and distribution of neuropathology when transmitted to mice, would be in keeping with the latter theory. However, increasing evidence is being accumulated in support of the prion hypothesis. It is clear that the agent, whatever its exact nature, possesses a high degree of resistance to many conventional inactivation procedures, including ultraviolet and ionizing irradiation, extremes of temperatures, ethanol, formaldehyde and standard autoclaving.

New variant Creutzfeldt-Jakob disease

In March 1996, 10 cases of a new variant of CJD (vCJD) were reported from the United Kingdom and, in April 1996, a young man died of vCJD in France. A further five definite and one probable case of vCJD have subsequently been identified in the United Kingdom. These unusually young patients exhibited an apparently novel and distinct clinicopathological phenotype and, from this, it was concluded that their disease was most likely to be associated with exposure to the BSE agent, probably with an incubation period of between 5 and 10 years. The hypothesis of a causal link with BSE is supported by the presence of pathological features similar to vCJD in macaques inoculated with BSE, and by the demonstration that vCJD is associated with a molecular marker that distinguishes it from other forms of CJD, while resembling that seen in BSE and in BSE transmitted to a number of other species. Very recent studies published in October 1997 provide further evidence that the vCJD may be caused by the agent that is responsible for BSE in cattle (2, 3).

In order to evaluate the situation, a consultation was convened at WHO in Geneva this year to evaluate the potential risks and the public health concerns associated with use of medicinal products and medical devices containing either bovine or human-derived materials. Over fifty scientists involved in this issue were present. The conclusions and recommendations of the meeting* are summarized on the following pages.

Medical products derived from bovine material
The use of bovine material in the manufacture of medicinal products should ideally be avoided. This applies equally to materials from other animal species in which TSEs occur naturally. In practice, avoidance may not always be feasible, and careful selection of source materials is the best way of assuring the safety of active substances, excipients and reagents.

Great care should be taken to determine the origin of imported material and to evaluate the risk posed by possible exposure to the BSE agent. Manufacturers should particularly determine the epidemiological status of BSE in countries prior to procurement of raw material of bovine origin. Depending upon the reliability of the source and type of material, additional measures should also be taken to bring the potential risk of contamination to an absolute minimum. These include careful selection of bovine materials and the introduction of procedures to inactivate or remove possible BSE contamination.

Selection of material of bovine origin
Careful selection of source material is the most important criterion for the safety of medical products. The most satisfactory source of materials is from countries which have not reported indigenous cases of BSE and have a compulsory BSE notification system, compulsory clinical and laboratory verification of suspected cases and a surveillance programme. It should also be ensured that there is no risk of BSE infection from the following factors: importation of cattle from countries where a high incidence of BSE has occurred nor the importation of the progeny of affected cows. In addition, it should be ensured that meat and bone meal containing any ruminant protein originating from countries with a high or low incidence of BSE, as classified by the Office International des Epizooties, is being avoided in ruminant feed.

Classification of bovine material
An indication of the infectivity of source materials comprising tissue or body fluids is set out in the table below and this should be borne in mind when selecting source materials. This information results from bioassays of mice injected intracerebrally with tissue from sheep and goats with clinical scrapie. Cell-lines known to be capable of concentrating or amplifying agents causing TSEs should not normally be used in the manufacture of medical products.

Categories of infectivity in bovine tissues and body fluids
(based on relative scrapie infectivity of tissues and body fluids from naturally infected sheep and goats with clinical scrapie)

<table>
<thead>
<tr>
<th>CATEGORY I</th>
<th>Brain, spinal cord, eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>High infectivity</td>
<td></td>
</tr>
<tr>
<td>CATEGORY II</td>
<td>Spleen, tonsil, lymph nodes, ileum, proximal colon, cerebrospinal fluid, pituitary gland, adrenal gland, dura mater, pineal gland, placenta, distal colon</td>
</tr>
<tr>
<td>Medium infectivity</td>
<td></td>
</tr>
<tr>
<td>CATEGORY III</td>
<td>Peripheral nerves, nasal mucosa, thymus, bone marrow, liver, lung, pancreas</td>
</tr>
<tr>
<td>Low infectivity</td>
<td></td>
</tr>
<tr>
<td>CATEGORY IV</td>
<td>Skeletal muscle, heart, mammary gland, milk, blood clot, serum, faeces, kidney, thyroid, salivary gland, saliva, ovary, uterus, testis, seminal testis, foetal tissue, colostrum, bile, bone, cartilaginous tissue, connective tissue, hair, skin, urine.</td>
</tr>
</tbody>
</table>
Conditions under which materials are collected
Potential risks will necessarily be influenced by circumstances under which tissues are removed. For example, the contamination of some tissues might be increased if infected animals are slaughtered by penetrative brain stunning or if the brain and/or spinal cord is sawed.

When cross contamination of a source tissue with a tissue from a higher risk category cannot be reasonable excluded, the higher risk category must be applied.

Procedures capable of reducing or removing infectivity
Where claims are made that the production process makes a significant contribution to the safety of the product, this claim should be validated.

Tallow should only be produced using raw material from a safe source. Materials derived from tallow that has been subjected to highly rigorous processes of extraction and purification, are unlikely to be contaminated.

Raw material used for the production of gelatin should be extracted from selected safe bovine material using a manufacturing process which removes or inactivates TSE infectivity. When this is done, gelatin can be considered safe for all purposes.

Amount of bovine material
Multiple exposure will increase the opportunity for infection and the quantity of bovine material present in the dose administered to humans should be carefully evaluated. Particular attention should be paid to implants and medical devices where the exposure time may be lengthy. The potential risks associated with such kinds of medical products can only be judged on a case-by-case basis.

Human-derived material
Transmission of TSE agents is most efficient where the species barrier is absent, or when the material consists of brain, spinal cord or related tissue potentially containing high titres of infectivity or when material is inserted directly into the brain.

For example, CJD has been transmitted by contaminated instruments in the course of neurosurgery. As a consequence, it is recommended that instruments used for neurosurgical and invasive ophthalmological procedures on patients with CJD should be discarded. If this is not possible, they should be immersed in 1 N NaOH for one hour, cleaned, and then autoclaved at 134°C for one hour.

Hormones, such as growth hormone and gonadotropin purified from the human pituitary gland, are also known to transmit CJD and should not be obtained from human pituitary glands. Over 50 cases of CJD have been reported following cadaveric dura mater grafts, and it is strongly recommended that dura mater no longer be used, especially in the case of neurosurgery, unless no alternative is available. If dura mater is to be used, only material from a non-pooled source originating from carefully screened donors and subject to validated inactivation treatment should be used.

On three occasions, CJD is known to have been transmitted by corneal transplants. Since there are no alternatives to this intervention, donors should be carefully selected and all collecting equipment scrupulously disinfected and sterilized.

The risk of transmission of CJD by blood and blood products
Although there is no documented instance of transmission of CJD by blood or blood products, increased awareness has raised concern about such a possibility. Epidemiological studies have yet to identify a case where CJD was transmitted by blood and it is reassuring that in groups highly exposed to specific blood products, such as haemophiliacs, no cases have been reported.

None the less, clinical and neuropathological observations suggest that vCJD may have distinctive biological features. Further studies of new variant cases are needed in order to determine whether or not the tissue distribution of infectivity in vCJD differs from that of classical CJD and, in particular, whether the infectious agent might be present in blood more frequently, or in greater amounts, than in the blood of patients with other forms of CJD. Continued surveillance is therefore of utmost importance.

Routine blood donor selection already excludes individuals suffering from Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI) or dementia. In addition, donors who have been treated with extracts derived from human pituitary glands, have a familial history of CJD, GSS or FFI, or who have received a human dura mater graft should also be excluded.
Countries have formulated varying policies for the management of plasma products derived from plasma pools which may contain donated blood from individuals with CJD. Batches of such plasma derivatives withdrawn in one country should never be exported to another country.

References


Data mining and drug safety

Professor I. Ralph Edwards

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The Uppsala Monitoring Centre and WHO Collaborating Centre for International Drug Monitoring collect adverse drug reaction reports from all over the world. It now has nearly two million entries stored in the data base of the WHO Programme for International Drug Monitoring. Data is entered based on a format established by the Programme, but the problem of getting early and useful adverse drug reaction (ADR) signals out of this "haystack" is one which has intrigued the members of the Programme since its inception in 1968.

Recently, the Centre has developed a data mining tool based on Bayesian, mutual information logic within a neural network (1) that allows the strength of all drug/ADR data associations to be quantified. The method is transparent and has proved to be robust, even when faced with the task of dealing with incomplete data. The starting point for Bayesian logic is the determination of an ‘a priori’ probability, such as finding a particular drug name within the data base. This probability can be modified by the addition of layers of qualifying information, such as how often a drug is associated with an ADR or, perhaps, a drug–ADR association with a certain age range, or even a drug–ADR–age-range association with the frequency of another drug used at the same time, or in a certain country.

Each time a new layer of information is added, a new ‘a posteriori’ probability is created and compared with the experience contained within the data base. In essence, the whole data base is being used as the control, and any significant new association will be reflected. In this case the size of the ‘haystack’ is an advantage, because the mass of reports it contains provides standard drug spontaneous reporting experiences for purposes of comparison. This latter point is very important for reasons given below, since it could change common approaches to ADR reporting.

It has been argued that free reporting could lead to confusion, or "noise", in the world’s ADR data bases which may mask important signals. In other words, the submission of too many reports which are clinically unsubstantiated can add a disproportionate amount of information to the "haystack" and confuse the identification of fact. As a result, national regulatory and pharmaceutical industry data bases may be crowded with ADR associations that have little value in themselves in raising new concerns. However, this may be overcome by using the Bayesian neural network for data mining.

In actual fact, under-reporting constitutes, overall, the greatest and most persistent problem in identifying signals. At the most recent meeting of national centres participating in the WHO Programme for International Drug Monitoring, the Uppsala Monitoring Centre reported a decline in the numbers of reports it was receiving, which not surprisingly reflects the same phenomenon in many member countries. This trend will adversely affect the data mining activity.

Before any regulatory action is taken as a result of reports, signals must be evaluated individually for their clinical significance. The ADR Signal Analysis Project (ASAP) which the UMC conducts in collaboration with IMS International and the University of Copenhagen, allows for nationally and internationally reported ADRs to be compared with appropriate drug sales and drug usage denominators. This project (supported by a European Union BIOMED grant) has resulted in a routine tool to evaluate the impact of signals on public health internationally (2, 3).

Developments in information technology, such as the data mining approach, require reporting of all ADR suspicions. Innovative methods can then be used to find signals. A signal is only a concern
about a drug and a reaction and the direct causal relationship is still an unproven possibility. We think that such an approach is now technologically feasible. Many other methods such as toxicological testing and pharmacoepidemiology may also need to be incorporated into the process of determining the nature of the signal, and the ASAP approach seems to be a useful way of beginning to understand more about the impact of a reported drug safety signal on international public health.

References

Developments in monitoring of antimicrobial resistance

*Dr Rosamund Williams, Division of Emerging and other Communicable Diseases Surveillance and Control, World Health Organization, Geneva*

The concept of monitoring resistance to antimicrobial agents is by no means new, and for many years the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance in Boston, USA, has been collecting and analysing data from many parts of the world.

In 1995, antimicrobial resistance and other emerging infections of public health importance were addressed in a resolution by the World Health Assembly and the Division of Emerging and other Communicable Diseases Surveillance and Control (EMC) was subsequently established within WHO to provide support to Member States. The programme on surveillance of antimicrobial resistance has now been reborn in EMC as the Antimicrobial Resistance Monitoring (ARM) Programme.

The goals of the ARM Programme are to:
- Assist countries to develop schemes for effective surveillance of antimicrobial resistance.
- Encourage more rational use of antimicrobials.
- Reduce the rate of emergence and spread of antimicrobial resistance.

Surveillance alone will not control the threat of antimicrobial resistance. In order to be effective, information must be translated into action and this will necessarily differ depending on the level at which it is taken. For example, local surveillance information can be used to guide empiric treatment, to identify outbreaks of resistant infections and to guide hospital antimicrobial policy, and the cost of drugs. Meanwhile, at national level, policies may be developed for the purchase and use of antimicrobials and thus reduce inappropriate drug use. At the global level, an analysis of the impact of resistance and monitoring of policies can be made, including development of advocacy and educational programmes, stimulation of appropriate development of new drugs and selection of drugs for the WHO Model List. The pharmaceutical industry also has a particular need for surveillance data for registration purposes, marketing strategies and development of new agents.

No truly global surveillance system of antimicrobial resistance so far exists, although a few countries do operate national systems coordinated by reference laboratories. Many local and some multicentre surveillance systems have been initiated but, at present, there is no repository for information about these systems nor coordination between them.

Linking national and international resistance networks is therefore crucial to improving the surveillance of resistance. The ARM Programme aims to provide as wide an access as possible to reliable resistance information by building a "network of networks". Because of the lack of a commonly-agreed laboratory method to detect resistance, and because of the many different forms which laboratory-based surveillance of resistance can take, the objective is to bring together information on resistance from different countries, while maintaining discrete data sets to avoid mixing "apples with pears". The use of an electronic format will eventually allow remote data entry and access. Through the ARM Programme, policies, guidelines,
bulletins and other information on resistance and surveillance will also be available in a resource bank of reference materials. Thus, sources of information can be shared and common tools developed. A series of meetings in each WHO region is planned to assist in the gathering and sharing of this information.

