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General Policy Topics

Adverse drug reaction monitoring: new issues

When a new drug reaches the market, patients expect it to be safe and effective. During development, preclinical and clinical studies usually provide sufficient evidence of the product's effectiveness, but this is not the case for its safety. Normally, no more than 3000 patients have been treated with the drug during the clinical trial phase, making it likely that adverse drug reactions with an incidence of less than one in 10 000 will remain undetected. Indeed, several examples serve to prove that pre-marketing clinical trials may fail to detect side effects that later manifest themselves as adverse drug reactions.

Adverse drug reactions can cause severe suffering, and are probably more frequent than many people think. They are estimated to cause 3–5% of all hospital admissions (1), and a survey carried out in 1971 (2) found that they may be responsible for 160 000 deaths each year in US hospitals alone. A more recent study has concluded that adverse drug reactions significantly prolong the length of hospitalization — which may double the cost — and are associated with an almost twofold risk of death (3).

Reporting of adverse drug reactions is therefore essential to obtain the necessary information on the safety of products. In addition, many subpopulations, such as young children, the old, pregnant women, and patients using other medicines concomitantly, or with complicated disease conditions, are not normally exposed to the drug in clinical trials during the development phase.

The origin of adverse drug reaction monitoring lies in the often-quoted thalidomide catastrophe (4), which created a new perception of drug control, accelerating the enforcement of already established, but sometimes dormant, regulatory systems in many countries. In 1967, the World Health Organization reacted to these events by setting up a project on the international monitoring of adverse reactions to drugs (5). Within a few years, this project was extended and developed into the **WHO Programme on International Drug Monitoring**.

Originally established by ten highly developed countries, the WHO Programme currently numbers fifty members. All of these countries possess a national centre for adverse drug reaction monitoring and a national programme. These national centres collect reports from health professionals and pass them on for entry into the international data base housed at the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden.

Over the last five years, some twenty new countries have joined the programme, and almost all of them are from the developing world. Several other countries have expressed the wish to join, and are currently in contact with the WHO Collaborating Centre, which offers the guidance necessary for setting up a national monitoring programme.

Development of a national programme requires special approaches, since these new centres often do not have an infrastructure that allows them to collect and follow-up large numbers of reports. In developed countries, however, people can build on the experience of others and the importance of adverse drug reaction monitoring can be emphasized in professional education. Specific training in drug safety can be more easily organized.

Reports of adverse drug reactions are traditionally collected from health professionals, mainly physicians — at the national level. Many countries, however, are now in the process of **decentralizing** their reporting systems, with the consequent establishment of regional centres for adverse drug reaction monitoring (6, 7). A regionalized system permits closer contact with the reporter, and is particularly suitable when pharmacists are also included in the monitoring process.

The WHO Collaborating Centre plays an essential role in the WHO Programme since it is responsible for maintaining the data base of reports received from those countries participating. At the present time, there are some 1 600 000 reports on file, and each year almost 200 000 new reports are added. The data base can, under certain conditions, be interrogated by third parties (8). It may also generate signals of potentially severe drug toxicity and provide confirmation of signals generated in

specific countries or regions. The Centre also acts as the guardian of the standardized terminology of adverse drug reactions in computerized systems (WHOART).

The **terminology** currently in use within the context of the programme was developed at an early stage, and has been continuously updated. It is used by national centres and by many pharmaceutical companies. None the less, it has become evident that the terminology no longer covers all areas of drug monitoring such as premarketing, clinical trial, or social history data. As a result, terminology that addresses the needs of the majority of drug regulatory authorities is now under development. The ultimate goal of this activity is to develop a truly global terminology with relevance for all countries. This would lead to considerable savings in terms of staff and resources, both within industry and regulatory authorities.

National and regional differences in medical culture and tradition, and availability of resources, result in different diagnostic and, consequently, pharmacotherapeutic practices (9). Because of the substantially different conditions in developing countries in terms of endemic diseases, overcrowding, poverty, malnutrition, and health services, the benefit-risk ratio for drugs determined in developed countries is often not relevant. In general, the benefits to be obtained from effective treatment or prophylaxis within developing countries may be so huge that the benefit-risk ratio is strongly positive, even when there is a substantial incidence of adverse reactions. For example, in a country with a high mortality rate associated with reproduction, the benefits of avoiding pregnancies are large, and will more than offset the risk associated with oral contraceptives. Moreover, many diseases, such as tropical diseases, are only prevalent in developing countries and the safety of innovative treatments can only be tested there.

In spite of budgetary constraints, several developing countries have set up well-organized, well-run adverse drug reaction monitoring programmes. These are often driven by the strong motivation of a handful of health professionals (10). Monitoring of adverse drug reactions in developing countries is of great importance. A good programme may detect signals that are specific for that country, but also for drugs — such as those used in tropical diseases (11) — that have often been on the market for many years in countries where there is no way of providing information on the potential risks.

Traditionally, the use of **herbal medicines** has been high in developing countries and is now taking up an increasing share of the health care market of the developed world. One explanation may be the popular belief that they do not cause adverse reactions. None the less, some herbal medicines are quite active and may even contain toxic compounds. For example, cases of hepatic veno-occlusion attributed to pyrrolizidine alkaloids in tea made from *Senecio* and *Symphytum* (comfrey) species have been reported in several countries, and patients have died of hepatic necrosis following overuse of herbal medicines derived from these plants. Attention must also be paid to possible interactions when administering other drug treatments. These safety aspects have resulted in restrictive regulatory measures in a number of Member States (12, 13).

Naturally occurring compounds may not be the only cause of toxicity from herbal products. Sometimes herbal drugs are dangerously adulterated or enriched by the addition of potent synthetic pharmaceuticals such as anabolic steroids, sedatives and nonsteroidal anti-inflammatory agents. Severe adverse effects have been reported in patients after consumption of such adulterated medication (14, 15). Continuous vigilance remains essential, but registration of adverse reactions to herbal medicines is complicated because of the lack of consistency in the composition of a product consisting of the different parts of several different herbal species.

Recently, the world was shocked by reports of many young children in Haiti dying after consumption of a cough mixture which proved to contain glycerol contaminated with diethylene glycol (16). This incident was not isolated; other cases involving diethylene glycol have been reported in the USA, India, Nigeria and Bangladesh, claiming the lives of uncountable numbers of children, and intoxicating many others (17, 18, 19). Other instances of **counterfeit or substandard medicines** have been reported such as antimalarials containing a trace amount of chloramphenicol, or eye drops manufactured using tap-water instead of sterile water (20). In view of the huge amounts of money involved and the relative ease of manufacture, transport and sale of medicinal products — in particular in insufficiently controlled markets — a decrease in the prevalence of counterfeits on the drug market is not to be expected. Efforts are needed to curb the problem, and drug monitoring programmes can be instrumental in this. For

example, an unexpected lack of efficacy may be spotted in a product which is then found to have no active ingredient, or unusual toxic effects may be caused by cheap adulterants inappropriately used by unscrupulous manufacturers. Patients reacting in an unusual way to relatively standard treatment should be reported as this can lead to the detection of counterfeit or substandard drugs.

Often, counterfeit drugs do not contain sufficient amounts of the active substance. Apart from providing unsatisfactory treatment, this may also lead to underdosing. In the case of infectious diseases, this can also contribute to the **emergence of antibiotic resistance**. Monitoring of the development of resistance is of vital importance, and national drug monitoring programmes can play an important role in this regard. Many other mechanisms may lead to antibiotic resistance and this can pose a threat to public health. Alarming outbreaks of tuberculosis in the USA have lately stirred public interest and concern. In 1993, the World Health Organization declared tuberculosis a global emergency (21) and cited the danger of multidrug resistance. Once again, reporting the absence of effect of long-established therapies may provide a clue to detection of a resistant strain.

Malaria kills between one and two million children every year. However, the number of drugs available for treatment is remarkably small and multidrug resistance diminishes the already not so rich armamentarium even further. Almost all tropical countries are now faced with the problem of an increasing number of ineffective antimalarials and even travellers returning from affected areas sometimes fail to respond to medication (22). Simple and sustainable systems for identification and evaluation of adverse reactions as well as reporting on lack of efficacy associated with antimalarial drugs are needed, but many tropical countries do not have the public health infrastructure to allow reporting (23).

Generally, **vaccines** are considered as safe and no major disasters have been reported. Since vaccines are administered to healthy people, mostly children, the impact of a perceived problem can be tremendous. Many will remember the scare when pertussis vaccine was reported to be associated with brain damage. Vaccination coverage decreased in the United Kingdom from 96% to 60% and only rose again when further studies demonstrated the absence of a causal relationship (24). It is consequently important to

collect information on the safety of vaccines to provide sound reference data in the event of a problem.

Because of these considerations, many countries have established a specific programme for the monitoring of adverse events following vaccination, and a field guide for vaccination programme monitors has been published by WHO (25).

In line with the general trend in our society to autonomy and the need to keep public health costs under control, more and more countries are allowing prescription-only drugs to be shifted to **over-the-counter (OTC)** status. This may result in a different rate of reporting of adverse effects, or even lack of reporting altogether, and monitoring centres should be on their guard.

Control of prescription medicines is the responsibility of the physician, or at least the dispensing pharmacist, whereas OTC drugs escape this kind of control (27). The possible risks associated with a switch from prescription-only to OTC include unexpected interactions when the product is used in combination with other treatments, and the missed opportunity for diagnosis of a possible serious ailment. This situation has primarily economic advantages, but it also provides the public with easier access to medication which is non-prescription (28). Consequences for drug monitoring programmes have not been sufficiently investigated, but initiatives are in hand to start the discussion.

A number of issues in adverse drug reaction monitoring have thus been identified that deserve more attention than received so far. It is fortunate that many developing countries are beginning to realize that they need to become active and collect information on the potential adverse effects of the drugs in their markets.

Although these initiatives may not avoid another disaster with absolute certainty, it is through effective monitoring and application of WHO guidelines that the risk associated with the use of medicines will be reduced to a minimum.

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Reports on Individual Drugs

Rotavirus vaccine nearing registration

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Rotavirus is responsible for more diarrhoeal disease than any other single agent. Most of the resulting 600 000 deaths each year are in the developing world, but rotavirus is a significant pathogen also in developed countries. Rotavirus diarrhoea is highly contagious and cannot be controlled by hygienic measures. This is a reason why rotavirus vaccination is attractive for both developed and developing countries. After fifteen years of studies, rotavirus vaccines are finally approaching registration status and may soon be considered for inclusion in the immunization programmes of many countries.

Rotavirus vaccination began by empirical use of the tissue-culture adapted bovine rotavirus strain RIT4237 in oral form. Studies in gnotobiotic piglets first showed cross-protection between bovine and human rotaviruses (1) and, thereafter, the vaccine was found safe, immunogenic, and efficacious during trials in human infants (2–3). In Finland, the RIT4237 vaccine induced 50–58% protection against any rotavirus gastroenteritis, and 82–88% protection against clinically significant forms (4). Thus, a high level of protection against severe rotavirus disease, moderate protection against mild disease, and no protection against rotavirus infection as such were seen. These findings have been consistent in most studies of oral rotavirus vaccines.

Despite the initial success in Finland, the RIT4237 vaccine was withdrawn. A report of a small study in Rwanda (5), and a preliminary analysis of a trial in Lima, Peru, indicated little or no protection and this led to the premature conclusion that the vaccine had failed in developing countries. Subsequently, a full analysis of the Peruvian trial showed protective efficacy of 40 % against any rotavirus disease, and 58–75% against severe forms (6) — which was in

fact only slightly less than in Finland. Another bovine rotavirus vaccine strain, WC3, showed a promising 76% protective efficacy in the United States (7), but was withdrawn because of unsatisfactory efficacy (17%) in another US trial (8) and virtually no efficacy when administered in the Central African Republic (9).

A bovine-human reassortant rotavirus vaccine based on the WC3 strain has been developed more recently. This quadrivalent vaccine contains reassortant rotaviruses expressing human rotavirus surface proteins VP7 (G types) G1, G2 and G4, and VP4 (P type) protein P[8] and has demonstrated 67% protection against all rotavirus disease in one trial (10). The number of subjects studied so far is, however, insufficient to come to any firm conclusions. A major advantage of the previous bovine rotavirus vaccines, as well as this reassortant vaccine, is their lack of reactogenicity.

Rhesus rotavirus (RRV) vaccine is more immunogenic than the bovine rotaviruses in humans (11). The vaccine titre is 10^4 – 10^5 per ml, as compared with 10^7 (WC3) or 10^8 (RIT4237) for the bovine rotavirus vaccines. RRV vaccine relies on virus multiplication to produce a sufficient amount of viral antigens for induction of an immune response and, as a result, causes febrile reactions (but no diarrhoea) at 3 to 4 days post-vaccination (12). The reactions are more frequent and severe in children who lack maternally acquired antibody, and are more commonly observed in developed countries where infants are less likely to receive rotavirus antibodies from the mother than in developing countries. High titre RRV vaccine was, in fact, efficacious in a study in Sweden, but caused a high rate of reactions in 5–12-month-old children (13); in other studies there has been a great variation in efficacy (14–17).

RRV was further improved by development of the rhesus-human reassortant rotaviruses (18), which contain 10 RNA segments from the rhesus rotavirus and one, encoding for the VP7 (G-type) surface protein, from human rotaviruses corresponding to the G-types 1, 2 or 4. Rhesus rotavirus itself is close to the human G-type 3 rotavirus (18). A mixture of the four viruses is named the rhesus rotavirus tetravalent (RRV-TV) vaccine.

The performance of RRV-TV vaccine in clinical trials has been consistent. In a multicentre trial in the USA, RRV-TV vaccine at titre level 4×10^4 PFU showed a 57% protective efficacy against any rotavirus diarrhoea, and up to 92 % protection against severe forms (19). In order to further improve vaccine efficacy a higher titre (4×10^5 PFU) RRV-TV vaccine was produced. In the USA, this high titre vaccine yielded a 49% efficacy for any rotavirus diarrhoea and 100% efficacy for dehydrating forms (20). In a recently completed trial in Finland, the high titre vaccine was 100% protective against hospitalization for rotavirus gastroenteritis*. In a large catchment trial in Caracas, Venezuela, the high titre RRV-TV vaccine showed good protection, with efficacy as high as in the USA and only slightly lower than in Finland**. This is perhaps the most encouraging result considering potential use in developing countries.

In contrast, the low titre RRV-TV was only 20% and 35% efficacious against any rotavirus diarrhoea in populations of low socioeconomic status in Lima, Peru (21), and Belém, Brazil (22), respectively, and, at best, 50–60 % efficacious against severe diarrhoea. An apparent reason was that the immunogenicity was low at both of these study sites.

At the moment, field trials are the only way to judge the performance of RRV-TV and other candidate rotavirus vaccines, as there is no satisfactory surrogate marker for protection. Overall immunogenicity is certainly of importance for clinical protection, but the role of the human rotavirus G- or P-type surface antigens present in the RRV-TV or bovine reassortant vaccines is less clear (23).

It is likely that RRV-TV vaccine will be licensed in the near future. Thereafter, the vaccine may be used by paediatricians in private practice in the USA and, gradually, in Europe. Acceptance for public health immunization programmes will depend on national considerations of disease burden and cost-benefit in each country. For example, many Latin American countries are likely to be interested in the RRV-TV vaccine. In these countries, rotavirus diarrhoea is a seasonal epidemic disease, causing considerable morbidity with some mortality. Many of the countries may be able to afford the vaccine if the price is reasonable. What may be needed to convince the decision-makers is a large-scale demonstration project showing effectiveness, rather than efficacy, and cost-benefit at the same time.

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In many Asian and African developing countries, where rotavirus disease is less seasonal, transmission occurs by the faecal-oral route, and the infectious dose is presumably large, the challenge for rotavirus vaccine is greater, but perhaps not impossible to meet. Even an efficacy level of 50–60% demonstrated by the low-dose RRV-TV against severe rotavirus disease — modest as it may sound — could prevent a large number of deaths. It would, however, be crucial to identify means to further increase the uptake of the RRV-TV vaccine in developing-country conditions.

