WHO DRUG INFORMATION

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INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

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WHO DRUG INFORMATION

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

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

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General Policy Topics

Fake drugs: a scourge on the system

The lesson of diethylene glycol

The *British Medical Journal* recently published a detailed report of an epidemic of acute renal failure among children in Bangladesh (1). Over a period of almost three years starting in January 1990, 339 children were admitted with unexplained renal failure to the Dhaka Shishu Hospital, the main children's hospital in Bangladesh; 70% of these died in hospital. Over 90% had recently been given a medicine for fever which, in one-third of the cases, was confirmed to be an elixir of paracetamol. Seven of 28 brands of this elixir were subsequently shown to contain diethylene glycol, which is highly toxic to the kidneys. Twelve months after the government had banned the sale of all elixirs of paracetamol, cases of unexplained renal failure presenting at the hospital had decreased by 80–90%.

Diethylene glycol is used widely in industrial processing as a solvent and an antifreeze. Its considerably more expensive congener, propylene glycol, is relatively non-toxic and is used legitimately in the preparation of liquid formulations of paracetamol and other medicines. The Bangladesh epidemic is the latest and apparently the most extensive of several tragedies that have occurred over the years as a result of substitution of diethylene glycol for propylene glycol in the manufacture of pharmaceuticals. The severe effects of diethylene glycol on the kidney first became apparent in the 1930s when it was used by a dispensing pharmacist in the United States to prepare an elixir of sulfanilamide (2). That incident resulted in the deaths of 76 children. It also inspired the 1938 US Food, Drugs and Cosmetics Act (3), which created a requirement for independent premarketing approval of new pharmaceutical products and established the US Food and Drug Administration in its current role.

The need for vigilance in assuring the quality of all materials used in the manufacture of pharmaceutical products has since been underscored time and again. Yet, over the years, other outbreaks of diethylene glycol poisoning have been reported from South Africa (4), Nigeria (5), India (6) and Argentina (6).

Ineffective antibiotics

Potentially just as lethal, but more insidious in its progression, is the emergence in many developing countries of fake drugs that contain little, if any, of the labelled active ingredient.

Over the past decade, WHO has received a perturbing number of unconfirmed reports of infiltration of products that are fraudulently labelled into drug distribution channels in countries with slender regulatory capacity. One internationally-organized survey recently conducted in three countries of equatorial Africa was directed principally to antibiotic and antiparasitic preparations (7). The results can only be described — by any reasonable standard — as catastrophic:

- of 26 analysed samples of chloramphenicol, 16 did not conform to specifications. Ten contained too little active ingredient, four contained none, and two tablet formulations failed disintegration testing;
- of 49 samples of trimethoprim/sulfamethoxazole tablets, six provided less than the labelled amount and a further six contained neither of the active ingredients;
- 8 of 28 samples of ampicillin contained too little of the active ingredient, and one contained none; and
- while 39 out of 41 samples of quinine met specifications, the remaining two failed seriously. One provided less than the labelled amount; the other contained not quinine but mepacrine.

This extraordinary prevalence of fraudulantly prepared antimicrobials is not unique to Africa: a recent analysis of samples of ampicillin and trimethoprim/sulfamethoxazole collected in different parts of Bangladesh has yielded similar results (8). This is a matter of international as well as national relevance. Not only are individual patients directly jeopardized, but a selection pressure favouring the emergence of drug-resistant pathogens threatens society at large.

In the absence of firm evidence, it is idle to speculate on who is taking callous advantage of frail regulatory structures in these countries. However, there is no doubt about the need for a resolute response. Since, time and again, the same defects occur in clusters which involve finished products from several companies within a single vicinity, the case for effective regulatory oversight of the importation and distribution of active ingredients and other starting materials has become compelling (1, 5). The time is past when responsibility for the quality of these substances can reasonably be accorded to the buyer rather than the manufacturer.

The reality is that many small drug manufacturers around the world are eager to seek out starting materials at bargain prices and have neither the equipment nor the staff to verify their authenticity, much less their quality. No country is immune from these risks: regulators around the world should take careful note of the measures proposed by the European Commission (set out on pages 156–157 of this journal) to assure greater transparency of trade in starting materials and to extend direct administrative control of the pharmaceutical industry to manufacturers of these substances. The message for less developed countries is that the creation of a domestically-based pharmaceutical industry imposes an onerous reponsibility for oversight, control and enforcement. Particularly vulnerable to the tragedies that stem from the distribution of fraudulent products are countries with a rapidly expanding industrial infrastructure in which large numbers of newly established companies are competing, sometimes recklessly, to gain a foothold in the market.