Training is one element of strengthening national capacity to detect antimicrobial resistance. Laboratory training courses are conducted by WHO teams using training materials developed in collaboration with WHO partners. These materials include the WHONET software which was designed to improve the use of laboratory data for monitoring trends and detecting outbreaks of resistant infections. Quality assurance is essential for the generation of reliable and reproducible data. Within the WHO Collaborating Centre for International Monitoring of Bacterial Resistance to Antimicrobial Agents in Atlanta, USA, a system is operating for external quality control and proficiency testing of laboratories prior to their enrolment into the ARM network.

As a step towards improving rational use of antimicrobial agents, a further aspect of strengthening national capacity is the development of sustainable policies for resistance monitoring and use of antimicrobials. The ARM Programme is working with other interested WHO divisions to sponsor national workshops aimed at improving communication and collaboration between policy makers and prescribers of antimicrobials and to develop national plans of action to address the threat of antimicrobial resistance.

The risk to human health from antimicrobial-resistant bacteria from animals and food of animal origin is still poorly defined. The ARM Programme, through working with experts in the many specialties involved, aims to identify the medical impact of antimicrobial agents used in animals and seek consensus on efficacious methods for monitoring and containment of resistant zoonotic bacteria.

The problem of antimicrobial resistance has triggered many responses at the local, national and international level. Sharing of information and expertise and creation of partnerships to optimize use of resources and avoid duplication are essential to combat this global threat. The ARM Programme is collaborating with many interested parties including ministries of health, nongovernmental organizations and professional societies as well as the pharmaceutical and diagnostics industries, to improve dialogue and encourage partnerships in surveillance, research and education. The Programme advocates appropriate regulation of the promotion and marketing of antimicrobial agents throughout Member States.
Regulatory Matters

Unapproved HIV test kits on Internet

United States of America — The Food and Drug Administration has warned consumers and pharmacists of two unapproved, fraudulently marketed home-use test kits.

The first kit, which is advertised on the Internet as a "personal HIV test kit" is distributed by Lei-Home Access Care, a division of Jin-Greene Biotechnology. The second is labelled as an "in-home hepatitis A test kit". Results from any unapproved tests for home use are unreliable and the FDA advises consumers to consult with a health professional who will advise on approved tests. The Agency also recommends that pharmacists remove any of these unapproved test kits from their stores.


Alendronic acid and oesophagitis

Australia — Alendronate has recently been approved for the treatment of osteoporosis in postmenopausal women and Paget’s disease of the bone. In the first half of 1997, 67 suspected adverse reactions have been reported to the Adverse Drug Reactions Advisory Committee (ADRAC). Of these, 22 reports document early onset oesophageal problems including oesophagitis, oesophageal ulceration, dysphagia, dyspepsia, indigestion, heartburn and epigastric, retrosternal or chest pain. Three reports indicate that these problems occurred despite compliance with precautions specified in the product information (1).

Similar cases have been reported previously from the United States of America (2).

References

Pethidine-associated convulsions

Australia — Since 1975, the Adverse Drug Reactions Advisory Committee (ADRAC) has received 35 reports describing convulsions in association with the administration of pethidine, an opioid analgesic. In 17 cases, pethidine was the only drug suspected and in 10 cases the total dose was high — either because of multiple intramuscular injections or prolonged intravenous infusion. Seven cases were confounded by the concomitant use of propofol, which is known to be associated with the development of convulsions.


Strict control for zopiclone and zolpidem

Sweden — The Medical Products Agency has proposed that, as from 1 October 1997, the two hypnotics, zopiclone and zolpidem, should be classified as narcotics requiring a special prescription form.


Drug-induced gynecomastia

Australia — 332 reports of drug-associated gynecomastia have been received in the past 25 years by the Adverse Drug Reactions Advisory Committee (ADRAC). The drugs most frequently cited are spironolactone, cimetidine, famotidine, ranitidine, digoxin and omeprazole.


Paracetamol and acetylsalicylic acid: restrictions on pack size

United Kingdom — The Medicines Control Agency has introduced a reduction in the size of paracetamol and acetylsalicylic acid packs sold to the public without prescription. As from September
1997, supermarkets and general stores are allowed to sell packs which contain no more than 16 tablets or capsules, rather than 24. Larger packs will be available from pharmacies, which may supply up to 100 tablets in "justifiable circumstances".

There are between 30–40 000 hospital referrals annually in the United Kingdom for paracetamol poisoning resulting in 100–150 deaths while acetylsalicylic acid overdose causes some 5000 hospital admissions and 60 deaths.

References

First fixed-combination drug for HIV

United States of America — The Food and Drug Agency has approved a fixed-combination of zidovudine (ZDV) and lamivudine (3TC), Combivir®, for treating AIDS and HIV infection. This fixed-combination is aimed to reduce pill intake, since these two drugs are frequently given as part of the "drug cocktail" for patients with HIV.


Clobetasol found in over-the-counter topical product

Belgium — The Pharmaceutical Inspectorate has recalled all batches of a product containing pyri-thione zinc (Skin-Cap®: Laboratorios Cheminova Internacional), because it also contains prescription-strength levels of a corticosteroid, clobetasol, which is not mentioned on the label. The product is used to treat dandruff, seborrhoeic dermatitis, psoriasis and other skin disorders. Patients have been advised to contact their physician immediately since abrupt discontinuation may cause potentially serious adverse reactions and worsen psoriasis.


Thalidomide recommended for approval

United States of America — The Food and Drug Administration is discussing with the company Celgene Inc. the possibility of approval of thalidomide for treatment of erythema nodosum leprosum which is a serious, severe complication of leprosy and for which no satisfactory alternative therapy is currently available.

At the present time, the Agency has determined that the benefits of this product outweigh the known risks for the treatment of erythema nodosum leprosum. However, before a final approval decision can be made, additional information must be submitted, reviewed and agreed upon by the Agency. If the product reaches the stage of final approval in the United States, it will be ruled by restricted distribution requirements which maximize the opportunities for health practitioners and patients to be made fully aware of the potential side effects of this product.


First COMT inhibitor for Parkinson's disease

United Kingdom, Germany and Switzerland — Tolcapone, a catechol-0-methyl transferase (COMT) inhibitor has been authorized for marketing for the adjunctive treatment of Parkinson's disease with levodopa. Tolcapone inhibits the enzyme responsible for metabolism of levodopa to a breakdown product, 3-0-methyladopha thus increasing the amount of levodopa to reach the brain.

Reference: Marketletter, 6 October 1997.

Phenolphthalein laxatives and cancer risk

United States of America — The Food and Drug Administration has proposed a ban on the OTC availability of phenolphthalein, an ingredient widely used in laxatives. A review of animal carcinogenicity studies showed that rats and mice fed high doses — approximately 50 to 100 times the recommended dose for humans — developed a variety of tumours. When fed 30 times the recommended human dose for six months, mice also developed genetic damage.

Given the fact that consumers have access to more than two dozen laxative products which do not contain phenolphthalein and that a potential cancer risk exists for people who use this ingredient at
higher than recommended doses or for extended periods of time, the Agency proposes to reclassify phenolphthalein. A final regulation will be issued following a review of comments.


**Warning of herbal products sold as abuse drugs**

**United Kingdom** — The Medicines Control Agency has warned traders that the sale or supply of unlicensed medicinal herbal products — which could be harmful — as alternatives to drugs of abuse is open to prosecution. Such products, which can contain ephedra, khat and yohimbe bark, are promoted as having similar effects to those of controlled drugs, such as cannabis and ecstasy.


**Dietary supplement products containing digitalis**

**United States of America** — The Food and Drug Administration has warned consumers not to purchase or ingest dietary supplements containing "plantain" because they may contain digitalis, a powerful heart stimulant that can cause life-threatening reactions including cardiac arrest. The Agency has published a list of distributors of herbal products whose products may contain digitalis.


**Medication errors involving HIV drugs**

**United States of America** — The United States Pharmacopeia has received reports of HIV patients receiving the wrong medication because of confusion over the names of drugs currently used to treat the infection. Mix-ups between the antiretroviral Retrovir® (zidovudine) and the protease inhibitor ritonavir, or between the anticonvulsant, lamotrigine, and the antiretroviral, lamivudine, have been problematic.

Both Retrovir® and ritonavir are available as 100 mg capsules, however, the maintenance dose for zidovudine is 500 to 600 mg daily compared with 600 mg twice daily for ritonavir. If one of these drugs is mistaken for the other, the patient may experience a subtherapeutic response, toxicity from an overdose, or unexpected drug interactions.

Another report describes an HIV patient who suffered a seizure requiring intensive care as a result of receiving an extremely high dose of Sinequan®, an antidepressant, instead of the prescribed HIV protease inhibitor, saquinavir.

WHO MODEL PRESCRIBING INFORMATION

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WHO Model Prescribing Information provides up-to-date and independent clinical information on essential drugs, including details of dosage, uses, contraindications, precautions and adverse effects. It is intended as source material for adaptation by national authorities, in particular in developing countries.

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Distribution and Sales, World Health Organization,
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Essential Drugs

WHO Model Formulary

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

Antibacterials: Antileprosy drugs

Leprosy is a chronic mycobacterial infection which affects people of all ages and both sexes. Paucibacillary and multibacillary leprosy are the two clinical forms of the disease. Single-lesion leprosy is a subclassification of paucibacillary leprosy.

In paucibacillary (PB) leprosy, peripheral nerve involvement may result in no more than minor, localized impairment of sensation but, in severe cases, extensive sensory and motor loss can induce trophic changes, muscle wasting and contractures. In multibacillary (MB) leprosy, nerve damage commonly occurs and, if left untreated, may lead to crippling deformities. Visual impairment or blindness is a frequent complication in both paucibacillary and multibacillary leprosy.

Dapsone, which is bacteriostatic or weakly bactericidal against \emph{M. leprae}, was the mainstay of treatment for leprosy for many years until widespread resistant strains appeared. Combination therapy has become essential to prevent the emergence of resistance. Rifampicin is now combined with dapsone to treat PB leprosy and rifampicin and clofazimine are now combined with dapsone to treat MB leprosy. The WHO Action Programme for the Elimination of Leprosy currently provides oral multidrug therapy (MDT) in blister packs which ensure better patient compliance. More recently, a one-time dose of combination therapy has been recommended to cure patients with single skin lesion leprosy. (WHO-recommended treatment regimens are set out in the tables on page 253).

Any patient with a positive skin smear should be treated with the MDT regimen for multibacillary leprosy. Never give the regimen for paucibacillary leprosy to a patient with multibacillary leprosy. If diagnosis in a particular patient is not possible, treat that patient with the MDT regimen for multibacillary leprosy.

Lepra reactions are episodes of sudden increase in the activity of leprosy and are often accompanied by neuritis. Reactions must always be treated promptly to prevent permanent nerve damage and disability. During a lepra reaction, continue giving leprosy multidrug therapy without interruption. This will reduce the frequency and severity of lepra reactions.

Type-1 lepra reactions, or reversal reactions, are delayed hypersensitivity reactions and may occur in either paucibacillary or multibacillary leprosy. If there is no nerve damage, treat type-1 reactions with analgesics, such as acetylsalicylic acid or paracetamol. If there is nerve involvement use corticosteroids, such as oral prednisolone.

The type-2 lepra reaction, also known as erythema nodosum leprosum (ENL), is an antibody response to dead leprosy bacteria and occurs only in multibacillary leprosy. Therapy for type-2 reactions may include analgesics, such as acetylsalicylic acid or paracetamol, and corticosteroids, such as oral prednisolone. In patients not responding to corticosteroids, thalidomide or clofazimine may be used under close medical supervision.

If a patient does not respond to lepra reaction treatment within 6 weeks or seems to become worse, the patient must be sent immediately to the nearest specialist centre.

Combination therapy prevents the organism from developing drug resistance. Experience with multi-
### WHO-recommended treatment regimens

#### Single-lesion paucibacillary (PB) leprosy

<table>
<thead>
<tr>
<th></th>
<th>Rifampicin</th>
<th>Ofloxacin</th>
<th>Minocycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult 50–70 kg</td>
<td>600 mg</td>
<td>400 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Child 5–14 years</td>
<td>300 mg</td>
<td>200 mg</td>
<td>50 mg</td>
</tr>
</tbody>
</table>

*a Adjust dose appropriately for child less than 5 years

#### 6-month regimen for paucibacillary (PB) leprosy

<table>
<thead>
<tr>
<th></th>
<th>Dapsone</th>
<th>Rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult 50–70 kg</td>
<td>100 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Child 10–14 years</td>
<td>50 mg</td>
<td>450 mg</td>
</tr>
</tbody>
</table>

*b Adjust dose appropriately for child less than 10 years. For example, dapsone 25 mg daily and rifampicin 300 mg given once a month under supervision

#### 12-month regimen for multibacillary (MB) leprosy

<table>
<thead>
<tr>
<th></th>
<th>Dapsone</th>
<th>Rifampicin</th>
<th>Clofazimine</th>
<th>Clofazimine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult 50–70 kg</td>
<td>100 mg</td>
<td>600 mg</td>
<td>50 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Child 10–14 years</td>
<td>50 mg</td>
<td>450 mg</td>
<td>50 mg</td>
<td>150 mg</td>
</tr>
</tbody>
</table>

*c Adjust dose appropriately for child less than 10 years. For example, dapsone 25 mg daily, rifampicin 300 mg given once a month under supervision, clofazimine, 50 mg given twice a week, and clofazamine 100 mg given once a month under supervision
drug therapy has shown that side-effects do not occur often and relapses are rare. Treatment can be considered as both safe and efficacious.