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Hearing loss from ototoxics

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Ototoxicity is the harmful effect of a drug or chemical substance on the organs of hearing and/or balance. Drugs and other chemicals that damage the cochlea — the organ of hearing in the inner ear — do so by destroying sound-sensitive hair cells, usually starting at the basal turn and progressing towards the apical turn. These drugs may also damage the end organs of balance in the semi-circular canals, utricle and saccule (vestibular apparatus). Ototoxic damage may be reversible initially but this generally depends on the particular agent and sometimes the dose. Aminoglycoside antibiotics, which are the commonest causes of drug-induced ototoxicity, usually produce permanent damage.

Most studies of ototoxicity have been hampered by difficulties in definition and measurement. A hearing loss of ≥ 15 dB at 2 or more frequencies or ≥ 20 dB at 1 or more frequencies following exposure to a potentially ototoxic substance is usually taken to indicate ototoxic damage. However, a recent study of aminoglycoside ototoxicity suggests that these levels could overestimate the incidence (1).

Cochlear toxicity often presents as tinnitus. Hearing loss may affect higher frequencies initially and patients may only become aware of a problem when their loss is at least 30 dB at frequencies from 3–4 kHz. Vestibular toxicity usually presents as unsteadiness (vertigo), or even oscillopsia (vertical “jiggling” of stationary objects). The vertigo may be so disabling that affected patients are often sick and bedridden (2).

Causes

The table below indicates the major causes of ototoxicity. Among systemically administered drugs, the aminoglycosides are probably the commonest cause, and some persons may have an inherited predisposition. Damage may be increased by poor renal function or during simultaneous administration of loop diuretics, which alone can also be ototoxic, especially when given by bolus injection. There is some evidence that aminoglycosides, especially streptomycin, may damage the fetus when given during pregnancy. The likelihood of this occurring may increase with the global resurgence of tuberculosis unless safer, alternative drug regimens are employed. Kanamycin given to pre-term infants has caused hearing loss and pre-term infants are hypersensitive to aminoglycoside ototoxicity during the period of anatomical and functional maturation of the inner ear. Neomycin, when used in the topical treatment of burns, may be absorbed and can cause irreversible ototoxic damage. Netilmycin may be less ototoxic than the other aminoglycosides.

Macrolide antibiotics such as erythromycin, and possibly azithromycin, can cause a reversible high-tone sensorineural hearing loss and tinnitus after high dosage (4 g/day for erythromycin). The risk is greater in the elderly or where there is kidney or liver dysfunction.

Salicylates, such as acetylsalicylic acid, have long been known to produce a reversible moderate

hearing loss and tinnitus. This is usually dose-dependent but idiosyncratic reactions have occurred. Some antimalarials are also ototoxic. Quinine, which is chemically similar to salicylates, can cause mild toxic symptoms — sometimes referred to as “cinchonism” — such as tinnitus, high-tone hearing loss, visual disturbances, nausea, giddiness and tremors when administered in therapeutic doses, and in excessive doses may cause permanent deafness or blindness as well as myocardial conduction abnormalities, hypoglycaemia and coma (3, 4). With the increase of chloroquine-resistant malaria, quinine is being used on a larger scale and in higher dosage, especially for cerebral malaria and the signs may be difficult to distinguish from quinine toxicity. Permanent hearing loss can also occur with high-dose chloroquine.

Anticancer agents, especially cisplatin, may be ototoxic. The hearing loss may not commence until many days after therapy, and occurs more commonly in adults with prior otologic disease. Affected patients may complain of otalgia, tinnitus and hearing loss. The chelating agent, deferoxamine, used to prevent iron overload in patients having multiple blood transfusions for conditions such as beta-thalassaemia, may produce auditory and visual neurotoxicity.

Many ototopical preparations, especially aminoglycosides, are potentially ototoxic. This has been demonstrated in animal studies, but the evidence in humans is less clear. Many otologists feel that the

Table of the main drugs causing ototoxicity

Aminoglycosides	gentamicin, streptomycin, kanamycin, amikacin, tobramycin, neomycin, netilmicin, polymyxin B
Macrolides	erythromycin, azithromycin, clarithromycin
Loop diuretics	furosemide, bumetanide, etacrynic acid
Salicylates	acetylsalicylic acid (aspirin)
Antimalarials	quinine, chloroquine (high dosage)
Nonsteroidal anti-inflammatory drugs	naproxen, indometacin (no definite findings)
Antineoplastic drugs	cisplatin, bleomycin, carboplatin
Chelating agents	deferoxamine
Topical otological preparations	antibiotic solutions: aminoglycosides, polymyxin B, chloramphenicol, fosfomycin anti-inflammatory: propylene glycol, hydrocortisone antiseptic: chlorhexidine, povidone iodine acidifying: acetic acid (2% solution)

risk of hearing loss from chronic otitis media is greater than from the ototopical antibiotics used to treat it. In fact, the ototoxic risk may be greater if such preparations are applied to a normal middle-ear mucosa, such as in a patient with a chronic perforation but only intermittent otorrhoea. The ototoxic potential of acetic acid and hydrocortisone has been questioned. Some traditional medicines may be ototoxic. For example infusions of various roots used as ear drops in Angola have been reported to be ototoxic (2).

Prevention

Ototoxic hearing loss and vestibulopathy are predominantly iatrogenic or self-induced conditions. Once ototoxic damage has occurred, it is frequently irreversible, and expensive and time-consuming audiological rehabilitation with hearing aids and speech training may be required. However, there is wide scope for prevention, and this is where the main activities for control should be targeted.

1. Health education and promotion

There is a general lack of knowledge and awareness of the potential ototoxic effects of certain drugs and chemicals. An increase in the public's understanding of the risk factors for ototoxicity and the improper use of such drugs could help to reduce the incidence of the problem, as was shown by a recent campaign in China (5).

2. Professional education

Much of the problem of ototoxicity results from the inappropriate and indiscriminate use of ototoxic drugs by health care providers, especially, but not only, at primary levels. Information on the dangers of potentially ototoxic drugs and the strategies for control should be included in basic and refresher training of all health professionals, particularly primary care workers, nurses, general practitioners, pharmacists, paediatricians, and internists. The importance of audiometric and other monitoring of patients at risk should be stressed. Lists of drugs published for use by health professionals and individual drug labelling and product information should include specific warnings of ototoxic potential.

3. Regulation and legislation

Many developing countries have inadequate control of the availability of potentially ototoxic drugs. In some countries, aminoglycosides and other antibiotics are available over-the-counter without the need for prescription. In others, there are regulations but they are not enforced. Regulations should

also include control of drugs donated for use in large-scale emergencies and disasters. Health authorities should ensure that adequate warnings written in the local language are provided with donated drugs.

4. Management and monitoring

If possible during treatment, ototoxic drugs should be avoided, particularly where other risk factors for ototoxicity are present. However this is not always possible because of the lack of alternative and affordable therapies. In situations where potentially ototoxic drugs must be used, the following precautions should be observed:

- Use the minimum effective dose and duration of therapy
- Use an appropriate route of drug administration; and
- Monitor the patient regularly and frequently.

This should be done by performing regular symptom checks, audiometric tests including high-frequency audiometry and otoacoustic emissions (if possible) and measurements of serum drug levels. Audiometry or serum testing may not be widely available in some developing countries, hence the need for constant clinical vigilance.

5. National surveillance systems

These should be set up, or integrated into other networks such as the WHO International Drug Monitoring Programme, in order to measure the extent and causes of the problem.

6. Research

The mechanism of ototoxicity and its incidence and prevalence, the development of affordable, alternative nontoxic drugs, and the need for substances that reduce damage caused by ototoxic drugs should be determined by research. The safe dosage and duration of treatment in high-risk patients need to be evaluated, in particular for those essential drugs that are potentially ototoxic.

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International study of hormone replacement therapy (HRT) announced

An international study involving more than 30 000 postmenopausal women will commence in 1997 to provide data on the long-term benefits and risks of HRT. The study is intended to complement the recent Women's Health Initiative study carried out in the United States. The Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) will be coordinated in the United Kingdom by the Medical Research Council's Epidemiology and Medical Care Unit and will extend over 20 years.

Participants in the study will take HRT or placebo for 10 years, and be followed up for a further 10 years. The first results of the trial are not expected before 2012 and will study, in particular, the risks of developing heart and other cardiovascular diseases, stroke, breast cancer and bone fractures caused by osteoporosis, as well as provide information on the quality of life and economic implications of HRT.

Reference: *Scip*, Number 2180, 1996. p. 27.

Betacarotene, vitamin A and E may not prevent cancer or cardiovascular diseases

Observations from epidemiological studies suggest that the risk of cancer and cardiovascular diseases is lower among persons who consume high dietary levels of vegetables, fruits and grains (1). A commonly accepted explanation for this, both among scientists and the public has been that antioxidant vitamins in vegetables and fruits prevent carcinogenesis and atherogenesis by interfering passively with oxidative damage to DNA and lipoproteins.

These theories have also been supported by observations in animal studies (2). As a result of these beliefs, many millions of dollars are spent annually on synthetic betacarotene and vitamin E (INN = tocofersolan) and A (INN = retinol) supplements.

Sceptics have long called for a large, long-term clinical intervention trial to demonstrate the benefits and risks of these prevention practices, and the results of four large-scale chemoprevention trials of betacarotene and related agents are now available. Their disappointing results reaffirm the importance of solid scientific evidence as a sound basis for any disease prevention strategies (3–6).

The Alpha-Tocopherol, Beta Carotene cancer prevention study (ATBC) (3) tested daily supplementation with 20 mg of betacarotene and 50 mg of tocofersolan in 29 133 male smokers (two-by-two factorial design). A total of 876 new cases of lung cancer were diagnosed and no reduction in the incidence of lung cancer was found among male smokers after five to eight years of dietary supplementation with tocofersolan or betacarotene. In fact the trial raised the possibility that these supplements may have both harmful and beneficial effects.

The Physicians' Health Study (4) tested supplementation with 50 mg of betacarotene on alternate days in 22 071 male physicians, 50% of whom were former smokers and 11 % of whom were currently smoking. In this trial, 170 new cases of lung cancer were diagnosed and 12 years of supplementation with betacarotene produced neither benefit nor harm in terms of the incidence of malignant neoplasms, cardiovascular disease, or death from all causes.

The betacarotene and retinol efficacy trial (CARET) tested daily supplementation with a combination of 30 mg betacarotene and 25 000 IU of retinol in a total of 18 314 smokers, former smokers and workers exposed to asbestos (5). There were 388 new cases of lung cancer and, after an average of four years of supplementation, the combination of betacarotene and retinol had no benefit and may have had an adverse effect on the incidence of lung cancer and on the risk of death from lung cancer, cardiovascular disease, and any cause in smokers and workers exposed to asbestos.

Finally, a study conducted in 34 486 postmenopausal women with no cardiovascular disease suggested that the intake of vitamin E from food is

inversely associated with the risk of death from coronary heart disease and that such women can lower their risk without using vitamin supplements (6). By contrast, the intake of retinol and ascorbic acid was not associated with lower risk of death from coronary disease.

In summary, the studies did not prove the value of antioxidant vitamin supplements for prevention of cancer or cardiovascular disease in a well-nourished population. Instead of buying and consuming antioxidant-vitamin supplements, people are advised to adhere to a healthy lifestyle. This is understood as eating sufficient fruit and vegetables, taking enough exercise, avoiding becoming overweight and refraining from smoking.

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Driving ability in cancer patients treated with morphine

Even a small single dose of an opioid in opioid-naive healthy volunteers is reported to reduce reaction speed and accuracy, muscular coordination, attentiveness and the ability to memorize, rendering the driver a traffic hazard. The question of whether stable doses of opioids in cancer treatment affect psychomotor functions in the same way is now raised in a study reported in the *Lancet* (1).

Two groups of cancer patients, one of 24 patients using slow-release morphine tablets in a mean daily dose of 209 mg, with dose stability established for at least two weeks, and a control group of 25 patients who had no pain and used no analgesics, performed a series of psychological, psychomotor and neurological tests originally designed to measure the vocational skills of professional drivers.

Although the morphine group did not perform quite as well as the control group in the tests, there were no significant differences between the two groups as far as measurement of intelligence, attentiveness, ability to concentrate, psychomotor speed and attention span were concerned. No significant drug effects were demonstrated in neurological tests measuring reaction speed, sensitivity to temperature variation, and keeping one's balance with the eyes open. The morphine group performed poorer only in the test for keeping balance with their eyes closed.

The authors concluded that the long-term use of stable doses of morphine does not essentially reduce driving skills. However, the observation relevant to driving was that there is a slight dose-dependent effect on the performance of tasks demanding special concentration.

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General Information

The implications of the TRIPS Agreement for the protection of pharmaceutical inventions*

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The Agreement establishing the World Trade Organization (WTO), including the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), came into force on 1 January 1995. The WTO is divided into three main parts: the Agreements on Trade in Goods, which includes a new General Agreement on Tariffs and Trade (GATT) and the various subsidiary agreements to it; a newly negotiated General Agreement on Trade in Services (GATS); and the Agreement on TRIPS. Any country wishing to be a Member of the WTO is obliged to accept all these agreements — as part of a package which reflects the trade-offs made during the negotiating process.

The TRIPS Agreement covers all the main areas of intellectual property — copyright and related rights, trademarks, geographical indications, industrial designs, patents, layout-designs of integrated circuits and undisclosed information or trade secrets. In respect of these areas, the Agreement contains three main sets of provisions.

Standards

The Agreement lays down minimum standards of substantive protection for each category of rights that must be provided in the national law of each Member. It defines each of the main elements of protection, namely the subject matter to be protected, the rights to be conferred and any permissible exceptions to those rights, and the minimum duration of protection. It does this by requiring that the substantive obligations of the World Intellectual Property Organization (WIPO) Conventions, the Paris Convention for the Protection of Industrial Property and the Berne Convention for the

Protection of Literary and Artistic Works, must be complied with and by adding a substantial number of additional obligations on matters where these Conventions are silent or were seen as being inadequate. This is particularly the case in the area of industrial property.

Enforcement

The second major characteristic of the Agreement is that, for the first time in international law, it requires Members to provide effective procedures and remedies for the enforcement of intellectual property rights, whether through the normal civil judicial process, through customs action against imports of counterfeit and pirated goods or through criminal procedures in respect of wilful counterfeiting and piracy on a commercial scale.

Dispute settlement

It makes disputes between governments about whether TRIPS obligations have been complied with subject to a strengthened version of the GATT dispute settlement system under the future World Trade Organization.

In addition the Agreement provides for certain basic principles, such as national treatment, and some general rules to ensure that procedural difficulties in acquiring or maintaining international patent rights do not negate the protection due. The obligations under the Agreement will apply equally to all member countries, but developing countries will have a longer period to phase them in. Special transition arrangements operate in the situation where a developing country does not presently provide product patent protection in the area of pharmaceuticals (see page 15).

Another general point about the Agreement should also be made. It is a minimum standards Agreement that leaves Members free to provide more extensive protection of intellectual property if they so wish — for purely domestic reasons or because they have concluded international agreements to this effect, whether bilateral, regional, as for example is the case in the European Communities and in the North American Free Trade Area (NAFTA), or multilateral, such as in WIPO. The TRIPS Agreement does, however, require, as a

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general rule, that any more extensive protection so implemented be extended to the nationals of all WTO Members on a national and most-favoured-nation treatment basis.

The TRIPS provisions on pharmaceutical patents

The question of the protection of pharmaceutical patents was one of the key issues in the negotiations as a whole and perhaps the key issue in the North-South axis of the negotiations. It was the last issue to be resolved in the negotiations prior to the tabling of the draft Agreement at the end of 1991. At that time, it was clear that there would be no TRIPS Agreement without a commitment to make available patent protection for twenty years in virtually all areas of technology, including pharmaceuticals, and that without a TRIPS Agreement it was doubtful that the Uruguay Round could be concluded. The question therefore that all delegations were willing to consider was: on what terms would they accept such an obligation, in particular in regard to such matters as the exhaustion of rights, compulsory licensing, the control of anti-competitive practices, test data protection and transitional arrangements?

Patentable subject matter

The basic rule is that patents must be available for any inventions, whether products or processes, in all fields of technology without discrimination, subject to the normal tests of novelty, inventiveness, industrial applicability and adequate disclosure. There are three exceptions to this basic rule.