Quality assurance: the foremost priority

Seven years have now passed since the World Health Assembly first formally acknowledged the threat to public health posed by the existence of fraudulent and substandard pharmaceuticals[1]. The idea that simple remedies may be at hand has long since been rejected. It is now generally accepted that the only viable recourse is to assist less developed countries in two ways: to help them organize small but effective national regulatory authorities that have a mandate to control both imported and locally manufactured products; and to create an efficient system for sharing between national authorities the information necessary to assure the quality of imported products and starting materials.[2,3]

WHO has responded to this challenge with a broad range of initiatives. Together with the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) it has set out a series of recommendations intended to curb illicit manufacture of pharmaceutical products (9). The Organization has issued guiding principles for setting up a small licensing authority (10); it has extended the scope of the WHO Certification Scheme, notably to cover active ingredients as well as finished pharmaceutical products (11); it has comprehensively updated its good manufacturing practices (12); it has prepared both provisional guidelines on the inspection of manufacturing facilities (12) and proposals for controlling the importation of pharmaceutical products (13); it has formulated a guideline on registration requirements to establish interchangeability of multi-source products (14); and it has engaged in a project to monitor the extent of illicit trade in pharmaceutical products and the impact of control measures on the prevalence of these products in the distribution chain.

For too long these documents have languished in obscurity. They will shortly be brought together by WHO in a twin-volume manual (15). These books will stand prominently on the bookshelves of regulators and company administrators around the world. It is vital that they be used and that their message be heeded.

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[2] World Health Assembly. Resolution WHA45.29, May 1992 which, *inter alia*, recognizes that "a comprehensive system of quality assurance including the WHO Certification Scheme must be founded on a reliable national system of licensing, independent analysis of the finished product and independent inspection to verify that all manufacturing operations are carried out in conformity with accepted norms, referred to as 'good manufacturing practices'".

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Reports on Individual Drugs

Eclampsia: magnesium sulfate favoured in anticonvulsant therapy

At least 500 000 women, overwhelmingly from developing countries, still die each year from causes related to pregnancy (1). Eclampsia — which now complicates only about 1 in 2000 pregnancies in developed countries, but which is associated with a high mortality (2) — is estimated to be a factor in about one in ten of these deaths (3, 4).

The pre-eclamptic syndrome of increasing blood pressure and proteinuria and its association with a risk of potentially fatal eclamptic convulsions during or immediately after pregnancy has been recognized by generations of clinicians. However, the cause of these events remains obscure. Symptomatic anticonvulsant management of eclampsia with diazepam or phenytoin has been essentially empiric and based on the assumption that "eclampsia is a seizure like any other seizure" (5).

Parenteral administration of magnesium sulfate offers an alternative approach which has been widely practised in the United States for the best part of a century (6, 7). Suggestions have been offered that it may exert a vasodilator or other effect that attenuates ischaemic brain damage (8–10). However, lack of a proven, physiologically-based therapeutic rationale for its action, and of any comparative assessment of its efficacy, has apparently frustrated its acceptance elsewhere (11). Choice of treatment has been claimed to be more a matter of faith than of objectivity (12). Clinicians have had to rely largely on experience conveyed in uncontrolled case series (6, 13–15), and on the outcome of a few small randomized trials (16–19), one of which decisively favoured magnesium sulfate in a comparison with phenytoin (17).

Eclampsia now complicates few pregnancies in developed countries. However, it has proved possible to organize a multicentre randomized comparative trial of these two approaches to treatment on a scale required to provide statistically secure results in hospital centres in Africa, Asia and South America (20). In these countries, eclampsia is still estimated to complicate as many as 1% of all deliveries (21–23).

The trial comprised two separate arms:

- diazepam was compared with magnesium sulfate in a sample of 910 women admitted to centres in Argentina, Brazil, Colombia, Ghana, India, Uganda, Venezuela and Zimbabwe; and
- phenytoin (administered after an initial loading dose of diazepam) was compared with magnesium sulfate in a sample of 777 women admitted to four centres in India and South Africa.