CLOFAZIMINE
Capsule: 50 mg, 100 mg

Uses: Multibacillary leprosy in combination with dapsone and rifampicin. For type-2 lepra reactions, as an alternative or in addition to analgesics, corticosteroids or thalidomide.

Dosage:
Multibacillary leprosy (in combination with dapsone and rifampicin)
Adults: 50 mg daily for 12 months, AND 300 mg once a month, supervised.
Children 10–14 years of age: 50 mg given on alternate days for 12 months, AND 150 mg once a month, supervised.
Children under 10 years of age: Adjust the dose. For example, clofazimine, 50 mg twice a week for 12 months AND 100 mg once a month, supervised.

Erythema nodosum leprosum (type-2 lepra reactions)
Adults and children: 200–300 mg daily in divided doses of twice or three times daily. 4–6 weeks may be needed before an effect is seen. Hospitalize a patient with severe type-2 lepra reactions for supervised medical care.

Precautions: Patients with pre-existing gastrointestinal disease require medical supervision. Liver function and creatinine clearance require monitoring.

Adverse effects: Reversible discoloration of skin, hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine may occur. Dose-related gastrointestinal symptoms include pain, nausea, vomiting and diarrhoea. Prolonged treatment with high doses may cause rare but severe mucosal and sub-mucosal oedema, severe enough to produce symptoms of subacute small-bowel obstruction needing supervised medical care.

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

DAPSONE
Tablet: 25 mg, 50 mg, 100 mg

Uses: Paucibacillary and multibacillary leprosy in combination with other antileprosy drugs.

Dosage:
Paucibacillary leprosy (in combination with rifampicin)
Adults: 100 mg daily for 6 months.
Children 10–14 years of age: 50 mg daily for 6 months.
Children under 10 years of age: Adjust the dose. For example, dapsone, 25 mg daily for 6 months.

Multibacillary leprosy (in combination with rifampicin and clofazimine)
Adults: 100 mg daily for 12 months
Children 10–14 years of age: 50 mg daily for 12 months.
Children under 10 years of age: Adjust the dose. For example, dapsone, 25 mg daily for 12 months

Contraindications: Known hypersensitivity to sulfones; severe anaemia.

Precautions: Treat pre-existing severe anaemia before therapy. Dapsone can induce haemolysis, particularly in glucose-6-phosphate dehydrogenase deficiency, and can cause dose-dependent methaemoglobinemia. These adverse effects are seen early in therapy. Monitor clinical response and blood count in susceptible patients during first weeks of treatment.

Adverse effects: Varying degrees of dose-related haemolysis and methaemoglobinemia are the most frequently reported adverse effects. A “dapsone syndrome”, which resembles mononucleosis is a rare hypersensitivity reaction. Symptoms include skin rash, fever, jaundice and eosinophilia. Occasionally, gastrointestinal irritation is reported and, uncommonly, headache, nervousness and insomnia, blurred vision, paraesthesia, reversible peripheral neuropathy, psychoses. Rarely, hepatitis and agranulocytosis occur.

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

RIFAMPICIN
Capsule or tablet 150 mg, 300 mg

Uses: Paucibacillary and multibacillary leprosy in combination with other antileprosy drugs.

Dosage:
Paucibacillary leprosy (in combination with dapsone).
Adults: A dose of 600 mg, supervised, once a month for 6 months.
Children 10–14 years of age: A single dose of 450 mg, supervised, once a month for 6 months.

Children under 10 years of age: Adjust the dose. For example, a single dose of 300 mg, supervised, once a month for 6 months.

**Multibacillary leprosy (in combination with dapsone and clofazimine)**

**Adults:** Once a month for 12 months, a single dose of 600 mg, which is supervised.

**Children 10–14 years of age:** A single dose of 450 mg, supervised, once a month for 12 months.

**Children under 10 years:** Adjust the dose. For example, a single dose of 300 mg, supervised, once a month for 12 months.

**Contraindications:** Hepatic dysfunction.

**Precautions:** Patients who re-take rifampicin again after a long interval may have serious immunological reactions, resulting in renal impairment, haemolysis, or thrombocytopenia. In this rare situation, stop rifampicin immediately. Do not ever give rifampicin again to this patient.

Monitor liver function in the elderly, in patients who are alcohol-dependent and in patients with hepatic disease. Rifampicin produces a red colour in urine, tears, saliva and sputum and may stain contact lenses permanently.

**Adverse effects:** In some patients, severe gastrointestinal disturbances may occur. Skin rashes, fever, influenza-like syndrome and thrombocytopenia are more likely to occur during intermittent therapy.

Moderate rises in serum concentrations of bilirubin and transaminases often occur at the start of treatment, are often transient and do not have clinical significance.

Potentially fatal, dose-related hepatitis may occur. Do not exceed the maximum recommended daily dose of 600 mg or 10 mg/kg.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary. Advise women taking oral contraceptives to use other nonsteroidal forms of contraception.

**MINOCYCLINE**

**Tablet, 50 mg, 100 mg**

**Uses:** Single-lesion paucibacillary leprosy in combination with rifampicin and ofloxacin.

**Dosage:**

**Adults:** A single dose of 100 mg.

**Children:** A single dose of 50 mg.

**Precautions:** Impaired liver function. Avoid exposure to sunlight.

**Contraindications:** Do not give with milk or milk products, antacids, or calcium, iron and magnesium salts.

**Adverse effects:** Vestibular disturbances which cause dizziness and vertigo are more common in women than in men. Gastrointestinal effects such as nausea, vomiting, and diarrhoea may occur. Headache or visual disturbances may indicate intracranial hypertension.

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

**OFLOXACIN**

**Tablets, 200 mg, 400 mg**

**Uses:** Single-lesion paucibacillary leprosy in combination with rifampicin and minocycline.

**Dosage:**

**Adults:** A single dose of 400 mg.

**Children:** A single dose of 200 mg.

**Precautions:** Use with extreme caution in patients with epilepsy, a history of epilepsy or a history of central nervous system disorders. Impaired renal or hepatic function. Avoid exposure to sunlight. Wait at least 4 hours before giving any product containing aluminium, iron or magnesium salts. Give with a full (250 ml) glass of water.

**Adverse effects:** May induce convulsions in patients with or without a history of convulsions. Nausea, vomiting, abdominal pain, diarrhoea, headache, visual disturbances, sleep disorders, rash, pruritus, fever, anaphylaxis.

**Drug Interactions:** Taking nonsteroidal anti-inflammatory drugs with ofloxacin may induce convulsions. Other drug interactions will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.
Antibacterials: Antituberculosis drugs

Tuberculosis is the leading infectious disease of adults and causes 26% of avoidable adult deaths in the developing world. More than 80% of tuberculosis cases are pulmonary (PTB). At least 30% of patients who are infected with HIV will also develop active tuberculosis. Left untreated, 50% of tuberculosis patients die within 5 years and most of the surviving patients with tuberculosis will be seriously debilitated. All patients represent a source of infection to others.

The essential tools against tuberculosis are detection and treatment, with priority given to infectious cases. Short-course therapy which lasts for 6 or 8 months, given under direct observation (DOTS), is one of the most important components of the WHO strategy against tuberculosis. Active tuberculosis, no matter how mild the case, must never be treated with a single drug because of the risk of acquired resistance.

The 6 antituberculosis drugs, isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol and thioacetazone, are used in various combinations as part of the WHO recommended treatment regimens set out in the table on page 257.

In countries with a high incidence of tuberculosis, routine drug susceptibility testing is not recommended and is not normally feasible for all patients. Drug susceptibility tests should be conducted only if the reliability and consistency of the results can be guaranteed by careful standardization and quality control.

In clinics where culture facilities and reliable drug susceptibility testing are available, testing may be useful in cases of treatment failure or relapse or for chronic cases. Testing should be used only after failure of standardized chemotherapy, given as DOTS, and should be used to assist in decision-making regarding the future therapy of a particular patient.

A change of drug regimen should be considered only if the patient fails to respond to treatment after 5 months of DOTS. Poor compliance is a far more common reason for failure of chemotherapy than is drug resistance. Alternative therapy, as set out in the table on page 258, may be administered as specified.

Worldwide, an important predisposing cause of immunosuppression leading to tuberculosis is human immunodeficiency virus (HIV) infection which increases the reactivation rate of tuberculosis. Preventive antituberculosis therapy of such persons is recommended.

Fixed-dose combination (FDC) tablets incorporate two or more drugs within the same dosage form. Use of single antituberculosis drugs increases the risk of emergence of drug-resistant organisms. FDCs provide a more effective regimen, decrease inadvertent medication errors and improve compliance.

Where the disease remains highly prevalent, routine immunization of infants within the first year of age with BCG vaccine is cost-effective. However, there is no evidence that BCG will protect children older than 15 years of age. Infants born to HIV-positive mothers should be vaccinated during the first year of life, provided they have no clinical signs suggestive of HIV.

Chemoprophylaxis with isoniazid can prevent the development of clinically apparent disease in persons in close contact with infectious patients, and in other persons at high risk. In countries with high tuberculosis prevalence, the recommended policy is to give isoniazid for at least 6 months to any child under 5 years of age who is in close contact with an infectious case of tuberculosis, provided the child is apparently healthy and does not have any symptoms of tuberculosis. Do not consider the BCG status of that child. In some countries or in populations with a high HIV prevalence, it is strongly recommended that chemoprophylaxis is given to patients who are HIV-positive and are also tuberculin positive.

The tuberculin test has limited diagnostic value. A positive tuberculin test indicates previous exposure to mycobacterial antigens through infection with one of the tubercle bacilli, or BCG vaccination. The tuberculin test does not distinguish between tuberculosis and other mycobacterial infection, between active and quiescent disease, or between acquired infection and seroconversion induced by BCG vaccination.

**ISONIAZID**

*Tablet: 100, 300 mg*

*Injection: 25 mg/ml in 2 ml ampoule*

**Uses:** A component of all combined antituberculosis regimens currently recommended by WHO. Occasionally used alone to prevent
transmission by close contact or high risk and to prevent progression of infection in recently infected, asymptomatic individuals, particularly those who are immunodeficient.

**Dosage:** Normally taken by mouth, but may also be administered intramuscularly to critically-ill patients.

**Treatment (combination therapy)**

*Adults and children:* 5 mg/kg (4–6 mg/kg) daily, maximum 300 mg or 10 mg/kg three times weekly or 15 mg/kg twice weekly.

**Prophylaxis**

*Adults:* 300 mg/kg daily for at least 6 months

*Children:* 5 mg/kg daily for at least 6 months. Maximum child’s dose is 300 mg daily for at least 6 months

**Contraindications:** Active hepatic disease.

### WHO recommended treatment regimen for tuberculosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase 1: 2 months</th>
<th>Phase 2: 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>5 mg/kg daily</td>
<td>10 mg/kg daily</td>
</tr>
<tr>
<td>rifampicin</td>
<td>10 mg/kg daily</td>
<td>10 mg/kg daily</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>25 mg/kg daily</td>
<td>10 mg/kg daily</td>
</tr>
<tr>
<td><em>together with</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>streptomycin</td>
<td>15 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethambutol</td>
<td>15 mg/kg daily</td>
<td></td>
</tr>
</tbody>
</table>

**OR**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase 1: 2 months</th>
<th>Phase 2: 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>10 mg/kg 3 times weekly</td>
<td>10 mg/kg 3 times weekly</td>
</tr>
<tr>
<td>rifampicin</td>
<td>10 mg/kg 3 times weekly</td>
<td>10 mg/kg 3 times weekly</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>35 mg/kg 3 times weekly</td>
<td></td>
</tr>
<tr>
<td><em>together with</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>streptomycin</td>
<td>15 mg/kg 3 times weekly</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethambutol</td>
<td>30 mg/kg 3 times weekly</td>
<td></td>
</tr>
</tbody>
</table>

### 8-month regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase 1: 2 months</th>
<th>Phase 2: 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>5 mg/kg daily</td>
<td>5 mg/kg daily</td>
</tr>
<tr>
<td>rifampicin</td>
<td>10 mg/kg daily</td>
<td>2.5 mg/kg daily</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>30 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td><em>together with</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>streptomycin</td>
<td>15 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethambutol</td>
<td>25 mg/kg daily</td>
<td>25 mg/kg daily</td>
</tr>
</tbody>
</table>

* Unless otherwise indicated, doses are suitable for both adults and children.