- One is for inventions contrary to public order or morality. This is subject to the condition that the commercial exploitation of the invention must also be prevented and this prevention must be necessary for the protection of public order or morality.
- The second exception is that Members may exclude from patentability diagnostic, therapeutic and surgical methods for the treatment of humans or animals.
- The third is that Members may exclude plants and animals other than microorganisms and processes for the production of plants or animals other than non-biological and microbiological processes. It is worth noting that this exception is considerably broader than the exceptions for life forms found in the patent laws of the United States, European countries and Japan. This

reflected a concern on the part of many developing countries not to be obliged to go further in this area of technology, at least for the time being.

Patent rights

The rights that must be conferred by a product patent include the usual ones of making, using and selling. Process patent protection must give rights over products obtained directly by the process. Patent owners must also have the right to prevent importation by third parties without their consent. The question of the international exhaustion of rights, that is to say the extent to which a right holder should have the possibility to assert his rights in respect of goods that he had authorized to be put on the market in another country, is of course not only related to the importation right; it applies equally in regard to the right to prevent sale or use of goods put on the market with his consent in another country. The negotiation on the issue of exhaustion was between those who favoured complete silence on this issue and those which wanted an explicit recognition of the right of countries to have their own exhaustion regimes. The outcome is the provision which makes it clear that the issue of exhaustion cannot be addressed in dispute settlement proceedings under the Agreement, except in regard to the national treatment and most favoured nation obligations. Thus, subject to these exceptions, what a country does in the area of exhaustion cannot be challenged through the WTO. However, the text does not specifically legitimize national discretion in this area and is interpreted by some as meaning that exhaustion practices are not covered by the restraint on the use of unilateral measures that the WTO dispute settlement provisions require.

Compulsory licensing

The main debate took place between those who wished to provide for a finite list of grounds on which compulsory licences could be granted, for example limiting compulsory licensing to situations of national emergency, anti-competitive practices and public non-commercial use, and those who did not consider such a finite list feasible or appropriate. A further important element in the negotiations was the insistence by a large number of countries that government use practices — use by or on behalf of the government — should be subject to rules equivalent to those applying to compulsory licensing. The outcome of these debates can be found in Article 31 of the TRIPS text. This contains a common set of rules applying

to both forms of use without the authorization of the right holder — that is to say compulsory licensing and government use — and does not limit the grounds on which compulsory licences can be granted. It does, however, contain, together with related provisions in Article 27.1, a number of conditions that have to be respected in order to protect the legitimate interests of the right holder. A number of these conditions are:

- Compulsory licences must not discriminate according to the field of technology. A number of countries have had special systems operating in the area of pharmaceuticals. These will have to be eliminated.
- Patents rights must be enjoyable without discrimination as to whether products are imported or locally produced. Failure to meet the reasonable needs of the market can remain a ground for the grant of a compulsory licence. But the compulsory licensing system must not provide for differential treatment according to whether the patent owner supplies the market through imports or local production.
- Applications for compulsory licences shall be considered on their individual merits. This means that countries must not provide automatic licences of right-type systems, but must consider each application in the light of the conditions set out in the TRIPS Agreement.
- As a general rule, applications must not be considered unless an unsuccessful attempt has been made to obtain a voluntary licence on reasonable terms and conditions within a reasonable period of time.
- The scope and duration of compulsory licences are limited to the purpose for which they were granted and such licences shall be liable, subject to adequate protection of the legitimate interests of the licensee, to be terminated if and when the circumstances which led to their being granted cease to exist and are unlikely to recur.
- The right holder shall be paid adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization.
- Decisions relating to remuneration and the legal validity of any decision to grant a licence shall be subject to judicial or other independent review.

- The requirements concerning the need to attempt first to negotiate a voluntary licence and the amount of remuneration are relaxed where a compulsory licence is granted to remedy a practice determined after judicial or administrative process to be anti-competitive.
- Compulsory licences on dependent patent grounds are permitted subject to a number of additional conditions.

Anti-competitive practices

The TRIPS Agreement contains a Section on the control of anti-competitive practices. This will be the first time that agreed language on such matters has been incorporated in a binding multilateral instrument. The Section recognizes that some licensing practices or conditions pertaining to IPRs which restrain competition may have adverse effects on trade and impede the transfer and dissemination of technology. The Section further recognizes the right of Members to adopt measures, consistently with the provisions of the Agreement, to prevent or control abusive anti-competitive practices and includes an illustrative list of such practices. The Section also establishes a consultation procedure by which a Member seeking to take action against abusive anti-competitive practices may seek the co-operation of the home government of the company in question, notably through the supply of information of relevance to the matter in question. These provisions essentially reflect the concerns expressed in the negotiations by representatives of developing countries. However, it is also worth noting that attitudes towards a general consideration of matters of competition law, including restrictive business practices, as they relate to the conditions of international trade have evolved in the GATT/WTO recently. The December 1996 Singapore Ministerial Conference decided to include this issue on the future work programme of the World Trade Organization.

Undisclosed information and test data

The TRIPS Agreement contains obligations on the protection of undisclosed information or trade secrets. These are not treated as a form of property; the protection that has to be given is against the use of such information in a manner contrary to honest commercial practices, i.e. against acts of unfair competition. Although the matter was somewhat contentious at the outset of the negotiations, delegations generally recognized that such protection was desirable and in many cases was already available in one form or another

through their national law. The information that should be protected is defined as information that is secret, that has commercial value because it is secret and that has been subject to reasonable steps under the circumstances to keep it secret.

Undisclosed test data and other data whose submission is required by a Member as a condition of approving the marketing of pharmaceutical or agricultural chemical products which use new chemical entities and whose origination involved a considerable effort must be protected against unfair commercial use. Earlier drafts of the Agreement had specified a period of time during which governments should not rely on such data for the approval of competing products without the agreement of the company submitting the original data. This, however, was removed in the final stages of the negotiations.

Transitional arrangements

The basic rule in this area is that, as of 1 January 1995, the date of entry into force of the WTO Agreement, developed countries had a one-year transition period (i.e. until the beginning of this year), and developing and least-developed countries generally have five- and eleven-year transition periods respectively in order to bring their legislation and practices into conformity with their TRIPS obligations. Countries in transition to a market economy may also benefit from a five-year transition period subject to certain conditions. All WTO Members have had to comply with the national treatment and most favoured nation obligations of the TRIPS Agreement since the beginning of this year. These transition periods are optional and many countries are making the necessary changes to their legislation in advance.

At the end of the relevant transition period, Members have to apply the TRIPS standards not only to new subject matter but also to existing subject matter under protection on that date. Thus, for example, any patent still in force on that date would benefit from the twenty-year term of protection from filing, from the rights specified in the TRIPS text and from the conditions on the use of compulsory licensing. There are certain exceptions to protect investments and arrangements already initiated prior to the acceptance of the WTO Agreement by a country; but, given the transition period, these are likely to be applicable only in developed countries.

Special transitional arrangements apply in the situation where a developing country does not

provide product protection in a given area of technology, such as pharmaceuticals, on the general date of application of this Agreement for that Member, i.e. in the year 2000. In such a situation, the country concerned may delay the application of the TRIPS obligations on product patents to that area of technology for an additional five years (i.e. to the year 2005). If this was all the TRIPS Agreement said on this matter, the effect would be that such a developing country would be obliged to start providing patent protection from the year 2005 for pharmaceutical product inventions which will be "new" as of that date. Given the delay between the date of filing applications for patents for new pharmaceutical products and those products receiving marketing approval, especially in developing countries, the practical commercial effect of the TRIPS provisions in the pharmaceutical sector would, in many such cases, not have become apparent until the year 2015 or so.

This was clearly not a negotiable prospect in the context of the Uruguay Round. It is for this reason that the TRIPS text also includes additional transitional arrangements in the situation where a country does not provide, as of the date of entry into force of the WTO Agreement, patent protection for pharmaceutical (and agricultural chemical) products commensurate with the TRIPS provisions. In such a situation, the country concerned must provide, as from the date of entry into force of the WTO Agreement, a means by which patent applications for such inventions can be filed.

These applications will not need to be examined for their patentability until the country starts applying product patent protection in that area, i.e. for a developing country, at the end of the ten-year transition period. However, at that time, the application must be examined by reference to the prior art as it existed at the time the application was made. If the application is successful, product patent protection would then have to be granted for the remainder of the patent term counted from the filing date of the application.

Given the lengthy delay between filing a patent application and obtaining marketing approval for a pharmaceutical product, most products that are the subject of this procedure would normally not be likely to get on the market in a developing country before the expiry of the ten-year transition period. However, in the, perhaps, rather rare situation where such a product does obtain marketing approval in a developing country benefiting from the

ten-year transition period, provision is made for the grant of an exclusive marketing right of up to five years to tide over the gap. This is subject to a number of safeguards to ensure that the product concerned is a genuine invention: subsequent to the entry into force of the WTO Agreement, a patent application must have been filed, a patent granted and marketing approval obtained in another Member for the product in question.

The net effect of these arrangements is that, in countries that do not currently grant product protection for pharmaceuticals, pharmaceutical inventions that meet the normal criteria for protection as of the date of entry into force of the Agreement for that country (normally 1 January 1995) must generally be protected, at least by the time that protection becomes of commercial significance. These transitional arrangements do not provide for pipeline protection, in the sense that there is no obligation for such countries to provide protection in respect of pharmaceutical inventions no longer meeting the normal criteria for protection on the date of entry into force, even if they have not yet been approved for marketing.

The TRIPS Agreement also regulates another transition issue, namely the extent to which patents still valid as of the end of a Member's transition period will benefit from the standards under the Agreement. The basic rule is that the obligations in the Agreement will apply to such patents. For example, an existing patent must benefit from the minimum term of 20 years from filing, even if it was originally granted for a shorter period. There is, however, an exception in situations where an act was commenced or in respect of which a significant investment was made before the date of acceptance of the WTO Agreement by a Member. If such an act becomes infringing as a result of the application of the rules of the Agreement, the Member State concerned may limit remedies available to the right holder to the payment of equitable remuneration. There is also a provision which states that the rules on compulsory licensing and government use need not be applied to authorizations granted before the date that the Agreement became known. In respect of patent applications pending at the end of the transition period, the applicant must be allowed to amend the application to claim any enhanced protection available under the provisions

of the Agreement, provided such amendments do not include new matter.

Dispute settlement

One of the major innovations of the TRIPS Agreement is that treaty obligations in the area of intellectual property will be subject for the first time to a functioning dispute settlement system. Under the World Trade Organization, an integrated dispute settlement system will apply to disputes in all of the areas covered. This system is a strengthened version of the existing GATT mechanism. The major element of strengthening has been the elimination of the means by which it has been possible for losing parties to be able to delay or block the dispute settlement process. As under the existing GATT system, any country which fails to bring itself into compliance with the findings adopted under the system will run the risk of the aggrieved country being authorized to retaliate, i.e. to withdraw obligations or concessions made to the offending country. Such retaliation can take place not only in the area that is the subject of the dispute but also, subject to certain conditions, in other areas covered by the WTO. Thus a country failing to live up to its TRIPS obligations would expose itself to the risk of losing market access rights. The issue of retaliation is important because it makes clear that in joining the WTO a country accepts international liability for meeting its obligations. However, it is also important to appreciate that retaliation has only once been authorized in the context of dispute settlement under the GATT and is more of a threat that gives credibility to the system than anything else.

Another important feature of the dispute settlement rules is that they contain commitments regarding the use of unilateral methods of dealing with disputes. WTO Members seeking redress of a violation of TRIPS or other WTO obligations commit themselves to have recourse to, and abide by, the multilateral WTO dispute settlement procedures. In such cases, they undertake not to make a determination that a violation has occurred except in accordance with these procedures and only to make such determinations consistent with the findings resulting from them. Moreover, they specifically commit themselves not to retaliate except in accordance with authorization from the WTO.

Regulatory Matters

Proposed withdrawal of terfenadine

United States of America — The Food and Drug Administration has announced its intention to withdraw approval of terfenadine (1), a non-sedating antihistamine that is also marketed in generic versions and in combination with pseudoephedrine, and is available on prescription only.

The Agency has determined that terfenadine is no longer the safest product available. Fexofenadine, an active metabolite of terfenadine, is now marketed and provides an alternative with essentially similar therapeutic advantages, but lacking the cardiotoxic risks.

Cases of potentially fatal cardiac arrhythmias, such as torsades de pointes or ventricular arrhythmias, have been reported in association with increased terfenadine levels in plasma, leading to prolongation of the QT interval (2). As a consequence, terfenadine is contraindicated in cases of hepatic dysfunction and when used concomitantly with drugs such as oral ketoconazole, itraconazole, erythromycin, clarithromycin, or troleandomycin. The product is not recommended for use with oral imidazole, antifungals, macrolide antibiotics, potential arrhythmogenic drugs such as neuroleptics and tricyclic antidepressants, or drugs which could produce an electrolyte imbalance (3).

The Food and Drug Administration advises patients currently taking terfenadine products to seek advice from their physicians concerning a change to alternative medication.

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France — In line with an opinion delivered by the National Pharmacovigilance Commission, the Medicines Agency has decided to suspend the product licence for terfenadine.

In 1992, a preliminary inquiry concerning the risk of rare but serious ventricular rhythm disorders led to a modification of the product information. Recent reappraisal has confirmed the continued risk of serious effects in spite an information campaign aimed at correct use of the medication. It is consequently considered that the benefit/risk ratio is no longer positive. The Medicines Agency has therefore suspended the product licence in France and has initiated a procedure at the European Community level for reappraisal of terfenadine. This should lead to a definitive and common position being taken by all European Union members.

Reference: Agence du Médicament. Press release, 13 February 1997.

European Union — The Committee for Proprietary Medicinal Products (CPMP) has stated that a procedure under Article 12 of Council Directive 75/319/EEC as amended, has been initiated by France. This procedure relates to terfenadine-containing medicinal products, the marketing of which has been suspended by France and Luxembourg.

Reference: *Press Release*, CPMP/182/97, February 1997.

Japan — The Ministry of Health & Welfare has advised WHO that terfenadine, which has been marketed in Japan since 1990, is contraindicated in patients with significant hepatic dysfunction or in concomitant administration with itraconazole, miconazole, or erythromycin. A boxed warning of a possible risk of QT prolongation and/or ventricular arrhythmias including torsades de pointes has been required since 1995.

Recent adverse reaction cases involving terfenadine have now been analysed by the Central Pharmaceutical Affairs Council, which has recommended that additional precautions should be included as part of the package insert stating that the product should not be administered to patients undergoing dialysis, or concomitantly with clarithromycin, antiarrhythmic drugs except beta-adrenoreceptor antagonists, diuretics, psychotropics or probucol, and in patients with cardiac failure, myocardial infarction or bradycardia.

The manufacturer has been requested to circulate a dear doctor letter highlighting the cardiotoxicity concerns.

Reference: Letter to WHO dated 13 February 1997 from Ministry of Health & Welfare, Japan.

Restrictions on use of sotalol

United Kingdom — The Medicines Control Agency (MCA) has re-evaluated the therapeutic indications for sotalol following publication of findings from the SWORD (the Survival With Oral *d*-Sotalol) study (1). The study was set up to evaluate the survival of patients with left ventricular dysfunction after myocardial infarction treated with *d*-sotalol and was discontinued for ethical and clinical reasons when mortality soon proved to be significantly higher in the treated group than in the placebo group (1).

Sotalol, a non-selective beta-adrenoreceptor antagonist, is known to have a dose-dependent arrhythmogenic effect. It prolongs the QT interval, which predisposes to the development of torsades de pointes (2). Worldwide, sotalol has been associated with 123 spontaneous reports of this complication.

In considering the available information, the MCA has decided (2) that the use of sotalol should be limited to either the treatment of ventricular arrhythmias or prophylaxis of supraventricular tachyarrhythmia. It should no longer be used for angina pectoris, hypertension, thyrotoxicosis or for secondary prevention after myocardial infarction.

References

1. Waldo, A.L., Camm, A.J., de Ruyter, H. et al. Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet*, **348**: 7–12 (1996).
2. Committee on Safety of Medicines/Medicines Control Agency. *Current Problems in Pharmacovigilance*, Volume 22, July 1996.

Fluoroquinolones and tendon rupture

United States of America — The Food and Drug Administration has requested manufacturers of products containing ciprofloxacin, enoxacin, lomefloxacin, norfloxacin or ofloxacin to revise the product information and package inserts to include the following warning: "Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair have been reported with these drugs".