Magnesium sulfate was administered as a slow intravenous loading injection of 4 g (5 g in South American centres) followed over the next 24 hours *either* by an intravenous infusion providing 1 g/hour, *or* by an immediate intramuscular dose of 10 g in divided dosage with a further 5 g every 4 hours (as long as respiratory rate, knee jerks and urinary output raised no suspicion of overdosage). Whenever a further convulsion occurred, an additional 2–4 g was given intravenously over 5 minutes.

Diazepam was administered as an intravenous loading dose of 10 mg over 2 minutes, followed by two consecutive 24-hour intravenous infusions delivering 40 mg and 20 mg respectively.

Since phenytoin is recommended only for prevention of convulsions, patients allocated to this drug were pretreated with the intravenous loading dose of diazepam. This was followed by a loading dose of phenytoin, 1 g intravenously over 20 minutes (with continuous cardiac monitoring) followed by 100 mg every 6 hours for 24 hours.

The results obtained are interpreted by the collaborators as "providing compelling evidence in favour of magnesium sulfate, rather than diazepam or phenytoin, for the treatment of eclampsia." In both settings maternal mortality was lower among women allocated magnesium sulfate, but these differences did not attain significance. The case for favouring magnesium sulfate is based essentially on the finding that this intervention approximately halved the risk of recurrent convulsions when compared with diazepam, and reduced it by a somewhat greater margin when compared with diazepam/phenytoin.

Magnesium sulfate held no statistically demonstrable advantage over diazepam in any other measure of serious maternal morbidity. However, it was less likely than phenytoin/diazepam to depress breathing or to be associated with pneumonia and the need for intensive care.

Most women convulsed after delivery. Some 250 infants were born to mothers treated before delivery and, among these, the overall mortality was 27%. Non-significant perinatal deaths occurred more among those exposed to phenytoin/diazepam than those allocated to magnesium sulfate (31% v. 26%). Live-born babies of women allocated magnesium sulfate were less likely than those in other treatment groups to have signs of respiratory depression, as reflected in Apgar scores, need for intubation and admission to special care nurseries.

These results, it is claimed, establish the superiority of magnesium sulfate in the routine anticonvulsant management of women with eclampsia beyond all reasonable doubt. The authors urge clinicians everywhere to align their practice with these results, and they call for WHO to accommodate parenteral magnesium sulfate within its list of essential drugs. Notwithstanding the failure of their study to demonstrate an advantage in survival of statistical significance, they estimate that several million women have died unnecessarily since magnesium sulfate was first proposed for the treatment of eclampsia.

In presenting their results the authors emphasize that "the only unbiased comparisons in this trial are of magnesium sulphate versus diazepam and of magnesium sulphate versus phenytoin". Other comparisons, they claim, are potentially misleading. This principle, however, does not absolve trialists from examining and accounting for evident bias whenever it emerges. The incidence of recurrent convulsions in women allocated to magnesium sulfate in one limb of the trial was 13.2%, yet in the other, it was only 5.7%. Such a large difference merits consideration and discussion. A search for possible factors contributing to this bias is unlikely to overturn the general conclusions of the study, but it might provide important insights into other determinants of eclampsia and, perhaps, into their management.

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Lymphatic filariasis: an eradicable disease

The prevalence of lymphatic filariasis, a mosquito-borne parasitic infection most frequently caused by the nematode worm, *Wuchereria bancrofti*, and focally by *Brugia malayi* and *B. timori*, is increasing globally. Unplanned urban development favours transmission and it is now estimated that at least 120 million people living in tropical and subtropical regions of Asia, Africa, the Western Pacific and some parts of the Americas are now infected (1, 2). Almost half of these cases are concentrated in India (3).

The need for substantial national effort

In contrast to this discouraging trend, the disease has already been eliminated from Japan, the Republic of Korea and Taiwan, while China is now far advanced with an effective control programme. These achievements have resulted in the disease being classed as "eradicable" by an International Task Force on Disease Eradication (4) — a decision intended to lend impetus to national chemotherapy programmes. However, the natural history of the disease and the limitations of classical dosage schedules of diethylcarbamazine (DEC), the only generally-available antifilarial drug, has precluded short-term solutions. Discontinuation in 1980 of a mass chemotherapy campaign which had been maintained in some Pacific islands for over 30 years has resulted in a return of the disease to pre-intervention levels in several islands (5, 6).