* 15 mg/kg maximum daily dose for children.

* Not suitable for children.
**Precautions:** Monitor hepatic function since isoniazid is associated with liver toxicity. Monitor serum concentrations of hepatic transaminases which indicate an increase in liver enzymes. If signs of liver disease appear, the patient must stop treatment and seek immediate medical attention. Patients at risk of peripheral neuropathy as a result of malnutrition, chronic alcohol dependence, chronic renal failure or diabetes should supplement their tuberculosis medication with pyridoxine (vitamin B₆), 10 mg daily. When the standard of health in the community is low, patients should routinely be given pyridoxine. Isoniazid may provoke epilepsy.

**Adverse effects:** Frequently produces gastrointestinal disturbances (nausea, diarrhoea, vomiting, stomach pain). To reduce gastrointestinal irritation, isoniazid should be taken with food, however, this may impair oral absorption and bioavailability.

### Alternative treatment regimen

<table>
<thead>
<tr>
<th>treatment category</th>
<th>Alternative TB treatment regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Initial phase (daily or 3 times weekly)</strong></td>
</tr>
<tr>
<td>1. New cases of smear-positive pulmonary tuberculosis (PTB) and new cases of smear-negative PTB with extensive parenchymal involvement. New cases of severe forms of extra-pulmonary TB.</td>
<td>2 EHRZ (SHRZ)</td>
</tr>
<tr>
<td></td>
<td>2 EHRZ (SHRZ)</td>
</tr>
<tr>
<td></td>
<td>2 EHRZ (SHRZ)</td>
</tr>
</tbody>
</table>

**H= isoniazid, R= rifampicin, Z=pyrazinamide, E=ethambutol, S=streptomycin.**


|                   | 2 SHRZE / 1 HRZE | 5 H,R,E³ |
|                   | 2 SHRZE / 1 HRZE | 5 HRE³ |

3. New smear-negative PTB (other than in 1); New less severe forms of extra-pulmonary TB.

|                   | 2 HRZ | 6 HE |
|                   | 2 HRZ | 4 HR |
|                   | 2 HRZ | 4 H₃R₃ |


**N.B.** Some authorities recommend a 7-month continuation phase with daily isoniazid and rifampicin (7HR) for Category 1 patients with the following forms of TB: TB meningitis, miliary TB, spinal TB with neurological signs.

A regimen consists of 2 phases, the initial phase and the continuation phase. The number before a phase is the duration of that phase in months. The number in subscript after a letter is the number of doses of that drug per week. If there is no number in subscript after a letter, then treatment with that drug is daily. An alternative drug(s) appears as a letter(s) in parentheses.
Occasionally, systemic or cutaneous hypersensitivity during first weeks of treatment may be experienced. Risk of peripheral neuropathy is reduced if patients take pyridoxine. Other, less common, neurological disturbances including optic neuritis, toxic psychosis and generalized convulsions, particularly during the later stages of treatment may occur. Isoniazid withdrawal may be necessary. Hypersensitivity reactions include skin eruptions, skin rash, fever, and joint pain.

Hepatitis is uncommon but potentially serious and, when this occurs, isoniazid should be stopped. Hepatitis is seen more often in patients over 35 years of age and in regular drinkers of alcohol. Fatigue may indicate liver damage. Patients who inactivate isoniazide slowly (slow acetylators) tend to have a higher incidence of adverse events, especially peripheral neuritis, and may require dose reduction.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary. If taking an aluminium-containing antacid, wait at least 1 hour after taking isoniazid.

**RIFAMPICIN**

_Capsule or tablet 150 mg, 300 mg_

**Uses:** A component of all 6 and 8-month antituberculosis regimens currently recommended by WHO.

**Dosage:**

_Adults and children:_ 10 mg/kg (8–12 mg/kg) daily two or three times weekly. Maximum dose is 600 mg daily.

Give at least 30 minutes before meals since rifampicin absorption is reduced when taken with food.

**Contraindications:** Hepatic dysfunction.

**Precautions:** Patients who re-take rifampicin again after a long interval may have serious immunological reactions resulting in renal impairment, haemolysis, or thrombocytopenia. In this rare situation, stop rifampicin immediately. Do not ever give rifampicin again to this patient.

Monitor liver function in the elderly, in patients who are alcohol-dependent and in patients with hepatic disease. Rifampicin produces a red colour in urine, tears, saliva and sputum and may stain contact lenses permanently.

**Adverse effects:** In some patients, severe gastrointestinal disturbances may occur. Skin rashes, fever, influenza-like syndrome and thrombocytopenia are more likely to occur during intermittent therapy. Exfoliative dermatitis is also observed in HIV-positive tuberculosis patients. Temporary oliguria, dyspnoea and haemolytic anaemia have been reported in patients taking rifampicin 3 times weekly. Conditions usually subside if rifampicin is reduced to once daily administration.

Moderate rises in serum concentrations of bilirubin and transaminases often occur at the start of treatment, are often transient and do not have clinical significance.

Potentially fatal, dose-related hepatitis may occur. Do not exceed the maximum recommended daily dose of 600 mg or 10 mg/kg.

**Drug interactions:** These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary. Advise women taking oral contraceptives to use nonsteroidal forms of contraception.

**RIFAMPICIN /ISONIAZID**

_Tablet: 150 mg rifampicin + 75 mg isoniazid and 300 mg rifampicin + 150 mg isoniazid._

_Tablet: 150 mg rifampicin + 150 mg isoniazid._

**Uses:** Both drugs are components of all 6- and 8-month antituberculosis regimens currently recommended by WHO.

**Dosage:** This fixed-dose combination tablet is used in the continuation phase of treatment. The combination tablet is not suitable for paediatric use.

For daily use

_Adults:_ Total daily dose of 450 mg rifampicin and 225 mg isoniazid.

For intermittent use (three times a week)

_Adults:_ Each dose of 450 mg rifampicin and 450 mg isoniazid.

**Contraindications, precautions, adverse effects and drug interactions:** Refer to information given for each individual substance.
PYRAZINAMIDE
Tablet: 400 mg, 500 mg

Uses: A component of all 6- and 8-month anti-tuberculosis regimens currently recommended by WHO.

Dosage: 
Adults and children: 25 mg/kg daily (20–30 mg/kg) or 35 mg/kg (30–40 mg/kg) three times weekly or 50 mg/kg (40–60 mg/kg) two times weekly.

Contraindications: Known hypersensitivity; severe hepatic impairment.

Precautions: Monitor blood glucose carefully in diabetic patients since this may change suddenly. Gout may be exacerbated.

Adverse effects: Moderate rises in serum transaminase concentrations are common during early phases of treatment. A degree of asymptomatic hyperuricaemia usually occurs. Arthralgia, particularly of the shoulders, is also common which can be treated with simple analgesics. Hyperuricaemia and arthralgia can be reduced by using regimens with intermittent administration of pyrazinamide. Gout requiring allopurinol treatment occasionally develops. Rarely, hypersensitivity is reported and some patients complain about skin flushing.

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

STREPTOMYCIN
Powder for injection: 1 gm (as sulfate) in vial

Uses: A component of several combined anti-tuberculosis regimens currently recommended by WHO.

Dosage: Administer streptomycin by deep intramuscular injection. Use only sterile needles and syringes.

Adults and children: 15 mg/kg (12–18 mg/kg) daily or two or three times weekly. Patients over 60 years may not tolerate more than 500–750 mg daily.

Contraindications: Auditory nerve impairment; myasthenia gravis.

Precautions: If possible, do not use streptomycin in children since the injections are painful, and irreversible auditory nerve damage may occur. Wear protective gloves to avoid sensitization dermatitis.

Withdraw if hypersensitivity occurs (commonly, during the first week of treatment). Monitor plasma levels periodically in the elderly and in patients with renal impairment. Adjust streptomycin dose to avoid dose-related toxic effects resulting from drug accumulation. Adjust dose to ensure that plasma concentrations, measured at maximum trough concentrations (just before the next dose is due) do not rise above 4 μg/ml (4 mg/litre).

Adverse effects: Painful and sterile abscesses at injection sites. Hypersensitivity reactions are common and can be severe. Streptomycin may produce otic toxicity. Vestibular ototoxicity presents as clumsiness, dizziness, vertigo, nausea and unsteadiness. Auditory ototoxicity includes hearing loss or ringing, buzzing or a feeling of fullness in the ears. Streptomycin affects vestibular function more often than auditory function but impairment of vestibular function appears to be uncommon with currently recommended doses.

Streptomycin may produce nephrotoxicity. Close monitoring of renal function is required. Halve the dose if urinary output falls, if albuminuria is seen, or if urine has tubular casts. Rarely produces haemolytic anaemia, aplastic anaemia, agranulocytosis; thrombocytopenia and lupoid reactions.

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

ETHAMBUTOL
Tablet: 100 mg, 400 mg (hydrochloride)

Uses: An optional component of several combined antituberculosis regimens currently recommended by WHO.

Dosage: This must always be calculated on a weight basis to avoid toxicity, and should be reduced in patients with impaired renal function. Adults: 15 mg/kg (15–20 mg/kg) daily, 30 mg/kg (25–35 mg/kg) three times weekly or 45 mg/kg (40–50 mg/kg) twice weekly. Children: Maximum 15 mg/kg daily.
**Contraindications**: Pre-existing optic neuritis from any cause; inability to report symptomatic visual disturbances creatinine clearance of less than 50 ml/minute.

**Precautions**: Ethambutol may damage the vision. Test vision before and regularly during administration. Ethambutol may produce optic neuritis, which causes eye pain, decreased visual acuity, general loss of vision, central and peripheral constriction of visual fields, and loss of red/green colour perception. If the patient has any indication that the perception of colour or the sight is deteriorating, treatment must be stopped immediately and the doctor consulted. Do not give ethambutol to any patient too young to understand this warning or who cannot communicate any visual problems.

Whenever possible, renal function should be assessed before and regularly during treatment. Ethambutol will increase serum concentration and prolong half-life in patients with renal impairment. In a patient with impaired kidney function, reduce ethambutol dose according to the drug serum concentration.

**Adverse effects**: Dose-dependent optic neuritis leading to impairment of visual acuity and colour vision. Early changes are usually reversible and prompt withdrawal may prevent blindness. Occasionally, signs of peripheral neuritis especially in the legs, have been reported. May precipitate attacks of gout, since ethambutol can increase uric acid concentration.

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

**THIOACETAZONE/ISONIAZID**

*Tablet: 50 mg thioacetazone + 100 mg isoniazid and 150 mg thioacetazone + 300 mg isoniazid*

**Uses**: A component of some of the longer antituberculosis regimens currently recommended by WHO.

**Dosage**: This fixed-dose combination tablet is used in the continuation phase of treatment.

*Adults*: 150 mg thioacetazone + 300 mg isoniazid daily. *Children*: 50 mg thioacetazone + 100 mg isoniazid daily.

**Contraindications**: Avoid in patients with HIV infection. Thioacetazone has been reported to produce a high incidence of serious and sometimes fatal cutaneous hypersensitivity reactions in HIV-infected patients. Do not give thioacetazone to patients with liver impairment or renal failure.

**Precautions**: The efficacy and toxicity of thioacetazone should be determined within a community before it is used since there appear to be geographical differences.

Withdraw immediately if rash or other signs related to hypersensitivity occur. Thioacetazone may potentiate the ototoxic effect of streptomycin.

**Adverse effects**: Refer to information given for isoniazid. Thioacetazone frequently causes gastrointestinal disorders (nausea, vomiting, diarrhoea), hypersensitivity reactions (including conjunctivitis), vertigo and skin rashes. The incidence of these adverse events appears to vary from country to country.

Fatal exfoliative dermatitis and acute hepatic toxicity with jaundice can occur. Thioacetazone may cause agranulocytosis, thrombocytopenia and aplastic anaemia. Acute haemolytic anaemia may occur. However, a large percentage of patients will have some minor degree of anaemia.

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

**ETHAMBUTOL/ISONIAZID**

*Tablet: 400 mg ethambutol + 150 mg isoniazid*

**Uses**: Ethambutol is an optional component of several combined antituberculosis regimens and isoniazid is a component of all combined antituberculosis regimens currently recommended by WHO. This fixed-dose combination can be substituted for the thioacetazone +isoniazid combination in patients, who have adverse effects due to thioacetazone.

**Dosage**: 800 mg ethambutol + 300 mg isoniazid. This fixed-dose combination tablet is used only in the continuation phase of treatment and is always given daily: do not give three times a week. The combination tablets are not suitable for paediatric use.

**Contraindications, precautions, adverse effects and drug interactions**: Refer to information given for each substance.
RIFAMPICIN/ISONIAZID/PYRAZINAMIDE

Tablet: 150 mg rifampicin + 75 mg isoniazid + 400 mg pyrazinamide
Tablet: 150 mg rifampicin + 150 mg isoniazid + 500 mg pyrazinamide

Uses: All three drugs are components of 6- and 8-month antituberculosis regimens recommended by WHO. This fixed-dose combination tablet is used in the initial phase of treatment.

Dosage: The combination tablets are not suitable for paediatric use. Doses shown are for a 45–55 kg patient during the initial phase of treatment.