Treatment should be discontinued if the patient experiences pain, inflammation or rupture of a tendon. The patient should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur at any time during or after therapy with these fluoroquinolone derivatives.

Reference: *FDA Medical Bulletin*, Volume 26, October 1996.

Fatal adverse drug reaction trends

United Kingdom — A total of 476 reports of fatal suspected adverse reactions were reported to the Committee on Safety of Medicines during 1995. 408 reactions were reported in 1994 and 471 in 1993. These figures relate to reports from health professionals using the voluntary adverse drug reaction reporting scheme.

Those drug substances most frequently associated with fatal reactions during 1995 were clozapine (34 cases), diclofenac (22), ethinylestradiol (21), fluoxetine (15), sertraline (12), paroxetine (12) amiodarone (10), nicorandil (9) and ibuprofen (9). Clozapine and diclofenac were also the top two drugs in the list for 1994.

Reference: *The Pharmaceutical Journal*, **257**: 145 (1996).

Aspartame: no apparent link with brain tumours

United States of America — The Food and Drug Administration has published a statement on the safety of the artificial sweetener, aspartame. A recently published medical journal article has again raised the possibility of a link with the incidence of brain tumours in the United States since 1981, when the FDA approved aspartame as a food additive.

A recent analysis of the public data base on cancer incidence in the United States (the SEER Program at the National Cancer Institute) did not support an association. Data showed an increase in overall incidence of brain tumours since 1973, which continued up to 1985. However, since 1985 the trend line has flattened and in 1991 to 1993 the incidence decreased slightly.

The FDA states that for the moment it upholds its original approval decision on aspartame, but remains ready to act on any credible scientific

evidence — as it would in the case of any product which it has approved.

Reference: *FDA Talk Paper*, T 96-74, November 1996.

Anthranoïds, herbal medicines and carcinogenic potential

Germany — The Federal Institute for Drugs and Medical Devices has restricted the indications and revised the contraindications of all medicinal products containing anthranoids (hydroxyanthracene derivatives) found in the plants *Andira*, *Cassia*, *Rhamnus*, *Rheum* and *Aloe* because experimental studies have shown evidence of potential genotoxicity and carcinogenicity.

Reference: Notification from the Federal Institute for Drugs and Medical Devices, Berlin, enclosing a press release of 31 July 1996.

Adrenal cortex extract associated with infections

United States of America — The Food and Drug Administration has announced a nationwide alert on injectable adrenal cortex extracts that have caused serious bacterial infections at the site of injection. Apparently these products may have been prepared from the adrenal glands of cattle, sheep or swine under conditions that could lead to contamination. The Food and Drug Administration has not approved adrenal cortex extract and is investigating how this product came to be manufactured and distributed. The Agency has also taken steps to remove the product promptly from the market.

Reference: *HHS News*, P96-13, August 1996.

Herbal medicines adulterated with antirheumatics

Singapore — Four Chinese herbal medicines have been found to be adulterated with diclofenac — a nonsteroidal anti-inflammatory drug. The products involved were Ba Bace Fen Ski, Huo Luo Dan and She Xiang Zhui Feng Ton Ou Wan, 101 Wei Yao Lin (Mei Hua brand) and Zhen Zhu Tong Ling (Fei Yien brand).

Reference: Communication from the Institute of Science and Forensic Medicine, Singapore, dated 18 July 1996.

Herbal hay-fever remedy and conventional drugs

A remedy for hay fever under the name of "podi" which was purchased from a street stall in New Delhi, India was analysed and found to contain tablets of chlordiazepoxide, a benzodiazepine, 5 mg, together with a packet of powder containing maize flour mixed with theophylline 30 mg, clorpheniramine 4 mg, and possibly prednisolone 0.5 mg, per dose.

Reference: *The Pharmaceutical Journal*, **258**: 105–106 (1997).

Withdrawal of blood products

United States of America — Centeon, the manufacturer of human albumin (Albuminar) and plasma protein fraction (Plasma Plex) has voluntarily withdrawn these two products as a precautionary measure because of possible contamination with bacterial agents.

Reference: *FDA Talk Paper*, T 96-69, October 1996.

Benzodiazepines, drug dependence and rebound effects

South Africa — The Medicines Control Council has stated that package inserts of benzodiazepines and benzodiazepine-like drugs should be revised to emphasize the risk of drug dependence during prolonged use and at high doses, and in particular when prescribed for patients with a history of alcohol or drug abuse.

The new information must state that a transient syndrome with symptoms similar to those that occur at the outset of drug treatment can occur on withdrawal. Mood changes, anxiety and restlessness may accompany the reaction and the risk of rebound effects is greater if treatment is discontinued abruptly. The duration of treatment should be minimized and should not exceed 4 weeks for insomnia, and 8–12 weeks for anxiety disorders.

Reference: Communication from the Medicines Control Council, Pretoria, 31 July 1996.

Carteolol and bronchial asthma

Japan — As in the case of other beta-adreno-receptor antagonists, carteolol-containing eye drops

have been reported to exacerbate bronchial asthma in patients with a history of this condition.

Reference: *Information on Adverse Reactions to Drugs*, Number 135, 1996.

Mucocutaneous reactions and carbamazepine

Malaysia — The Adverse Drug Reaction Advisory Committee has received 103 reports, between 1988 and 1996, associated with the use of carbamazepine. In 96 of the reports, carbamazepine was identified as the sole suspected drug.

Mucocutaneous reactions were the most commonly reported findings ranging from maculopapular rash (25 cases) to more serious and potentially life-threatening reactions such as Stevens Johnson syndrome (48) and toxic epidermal necrolysis (2). Other reactions included exfoliative dermatitis (3), erythema multiforme (2), fixed eruption (2), bullous eruptions (2), angio-oedema (3), oral lesions (5), and ocular lesions (2).

Reference: *Barita Ubat-Ubatan*, Volume 10, 1996.

Mebendazole deregulated to over-the-counter (OTC) status

Norway — The anthelmintic, mebendazole, in either mixture or tablet form is now available without prescription for treatment of various types of intestinal worm infestations in adults and children. None the less, instruction or counselling by a physician is still required for treatment during pregnancy or for use in children under two years of age.

Reference: *Nytt on legemidler*, Number 4, 1996.

Donepezil: new treatment for Alzheimer disease

United States of America — The Food and Drug Administration has approved donepezil for the treatment of mild to moderate symptoms of Alzheimer disease.

Alzheimer disease is estimated to affect over four million Americans and is a progressive condition affecting memory, judgement and the ability to reason. Donepezil is a cholinesterase inhibitor that

increases levels of acetylcholine, a neurotransmitter important in cognitive functions. Although the drug has not been shown to have an effect on the underlying cause of the disease, it may moderate some of the symptoms.

Clinical trials reported side effects such as diarrhoea, syncope and nausea. The labelling also warns that the drug has the potential to cause bradycardia (arrhythmias), especially in patients with underlying cardiac conduction conditions.

Following approval of tacrine in 1993, donepezil is only the second drug available to treat the symptoms of this disease.

Reference: *FDA Talk Paper*, T96-78, November 1996.

Whole-oat foods and heart disease

United States of America — The Food and Drug Administration will allow health claims on packaging of foods containing soluble fibre from whole oats (rolled oats, oat bran and oatflour) stating that when used as part of a diet low in saturated fat and cholesterol, these foods may reduce the risk of heart disease.

The Agency has concluded that the betaglucan soluble fibre of whole oats is the primary component responsible for the total and LDL blood cholesterol-lowering effects of diets that contain these foods.

Reference: *FDA Talk Paper*, T97-5, 1997.

Nifedipine: restricted use

Ireland — Recent studies suggest that there is an increased risk of cardiovascular events and mortality in patients treated with the short-acting calcium channel blocker, nifedipine, for unstable angina pectoris or following myocardial infarction (1-3).

Following a review and evaluation of data, the Irish Board of Medicines has recommended that use of nifedipine in ischaemic heart disease should be restricted to the prophylaxis of stable angina and is contraindicated in patients with unstable angina (4).

Prescribers are reminded that treatment of hypertension with short-acting nifedipine may induce an abrupt fall in blood pressure as well as tachycardia.

References

1. Furberg, C.D. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation*, **92**: 1326–1331 (1995).
2. Psaty, B.M. The risk of myocardial infarction associated with antihypertensive drug therapies. *Journal of the American Medical Association*, **275**: 620–625 (1995).
3. Nifedipine: danger of short-acting formulations. *WHO Drug Information*, **9**: 220–221 (1995).
4. Irish Medicines Board. *Drug Safety*. Number 2, May 1996.

Emergence of multidrug-resistant salmonella

WHO has issued a statement on the increasing resistance of *Salmonellosis typhimurium* to a range of antibiotics that threatens to become a serious public health problem. Resistance is expected to continue to rise at a similar or even greater rate in the future as antimicrobial agents lose their effectiveness.

Multidrug-resistant *Salmonella typhimurium* DT 104 initially emerged in cattle in 1988 in England and Wales. Subsequently, the strain has been isolated from poultry, sheep, pigs and horses. Antimicrobial therapy is used extensively to combat salmonella infection in animals. The evolution of a strain resistant to the commonly used antibiotics has made infection with *S. typhimurium* in food animals difficult to control and it will likely remain an animal health problem for quite some time.

The primary route by which humans acquire infection is by consumption of contaminated food of animal origin. Unlike *S. enteritidis*, which is mainly associated with poultry and eggs, multidrug-resistant *S. typhimurium* DT 104 can be found in a broad range of foodstuffs such as poultry, meat and meat products, and unpasteurized milk. Human cases have also occurred where individuals have been in contact with infected cattle or pets.

An increase in the overall number and percentage of multidrug-resistant *S. typhimurium* DT 104 cases has been reported from several European countries. In England and Wales, a tenfold increase in the number of human cases of multidrug-resistant *S. typhimurium* DT 104 has been reported during a six-year period from 1990 to 1996 rising from 300 to 3500 cases per year. Resistance

has developed to some of the most common antibiotics such as ampicillin, chloramphenicol, streptomycin, the sulfonamides and tetracycline. Since 1994, an increasing number of isolates with additional resistance to trimethoprim and a few with additional resistance to ciprofloxacin, have also been reported. Moreover, infection with multidrug-resistant *S. typhimurium* DT 104 has been associated with hospitalization rates which are twice that of other zoonotic foodborne salmonella infections, with ten times higher case-fatality rates.

In Germany, *S. typhimurium* DT 104 accounted for up to 10% of almost 10 000 salmonella samples from human sources examined in 1995; and 18% of those examined in 1996. Almost all DT 104 isolates were multidrug-resistant, with the same resistance pattern as in England and Wales — although resistance to ciprofloxacin has not yet been observed in Germany. DT 104 was recently detected in the United States but little is currently known concerning its prevalence and means of transmission. A rise in salmonellosis incidence has been reported in all countries in Europe and in a number of countries in the Eastern Mediterranean and South-east Asia.

WHO's statement concludes that existing knowledge and technology cannot provide consumers with pathogen-free raw meat and poultry, and it is very unlikely that the eradication of salmonellae in domestic animals is possible in the foreseeable future. The increased occurrence of drug-resistant pathogens in food of animal origin emphasizes the need to cook foods thoroughly prior to consumption. Education of food-handlers in the principles of safe food-handling is an essential step towards reducing the incidence of foodborne disease resulting from cross-contamination during processing and preparation of foods. Education of farmers and their families regarding the risks of occupationally acquired infections is also an important step in the control of human infection from *S. typhimurium* DT 104. Finally, the avoidance of unnecessary antibiotic use in food animals is vital.

Reference: *WHO Fact Sheet*, Number 139, 1997.

Tolrestat: hepatic necrosis

Argentina — Tolrestat is a new aldose-reductase inhibitor indicated in the treatment of serious complications of diabetes such as neuropathy, retinopathy and nephropathy.

In March 1995, the National Pharmacovigilance System received notification of the death of a 41-year-old woman patient from hepatic necrosis following treatment with tolrestat. The patient died 80 days after treatment was started and 30 days after the drug was withdrawn because of abdominal pain and jaundice.

In October 1996, the manufacturer of tolrestat (John Wyeth Laboratory) withdrew the product from the market worldwide following reports of two other deaths from hepatic necrosis and poor efficacy in clinical trials.

Reference: Communication to WHO from the Administración Nacional de Medicamentos, Alimentos y Tecnología (ANMAT), Buenos Aires, 5 November 1996.

Somatropin for wasting syndrome in AIDS

United States of America — The Food and Drug Administration has approved somatropin for treatment of AIDS-wasting syndrome in HIV-infected patients to increase lean body mass. This illness is a metabolic disorder characterized by weight loss and leads to muscle weakness and organ failure, contributing to a fatal outcome.

Reference: *FDA Talk Paper*, T96-59, August 1996.

Ivermectin approved for human use

United States of America — The Food and Drug Administration has approved ivermectin for treatment of two human parasitic infections: strongyloidiasis and onchocerciasis.

Strongyloidiasis is an infection usually confined to the small intestine. The disease is common in many tropical countries and, among Americans, it is usually a disease of immigrants, travellers, and former prisoners of war — but it can occasionally be acquired in some areas of the United States. If the immune system is normal, the infection remains in the intestine, often for years, causing abdominal pain, diarrhoea and blood eosinophilia. The infection can spread throughout the body and is fatal if the person has a weakened immune system. In controlled clinical trials a single dose of ivermectin has cured between 64 and 100% of patients infected with intestinal strongyloidiasis, when the immune system was normal.

Onchocerciasis, also known as river blindness, is prevalent in many countries of Africa as well as South and Central America. The parasites can migrate to the eyes, causing inflammation and blindness. In onchocerciasis, a single dose of ivermectin reduced the number of larvae in the skin by 83% at three days and 99.5 % at three months following drug intake.

Reference: *FDA Talk Paper*, T96-77, November 1996.

Naproxen available over-the-counter (OTC)

Norway — The nonsteroidal anti-inflammatory drug, naproxen, has been deregulated to non-prescription status and is available in tablet form in packages containing a maximum of 20 tablets of 250 mg each. The product is indicated for primary dysmenorrhoea or dysmenorrhoea associated with use of an IUD.

Reference: *Nytt on legemidler*, Number 3, 1996.

Influenza virus vaccines for 1997–1998

World Health Organization — The recommended composition of influenza virus vaccines for use in the 1997–1998 season has been announced as the following:

Trivalent vaccines are recommended, with the following composition:

- an A/Wuhan/359/95(H3N2)-like strain*
- an A/Bayern/7/95(H1N1)-like strain
- a B/Beijing/184/93-like strain.**

* The most widely used vaccine strain is A/Nanchang/933/95.

** The most widely used vaccine strain is B/Harbin/7/94.

Reference: *Weekly Epidemiological Record*, 28 February 1997.

Essential Drugs

WHO Model Formulary

Since publication of the first *Model List of Essential Drugs* in 1977, WHO has made a significant contribution to rationalizing the use of drugs. The List has now been revised eight times and still includes fewer than 300 drugs which are considered sufficient to satisfy the basic health needs of the majority of the population in most countries.

Needless to say, a list alone is not sufficient to ensure good prescribing practice, and doctors and health care workers are in need of information on how to use these drugs. Access to independent and accurate information varies widely from one country to another, and few countries have developed sources of independent information which are fully consistent with their needs.

Members of the WHO Expert Committee on the Use of Essential Drugs are aware of this situation and, at the last meeting in December 1995, discussed possible options available to further improve the rational use of drugs. As a consequence, it was recommended that a *WHO Model Formulary* should be developed to complement the *Model List of Essential Drugs*. The purpose of such a formulary would be to provide general information, complemented by information on the prototype drug as it appears in the List. Countries could then adapt this information according to their own needs — thereby providing a key element in the implementation of rational drug use.

This work is now in hand and draft texts of the *WHO Model Formulary* will be published regularly in *WHO Drug Information* with a view to obtaining a response to the draft material proposed for publication. Comments on the following section related to anticonvulsants/antiepileptics should be addressed to: Drug Selection and Information (DSI), Division of Drug Management & Policies, World Health Organization, 1211 Geneva 27, Switzerland.