The basic problem is lack of a drug that efficiently destroys all the adult nematode worms, or macrofilariae, which develop and live for many years in the pelvic and periaortic lymphatics. Repeated infection results in progressive accumulation of these worms which leads to the lymphatic dysfunction that produces the classic signs of elephantiasis and hydrocele. However, it is the microfilariae which the adult worms produce in abundance, and which are taken up from the peripheral blood by mosquitos, that assures transmission of infection. DEC is active against microfilariae and, to a lesser extent, against adult worms when administered in classical regimens of 6 mg/kg daily for 12 days (*W. bancrofti*) or 6 days (*B. malayi*) (7). None the less, even after these repeated standard courses of DEC, some adult worms are likely to survive (8).

A changing role for DEC

DEC can cause dose-related gastrointestinal symptoms (9). More important are the adverse effects that exclude its use at classical dosage in areas where other filarial diseases co-exist. Sudden and massive destruction of microfilariae can have serious consequences in patients with onchocerciasis or loiasis. Use of DEC in patients with onchocerciasis is commonly complicated by severe cutaneous, or Mazzotti, reactions (10) and occasionally by an exacerbation of optic neuropathy (11, 12), while in patients with loiasis it can cause potentially-fatal acute encephalitis (13).

Because of these shortcomings, DEC has been increasingly used in recent years at relatively low doses in "mass distribution" programmes. The aim is to frustrate transmission by reducing the microfilarial load and the success of this approach has far exceeded initial expectation:

- *In control programmes involving large populations* in China, India and Taiwan, family use of medicated cooking and table salt containing DEC, 0.1 to 0.6%, for 6–12 months has consistently decreased microfilarial prevalence in both bancroftian and brugian filariasis by 70 to 100% (14–18). A comparable and sustained decrease in the prevalence of infected mosquitos has also been reported in the wake of a programme that was sustained in southern India for 4 years (18).

- Data generated principally within the Pacific islands and Indonesia show that community administration of single doses of DEC, 6 mg/kg, administered at intervals of up to one year are as effective as classical 12-day courses in reducing microfilarial density (19–22) and are considerably less likely to induce adverse effects (9).

The profound and long-lasting reduction in the microfilarial load that characterizes these studies suggests that DEC not only destroys microfilariae but also interferes with their generation by reducing the reproductive capacity of the adult worm population. Ultimately, however, in the absence of further therapy, the microfilarial density rises towards pre-treatment levels. Few, if any, infections are cured by a single course of therapy and it remains uncertain whether long-term or repeated use of DEC in mass distribution programmes can be expected to eradicate infection (8). For this reason, until direct evidence is generated to support other approaches, WHO continues to recommend the classical courses of DEC for treatment of individual patients to arrest lymphatic and renal damage in the early treatment of asymptomatic disease (2).

Ivermectin: an important ancillary role

Despite the difficulties, optimism regarding the prospects of eradicating the disease is rising. Community trials of widely-spaced single doses of DEC have generated consistently positive results wherever they have been conducted, and confirmation has been obtained that comparable results can be achieved with the macrolide antibiotic, ivermectin, now securely established in the community control of onchocerciasis. Massive reductions in mean microfilarial densities have been sustained for one year or more after the administration of either drug (8, 19, 22–28). However, since microfilariae remain detectable in many patients, doubt persists that the means is yet available to definitively cure patients with long-established disease.

Ivermectin alone apparently offers no advantage in potency over DEC as a microfilaricide in *W. bancrofti* or *B. Malayi* infections. (24, 25). It may, however, act synergistically with DEC to enhance clearing of microfilariae (25–28) or to reduce any risk of emergence of resistant strains (27–29). Most importantly, given that it is not associated with the serious adverse effects associated with the use of DEC in patients infected with other filarial nematodes (30–32), it may offer an acceptably safe alternative to DEC in the community management of lymphatic filariasis in areas where either onchocerciasis or loiasis co-exist (33–36).

Much testing remains to be carried out to define regimens that are well tolerated, result in sustained and profound suppression of microfilaraemia, and can be administered in a single dose. None the less, these vital targets may well soon be attainable.

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More on malaria vaccination

Disappointing interim results have been generated in a trial of the SPf66 polymeric synthetic peptide malaria vaccine in Gambian infants (1).