For daily administration: 450 mg rifampicin + 225 mg isoniazid + 1200 mg pyrazinamide.

For 3 times weekly administration: 450 mg rifampicin + 450 mg isoniazid + 1500 mg pyrazinamide for each administration.

Contraindications, precautions, adverse effects and drug interactions: Refer to information given for each substance.

BCG VACCINE (DRIED)

Intradermal injection

Uses: To confer active immunity against tuberculosis.

Dosage: Inject the vaccine intradermally. Be careful not to inject vaccine subcutaneously.

Neonates and infants: 0.05 ml by intradermal injection in the arm over the insertion of the deltoid muscle.

Children over 1 year of age: 0.1 ml by intradermal injection in the arm over the insertion of the deltoid muscle.

Contraindications: Generalized oedema; hypogammaglobulinaemia and immunodeficiency resulting from treatment with antimetabolites, irradiation or systemic corticosteroids.

Precautions: Do not inject into skin sites with infectious dermatosis such as scabies.

Adverse effects: Lymphadenitis, osteitis and localized necrotic ulceration may occur. Very rarely, cases of disseminated BCG infection have been reported in immunodeficient patients.

TUBERCULIN (PURIFIED PROTEIN DERIVATIVE)

Intradermal injection

Uses: A diagnostic agent for detecting cell-mediated skin-reactivity to tuberculin.

Dosage and administration: Mantoux test: A special tuberculin syringe is used to inject 0.1 ml of tuberculin (5 IU) intradermally into the flexor surface of the upper forearm after cleansing with acetone or ether. The needle is held parallel to the skin and downward pressure applied until the point penetrates the superficial layers of the skin. It is then moved forward to the intended site of injection where a weal of 7 mm in diameter is raised. The test, which is read after 48–72 hours, is regarded as positive if an area of more than 10 mm diameter around the injection site is indurated.

Precautions: Avoid contact with open cuts, abraded or diseased skin, the eyes or mouth.
International Nonproprietary Names for Pharmaceutical Substances (INN)

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

Lists of Proposed (1–73) and Recommended (1–35) International Nonproprietary Names can be found in Cumulative List No. 9, 1996. The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

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

On trouvera d'autres listes de Dénominations communes internationales proposées (1–73) et recommandées (1–35) dans la Liste récapitulative No. 9, 1996. Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–73) y Recomendadas (1–35) se encuentran reunidas en Cumulative List No. 9, 1996. Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.
Proposed International Nonproprietary Names: List 78
Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in WHO Drug Information, i.e., for List 78 Proposed INN not later than 15 May 1998.

Dénominations communes internationales proposées: Liste 78
Des observations ou des objections formelles à l’égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l’Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans WHO Drug Information, c’est-à-dire pour la Liste 78 de DCI Proposées le 15 mai 1998 au plus tard.

Denominaciones Comunes Internacionales Propuestas: Lista 78
Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en WHO Drug Information, es decir, para la Lista 78 de DCI Propuestas el 15 de mayo de 1998 a más tardar.

<table>
<thead>
<tr>
<th>Proposed INN (Latin, English, French, Spanish)</th>
<th>Chemical name or description: Action and use: Molecular formula</th>
<th>Chemical Abstracts Service (CAS) registry number: Graphic formula</th>
</tr>
</thead>
</table>
| abarelixum                                    | N-acetyl-3-(2-naphthyl)-o-alanyl-4-chloro-o-phenylalanyl-3-(3-pyridyl)-o-alanyl-
|                                              | l-seryl-N-methyl-l-tyrosyl-l-leucyl-N^6-isopropyl-l-lysyl-l-prolyl-o-
|                                              | alanimamide                                                   |
| abarelix                                      | luteinizing-hormone-releasing-hormone inhibitor               |
| abarélix                                      | luteinizing-hormone-releasing-hormone inhibitor               |
| abarelx                                       | luteinizing-hormone-releasing-hormone inhibitor               |
| abarelix                                      | N-acetil-3-(2-naftil)-o-alanil-4-cloro-o-fenilalani-3-(3-piridil)-o-alanil-L-seril-N-
|                                              | metil-l-tirosil-o-asparaginil-l-leucil-N^6-isopropil-l-lysil-l-prolil-o-alaninamida |
|                                              | inhibidor de la hormona de liberación de hormona luteinizante |
|                                              | C_{72}H_{95}ClN_{14}O_{14} 183552-39-7                        |

![Diagram](image)

268
**acidum minodronicum**
minodronic acid

(1-hydroxy-2-imidazo[1,2-a]pyridin-3-yl)ethylidene)diphosphonic acid
calcium regulator

**acide minodronique**
acide (1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)éthylidène)diphosphonique
régulateur du calcium

**ácido minodránico**
ácido 1-hidroxi-2-imidazo[1,2-a]piridin-3-ilétilideno)difosfónico
regulador del calcio

C$_3$H$_2$N$_2$O$_7$P$_2$ 127657-42-5

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**atreleutonum**
atreleuton

1-[(R)-3-{5-(p-fluorobenzyl)-2-thienyl}-1-methyl-2-propynyl]-1-hydroxyurea
antiasthmatic

**atréleuton**
1-[(1R)-3-{5-(4-fluorobenzyl)thiophén-2-yl}-1-méthylprop-2-ynyl]-1-hydroxyurée
antiasthmatique

**atroleutón**
1-[(R)-3-{5-(p-fluorobenzi)-2-tienil]-1-metil-2-propinil]-1-hidroxiurea
antiasmático

C$_{16}$H$_{15}$FN$_2$O$_2$S 154355-76-7

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**aviptadilum**
aviptadil

vasodilator

**aviptadil**
vasodilatateur
aviptadil

\[ \text{His-Ser-Asp-Ala-Val-Phen-Thr-Leu-Asn-Tyr-Thr-Arg-Leu-Arg-} \]

\[ \text{Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Val-Ile-Leu-Asn} \]

bepotastinum

bepotastine

\[ (+4)-4-[[S]-p\text{-chloro-2-piryrdilbenzyl}oxy]-1\text{-piperidinebutyric acid} \]

antiallergic

bépotastine

acide \[ (+4)-4-[[S]-p\text{-chlorophényl}(pyridin-2-y)\text{méthoxy}pîpêrdin-1-yl]pîpêrdin-1-yl\]

antiallergique

bepotastina

ácido \[ (+4)-[[S]-p\text{-cloro-2-pindilbencil}o]xil]-1\text{-piperidinabútico} \]

antialérgico

\[ \text{C}_{21}\text{H}_{25}\text{ClIN}_{2}\text{O}_{3} \]

\[ \text{125602-71-3} \]

bibapcitidum

bibapcitide

\[ 13,13'\text{-oxybis[méthylène}(2,5\text{-dioxo}-1,3\text{-pyrrolidinediy})]\text{bis}[N\text{-mercaptoacetyl}-\]

D-tyrosyl-S-(3-aminopropyl)-L-cystéinylglycyl-L-cystéinylglycyl-S-(acetamidométhyl)-L-cystéinylglycyl-S-(acetamidométhyl)-L-cystéinylglycyl-L-cystéinamide cyclic (1-5),(1'-5')-bis(sulfide) \]

diagnostic agent

bibapcitide

\[ (1-5),(1'-5')\text{-bis(sulfure cyclique) du 13,13'\text{-oxybis[méthylène}(2,5\text{-dioxo}-1,3\text{-pyrrolidinediy})}\text{bis}[N\text{-sulfanylacétyl}-\]

D-tyrosyl-S-(3-aminopropyl)-L-cystéinylglycyl-L-cystéinylglycyl-S-(acétylaminométhyl)-L-cystéinylglycyl-S-(acétylaminométhyl)-L-cystéinylglycyl-glycyl-L-cystéinamide \]

produit à usage diagnostique

bibapcictada

\[ (1-5),(1'-5')\text{-bis}sulfurocicNco)de13,13'-\text{oxybis[méthylène}(2,5\text{-dioxo}-1,3\text{-pyrrolidinediy})]\text{bis}[N\text{-mercaptoacetyl}-\]

D-tyrosyl-S-(3-aminopropyl)-L-cystéinylglycyl-L-cystéinylglycyl-S-(acetamidométhyl)-L-cystéinylglycyl-glycyl-L-cystéinamide \]

ágent de diagnóstico
**biricodarum**

4-(3-pyndyl)-1-[3-(3-pyridyl)propyl]butyl (S)-1-[3,4,5-trimethoxyphenyl]glyoxyloyl]pipecolate

*multidrug resistant inhibitor, antineoplastic*

**carafibanum**

ethyl (S)-β-[[2-[[S]-4-(p-amidinophenyl)-4-methyl-2,5-dioxo-1-imidazolidinyl]acetamido]hydrocinnamate

*fibrinogen receptor antagonist*
Clevudinum

Clevudine

Clévudine

Clevudina

Declopramidum

Declopramide

Déclopramide

Declopramida

Declopramida

\[
\text{Clevudinum:} \quad \text{1-(2-deoxy-2-fluoro-\(\beta\)-arabinofuranosyl)thymine antiviral}
\]

\[
\text{Clevudine:} \quad \text{1-(2-fluoro-2-désoxy-\(\beta\)-arabinofuranosyl)-5-méthylpyrimidine-2,4(1H,3H)-dione antiviral}
\]

\[
\text{Clevudina:} \quad \text{1-(2-desoxi-2-fluoro-\(\beta\)-arabinofuranosil)timina antiviral}
\]

\[
\text{Declopramidum:} \quad \text{4-amino-3-chloro-N-[2-(diethylamino)ethyl]benzamide radiosensitizing agent}
\]

\[
\text{Declopramide:} \quad \text{4-amino-3-chloro-N-[2-(diéthylamino)éthyl]benzamide radiosensibilisant}
\]

\[
\text{Declopramida:} \quad \text{4-amino-3-cloro-N-[2-(dietilamino)etil]benzamida agente sensibilizante para radioterapia}
\]
**denileukinum diftitoxum**

*denileukin diftitox*

\( N\)\(-\)l-methionyl-387-\( L\)\(-\)histidine-388-\( L\)\(-\)alanine-1-388-toxin (Corynebacterium diphtheriae strain C7) (388-2')-protein with 2-133-interleukin 2 (human clone pTIL2-21a)

**immunomodulator**

**déniléukine diftitox**

\( N\)\(-\)l\(-\)méthionyl\-[387-\( L\)\(-\)histidine-388-\( L\)\(-\)alanine]-{1-388}-toxine (souche C7 de Corynebacterium diphtheriae)-(388-2')-(2-133)-interleukine 2 (clone pTIL2-21a humain)

**immunomodulateur**

**denileukina diftitox**

\( N\)\(-\)l-metionil-387-\( L\)\(-\)histidina-388-\( L\)\(-\)alanina-1-388-toxina (cepa C7 de Corynebacterium diphtheriae) (388-2')-(2-133)-interleukin 2 (clon humano pTIL2-21a)

**inmunomodulador**

\( \text{C}_{2558}\text{H}_{4036}\text{N}_{678}\text{O}_{799}\text{S}_{17} \) 173146-27-5

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**dutasteridum**

*duasteride*

\( \alpha,\alpha,\alpha',\alpha'\)\(-\)hexafluoro-3\(-\)oxo-4\(-\)aza\(-\)5\(-\)\( \alpha\)\(-\)androst\(-\)1\(-\)ene\(-\)17\(-\)l\(-\)carboxy\(-\)2',5\(-\)xylidide

**testosterone reductase inhibitor**

**dutaséride**

\( N\)\-[2,5-bis\( (\text{trifluoromethyl})\)phényl]-3-oxo-4-aza-5\(-\)\( \alpha\)\(-\)androst\(-\)1\(-\)ène\(-\)17\(-\)l\(-\)carboxamide

**inhibiteur de la réductase de la testostérone**

**dutasterida**

\( \alpha,\alpha,\alpha',\alpha'\)\(-\)hexafluoro-3\(-\)oxo-4\(-\)aza\(-\)5\(-\)\( \alpha\)\(-\)androst\(-\)1\(-\)ene\(-\)17\(-\)l\(-\)carboxo\(-\)2',5\(-\)xilidida

**inhibidor de la reductase de la testosterona**
ecenofloxacium
ecenofloxacin
(+)-7-[(1R,5S,6S)-6-amino-1-methyl-3-azabicyclo[3.2.0]hept-3-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid antibacterial

écénofloxacine
acide (+)-7-[(1R,5S,6S)-6-amino-1-méthyl-3-azabicyclo[3.2.0]hept-3-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphtyrindine-3-carboxylique

ecenofloxacino
ácido (+)-7-[(1R,5S,6S)-6-amino-1-metil-3-azabicielo[3.2.0]hept-3-il]-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridina-3-carboxílico

C_{19}H_{21}FN_{4}O_{3} 162301-05-5

efavirenzum
efavirenz
(S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoazizin-2-one
antiviral