Anticonvulsants/antiepileptics

Treatment should always be started with a single drug, but the choice of an anticonvulsant can only

be made on an individual basis and will depend on the efficacy of the drug and the patient's tolerance of treatment. If one drug fails to control the seizures after it has been used in full therapeutic dosage for an adequate period, or if it is not well tolerated, it should be gradually substituted with another. If monotherapy is ineffective, two drugs should be given in combination and several regimens may need to be tried before the most appropriate is determined.

Dosage should be increased gradually until an effective response is obtained. Where the necessary laboratory facilities exist, it can be useful to measure plasma concentrations as an aid to dose adjustment or to determine whether the patient is complying with treatment. Patients should ideally remain under supervision throughout treatment.

Withdrawal

Treatment is normally continued for a minimum of two years after the last seizure. Withdrawal should be extended over a period of several months since abrupt withdrawal can lead to complications such as status epilepticus. Abrupt discontinuation is therefore never warranted. Many adult patients relapse once treatment is withdrawn and it may be justified to continue treatment indefinitely, particularly when the patient's livelihood can be endangered by recurrence of a seizure.

Pregnancy and lactation

There is an increased risk of birth defects with the use of anticonvulsants, particularly carbamazepine, valproic acid and phenytoin. In view of the risks of neural tube and other defects, patients who may become pregnant should be informed of the risks and referred for advice, and pregnant patients should be offered counselling and antenatal screening. To counteract the risk of neural tube defects, adequate folate supplements are advised for women before and during pregnancy. In view of the risk of neonatal bleeding associated with carbamazepine, phenobarbital and phenytoin, prophylactic vitamin K₁ (INN = phytomenadione) is recommended for the neonate and the mother before delivery. Antiepileptic drugs can be used safely during lactation, with the possible exception of phenobarbital and ethosuximide.

Generalized tonic-clonic, simple partial and complex partial seizures

Phenobarbital, phenytoin, carbamazepine and valproic acid are widely used in the treatment of these conditions. However, each of these drugs is associated with dose-related and idiosyncratic adverse effects and monitoring of haematological, hepatic and renal function is advised.

Absence seizures

Both ethosuximide and valproic acid are widely used in the treatment of absence seizures and are usually well accepted. However, ethosuximide can, rarely, cause lupus erythematosus and psychoses which call for immediate, but cautious, discontinuation. Absence seizures are commonly associated with tonic-clonic seizures and valproic acid is preferred since it is effective in both disorders.

Tonic, atonic and atypical absence seizures

Phenobarbital or phenytoin is widely used for tonic seizures, valproic acid or clonazepam for atonic seizures, and clonazepam for atypical absence seizures.

Myoclonic seizures

Valproic acid is widely used for juvenile myoclonic seizures. Although this drug is the most effective, it is associated with a high relapse rate and it is often necessary to continue therapy indefinitely. Other myoclonic seizures are often resistant to treatment and some do not have an epileptic basis. Valproic acid or clonazepam can be of value in this case and other antiepileptic drugs may be useful in intractable cases. Both drugs are generally well accepted, although tolerance to clonazepam has been reported.

Infantile spasm (infantile myoclonic epilepsy)

Infantile spasms, which are often associated with severe brain damage, can be resistant to anti-epileptic drugs. However, they may be responsive to intramuscular adrenocorticotrophic hormone (ACTH) which holds advantage over corticosteroids. Clonazepam is sometimes of value in resistant cases.

Febrile convulsions

Febrile convulsions usually respond to sponging with tepid water and antipyretics such as paracetamol. Rectal diazepam is needed for severe attacks. Prolonged treatment is advisable when repeated seizures occur during the first 18 months of life or when the child has evident neurological abnormalities. Phenobarbital is used for this purpose but

careful clinical monitoring and dosage adjustment are necessary to minimize the risk of adverse effects. Valproic acid, although also effective, is not recommended because of the greater risk of hepatotoxicity in this age group. Alternatively, intermittent prophylaxis with rectal diazepam during febrile episodes can also be effective.

Status epilepticus

Status epilepticus is a medical emergency which carries a high mortality rate. Maintenance of the airway and assisted ventilation are crucial even when the seizures are controlled, since the drugs used in its management may also depress respiration. Unresponsive patients require intensive care. Intravenous diazepam or clonazepam is often effective. Diazepam, which is rapid-acting, can be administered first and should be followed immediately by phenytoin which has a longer-acting effect. When cannulation is impossible, diazepam may be administered rectally. Intravenous phenobarbital is also effective and is preferred when status epilepticus occurs during withdrawal of oral phenobarbital. If seizures continue despite treatment, general anaesthesia may be required. The underlying cause must be identified and remedied in all cases.

CARBAMAZEPINE

Anticonvulsant agent

Scored tablets: 100 mg, 200 mg

Uses: Generalized tonic-clonic, simple partial and complex partial seizures.

Dosage: *Adults:* Initially 100 mg twice daily, or 50 mg twice daily in frail or elderly patients. This is increased gradually according to response, to a maximum of 2 g daily in divided dosage. Exceptionally, even higher doses have been used.

Children: Daily maintenance doses usually lie between 10 and 20 mg/kg. Twice daily dosage is often adequate but six or eight-hourly administration is advisable at higher dosages to avoid large fluctuations in plasma concentrations. Therapeutic plasma concentrations are in the region of 4–12 mg/ml (17–50 micromol/l). Lower blood levels are attained when carbamazepine is used with phenytoin or phenobarbital as a result of increased rates of inactivation of the liver.

Contraindications: Known hypersensitivity to carbamazepine or tricyclic antidepressants; atrio-ventricular conduction abnormalities, concomitant use with monoamine oxidase (MAO) inhibitors or within two weeks of using the latter.

Precautions: See notes on page 23 for precautions concerning pregnancy. The white blood cell count should be monitored during the first month. Patients should be asked to report sore throat or fever to the physician since this may be indicative of bone-marrow depression and may mean that medication should be changed.

Adverse effects: Dose-related reactions include gastrointestinal intolerance, dryness of the mouth, drowsiness, dizziness, blurred vision, diplopia and ataxia. Frequently, cutaneous eruptions and, rarely, more serious skin conditions such as Stevens-Johnson syndrome occur. Severe idiosyncratic reaction usually presents with dermatitis, in which case hospitalize the patient immediately. Rarely, bone-marrow depression or hepatic dysfunction is reported.

Drug interactions: Plasma concentrations of clonazepam, ethosuximide, phenytoin and valproic acid may be lowered. Other important interactions will appear in tabulated form in the appendix of the published edition of the model formulary.

CLONAZEPAM

Anticonvulsant agent.

Scored tablets: 0.5 mg

Uses: Atonic and myoclonic seizures, atypical absence seizures, absence seizures resistant to ethosuximide or valproic acid; infantile spasms.

Dosage:

Adults: Initially 1 mg at night for 4 days or 0.5 mg in frail or elderly patients. The dosage is increased gradually over 2–4 weeks to 4–8 mg daily in divided doses depending on the patient's response.

Children under 1 year: 0.25 mg initially, and up to 0.5–1 mg daily. *Children 1–5 years:* 0.25 mg initially and up to 1–3 mg daily. *Children 5–12 years:* 0.5 mg initially and up to 3 mg daily.

Contraindications: Known hypersensitivity to benzodiazepines.

Precautions: Use with caution in patients with renal or hepatic impairment. Avoid alcohol. Do not operate machinery. Avoid abrupt withdrawal because of status epilepticus.

Adverse effects: Frequently drowsiness, lethargy, ataxia and, less frequently, aggression, irritability and mental changes are reported. Rarely, blood disorders and abnormal hepatic function tests or excessive salivation may occur.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the model formulary.

DIAZEPAM

Anticonvulsant agent

Injection: 5 mg/ml in 2-ml ampoule (intravenous or rectal)

Uses: Status epilepticus, emergency management of recurrent seizures including febrile convulsions, seizures associated with poisoning and drug withdrawal, symptomatic treatment of alcohol withdrawal.

Dosage:

Status epilepticus

Adults: Initially 10–20 mg (0.15–0.3 mg/kg) by slow intravenous injection at a rate of 5 mg per minute. This can be repeated, if necessary to a maximum of 50 mg over a 60-minute period. In resistant cases, a slow IV infusion of up to 3 mg/kg over a 24-hour period may be necessary provided that facilities for assisted ventilation in the event of hypotension and dysrhythmia are immediately available.

Children: 0.2–0.3 mg/kg by slow intravenous infusion or, as necessary, to a maximum of 5 mg a day in children less than 3 years and 10 mg a day in children over 3 years.

Diazepam may alternatively be administered rectally at a dosage of 0.2–0.4 mg/kg, up to a maximum of 10 mg a day, using a cannula or catheter fitted to the syringe.

Emergency treatment of rapidly recurrent (or closely spaced) seizures.

Adults: 10–20 mg (0.15–0.3 mg/kg) by slow intravenous injection or rectally.

Children: (1–3 years) and *elderly patients:* 0.2–0.3 mg/kg by slow intravenous injection or rectally.

Febrile convulsions

0.5 mg/kg administered rectally. This may be repeated, if necessary, after 30 minutes up to a maximum of 10 mg a day.

Seizures associated with poisoning, drug and alcohol withdrawal.

10 mg IV repeated, if necessary, after 4 hours.

Contraindications, precautions and adverse effects will appear in the section on psychotherapeutic drugs of the published edition of the model formulary.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the model formulary.

ETHOSUXIMIDE

Anticonvulsant agent

Capsule: 250 mg

Syrup: 250 mg/5 ml

Uses: Generalized absence seizures

Dosage: The optimum plasma concentration lies between 50 and 100 mg/ml (350 and 700 micro-mol/l). Inadequate dosage is the major cause of therapeutic failure.

Adults and children over 6 years: Initially, 500 mg daily, subsequently adjusted according to response. Increments should be made in steps of 250 mg every 4 to 7 days to a maximum of 2 g daily, or until an adequate response is obtained. The daily maintenance dose is usually within the range 20–30 mg/kg. Amounts of 1g or more should be taken in 2 or more divided doses.

Children under six years: Infants and young children metabolize ethosuximide more rapidly than adults. They therefore require relatively higher and more frequent dosage: initially, 10 mg/kg daily adjusted as above according to requirements to a maximum of 40 mg/kg daily.

Contraindications: Hypersensitivity to ethosuximide, mesuximide or phensuximide.

Precautions: Monitor plasma concentrations in patients with impaired hepatic or renal function. See notes on page 23 for precautions concerning pregnancy.

Adverse effects: Gastrointestinal disturbances include anorexia, hiccoughs, nausea and vomiting, epigastric pain (particularly during the initial phases of treatment); weight loss, drowsiness, dizziness, ataxia, headache, depression and mild euphoria may be troublesome. Rarely, psychotic states, rashes including erythema multiforme and the more serious Stevens Johnson syndrome, lupus erythematosus, disturbances of liver function and haematological disorders, including leukopenia, agranulocytosis and bone-marrow depression have been reported.

Drug interactions: Plasma concentrations of phenytoin may be raised. Other interactions will appear in tabulated form in the appendix of the published edition of the model formulary.

PHENOBARBITAL

Anticonvulsant agent

Injection: 60 mg/ml

Tablet: 15–100 mg

Elixir: 15 mg/5ml

Uses: Generalized tonic-clonic seizures, simple partial and complex partial seizures, neonatal seizures and febrile seizures, status epilepticus occurring only during withdrawal of phenobarbital, in patients unresponsive to diazepam or phenytoin.

Dosage:

All indications other than status epilepticus.

Oral dosage forms.

The optimum plasma concentration usually lies between 10 and 30 mg/ml (45 and 130 mmol/l).

Adults: Initially 2 mg/kg daily (to a maximum of 100 mg) as a single dose at night. If necessary, this may be increased incrementally, according to the response, to a maximum of 6 mg/kg daily in 2 or more divided doses.

Children: Initially 3–4 mg/kg, but in infants up to 8 mg/kg may be required in order to achieve therapeutic plasma concentrations.

Status epilepticus.

Injectable dosage forms

Adults and children: 10–20 mg/kg is infused intravenously at a rate not exceeding 30 mg per minute until an adequate response is obtained. Care should be taken that hypotension and respiratory depression do not occur. In general, children and neonates tend to require higher dosages. Intravenous therapy should be discontinued as soon as seizures are controlled.

Contraindications: Hypersensitivity to barbiturates, MAO inhibitors. Acute intermittent porphyria.

Precautions: Avoid driving or operating machinery because of sedative effects. The use of phenobarbital in children needs to be considered with regard to the possibility of behavioural changes and hyperactivity. Monitor dosage in the elderly and in patients with reduced respiratory capacity or renal insufficiency. See notes on page 23 for precautions concerning pregnancy.

Adverse effects: Dose-related reactions include sedation, nystagmus and ataxia. Impairment of learning ability and understanding, irritability, behavioural problems and hyperactivity may occur in children. Commonly, confusion in the elderly, rashes and other signs of allergy may occur.

Rarely, serious hypersensitivity reactions including exfoliative dermatitis. Occasionally, megaloblastic anaemia and osteomalacia (resulting from prolonged therapy), phenobarbital dependence, status epilepticus (on discontinuation of treatment). As a result of local extravasation, extensive necrosis and, during injection, spasm, severe pain and possibly gangrene. On rapid intravenous injection, respiratory depression or hypotension.

Drug interactions: Plasma concentrations of carbamazepine, ethosuximide, phenytoin and valproic acid may be lowered. Other interactions will appear in tabulated form in the appendix of the published edition of the model formulary.

PHENYTOIN

Anticonvulsant agent

Capsule or tablet: 25 mg, 50 mg, 100 mg (sodium salt)

Injection: 50 mg (sodium salt)/ml in 5-ml vial

Uses: Generalized tonic-clonic, simple partial and complex partial seizures; status epilepticus.

Dosage:

All indications other than status epilepticus

Oral dosage forms

Adults. Initially 4–5 mg/kg/day. This is frequently given as 100 mg two or three times daily. However, many seizures in adult patients can be adequately controlled on one daily dose. This should be increased by 25 mg daily at two-weekly intervals, according to the response, to a maximum of about 8 mg/kg daily.

Children. Initially 5 mg/kg daily administered in two divided doses and increased gradually to a maximum of 8 mg/kg.

The optimum plasma concentration usually lies between 10 and 20 mg/ml (40–80 micromol/l). Protein binding is reduced in neonates and patients with impaired renal or hepatic function and lower plasma concentrations are generally effective.

Status epilepticus:

Injectable dosage forms:

Administration of phenytoin is normally preceded by an initial IV injection of diazepam.

Adults. 15–18 mg/kg as a loading dose by IV injection at a rate not exceeding 50 mg per minute. An additional 5 mg/kg may be given after 12 hours if necessary.

Children. 10–15 mg/kg by IV injection at a rate of 0.5–1.5 mg/kg per minute. In refractory cases, use

of IV barbiturates, rectal paraldehyde or general anaesthesia should be considered.

Contraindications: Hypersensitivity to hydantoin. Avoid parenteral phenytoin in patients with sinus bradycardia, sino-atrial block, or second or third degree atrioventricular block.

Precautions: Diplopia and ataxia are indications for lowering dosage. Withdraw or reduce dosage at a rate not greater than 25 mg in any 7-day period. Preferably, a plan should be adopted to phase out dosage over a 6-month period. See notes on page 23 for precautions concerning pregnancy.

Adverse effects: Gastric intolerance, sleeplessness and agitation are sometimes troublesome (during the initial phases of treatment), dose-related functional neurological disturbances including sedation, confusion, blurred vision, ataxia, nystagmus, diplopia, vertigo, cerebellar-vestibular symptoms, behavioural disturbances and hallucinations, non-dose-related adverse effects include mucocutaneous changes (gingival hyperplasia, skin eruptions, coarse facies, hirsutism), neurological changes (peripheral neuropathy, choreiform movements, impaired learning and understanding), osteomalacia and occasionally rickets associated with reduced plasma calcium levels, hyperglycaemia, megaloblastic anaemia, hypersensitivity reactions including erythema, generalized lymph-node enlargement and, very rarely, Stevens-Johnson syndrome, systemic lupus erythematosus, hepatic necrosis, nephrosis and polyarthropathy, haematological reactions including leukopenia and rarely, thrombocytopenia, agranulocytosis and bone-marrow depression; hypotension and ventricular dysrhythmias (resulting from parenteral administration).