étavirenz
(4S)-6-chloro-4-(cyclopropylethynyl)-4-(trifluorométhyl)-1,4-dihydro-2H-3,1-benzoazizin-2-one
antiviral

efavirenzo
(S)-6-cloro-4-(ciclopropiletinil)-1,4-dihidro-4-(trifluorometil)-2H-3,1-benzoxazinin-2-ona
antiviral
**embusartanum**  
Embustaran  
methy1 6-butyl-1-[2-fluoro-4-(o-1H-tetrazol-5-ylphenyl) benzyl]-1,2-dihydro-2-oxoisonicotinate  
angiotensin II receptor antagonist

**embusartan**  
6-butyl-1-[3-fluoro-2'-(1H-tetrazol-5-yl)biphenyl-4-yl]méthyl]-2-oxo-1,2-dihydropyridine-4-carboxylate de méthyle  
antagoniste du récepteur de l’angiotensine II

**embusartán**  
6-butil-1-[(3-fluoro-2'-(1H-tetrazol-5-ilfenil)bencil]-1,2-dihidro-2-oxoisonicotinato de metilo  
antagonista del receptor de angiotensina II

**eptifibatidum**  
Eptifibatide  
N⁶-amidino-N²-(3-mercaptopropionyl)-c-lysylglycyl-L-α-aspartyl-L-triptofyl-L-proliyl-L-cysteinamide, cyclic (1-6)-disulfide  
platelet aggregation inhibitor, fibrinogen receptor antagonist

**eptifibatide**  
(1-6)-disulfure cyclique de [N⁶-carbamimidoyl-N²-(3-sulfanylpropanoyl)-c-lysyl]-glycyl-L-α-aspartyl-L-triptofyl-L-proliyl-L-cysteinamide  
antagrégant plaquettaire; antagoniste du récepteur du fibrinogène

**eptifibatida**  
(1-6)-disulfuro cíclico de N⁶-amidino-N²-(3-mercaptopenoponio)-c-isligilo-L-α-aspartili-L-triptofi-L-proli-L-cisteinamida  
inhibidor de la agregación plaquetaria; antagonista del receptor del fibrinógeno

C₃₅H₄₉F₅N₁₁O₉S₂  148031-34-9
**fandofloxacinum**  
*fandofloxacin*  
6-fluoro-1-(5-fluoro-2-pyridyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid  
*antibacterial*

**fandofloxacin**  
acide 6-fluoro-1-(5-fluoropyridin-2-yl)-7-(4-méthylpipérazine-1-yl)-4-oxo-1,4-dihydroquinoléine-3-carboxylique  
*antibacterien*

**fandofloxacino**  
ácido 6-fluoro-1-(5-fluoro-2-piridil)-1,4-dihidro-7-(4-metil-1-píperazinil)-4-oxo-3-quinolinacarboxílico  
*antibacteriano*

C_{20}H_{18}F_{2}N_{4}O_{3}  164150-85-0

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**fasoracetamum**  
*fasoracetam*  
(+)-1-[[[(R)-5-oxo-2-pyrrolidinyl]carbonyl]pipendine  
nootropic agent

**fasoracétam**  
(+)-1-[[[2R]-5-oxopyrrolidin-2-yl]carbonyl]pipéridine  
nootrope

**fasoracetam**  
(+)-1-[[[(R)-5-oxo-2-pirrolidinil]carbonil]piperidina  
nootrope

---

**fidarestatum**  
*fidarestat*  
(+)-(2S,4S)-6-fluoro-2',5'-dioxospiro[chroman-4,4'-imidazolidine]-2-carboxamide  
*aldose reductase inhibitor*

**fidarestat**  
(+)-(2S,4S)-6-fluoro-2',5'-dioxo-2,3-dihydropyrrol-4H-chromène-4,4'-imidazolidine]-2-carboxamide  
inhibiteur de l'aldose réductase

**fidarestat**  
(+)-(2S,4S)-6-fluoro-2',5'-dioxoespiro[4H-chroman-4,4'-imidazolidina]-2-carboxamida  
inhibidor de la reductasa de aldosas
**frovatriptanum**

frovatriptan  
(R)-5,6,7,8-tetrahydro-6-(methylamino)carbazole-3-carboxamide  
serotonin receptor agonist

**fulvestrantum**

fulvestrant  
7α-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol  
antiestrogen

**C₁₂H₇FN₃O₄**  
136067-85-9

![frovatriptan structure](image1)

![fulvestrant structure](image2)
**ibutamorenum**

*ibutamoren*

2-amino-N\(^{(R)}\)-2-(benzyloxy)-1-[[1-(methylsulfonyl)spiro[indoline-3,4'-piperidin]-1'-yl]carbonyl]ethyl]-2-methylpropionamide

*growth hormone release stimulating peptide*

**ipamorelinum**

*ipamorelin*

2-methylalanyl-L-histidyl-3-(2-naphthyl)-D-alanyl-D-phenylalanyl-L-lysinamide

*growth factor*

**levocetirizinum**

*levocetirizine*

[2-[4-[(R)-p-chloro-\(\alpha\)-phenyibenzyl]-1-piperazinyl]ethoxy]acetic acid

*histamine H\(_1\)-receptor antagonist*
levosalbutamol
levosalbutamol
\((R)\-\alpha^1\-\{(\text{tert-butylamino})\text{methyl}\}-4\text{-}\text{hydroxy-}\text{m}\text{-xylene}\-\alpha,\alpha^\prime\text{-dil}
\text{antiasthmatic}
levosalbutamol
\((1\ R)\-2\-\{(1,1\text{-diméthyléthyl})\text{amino}\}\-1\-\{4\text{-}\text{hydroxy-3-}
\text{hydroxyméthyl}\text{phényl}\}\text{éthanol}
\text{antiasthmatique}
levosalbutamol
\((R)\-\alpha^1\-\{(\text{terc-bLitilamino})\text{metil}\}-4\text{-}\text{hidroxi-m-xileno}\-\alpha,\alpha^\prime\text{-diol}
\text{antiasmático}
C_{13}H_{21}NO_3 34391-04-3

lodenosinum
lodenosine
\(9\-\{(2,3\text{-}d\text{ideoxy-2-fluoro-}\beta\-\text{c}\text{-threo-pentoluranosyl})\text{adenine}
\text{antiviral}
lodénosine
\(9\-\{(2\text{-}fluo-2,3\text{-}d\text{iiésoxy-}\beta\-\text{c}\text{-thréo-pentofuranosyl})\-9\text{H-purine-6-amine}
\text{antiviral}
lodenosina
\(9\-\{(2,3\text{-}d\text{idesoxi-2-fluoro-}\beta\-\text{c}\text{-treo-pentofuranosil})\text{adenina}
\text{antiviral}
C_{10}H_{12}FN_5O_2 110143-10-7
lotrafibanum
lotrafiban
(S)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[(4-(4-piperidyl)piperidino)carbonyl]-1H-1,4-benzodiazepine-2-acetic acid
fibrinogen receptor antagonist

lotrafiban
acide 2-[(2S)-7-[(4,4'-bipiperidinyl-1-yl)carbonyl]-4-méthyl-3-oxo-2,3,4,5-tétrahydro-1H-1,4-benzodiazépin-2-yl]acétique
antagoniste du récepteur du fibrinogène

lotrafibán
ácido (S)-2,3,4,5-tetrahidro-4-metil-3-oxo-7-[(4-(4-pipendil)pipendino)carbonil]-1H-1,4-benzodiazepina-2-acético
antagonista del receptor del fibrinógeno

C<sub>22</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub> 171049-14-2

meluadrinum
meluadrine
(−)-(R)-α-[[(tert-butylamino)methyl]-2-chloro-4-hydroxybenzyl alcohol
β-adrenoceptor agonist

méluadrine
(−)-(1R)-1-(2-chloro-4-hydroxyphényl)-2-[(1,1-diméthyléthyl)amino]éthanol
agoniste β-adrénergique

meluadrina
alcohol (−)-(R)-α-[(terc-butilamino)metil]-2-cloro-4-hidroxibencilico
agonista de los receptores β-adrenérgicos

C<sub>12</sub>H<sub>18</sub>CINO<sub>2</sub> 134865-33-1

mespiperonum (11C)
mespiperone (11C)
8-[3-(p-fluorobenzoyl)propyl]-3-[11C]méthyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one
radiodiagnostic agent

mespipérone (11C)
8-[4-(4-fluorophényl)-4-oxobutyl]-3-[11C]methyl-1-phényl-1,3,8-triazaspiro[4.5]decan-4-one
produit à usage radiodiagnostique

mespiperona (11C)
8-[3-(p-fluorobenzoi)propil]-3-[11C]metil-1-fenil-1,3,8-triazaspiro[4.5]decan-4-on
agente de radiodiagnóstico
mitiglinidum
mitiglinide
(-)-(2S,3a,7a-cis)-α-benzylhexahydro-γ-oxo-2-isindolinebutyric acid
antidiabetic

mitiglinide
(-)-acide (2S)-2-benzyl-4-[(3aR,7aS)-octahydro-2H-isindol-2-yl]-4-oxobutanole(que)
antidiabétique

mitiglinida
ácido (−)(2S,3a,7a-cis)-α-bencilhexahidro-γ-oxo-2-isindolinaclusão
antidiabético

\[ C_{28}H_{32}FN_{2}O_{14} \] 94153-50-1

moxifloxacín
moxifloxacin
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-
pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinocarboxylic acid
antibacterial

moxifloxacine
acide 1-cyclopropyl-6-fluoro-8-méthoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-
b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique
antibactérien

moxifloxacina
ácido 1-ciclopropil-6-fluoro-1,4-dihidro-8-metoxi-7-[(4aS,7aS)-octahidro-6H-
pirrolo[3,4-b]pindin-6-il]-4-oxo-3-quinolinacboxílico
antibacteriano

\[ C_{21}H_{24}FN_{3}O_{4} \] 145375-43-5

\[ C_{21}H_{23}FN_{3}O_{4} \] 151096-09-2
**moxilubantum**
moxilubant

4-[[5-(p-amidinophenoxy)pentyl]oxy]-N,N-diisopropyl-3-methoxybenzamide
leukotriene receptor antagonist

**moxilubant**

4-[[5-(4-carbamimidoylphenoxy)pentyl]oxy]-3-méthoxy-N,N-bis(1-méthyléthyl)benzamide
antagoniste du récepteur des leucotriènes

**moxilubant**

4-[[5-(p-amidonofenoxi)pentil]oxi]-N,N-dnsopropil-3-metoxibenzamida
antagonista del receptor de leucotrienos

C_{26}H_{37}N_{3}O_{4}  147398-01-4

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**netzarabinum**

netzarabine

2-amino-β-D-arabinofuranosyl-6-methoxy-9H-purine
antineoplastic

nélzarabine

9-(β-D-arabinofuranosyl)-6-méthoxy-9H-purin-2-amine
antinéoplasique

neztarabina

2-amino-β-D-arabinofuranosil-6-metoxi-9H-purina
antineoplásico

C_{11}H_{15}N_{5}O_{5}  121032-29-9

---

**nepadutantum**

nepaduant

cyclo[N-{2-acetamido-2-deoxy-β-D-glucopyranosyl}-L-asparaginyl-L-α-aspartyl-L-tryptophyl-L-phenylalanyl-L-2,3-diaminopropionyl-L-leucyl], cyclic (2-5)-peptide
tachykinin receptor antagonist

népaduant

(2-5)-peptide cyclique du cyclo[N{2-(acétylamino)-2-désoxy-β-D-glucopyranosyl}-L-asparaginyl-L-α-aspartyl-L-tryptophyl-L-phenylalanyl-L-3-amino-L-alanyl]-L-leucyl]
antagoniste de récepteurs de la tachykinine
**nepaduant**

(2-5)-péptido cíclico de ciclo[N-(2-acetamido-2-desoxi-β-D-glucopiranósido)-L-asparaginil-L-α-aspartil-L-triptofil-L-fenilalanilil-2,3-diaminoproponil-L-leucil]

antagonista del receptor de la quinina

C_{45}H_{58}N_{10}O_{13}  183747-35-5

**nepafenacum**

nepafenac  2-(2-amino-3-benzoylphenyl)acetamide

non-steroid anti-inflammatory

népafénac  2-(2-amino-3-benzoylphényl)acétamide

anti-inflammatoire non stéroïden

nepafenaco  2-(2-amino-3-benzoílenil)acetamida

antiinflamatorio no esteroideo

C_{15}H_{14}N_{2}O_{2}  78281-72-8

**nepicastatum**

nepicstat  5-(aminomethyl)-1-[(S)-5,7-difluoro-1,2,3,4-tetrahydro-2-naphthyl]-4-imidazoline-2-thione
dopamine β-hydroxylase inhibitor

népicstat  5-(aminométhyl)-1-[(2S)-5,7-difluoro-1,2,3,4-tétrahydronaphtalén-2-yl]-1,3-dihydro-2H-imidazole-2-thione

inhibiteur de la dopamine β-hydroxylase

nepcastat  5-(aminometil)-1-[(S)-5,7-difluoro-1,2,3,4-tetrahdro-2-naftil]-4-imidazolina-2-thiona

inhibidor de la dopamina β-hydroxilasa
nitisinonum

2-(α,α,α-trifluoro-2-nitro-p-toluoyl)-1,3-cyclohexanedione
4-hydroxyphenylpyruvate dioxygenase inhibitor

C_{14}H_{15}F_{2}N_{2}S

nitisinone

2-(2-nitro-4-(trifluorométhyl)benzoyl)cyclohexane-1,3-dione
inhibiteur de la 4-hydroxyphénylpyruvate dioxygénase

C_{14}H_{10}F_{3}NO_{5}

nitisinona

2-(α,α,α-trifluoro-2-nitro-p-toluoyl)-1,3-ciclohexanodiona
Inhibidor de la dioxigenasa del 4-hidroxifenilpyruvato

C_{14}H_{10}F_{3}NO_{5}

nolatrexedum

2-amino-6-methyl-5-(4-pyridylthio)-4(3H)-quinazolinone
antineoplastic

C_{14}H_{12}N_{4}O_{5}S

nolatrexed

2-amino-6-méthyl-5-[pyridin-4-yl)sulfanyl]quinazolin-4(1H)-one
antinéoplasique

nolatrexed

2-amino-6-metil-5-(4-piridilitio)-4(3H)-quinazolinona
antineopfásico

C_{14}H_{12}N_{4}O_{5}S
omapatrilatum

omapatrilat

\((4S,7S,10aS)\)-octahydro-4-(((S)-\(\alpha\)-mercaptohydrocinnamamido)-5-oxo-7H-pyrido[2,1-b][1,3]thiazepine-7-carboxylic acid
angiotensin-converting enzyme inhibitor, endo peptidase inhibitor

omapatrilate

acide \((4S,7S,10aS)\)-5-oxo-4-(((2S)-3-phényl-2-sulfanylpropanoyl)amino)-octahydro-7H-pyrido[2,1-b][1,3]thiazépine-7-carboxylique
inhibiteur de l'enzyme de conversion de l’angiotensine, inhibiteur de l'endopeptidase

omapatrilat

ácido \((4S,7S,10aS)\)-octahidro-4-(((2S)-3-mercaptohidrocinamamido)-5-oxo-7H-pirido[2,1-b][1,3]tiazepma-7-carboxilico
inhibidor de la enzima conversora de la angiotensina, inhibidor de la endopeptidasa

\(C_{19}H_{24}N_{2}O_{4}S_{2}\) 167305-00-2

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pamiteplasum

pamiteplase

275-L-glutamic acid-(1-91)-(174-527)-plasminogen activator (human tissue-type protein moiety)
plasminogen activator

pamitéplase

[275-acide L-glutamique]-(1-91)-(174-527)-activateur du plasminogène (de type tissulaire humain)
activateur du plasminogène

pamiteplasa

275-ácido L-glutámico -(1-91)-(174-527)-activador del plasminógeno (tipo tísular humano fracción proteica)
activador del plasminógeno

\(C_{2172}H_{3309}N_{627}O_{658}S_{34}\) 151912-42-4
paricalcitolum
paricalcitol
paricalcitol
paricalcitol

(7E,22E)-19-nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol vitamin D analogue

(7E,22E)-(1R,3R)-19-nor-9,10-secoergosta-5,7,22-triene-1,3,25-triol analogue de la vitamine D

(7E,22E)-19-nor-9,10-secoergosta-5,7,22-trieno-1α,3β,25-trol analogo de la vitamina D

C_{27}H_{44}O_3 131918-61-1
pemetrexedum

pemetrexed  \( N\)-(p-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid

antineoplastic

pémétrexed  acide (2S)-2-[[4-[2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzy]amino]pentanédioïque

antineoplasique

pemetrexed  ácido \( N\)-(p-[2-(2-amino-4,7-dihidro-4-oxo-1H-pirrQlo[2,3-fí|p¡r¡mid¡n-5-

il)etil]benzoil]-L-glutámico

antineoplásico

\( C_{20}H_{21}N_{5}O_{6} \)

137281-23-3

\[
\begin{align*}
\text{CO}_2\text{H} \\
\text{H}_2\text{N}-
\end{align*}
\]

perflenapentum

perflenapent  dodecafluoropentane

ultrasound contrast agent

perflénapent  dodécafluoropentane

produit de contraste pour des analyses ultrasoniques

perflenapent  dodecafluoropentano

medio de contraste para análisis por ultrasonido

\( C_{5}F_{12} \)

678-26-2

\[
\begin{align*}
\text{CF}_3 \\
\text{F}_3\text{C}
\end{align*}
\]

perflisopentum

perflisopent  nonaffluoro-2-(trifluoromethyl)butane

ultrasound contrast agent

perflisopent  nonafluoro-2-(trifluorométhyl)butane

produit de contraste pour des analyses ultrasoniques

perflisopent  nonafluoro-2-(trifluorometil)butano

medio de contraste para análisis por ultrasonido
perifosinum
perifosine
4-hydroxy-1,1-dimethylpiperidinium hydroxide, octadecyl hydrogen phosphate, inner salt
antineoplastic

pénfosine
1,1-diméthyl-4-[[octadécyloxy]oxydophosphoryloxy]pipéridinium
antinéoplasique

perifosina
1,1-dimetil-4-[[octadectloxi]oxido fosforiloxy]piridinio
antineoplásico

C_{25}H_{52}NO_{4}P 157716-52-4

\[
\begin{align*}
\text{isoleucyl-L-leucyl-L-lysyl-L-lysylamid}
\end{align*}
\]

antibacterial

\[
\begin{align*}
\text{isoleucyl-L-leucyl-L-lysyl-L-lysylamid}
\end{align*}
\]

antibacterien

\[
\begin{align*}
\text{isoleucyl-L-leucyl-L-lysyl-L-lysylamid}
\end{align*}
\]

antibacteriano

C_{122}H_{210}N_{32}O_{22} 172820-23-4

Gly-Ile-Gly-Lys-Phe-Leu-Lys-Lys-Ala-Lys-Lys-Phe-
10
Gly-Lys-Ala-Phe-Val-Lys-Ile-Leu-Lys-Lys-NH₂
20
**pibutidinum**

3-amino-4-[[[(Z)-4-[4-(piperidinomethyl)-2-pyridyl]oxy]-2-butenyl]amino]-3-cyclobutene-1,2-dione

*histamine H₂-receptor antagonist*

**pibutidine**


*antagoniste des récepteurs H₂ de l’histamine*

**pibutidina**

3-amino-4-[[[(Z)-4-[4-(piperidinomethyl)-2-piridil]oxo]-2-butenil]arnino]ciclobuteno-1,2-diona

*antagonista de los receptores H₂ de la histamina*

C₁₉H₂₂N₄O₃  103922-33-4

![Chemical Structure](image)

**pregabalinum**

(S)-3-(aminomethyl)-5-methylhexanoic acid

*anticonvulsant*

**pregabalin**

acide (3S)-3-(aminométhyl)-5-méthylhexanoïque

*anticonvulsivant*

**pregabalina**

ácido (S)-3-(aminometil)-5-met/hexanónico

*anticonvulsivo*

C₈H₁₇NO₂  148553-50-8

![Chemical Structure](image)

**prucalopridum**

4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidyl]-7-benzoturancarboxamide

*prokinetic agent*

**prucalopride**

4-amino-5-chloro-N-[1-(3-méthoxypropyl)pipéridin-4-y]l-2,3-dihydrobenzoturane-7-carboxamide

*accélérateur du transit intestinal*

**prucaloprida**

4-amino-5-cloro-2,3-dihidro-N-[1-(3-metoxipropil)-4-piperidil]-7-benzofurancarboxamida

*estimulante de la motilidad intestinal*
rapacuronium bromide
1-allyl-1-(3α,17β-dihydroxy-2β-piperidino-5α-androstan-16β-yl)piperidinium bromide, 3-acetate 17-propionate
neuromuscular receptor antagonist

bromure de rapacuronium
bromure de 1-(3α-(acétyloxy)-28-(piperidin-1-yl)-17β-(propanoïtoxy)-5α-androstan-16β-yl)-1-(prop-2-ényl)piperidinium
antagoniste des récepteurs neuro-musculaires

bromuro de rapacurônio
bromuro de 1-allyl-1-(3α,17β-dihidroxi-2β-piperidino-5α-androstan-16β-il)piperidinio, 3-acetato 17-propionato
antagonista de los receptores neuromusculares

rifalazilum
rifalazil
table striptetraquinoïén
rifalazilo
antibacteriano
**robalzotanum**

**(R)-3-(dicyclobutylamino)-8-fluoro-5-chroman-carboxamide**

*serotonin receptor agonist*

**robalzotan**

**(3R)-3-(dicyclobutylamino)-8-fluoro-3,4-dihydro-2H-chromène-5-carboxamide**

*agoniste des récepteurs de la sérotonine*

**robalzotán**

**(R)-3-(diciclobutilamino)-8-fluoro-5-cromancarboxamida**

*agonista de los receptores de la serotonina*

C18H23FN2O2 169758-66-1

**rosiglitazonum**

**(±)-5-[p-[2-(methyl-2-pyndylamino)ethoxy]benzyl]-2,4-thiazolidinedione**

*antidiabetic*

**rosiglitazone**

**(5RS)-5-[4-[2-[(méthyl(pyndin-2-yl)amino]éthoxy]benzyl]thiazolidine-2,4-dione**

*antidiabétique*

**rosiglitazona**

**(±)-5,5-[2-methyl-2-piridilamino)etoxi]benzi]-2,4-tiazolidinadiona**

*antidiabético*
seocalcitolum
(5Z,7E,22E,24E)-24a,26a,27a-trihomo-9,10-secocholesta-5,7,10(19),22,24-pentaene-1ß,3α,25-triol
vitamin D analogue

séocalcitol
(5Z,7E,22E,24E)-(1S,3R)-24a,26a,27a-trihomo-9,10-sécocholesta-5,7,10(19),22,24-pentaéne-1,3,25-triol
analogue de la vitamine D

seocalcitol
(5Z,7E,22E,24E)-24a,26a,27a-trihomo-9,10-secocholesta-5,7,10(19),22,24-pentaeno-1α,3β,25-triol
análogo de la vitamina D

silperisonum
1-[[p-fluorobenzyl[dimethylsilyl]methyl]piperidine
central muscle relaxant

dentral relaxant muscle

silpérisone
1-[[4-fluorobenzyl[diméthylsilyl]méthyl]pipéridine
myorelaxant central

silperisona
1-[[p-fluorobencil]dimetilsíil]metil]pipendina
miorelajante central

C_{15}H_{24}FNSi
140944-31-6
**sinapultidum**

**sinapultide**


*pulmonary surfactant*

**sinapultide**


*pulmonary surfactant*

**sinapultida**

\[\text{L-lisil-L-leucil-L-leucil-L-leucil-L-leucil-L-lisil-L-leucil-L-leucil-L-leucil-L-leucil-L-lisil-L-leucil-L-leucil-L-leucil-L-leucil-L-lisina}\]

*tensioactivo pulmonar*

\[\text{C}_{126}\text{H}_{238}\text{N}_{26}\text{O}_{22}\]

138531-07-4


\[\text{Leu-Leu-Leu-Leu-Leu-Leu-Leu-Lys}\]

**sivelestatum**

**sivelestat**

\[\text{o-\(p\)-hydroxybenzenesulfonamido)hippuric acid, pivalate (ester)}\]

*elastase inhibitor*

**sivelestat**

\[\text{ácido o-\(p\)-hidroxibencenosulfonamido)hipúrico, pivalato (éster)}\]

*inhibidor de la elastasa*

\[\text{C}_{20}\text{H}_{22}\text{N}_{2}\text{O}_{7}\text{S}\]

127373-66-4

**sunepitronum**

**sunepitron**

\[\text{N-\([7S,9aS]-octahydro-2-(2-pyrimidinyl)-2H-pyrido[1,2-a]pyridin-7-yl\)methyl]succinimide}\]

*anxiolytic, antidepressant*

**sunépiron**

\[\text{1-\([7S,9aS]-2-(pyrimidin-2-yl)octahydro-2H-pyrido[1,2-a]pyridin-7-yl\)méthyl]pyrroldione-2,5-dione}\]

*anxiolytique, antidépresseur*

**sunepitrón**

\[\text{N-\([7S,9aS]-octahidro-2-(2-pteridinil)-2H-pirido[1,2-a]pirazin-7-il\)metil]succinimida}\]

*ansiolítico, antidepressivo*
**C17H23N5O2  148408-65-5**

[targinum]

**targinine**

$N^5$-(methylamidino)-L-ornithine  
*nitric oxide synthase inhibitor*

[targinina]

**targinina**  
$N^5$-(metilamidino)-L-ornitina  
*Inhibidor de la sintetasa del óxido nítrico*

**technetium (99mTc)apcitidum**

technetium (99mTc) apcitide

**technétium (99mTc) apcitide**

sodium hydrogen $[N$-(mercaptoacetyl)-D-tyrosyl-S-(3-aminopropyl)-L-cysteinylglycyl-L-aspartyl-L-cysteinylglycyl-S-(acetamidomethyl)-L-cysteinylglycyl-S-(acetamidomethyl)-L-cysteinylglycylglycyl-L-cysteinamide cyclic (1-5)-sulfidato(5-)$-N^1$,N^2$,N^3$,S^3]$oxo$[99mTc]$technetate(V)