Drug interactions: Plasma concentrations may be lowered of carbamazepine, clonazepam, ethosuximide, and valproic acid. Other interactions will appear in tabulated form in the appendix of the published edition of the model formulary.

VALPROIC ACID

Anticonvulsant agent

Enteric coated tablet: 200 mg, 500 mg (sodium salt)

Uses: Generalized absence seizures; generalized tonic-clonic, simple partial and complex partial seizures, myoclonic and atonic seizures.

Dosage:**All indications**

Adults: Initially 15 mg/kg in one or two divided doses increased, according to the response, by 200 mg daily at twice weekly intervals. Daily doses in excess of 30 mg/kg are rarely needed.

Infants and children: Initially 15 mg/kg daily in divided doses, increasing according to response. Rarely, daily doses of more than 30 mg/kg are needed in children and infants may require up to 40 mg/kg. The effective plasma concentration is in the region of 40–100 mg/ml (280–690 micromol/l). However, the correlation between therapeutic efficacy and plasma levels is poor and the latter have limited value in management, except as an indication of noncompliance or to monitor the effects of a change in dosage or the addition of another drug to the regimen.

Contraindications: Hypersensitivity to valproic acid, pre-existing impaired hepatic or pancreatic function, bleeding disorders. First trimester pregnancy.

Precautions: Increased risk of neural tube defects if given during the first trimester of pregnancy. See

notes on page 23 for other precautions concerning pregnancy. Because of the risk of hepatic failure, which can be fatal, hepatic function should be monitored and the drug withdrawn if there are signs of loss of seizure control, malaise, weakness, lethargy, facial oedema and vomiting. Withdraw the drug immediately if spontaneous bruising or bleeding indicative of thrombocytopenia occurs. Monitor the bleeding time and platelet count before surgery or anticoagulant administration.

Adverse effects: Rarely, potentially fatal hepatic failure, thrombocytopenia, pancreatitis; other adverse effects include weight gain resulting from increased appetite, partial or complete hair loss, tremor, paraesthesia, drowsiness and ataxia; commonly, sedation (when used with phenobarbital).

Drug interactions: Plasma concentrations of ethosuximide, phenobarbital and phenytoin may be raised. Other interactions will appear in tabulated form in the appendix of the published edition of the model formulary.

Recent Publications

Nordic statistics on medicines: 1993–1995

National consumption statistics have been published for the Nordic countries by the Nordic Council on Medicines (NLN) covering Denmark, Finland, Iceland, Norway and Sweden. Their purpose is to make data on drug consumption more generally available. The new publication provides comparative data between countries, and illustrates trends in drug consumption with emphasis on national differences. In order to give a perspective to the data, the statistics are compared to those of Australia, Estonia and Spain.

NLN Publication No. 43. Nordiska Läkemedelsnämnden, Nordic Council on Medicines, Uppsala, Sweden. ISBN 91-86432-42-7

Pharmacological action and therapeutic use of drugs – list of terms

Since 1989, members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated to deal with the selection of INNs have recognized that the terms describing the pharmacological action and therapeutic use of pharmaceuticals were in need of harmonization.

A review of the situation has indicated that the lack of a unique, generally accepted reference list can lead to use of various terminologies originating from different sources of information. This diversity is reflected in inconsistencies in numerous documents and information material issued such as drug monitoring reports and newsletters, and many other documents and publications related to pharmaceuticals.

A standard list of terms was therefore drawn up after a comparison had been made of terminologies used around the world. Despite the diversity of the references, it soon became evident that the vast majority of terms could be traced back to a dozen or so internationally recognized reference sources. It furthermore became apparent that nuances in meaning were usually attached to the terms used by individuals so that while concepts were largely comparable, the specific terms were no longer synonymous. As a consequence, a cumulative list of terms with an accompanying grouping by concept was felt necessary. In each conceptual group, a candidate preferred term has been selected.

The current list therefore features preferred terms, printed in bold, arranged in alphabetical order in English, French and Spanish. The corresponding equivalents are listed and any synonyms — as they appear in the literature — are set out below. Simple rules were followed to ensure maximum consistency in the selection of preferred terms. To be concise, single-word terms were chosen whenever possible. For example, the action exerted on various receptors is described as “agonist” or “antagonist”. “Inhibitor” is used to describe the action on enzymes, and “hormone inhibitor” and “enzyme inhibitor” refer to general action. Specific hormone or enzyme names should be used to describe the corresponding action. Finally, the systemic impact of a given drug is implied by its specific therapeutic use. Additional qualifications in the form of adjectives may be added, as necessary, for further accuracy.

Pharmacological action and therapeutic use of drugs — list of terms, (WHO/PHARM/97.594) can be obtained free of charge in English, French and Spanish from the Programme on International Nonproprietary Names, Division of Drug Management & Policies, WHO, 1211 Geneva 27, Switzerland.

Please note that henceforth lists of recommended International Nonproprietary Names (INNs) will appear twice yearly, in alternance with the proposed INNs. An added feature of the lists will be the inclusion of graphic formulae.



**WHO Programme on International Nonproprietary
Names (INN) for Pharmaceutical Substances
Division of Drug Management & Policies
World Health Organization
1211 Geneva 27, Switzerland
e mail: koppkubels@who.ch
Fax: +41 22 791 0746
Telephone: +41 22 7913636**

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 37

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

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES (DCI Rec): Liste 37

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9)] les dénominations ci-dessous sont 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*.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 37

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, **60**, 3 (Resolución EB15.R7); 1969, **173**, 10 (Resolución EB43.R9)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1-73) y Recomendadas (1-35) se encuentran reunidas en *Cumulative List No. 9, 1996*.

MODIFICATION

This is to inform you that WHO will henceforth publish lists of recommended INNs **twice a year**.

This new measure is intended to provide information as soon as possible on the names that have reached the status of recommended INNs.

MODIFICATION

L'OMS publiera désormais les listes des DCI recommandées **deux fois par an**.

Cette nouvelle mesure est destinée à informer les lecteurs dès que possible au sujet des dénominations ayant atteint le statut de DCI recommandée.

MODIFICACION

De ahora en adelante, la OMS publicará **dos veces por año** las listas de DCI recomendadas.

Con esta nueva medida se quiere facilitar lo antes posible la información sobre las denominaciones a las que se ha asignado la condición de DCI recomendadas.

Latin, English, French, Spanish:

Recommended INN

Chemical name or description; Molecular formula; Graphic formula

DCI Recommandée

Nom chimique ou description; Formule brute; Formule développée

DCI Recomendada

Nombre químico o descripción; Fórmula empírica; Fórmula desarrollada

agomelatinum

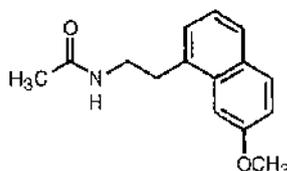
agomelatine

N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide

agomélatine

N-[2-(7-méthoxynaphtalén-1-yl)éthyl]acétamide

agomelatina

N-[2-(7-metoxi-1-naftil)etil]acetamidaC₁₅H₁₇NO₂**alatrofloxacinum**

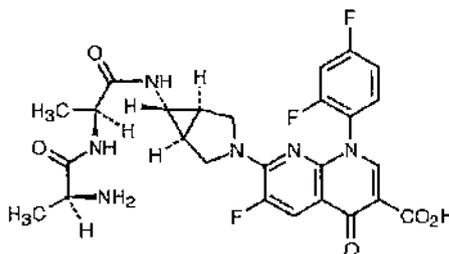
alatrofloxacin

7-[(1*R*,5*S*,6*S*)-6-[(*S*)-2-[(*S*)-2-aminopropionamido]propionamido]-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

alatrofloxacine

acide 7-[(1*R*,5*S*,6*S*)-6-[[2*S*]-2-[[2*S*]-2-aminopropanoyl]amino]propanoyl]-amino]-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophényl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphtyridine-3-carboxylique

alatrofloxacino

ácido 7-[(1*R*,5*S*,6*S*)-6-[(*S*)-2-[(*S*)-2-aminopropionamido]propionamido]-3-azabicyclo[3.1.0]hex-3-il]-1-(2,4-difluorofenil)-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridina-3-carboxílicoC₂₆H₂₅F₃N₅O₅

aripiprazolum

aripiprazole

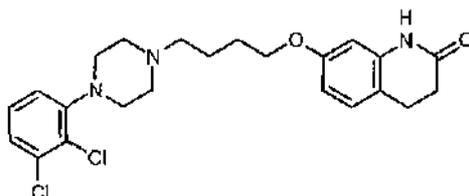
7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrl

aripiprazole

7-[4-[4-(2,3-dichlorophényl)piperazin-1-yl]butoxy]-3,4-dihydroquinoléin-2(1*H*)-one

aripiprazol

7-[4-[4-(2,3-dichlorofenil)-1-piperazinil]butoxi]-3,4-dihydrocarbostiril

 $C_{23}H_{27}Cl_2N_5O_2$ **arofyllinum**

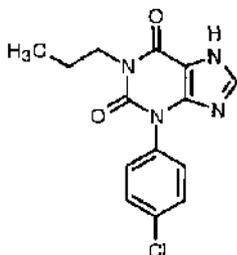
arofylline

3-(*p*-chlorophenyl)-1-propylxanthine

arofylline

3-(4-chlorophényl)-1-propyl-3,7-dihydro-1*H*-purine-2,6-dione

arofilina

3-(*p*-clorofenil)-1-propilxantina $C_{14}H_{13}ClN_4O_2$ **atiprimodum**

atiprimod

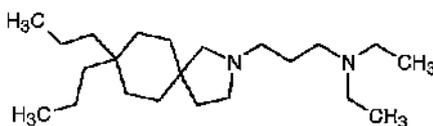
2-[3-(diethylamino)propyl]-8,8-dipropyl-2-azaspiro[4.5]decane

atiprimod

3-[8,8-di(2-propyl)-2-azaspiro[4.5]déc-2-yl]-*N,N*-diéthylpropan-1-amine

atiprimod

2-[3-(diéthilamino)propil]-8,8-di(2-propil)-2-azaspiro[4.5]decano

 $C_{22}H_{44}N_2$ 

bectumomabum

bectumomab

immunoglobulin G 2a (mouse monoclonal IMMU-LL2 Fab' fragment γ -chain anti-human antigen CD 22), disulfide with mouse monoclonal IMMU-LL2 light chain

bectumomab

immunoglobuline G 2a (chaîne γ du fragment Fab' de l'anticorps monoclonal de souris IMMU-LL2 anti-antigène CD 22 humain), disulfure avec la chaîne légère de l'anticorps monoclonal de souris IMMU-LL2

bectumomab

inmunoglobulina G 2a (cadena γ del fragmento Fab' del anticuerpo monoclonal de ratón IMMU-LL2 anti-antígeno CD 22 humano), disulfuro con la cadena ligera del anticuerpo monoclonal de ratón IMMU-LL2

beloxepinum

beloxepin

(±)-*cis*-1,3,4,13b-tetrahydro-2,10-dimethyldibenz[2.3:6,7]oxepino=[4,5-*c*]pyridin-4a(2*H*)-ol

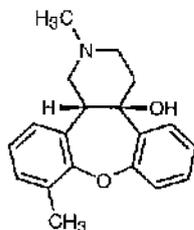
béloxépine

(4a*RS*,13b*RS*)-2,10-diméthyl-1,3,4,13b-tétrahydrodibenzo[2,3:6,7]oxépino=[4,5-*c*]pyridin-4a(2*H*)-ol

beloxepina

(±)-*cis*-1,3,4,13b-tetrahidro-2,10-dimetilidibenz[2,3:6,7]oxepino=[4,5-*c*]piridin-4a(2*H*)-ol

$C_{19}H_{21}NO_2$



and enantiomer
et l'énantiomère
y enantiómero

bemiparinum natricum

bemiparin sodium

Sodium salt of depolymerized heparin obtained by alkaline degradation of quaternary ammonium salt of heparin from pork intestinal mucosa; the majority of the components have a 2-*O*-sulfo-4-ene-pyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo- α -glucosamine structure at the reducing end of their chain; the average relative molecular mass is about 3600 (3000 to 4200); the degree of sulfatation is about 2 per disaccharidic unit.

bémparine sodique

Sel de sodium d'héparine dépolymérisée obtenue par fragmentation alcaline d'un sel d'ammonium quaternaire d'héparine de muqueuse intestinale de porc. La majorité des composants présentent une structure acide 2-*O*-sulfo-4-ène-pyranosurionique à l'extrémité non réductrice et une structure 2-*N*,6-*O*-disulfo- α -glucosamine à l'extrémité réductrice de leur chaîne. La masse moléculaire relative moyenne est voisine de 3600 (3000 à 4200). Le degré de sulfatation est voisin de 2 par unité disaccharide.

bemiparina sódica

Sal de sodio de heparina despolimerizada obtenida por fragmentación alcalina de una sal de amonio cuaternario de heparina de mucosa intestinal de cerdo. La mayoría de los componentes presentan una estructura ácido 2-*O*-sulfo-4-enopiranosurónico en el extremo no reductor y una estructura 2-*N*,6-*O*-disulfo- α -glucosamina en el extremo reductor de su cadena. La masa molecular relativa media es aproximadamente 3600 (de 3000 a 4200). El grado de sulfatación es aproximadamente 2 por unidad de disacárido.

cemadotinum

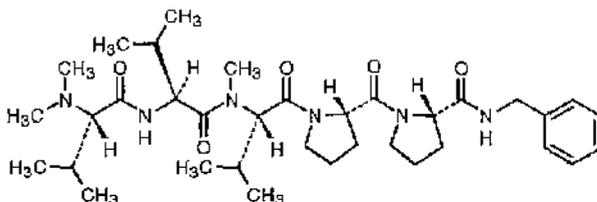
cemadotin

N,N-dimethyl-L-valyl-L-valyl-*N*-methyl-L-valyl-L-protyl-*N*-benzyl-L-prolinamide

cémadotine

(*N,N*-diméthyl-L-valyl)-L-valyl-(*N*-méthyl-L-valyl)-L-protyl-(*N*-benzyl-L-prolinamide)

cemadotina

N,N-dimetil-L-valil-L-valil-*N*-metil-L-valil-L-protil-*N*-bencil-L-prolinamidaC₃₅H₆₆N₆O₅**choriogonadotropinum alfa**

choriogonadotropin alfa

human chorionic gonadotropin (protein moiety reduced), glycoform α -subunit;chorionic gonadotropin (human α -subunit protein moiety reduced) β -subunit:chorionic gonadotropin (human β -subunit protein moiety reduced)

choriogonadotropine alfa

gonadotropine chorionique humaine (partie protéique réduite), forme glycosylée α sous-unité α gonadotropine chorionique (partie protéique réduite de la sous-unité α humaine)sous-unité β :gonadotropine chorionique (partie protéique réduite de la sous-unité β humaine)

coriogonadotropina alfa

gonadotropina coriónica humana (fracción proteica reducida), glucoforma α subunidad α :gonadotropina coriónica (fracción proteica reducida de la subunidad α humana)subunidad β :gonadotropina coriónica (fracción proteica reducida de la subunidad β humana) α : C₄₃₇H₆₈₂N₁₂₂O₁₃₄S₁₃ β : C₃₆₆H₁₀₆₀N₁₉₆O₂₀₃S₁₃

APDVQDCPEC TLQENPFFSQ PGAPILQCMG CCFSRAYPTP
 LRSKKTMLVQ KNVTSSESTCC VAKSYNRVTV MGGPKVENHT
 ACHCSTCYH KS
 SKEPLRPRCR PINATLAVEK EGCPVCITVN TTICAGYCPT
 MTRVLQGVLP ALPQVVCNYR DVRFESIRLP GCPRGVNPPV
 SYAVALSCQC ALCRRSTTDC GGPKDHPLTC DDPRFQDSSS
 SKAPPSLPS PSRLPGPSDT PILPQ

clevidipinum

clevidipine

(±)-hydroxymethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, butyrate (ester)