*radiodiagnostic agent*

**tecnecio (99mTc) apcitida**

tecnecio ($^{99m}$Tc) apcitida

hidrógeno $[N$-(mercaptoacetil)-D-tirosil-S-(3-aminopropil)-L-cisteiniliglicil-L-$\alpha$-asparili-L-cisteiniligliciliglicil-S-(acetamidometil)-L-cisteiniligliciliglicil-S-(acetamidometil)-L-cisteiniligliciliglicil-l-cisteinamida (1-5)-sulfidato cíclico (5-)$-N^1$,N^2$,N^3$,S^3]$oxo$[99mTc]$technetato(V) de sodio

*agente de radiodiagnóstico*
temocaprilatum

(+)-(2S,6R)-6-[(1S)-1-carboxy-3-phenylpropyl]amino]tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5H)-acetic acid
angiotensin-converting enzyme inhibitor

thyrotropinum alfa

thyrotropin (human β-subunit protein moiety), complex with choriionic gonadotropin (human α-subunit protein moiety)
thyrotropin releasing hormone (TRH) analog
tifacoginum

tifacogin

N-L-alanylblood-coagulation factor LACI (human clone \( \lambda P9 \) protein moiety reduced)
anticoagulant

.tifacogine

N-L-alanylfacteur de coagulation sanguine LACI (partie protéique réduite produite par le clone humain \( \lambda P9 \))
anticoagulant

tifacogina

N-L-alanilfactor de coagulación sanguínea LACI (fracción protéica reducida producida por el clón humano \( \lambda P9 \))
anticoagulante

C_{1400}H_{2167}N_{395}O_{422}S_{23} \quad 148883-56-1

.tifacillinum

tobicillin

(+)\( \alpha \)-hydroxy-\( m \)-toly(2S,5R,6R)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, isobutyrate (ester)
antibiotic (vet)

.tifobicillium

tobicillin

(2S,5R,6R)-3,3-diméthyl-7-oxo-6-\{(2-phénylacétyl)amino\}-4-thia-1-azabiclo[3.2.0]heptano-2-carboxilato de \((+)\-ácido hidroxi-\( m \)-tolylo, isobutirato (éster)
antibiotico (vet)
**trastuzumabum**

**trastuzumab**

Immunoglobulin G1 (human-mouse monoclonal rhuMab HER2 γ1-chain anti-human p185c-erbB2 receptor), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer

**trastuzumab**

Immunoglobuline G1 (chaîne γ1 de l'anticorps monoclonal de souris humanisé rhuMab HER2 dirigé contre le récepteur humain p185c-erbB2), dimère du disulfure avec la chaîne légère de l'anticorps monoclonsal de souris humanisé rhuMab HER2

**trastuzumab**

Immunoglobulina G1 (cadena γ1 del anticuerpo monoclonal humanizado de ratón rhuMab HER2 dirigido contra el receptor humano p185c-erbB2), dimero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de ratón rhuMab HER2

180288-69-1

**tremacamrum**

**tremacamra**

1-453-glycoprotein ICAM1 (human reduced)

Antiviral

Glycoprotéine comprenant 453 acides aminés, constituée du domaine extracellulaire de la molécule d'adhésion intracellulaire-1 humaine (ICAM-1), obtenue par génie génétique

Antiviral

**tremacamra**

1-453-glicoproteina ICAM1 (humana reducida)

Antiviral

295
valganciclovirum

valganciclovir

L-valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine antiviral

(2S)-2-amino-3-méthylbutanoate de (2RS)-2-[[2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl]méthoxy]-3-hydroxypropyle antiviral

L-valinato de 9-[[2-hidroxi-1-(hidroximetil)etoxi]métile]guanina antiviral

C<sub>14</sub>H<sub>22</sub>N<sub>6</sub>O<sub>5</sub> 175865-60-8

[Chemical structure of valganciclovir]

and epimer at C<sup>*</sup> et l'épimère en C<sup>*</sup> y el epímero al C<sup>*</sup>

xaliprodenum

xaliprodan

1,2,3,6-tetrahydro-1-[2-(2-naphthyl)ethyl]-4-α,α,α-trifluoro-m-tolyl]pyridine nootropic agent

xaliprodène

1-[2-(naphthalén-2-yl)éthyl]-4-[3-(trifluorométhyl)phényl]-1,2,3,6-
tétrahydropropyldine nootrope
xaliprodeno

1,2,3,6-tetrahydro-1-[(2-(2-naphthyl)-ethyl)-4-(α,α,α-trifluoro-m-tolyl)]piridina
nootropo
C_{24}H_{22}F_{3}N

ziconotidum

ziconotide

cyclic (1-16), (8-20), (15-25)-tris(disulfide)
analgesic, neural anti-ischemic

ziconotide

analgésique, anti-ischémique neural

ziconotida

analgésico, anti-isquémico neural
C_{102}H_{172}N_{36}O_{32}S_{7}

107452-89-1
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

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

p. 20  reviparinum natricum
reviparin sodium

replace the definition by the following:
Sodium salt of a low molecular mass heparin that is obtained by nitrous acid
depolymerization of heparin from porcine intestinal mucosa; the majority of the
components have a 2-O-sulfo-α-L-idopyranosuronic acid structure at the non-
reducing end and a 6-O-sulfo-2,5-anhydro-α-D-mannitol structure at the reducing
end of their chain; the mass-average molecular mass ranges between 3150
and 5150, with a characteristic value of about 4150; the degree of sulfatation is
about 2.1 per disaccharidic unit.

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

p. 20  reviparinum natricum
réviparine sodique

remplacer la description suivante:
Sel sodique d’une héparine de basse masse moléculaire obtenue par
dépolymérisation, au moyen d’acide nitrique, d’héparine de muqueuse
intestinale de porc; la majorité des composants de la réviparine sodique
possèdent une structure acide 2-O-sulfo-α-L-idopyranosuronique à l’extrémité
non réductrice de leur chaîne et une structure 6-O-sulfo-2,5-anhydro-α-
mannitol à l’extrémité réductrice de leur chaîne; la masse moléculaire relative
moyenne est de 3150 à 5150, avec une valeur caractéristique de 4150 environ;
le degré de sulfatation est 2.1 environ par unité disaccharidique.

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

p. 20  reviparinum natricum
reviparina sódica

sustituya la descripción por la siguiente:
Sal sódica de una heparina de baja masa molecular obtenida por
despolimerización con ácido nítrico de la heparina de la mucosa intestinal del
cerdo; la mayoría de los compuestos tienen una estructura de ácido 2-O-sulfo-
α-L-idopiranosurónico en el extremo no reductor y una estructura de 6-O-sulfo-
2,5-anhidro-α-D-mannitol en el extremo reductor de la cadena; la masa molecular
relativa media está entre 3150 y 5150; un valor característico de 4150
aproximadamente; el grado de sulfatación es de 2.1 por unidad de disacárido.
Proposed International Nonproprietary Names (Prop. INN): List 71

Dénominations communes internationales proposées (DCI Prop.): Liste 71
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Liste 71

(WHO Drug Information, Vol. 8, No. 2, 1994)

p. 8  delete/supprimer/suprimase  insert/insérer/insértase
dacliximaburn  daclizumaburn
dacliximab  daclizumab
dacliximab  daclizumab
dacliximab  daclizumab

p. 20  teverelixum  replace the chemical name and the graphic formula by the following.
teverelix  N-acetyl-3-(2-naphthyl)-D-alanyl-p-chloro-o-phenylalanyl-3-(3-pyridyl)-o-alanyl-
tévérélix  remplacer le nom chimique et la formule développée par:

\[
\text{[N-acétyl-3-(naphtalén-2-yl)-D-alanil]-[4-chloro-o-phénytalanil]-[3-(pyridin-3-yl)-}
\text{o-alanil]-l-séryl]-l-tyrosyl-[N}\text{6-(carbamoyl)-o-lysyl]-L-lysyl-[N}\text{6-}
\text{(1-méthyléthyl)-o-lysyl]-L-prolyl-o-alaninamide}
\]
teverelix  sustituyase el nombre químico y la fórmula desarrollada por.

\[
\text{[N-acetil-3-(naftalen-2-il)-o-alanil]-[4-cloro-o-fenilalanil]-[3-[piridín-3-il]-o-alanil]-}
\text{l-seril-l-tirosil-[N}\text{6-(carbamoil)-o-lisil]-l-leucil-[N}\text{6-(1-metiletil)-o-lisil]-L-prolyl-
\text{o-alaninamida}
\]

Proposed International Nonproprietary Names (Prop. INN): List 75

Dénominations communes internationales proposées (DCI Prop.): Liste 75
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Liste 75


p. 91  delete/supprimer/suprimase  insert/insérer/insértase
anseculinum  ensaculinum
anseculin  ensaculin
anséculine  ensaculine
anseculina  ensaculina
Proposed International Nonproprietary Names (Prop. INN): List 76
Dénominations communes internationales proposées (DCI Prop.): Liste 76
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): List 76
(WHO Drug Information, Vol. 10, No. 4, 1996)

p. 196  delete/supprimer/suprimase  insert/insérer/insértase
balaperidonum  belaperidonum
balapendone  belapendone
balapéridone  bélapéridone
balapendona  belaperidona

p. 197  bimocliomolum  bimocliomol
replace the chemical name by the following:
(±)-N-(2-hydroxy-3-piperidinopropoxy)nicotinimidoyl chloride

p. 213  oprotonii iodidum  opratonium iodide
replace the chemical name by the following:
trimethyl(3-(10-undecenamido)propyl)ammonium iodide
sustituyase el nombre químico por lo siguiente.
iодуро de opratonio

p. 216  sabcomelinum  sabcomeline
replace the action and use statement by the following:
muscarinic receptor agonist
sustituyase el término de acción farmacológica por el siguiente:
sabcomélina

p. 217  tasonerminum  tasonermin
replace the graphic formula by the following:
remplacer la formule développée par la suivante:
tasonermina

VRSSSRTPSD KFVAHVVPNQ QARGQLWQLS RANALLANG
VELRNQILV PQSEGLYLYS QVLFKGQGCP STHVLLHTHT
SRIAVSYQTK VNLSSAIKSP CQRETPBGAQ AKFWYEPYLY
GGVQOLEKGD RLXAEINRPD YLDFAESQGY YFGIAL
Proposed International Nonproprietary Names (Prop. INN): List 77
Dénominations communes internationales proposées (DCI Prop.): Liste 77
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 77
(Who Drug Information, Vol. 11, No. 2, 1997)

p. 90  eplerenonum  
éplérénone  
remplacer l'indication par la suivante:  
antagoniste de récepteurs de l'aldostérone  
eplerenona  
sustituyase la acción y uso por la siguiente:  
antagonista de los receptores de aldosterona

p. 96  opanixilum  
opanixil  
remplacer l'indication par la suivante:  
antihyperlipidémiant

p. 104  nadroparinum calcium  
nadroparin calcium  
replace the definition by the following:  
Calcium salt of a low molecular mass heparin obtained by nitrous acid depolymerization of heparin from pork intestinal mucosa, followed by fractionation to eliminate selectively most of the chains with a molecular mass lower than 2000; the majority of the components have a 2-O-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-O-sulfo-2,5-anhydro-α-D-mannitol structure at the reducing end of their chain; the mass-average molecular mass ranges between 3600 and 5000 with a characteristic value of about 4300; the degree of sulfatation is about 2.1 per disaccharidic unit.

p. 109  nadroparine caldque  
nadroparina cálcica  
remplacer la description par la suivante:  
Sel calcique d'une héparine de basse masse moléculaire obtenue par dépolymerisation, au moyen d'acide nitreux, d'héparine de muqueuse intestinale de porc; la majorité des composants de la nadroparine sodique possèdent une structure acide 2-O-sulfo-α-L-idopyranosuronic à l'extrémité non réductrice de leur chaîne et une structure 6-O-sulfo-2,5-anhydro-α-D-mannitol à l'extrémité réductrice de leur chaîne; la masse moléculaire relative moyenne est de 3600 à 5000, avec une valeur caractéristique de 4300 environ; le degré de sulfatation est 2.1 environ par unité disaccharidique.

p. 110  nadroparina cálcica  
Sal cálcica de una heparina de baja masa molecular obtenida por despolimerización con ácido nitroso de la heparina de la mucosa intestinal de cerdo seguida de fraccionamiento a fin de eliminar selectivamente la mayor parte de las cadenas de masa molecular inferior a 2000; la mayoría de los componentes tienen una estructura de ácido 2-O-sulfo-α-L-idopiranosurónico en el extremo no reductor y una estructura de 6-O-sulfo-2,5-anhidro-α-D-mannitol en el extremo reductor de la cadena; la masa molecular relativa media es de 3600 a 5000, con un valor característico de 4300 aproximadamente; el grado de sulfatación es de 2.1 por unidad de disacárido.
Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

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

Les textes de la Procédure à suivre en vue de choix de dénominations communes internationales recommandées pour les substances pharmaceutiques et des Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques ont été publiés avec la liste 77 des DCI proposées et seront, à nouveau, publiés avec la prochaine liste.

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