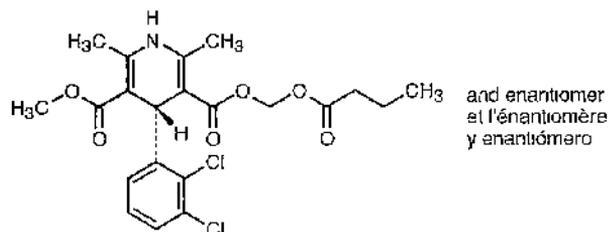
clévidipine

(4*RS*)-4-(2,3-dichlorophényl)-2,6-diméthyl-1,4-dihydropyridine-3,5-dicarboxylate de butanoyloxyméthyle et de méthyle

clevidipino

(±)-4-(2,3-diclorofenil)-1,4-dihidro-2,6-dimetil-3,5-piridinadicarboxilato de butiriloximetilo y metilo

$C_{21}H_{25}Cl_2NO_6$

**domitrobanum**

domitroban

(+)-(Z)-7-[(1*R*,2*S*,3*S*,4*S*)-3-benzenesulfonamido-2-norbornyl]-5-heptenoic acid

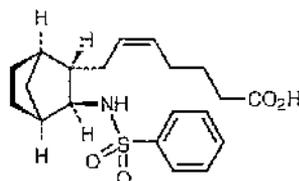
domitroban

acide (+)-(Z)-7-[(1*R*,2*S*,3*S*,4*S*)-3-[(phénylsulfonyl)amino]bicyclo[2.2.1]hept-2-yl]hept-5-énoïque

domitrobán

ácido (+)-(Z)-7-[(1*R*,2*S*,3*S*,4*S*)-3-bencensulfonamido-2-norbornil]-5-heptenoico

$C_{20}H_{27}NO_4S$



donepezilum

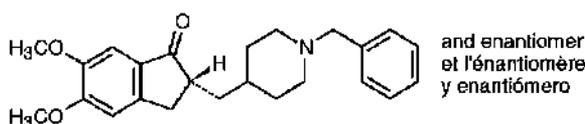
donepezil

 (\pm) -2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone

donépázil

 $(2R)$ -2-[(1-benzylpiperidin-4-yl)méthyl]-5,6-diméthoxy-2,3-dihydro-1*H*-indén-1-one

donepezilo

 (\pm) -2-[(1-bencil-4-piperidil)metil]-5,6-dimetoxi-1-indanona $C_{24}H_{29}NO_3$ **dronedaronum**

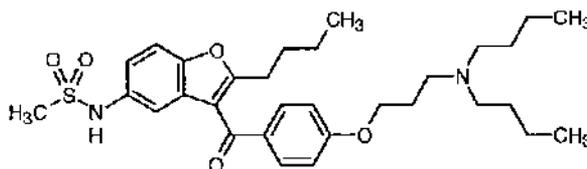
dronedarone

N-[2-butyl-3-[*p*-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]=methanesulfonamide

dronédarone

N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]benzofuran-5-yl]méthanesulfonamide

dronedaronna

N-(2-butil-3-[*p*-[3-(dibutilamino)propoxil]benzoiil]-5-benzofuranil)=metanosulfonamida $C_{31}H_{44}N_2O_5S$ **ecamsulum**

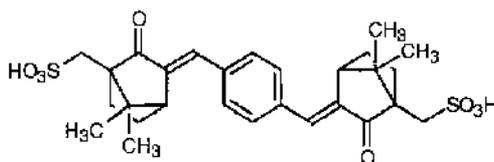
ecamsule

 (\pm) -(3*E*,3'*E*)-3,3'-(*p*-phenylenedimethylidene)bis[2-oxo-10-bornanesulfonic acid]

écamsule

acide [[1,4-phénylènediméthylidyne]bis[(3*E*,3'*E*)-7,7-diméthyl-2-oxobicyclo[2.2.1]heptan-3,1-diyl]]diméthanesulfonique

ecamsul

 (\pm) -(3*E*,3'*E*)-3,3'-(*p*-fenilènodimetilidino)bis[ácido 2-oxo-10-bornanosulfónico] $C_{28}H_{34}O_8S_2$ 

efepriştinum

efepriştin

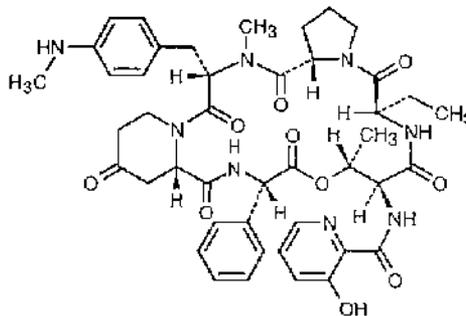
N-[(6*R*,9*S*,10*R*,13*S*,15*aS*,22*S*,24*aS*)-6-ethyl-docosahydro-10,23-dimethyl-22-[*p*-(methylamino)benzyl]-5,8,12,15,17,21,24-hepta-oxo-13-phenyl-12*H*-pyrido[2,1-*f*]pyrrolo[2,1-*h*][1,4,7,10,13,16]oxapentaazacyclononadecin-9-yl]-3-hydroxypicolinamide

éfépriştine

N-[(6*R*,9*S*,10*R*,13*S*,15*aS*,22*S*,24*aS*)-6-éthyl-10,23-diméthyl-22-[4-(méthylamino)benzyl]-5,8,12,15,17,21,24-hepta-oxo-13-phényldocosahydro-12*H*-pyrido[2,1-*f*]pyrrolo[2,1-*h*][1,4,7,10,13,16]oxapentaazacyclononadécén-9-yl]-3-hydroxypyridine-2-carboxamide

efepriştina

N-[(6*R*,9*S*,10*R*,13*S*,15*aS*,22*S*,24*aS*)-6-etildocosahidro-10,23-dimetil-22-[*p*-(metilamino)benzil]-5,8,12,15,17,21,24-hepta-oxo-13-fenil-12*H*-pirido[2,1-*f*]pirrolo[2,1-*h*][1,4,7,10,13,16]oxapentaazaciclono-nadecin-9-il]-3-hidroxicolinamida

C₄₄H₅₂N₈O₁₀**elinafidum**

elinafide

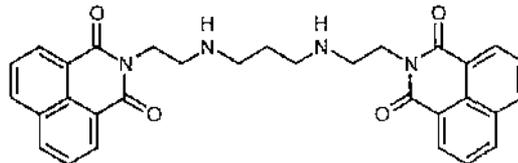
N,N'-[trimethylenebis(iminoethylene)]dinaphthalimide

élinafide

2,2'-[propane-1,3-diylbis(iminoéthylène)]bis[1*H*-benzo[*d*]isoquinoléine-1,3(2*H*)-dione]

elinafida

N,N'-[trimetilénobis(iminoetileno)]dinaftalimida

C₃₁H₂₈N₄O₄

filaminastum

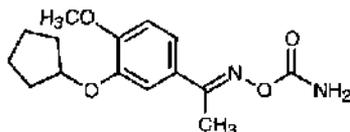
filaminast

3'-(cyclopentyloxy)-4'-methoxyacetophenone (*E*)-*O*-carbamoyloxime

filaminast

1-[3-(cyclopentyloxy)-4-méthoxyphényl]éthanone (*E*)-*O*-carbamoyloxime

filaminast

3'-(ciclopentiloxi)-4'-metoxiacetofenona (*E*)-*O*-carbamoiloximaC₁₅H₂₀N₂O₄**filbanserinum**

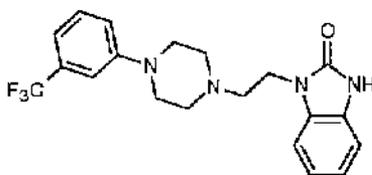
filbanserin

1-[2-[4-(α,α,α -trifluoro-*m*-tolyl)-1-piperazinyl]éthyl]-2-benzimidazolinone

filbansérine

1-[2-[4-(3-(trifluorométhyl)phényl)pipérazin-1-yl]éthyl]-1,3-dihydro-2*H*-benzimidazol-2-one

filbanserina

1-[2-[4-(α,α,α -trifluoro-*m*-tolil)-1-piperazinil]etil]-2-benzimidazolinonaC₂₀H₂₁F₃N₄O**fludarabinum**

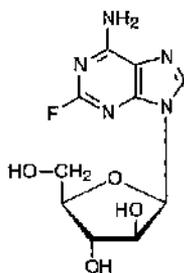
fludarabine

9- β -D-arabinofuranosyl-2-fluoroadenine

fludarabine

9-(β -D-arabinofuranosyl)-2-fluoro-9*H*-purin-6-amine

fludarabina

9- β -D-arabinofuranosil-2-fluoroadeninaC₁₀H₁₂FN₅O₄

fomivirsenum

fomivirsen

2'-deoxy-*P*-thioguanilyl-(5'→3')-2'-deoxy-*P*-thiocytidylyl-(5'→3')-2'-deoxy-*P*-thioguanilyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-deoxy-*P*-thioguanilyl-(5'→3')-2'-deoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-deoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-deoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-deoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-deoxy-*P*-thioguanilyl-(5'→3')-2'-deoxy-*P*-thiocytidylyl-(5'→3')-2'-deoxyguanosine

fomivirsen

2'-désoxy-*P*-thioguanilyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-2'-désoxy-*P*-thioguanilyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thioguanilyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-*P*-thiothymidylyl-(5'→3')-2'-désoxy-*P*-thioguanilyl-(5'→3')-2'-désoxy-*P*-thiocytidylyl-(5'→3')-2'-désoxyguanosine

fomivirseno

2'-desoxi-*P*-thioguanilil-(5'→3')-2'-desoxi-*P*-thiocitidilil-(5'→3')-2'-desoxi-*P*-thioguanilil-(5'→3')-*P*-tiotimidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-thioguanilil-(5'→3')-2'-desoxi-*P*-thiocitidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-thiocitidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-thiocitidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-thiocitidilil-(5'→3')-*P*-tiotimidilil-(5'→3')-2'-desoxi-*P*-thioguanilil-(5'→3')-2'-desoxi-*P*-thiocitidilil-(5'→3')-2'-desoxiguanosina

C₂₀₄H₂₆₃N₆₃O₁₁₄P₂₀S₂₀**foropafantum**

foropafant

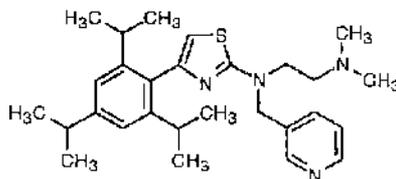
3-[[[2-(diméthylamino)éthyl][4-(2,4,6-trisopropylphényl)-2-thiazolyl]amino]=méthyl]pyridine

foropafant

N,N-diméthyl-*N'*-[(pyridin-3-yl)méthyl]-*N'*-[4-[2,4,6-tris(1-méthyléthyl)phényl]thiazol-2-yl]éthane-1,2-diamine

foropafant

3-[[[2-(diméthylamino)etil][4-(2,4,6-trisopropilfenil)-2-tiazolil]amino]=metil]piridina

C₂₈H₄₀N₄S

icopezilum

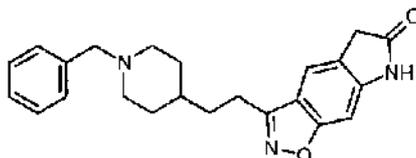
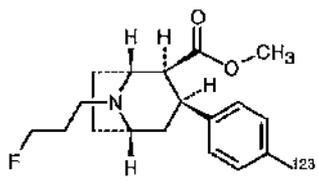
icopezil

3-[2-(1-benzyl-4-piperidyl)ethyl]-5,7-dihydro-6*H*-pyrrolo[3,2-*f*]-1,2-benzisoxazol-6-one

icopézil

3-[2-(1-benzylpiperidin-4-yl)éthyl]-5,7-dihydro-6*H*-pyrrolo[3,2-*f*]-1,2-benzisoxazol-6-one

icopezilo

3-[2-(1-benzil-4-piperidil)etil]-5,7-dihidro-6*H*-pirolo[3,2-*f*]-1,2-benzisoxazol-6-ona $C_{23}H_{25}N_3O_2$ **ioflupanum** (¹²³I)ioflupane (¹²³I)methyl 8-(3-fluoropropyl)-3β-(*p*-iodo-¹²³I-phenyl)-1*αH*,5*αH*-nortropane-2β-carboxylateioflupane (¹²³I)(1*R*,2*S*,3*S*,5*S*)-8-(3-fluoropropyl)-3-[4-¹²³I]iodophényl]-8-azabicyclo[3.2.1]octane-2-carboxylate de méthyleioflupano (¹²³I)8-(3-fluoropropil)-3β-(*p*-iodo-¹²³I-fenil)-1*αH*,5*αH*-nortropano-2β-carboxilato de metilo $C_{18}H_{23}F^{123}INO_2$ **ivabradinum**

ivabradine

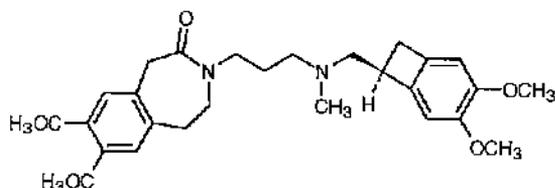
3-[3-[[[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]méthyl]=méthylamino]propyl]-1,3,4,5-tétrahydro-7,8-diméthoxy-2*H*-3-benzazépin-2-one

ivabradine

3-[3-[[[(7*S*)-3,4-diméthoxybicyclo[4.2.0]octa-1,3,5-trién-7-yl]méthyl]=méthylamino]propyl]-7,8-diméthoxy-1,3,4,5-tétrahydro-2*H*-3-benzazépin-2-one

ivabradina

3-[3-[[[(7*S*)-3,4-dimetoxybicyclo[4.2.0]octa-1,3,5-trien-7-il]metil]metilamino]=propil]-1,3,4,5-tetrahidro-7,8-dimetoxi-2*H*-3-benzazepin-2-ona

$C_{27}H_{36}N_2O_5$ **lagatidum**

lagatide

L-prolyl-L-valyl-L-threonyl-L-lysyl-L-prolyl-L-glutaminy-D-alaninamide

lagatide

L-prolyl-L-valyl-L-thréonyl-L-lysyl-L-prolyl-L-glutaminy-D-alaninamide

lagatida

L-profil-L-valil-L-treonil-L-lysil-L-profil-L-glutaminil-D-alaninamida

 $C_{23}H_{35}N_{10}O_9$ H-Pro-Val-Thr-Lys-Pro-Gln-D-Ala-NH₂**landiololum**

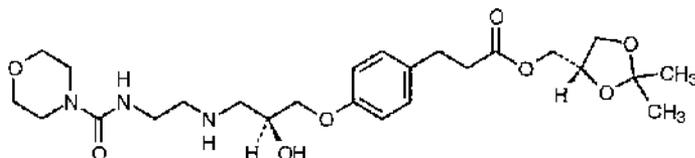
landiolol

(-)-[(S)-2,2-diméthyl-1,3-dioxolan-4-yl]méthyl *p*-[(S)-2-hydroxy-3-[[2-(4-morpholinocarboxamido)éthyl]amino]propoxy]hydrocinnamate

landiolol

(-)-3-[4-[(2*S*)-2-hydroxy-3-[[2-[(morpholin-4-ylcarbonyl)amino]éthyl]amino]=propoxy]phényl]propanoate de [(4*S*)-2,2-diméthyl-1,3-dioxolan-4-yl]méthyle

landiolol

p-[(*S*)-2-hidroxi-3-[[2-(4-morfolinocarboxamido)etil]amino]propoxi]=hidrocinnamato de (-)-[(*S*)-2,2-dimetil-1,3-dioxolan-4-il]metil $C_{25}H_{33}N_3O_6$ **lefradafibanum**

lefradafiban

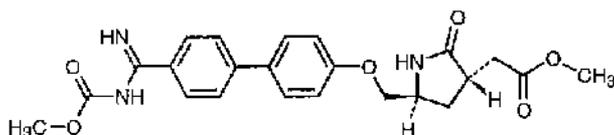
(3*S*,5*S*)-5-[[[4'-(carboxyamidino)-4-biphényl]oxy]méthyl]-2-oxo-3-pyrrolidineacetic acid, dimethyl ester

lefradafiban

2-[(3*S*,5*S*)-5-[[[4'-(rimino(méthoxycarbonyl)amino)méthyl]biphényl-4-yl]oxy]méthyl]-2-oxopyrrolidin-3-yl]acétate de méthyle

lefradafibán

éster dimetilico del ácido(3*S*,5*S*)-5-[[[4'-(carboxyamidino)-4-bifenilil]oxi]metil]-2-oxo-3-pirrolidinacético

C₂₃H₂₅N₃O₆**marimastatum**

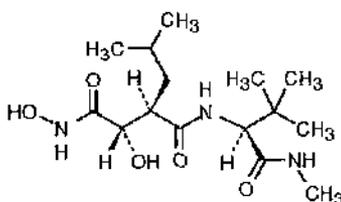
marimastat

(2*S*,3*R*)-3-[[[(1*S*)-2,2-diméthyl-1-(méthylcarbamoyl)propyl]carbamoyl]-2-hydroxy-5-méthylhexanohydroxamique acid

marimastat

(2*R*,3*S*)-*N*'-[[[(1*S*)-2,2-diméthyl-1-(méthylcarbamoyl)propyl]-*N*⁴,3-dihydroxy-2-(2-méthylpropyl)butanediamide

marimastat

ácido (2*S*,3*R*)-3-[[[(1*S*)-2,2-dimetil-1-(metilcarbamoil)propil]carbamoil]-2-hidroxi-5-metilhexanohidroxámicoC₁₅H₂₃N₃O₅**maxacalcitolum**

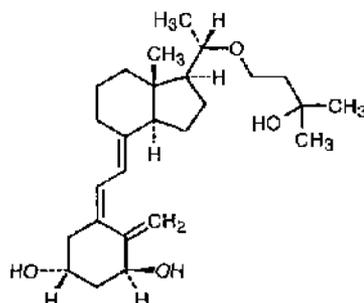
maxacalcitol

(+)-(5*Z*,7*E*,20*S*)-20-(3-hydroxy-3-méthylbutoxy)-9,10-secopregna-5,7,10(19)-triène-1 α ,3 β -diol

maxacalcitol

(+)-(5*Z*,7*E*)-(20*S*)-20-(3-hydroxy-3-méthylbutoxy)-9,10-sécoprégna-5,7,10(19)-triène-1 α ,3 β -diol

maxacalcitol

(+)-(5*Z*,7*E*,20*S*)-20-(3-hidroxi-3-metilbutoxi)-9,10-secopregna-5,7,10(19)-trieno-1 α ,3 β -diolC₂₆H₄₂O₄

mazokalimum

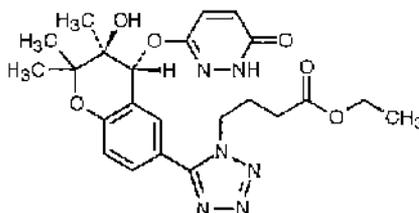
mazokalim

ethyl 5-[(3*S*,4*R*)-4-[(1,6-dihydro-6-oxo-3-pyridazinyl)oxy]-3-hydroxy-2,2,3-triméthyl-6-chromanyl]-1*H*-tetrazol-1-butyrate

mazokalim

4-[5-[(3*S*,4*R*)-3-hydroxy-2,2,3-triméthyl-4-(6-oxo-1,6-dihydropyridazin-3-yloxy)-3,4-dihydro-2*H*-chromén-6-yl]-1*H*-tétrazol-1-yl]butanoate d'éthyle

mazokalim

5-[(3*S*,4*R*)-4-[(1,6-dihidro-6-oxo-3-piridazinil)oxi]-3-hidroxi-2,2,3-trimetil-6-cromanil]-1*H*-tetrazol-1-butirato de etiloC₂₃H₂₉N₅O₆**nifekalantum**

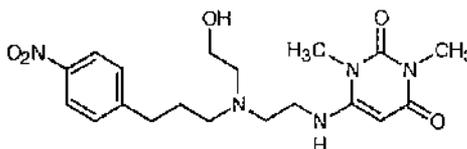
nifekalant

6-[[2-[(2-hydroxyethyl)[3-(*p*-nitrophenyl)propyl]amino]éthyl]amino]-1,3-diméthyluracil

nifekalant

6-[[2-[(2-hydroxyéthyl)[3-(4-nitrophényl)propyl]amino]éthyl]amino]-1,3-diméthylpyrimidin-2,4(1*H*,3*H*)-dione

nifekalant

6-[[2-[(2-hidroxietil)[3-(*p*-nitrofenil)propil]amino]etil]amino]-1,3-dimeetiluraciloC₁₃H₂₇N₅O₅**nolpitantil besilas**

nolpitantium besilate

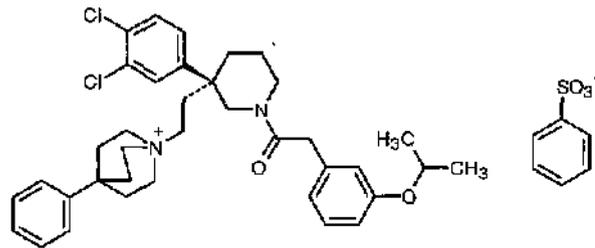
1-[2-[(*S*)-3-(3,4-dichlorophenyl)-1-[(*m*-isopropoxyphenyl)acetyl]-3-piperidyl]éthyl-4-phenylquinuclidinium benzenesulfonate

bésilate de nolpitantium

benzènesulfonate de 1-[2-[(3*S*)-3-(3,4-dichlorophényl)-1-[2-[3-(1-méthyléthoxy)phényl]acétyl]pipéridin-3-yl]éthyl]-4-phényl-1-azoniabicyclo[2.2.2]octane

besiato de nolpantio

benzenosulfonato de 1-[2-[(*S*)-3-(3,4-diclorofenil)-1-[(*m*-isopropoxifenil)acetyl]-3-piperidil]etil-4-fenilquinuclidinio

C₄₃H₅₀Cl₂N₂O₅S**orbofibanum***orbofiban*

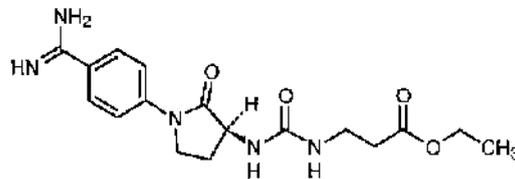
N-[[[(3*S*)-1-(*p*-aminophenyl)-2-oxo-3-pyrrolidinyl]carbamoyl]-
β-alanine, ethyl ester

orbofiban

3-[3-[(3*S*)-1-(4-carbamimidoylphényl)-2-oxopyrrolidin-3-yl]uréido]propanoate
d'éthyle

orbofiban

éster etílico de la *N*-[[[(3*S*)-1-(*p*-aminofenil)-2-oxo-3-pirrolidinil]carbamol]-
β-alanina

C₁₇H₂₃N₅O₄**pranazepidum***pranazepide*

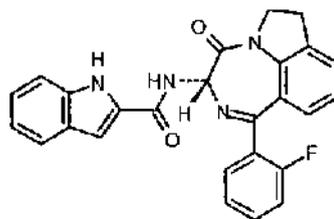
(-)-*N*-[(*S*)-1-(*o*-fluorophenyl)-3,4,6,7-tetrahydro-4-oxopyrrolo=
[3,2,1-*ik*][1,4]benzodiazepin-3-yl]indole-2-carboxamide

pranazépide

(-)-*N*-[(3*S*)-1-(2-fluorophényl)-4-oxo-3,4,6,7-tétrahydropyrrolo=
[3,2,1-*ik*][1,4]benzodiazépin-3-yl]-1*H*-indole-2-carboxamide

pranazepida

(-)-*N*-[(*S*)-1-(*o*-fluorofenil)-3,4,6,7-tetrahydro-4-oxopirrolo=
[3,2,1-*ik*][1,4]benzodiazepin-3-yl]indol-2-carboxamida

C₂₆H₁₉FN₄O₂

rizatriptanum

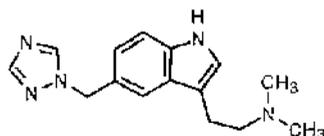
rizatriptan

3-[2-(dimethylamino)ethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl)indole

rizatriptan

N,N-diméthyl-2-[5-[(1*H*-1,2,4-triazol-1-yl)méthyl]-1*H*-indol-3-yl]éthanamine

rizatriptán

3-[2-(dimetilamino)etil]-5-(1*H*-1,2,4-triazol-1-ilmetil)indolC₁₅H₁₉N₅**saredutantum**

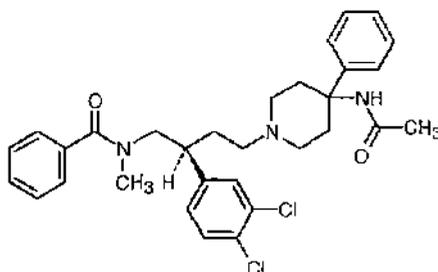
saredutant

N-[(*S*)-β-[2-(4-acetamido-4-phenylpiperidino)ethyl]-3,4-dichlorophenethyl]-*N*-methylbenzamide

sarédutant

N-[(2*S*)-4-[4-(acétylamino)-4-phénylpipéridin-1-yl]-2-(3,4-dichlorophényl)butyl]-*N*-méthylbenzamide

saredutant

N-[(*S*)-β-[2-(4-acetamido-4-fenilpiperidino)etil]-3,4-diclorofenetil]-*N*-metilbenzamidaC₃₁H₃₅Cl₂N₃O₂**sifaloxicinum**

sifaloxacin

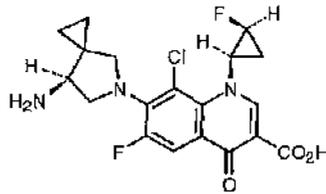
(-)-7-[(7*S*)-7-amino-5-azaspiro[2.4]hept-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

sifaloxicine

acide (-)-7-[(7*S*)-7-amino-5-azaspiro[2.4]hept-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-4-oxo-1,4-dihydroquinoléin-3-carboxylique

sifaloxicino

ácido (-)-7-[(7*S*)-7-amino-5-azaspiro[2.4]hept-5-il]-8-cloro-6-fluoro-1-[(1*R*,2*S*)-2-fluorociclopropil]-1,4-dihidro-4-oxo-3-quinolinacarboxílico

**sulesomabum**

sulesomab

immunoglobulin G 1 (mouse monoclonal IMMU-MN3 Fab' fragment γ -chain anti-human NCA-90 granulocyte cell antigen), disulfide with mouse monoclonal IMMU-MN3 light chain

sulésomab

immunoglobuline G 1 (chaîne γ du fragment Fab' de l'anticorps monoclonal de souris IMMU-MN3 anti-antigène de granulocyte humain NCA-90), disulfure avec la chaîne légère de l'anticorps monoclonal de souris IMMU-MN3

sulesomab

immunoglobulina G 1 (cadena γ del fragmento Fab' del anticuerpo monoclonal de ratón IMMU-MN3 anti-antígeno de granulocito humano NCA-90), disulfuro con la cadena ligera del anticuerpo monoclonal de ratón IMMU-MN3

taltirelinum

taltirelin

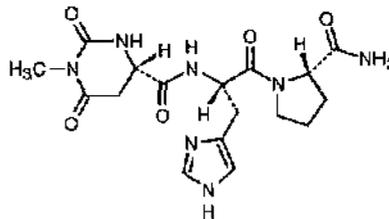
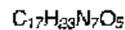
(-)-N-[[[(S)-hexahydro-1-methyl-2,6-dioxo-4-pyrimidinyl]carbonyl]-L-histidyl]-L-prolinamide

taltiréline

(-)-(2S)-1-[[[(2S)-3-(1H-imidazol-4-yl)-2-[[[(4S)-1-méthyl-2,6-dioxohexahydro=pyrimidin-4-yl]carbonyl]amino]propanoyl]pyrrolidine-2-carboxamide

taltirelina

(-)-N[[[(S)-hexahidro-1-metil-2,6-dioxo-4-pirimidini]carbonil]-L-histidil]-L-prolinamida

**talviralinum**

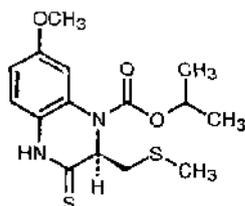
talviraline

isopropyl (2S)-3,4-dihydro-7-methoxy-2-[(methylthio)methyl]-3-thioxo-1(2H)-quinoxalinecarboxylate

talviraline

(2S)-7-méthoxy-2-[(méthylsulfanyl)méthyl]-3-thioxo-3,4-dihydroquinoxaline-1(2H)-carboxylate de 1-méthyléthyle

talviralina

(2*S*)-3,4-dihidro-7-metoxi-2-[(metilitio)metil]-3-tioxo-1(2*H*)-quinoxalinacarboxilato de 1-metilsetilo $C_{15}H_{20}N_2O_3S_2$ technetium (^{99m}Tc) pintumomabum
technetium (^{99m}Tc) pintumomabimmunoglobulin G 1 (mouse monoclonal 170 γ -chain anti-human adenocarcinoma antigen), disulfide with mouse monoclonal 170 κ -chain, dimer, [^{99m}Tc]technetium salttechnétium (^{99m}Tc) pintumomabsel de [^{99m}Tc]technétium de l'immunoglobulina G 1 (chaîne γ de l'anticorps monoclonal de souris 170 anti-antigène associé à l'adénocarcinome humain), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris 170technetium (^{99m}Tc) pintumomabsal de [^{99m}Tc]technetium del immunoglobulina G 1 (cadena γ del anticuerpo monoclonal de ratón 170 anti-antígeno asociado al adenocarcinoma humano), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón 170

terbogrelum

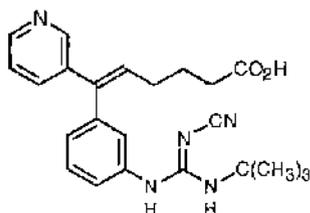
terbogrel

(5*E*)-6-[*m*-(3-*tert*-butyl-2-cyanoguanidino)phenyl]-6-(3-pyridyl)-5-hexenoic acid

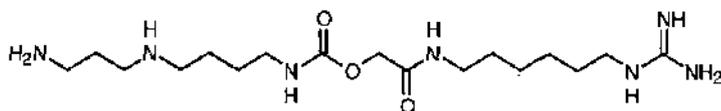
terbogrel

acide (5*E*)-6-[3-[2-cyano-3-(1,1-diméthyléthyl)guanidino]phényl]-6-(pyrid-3-yl)hex-5-énoïque

terbogrel

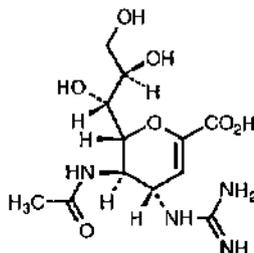
ácido (5*E*)-6-[*m*-(3-*tert*-butil-2-cianoguanidino)fenil]-6-(3-piridil)-5-hexenóico $C_{23}H_{27}N_5O_2$ tresperimusum
tresperimus[4-[(3-aminopropyl)amino]butyl]carbamic acid, ester with *N*-(6-guanidinohexyl)glycolamide

trespérimus	[4-[(3-aminopropyl)amino]butyl]carbamate de 2-[(6-guandinohexil)amino]-2-oxoéthyle
tresperimus	[4-[(3-aminopropil)amino]butil]carbamato de [(6-guandinohexil)carbamoi]=metilo
	C ₁₇ H ₃₇ N ₇ O ₃



vinfluninum	4'-deoxy-20',20'-difluoro-8'-norvincalécoblastine
vinflunine	20',20'-difluoro-4'-désoxy-8'-norvincalécoblastine
vinflunine	20',20'-difluoro-4'-désoxy-8'-norvincalécoblastine
vinflunina	4'-desoxi-20',20'-difluoro-8'-norvincalécoblastina
	C ₄₅ H ₅₄ F ₂ N ₄ O ₈

zanamivirum	5-acetamido-2,6-anhydro-3,4,5-tridésoxi-4-guandino-D-glycero-D-galacto-non-2-énico acid
zanamivir	acide (4 <i>S</i> ,5 <i>R</i> ,6 <i>R</i>)-5-(acétylamino)-4-guandino-6-[(1 <i>R</i> ,2 <i>R</i>)-1,2,3-trihydroxypropyl]-5,6-dihydro-4 <i>H</i> -pyrane-2-carboxylique
zanamivir	ácido 5-acetamido-2,6-anhidro-3,4,5-tridesoxi-4-guandino-D-glicero-D-galacto-non-2-énico
	C ₁₂ H ₂₀ N ₄ O ₇



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* seront publiés seulement dans les listes impaires des DCI proposées.

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