In a randomized, double-blind, placebo-controlled study 630 children aged 6–11 months at the time of enrolment received three doses of either SPf66 or of injectable polio vaccine at 0, 4 and 26 weeks. SPf66 antibody was detectable in 55 of 56 serum samples obtained 3 weeks after administration of the third dose of vaccine. However, at the end of a further 12 weeks (a period which was planned to coincide with the relatively short transmission season in the Gambia) it was concluded that this immunogenic response did not confer significant protection against clinical episodes of malaria, nor did it demonstrably reduce levels of parasitaemia. Almost 350 clinical attacks of malaria were recorded among the children while they remained under surveillance, and the adjusted vaccine efficacy against all detected episodes of malaria was estimated to be no more than 3% (95% confidence interval: –24 to +24).

These results are at variance with those obtained in a trial of comparable size involving children aged between 1 and 5 years living in an area of intense perennial malaria transmission in southern Tanzania (2, 3). In this earlier study, the number of episodes of clinical malaria was reduced by about one-third among the vaccinated children within the twelve-month period following the third dose.

No explanation for these divergent results can yet be offered with confidence. It was considered unlikely that this vaccine would be less immunogenic among the infants admitted to the Gambia study, and this expectation has been borne out by the antibody responses to SPf66. The possibility remains, however, that prior exposure to malaria — which is certain to have been much less among the substantially younger Gambian infants — may be an important determinant of the protective response to vaccination.

It is also possible that protection conferred by SPf66 becomes apparent only after a latent interval greater than the period of surveillance in the Gambian trial. Indeed, in the Tanzanian study the protective effect could be discerned only 48 weeks after the third dose of vaccine. Children in the Gambian study will consequently be followed again during the 1995 malaria transmission season. The snag is that by this time the mean SPf66 antibody titre is expected to have returned to near pre-vaccination levels (4).

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Cerebral cysticercosis: what can be expected of cysticidal drugs?

In an earlier article in this journal on the use of albendazole and praziquantel as cysticidal agents

in cerebral cysticercosis (1) attention was focused on the outcome of a survey of Mexican patients with multiple parenchymal cysts who were followed for periods of some 7 to 8 years (2).

The broad conclusions drawn from this study were that, in patients with no evidence of a destructive inflammatory response to the cysts, treatment with anti-epilepsy drugs alone was of little value in the longer term. In a series of 49 patients, the number of cysts tended gradually to increase — presumably as a consequence of re-infection — and the frequency of seizures showed no tendency to decrease. In contrast, treatment of 118 such patients with a cysticidal drug resulted in the eventual disappearance of most cysts. Over half the patients became seizure-free shortly after treatment and most of these were successfully withdrawn from anti-epilepsy drugs.

Evidence of pericystic inflammation on radiographs was also confirmed to have important and positive prognostic significance (3). Among 58 such patients who were treated with ant-iepilepsy drugs alone, some three-quarters of the brain cysts eventually degenerated spontaneously. Over 30% became seizure-free, and a slightly higher proportion was withdrawn from anti-epilepsy therapy. None the less, the authors recommended that such patients should receive cysticidal therapy in order to accelerate resorption and reduce scarring and granuloma formation which can perpetuate focal epilepsy (4–8).

In their experience, cysticidal therapy (praziquantel, 50 mg/kg daily for 15 days, or albendazole 15 mg/kg daily for 30 days) was well tolerated. Some 20% of patients required steroid cover (8 mg dexamethasone intramuscularly every 8 hours) to suppress headache, vomiting, seizures, and focal neurological signs attributed to an acute inflammatory reaction. These signs regressed rapidly and no patient required steroids for more than 2–3 days.

The conclusion drawn by the authors was categorical: "treatment of the parenchymal lesions in the brain greatly improves the prognosis of patients with epilepsy due to cysticercosis".

Similarly positive results had been presented in the past. An overview of six open uncontrolled studies of praziquantel used in daily doses ranging from 5 to 75 mg/kg over periods of 6 to 21 days (9) concluded that almost 90% of patients ultimately benefit from cysticidal therapy. In these trials, however, it seems that inflammatory reactions were frequently troublesome.

Other commentators had challenged the routine use of cysticidal therapy (10–13). Sudden destruction of the parasite, in their experience, could dangerously intensify a pre-existing inflammatory reaction (10). Moreover, they had found that parenchymal cysts often disappear spontaneously within 2 to 3 years, and that many patients respond well to antiepilepsy drugs (11–13). All of these findings contrasted inexplicably with the experience of the Mexican group.

In the absence of any large randomized study of the effects of cysticidal therapy, uncertainty and division of opinion still persists over the circumstances in which cysticidal treatment should be recommended in parenchymal cysticercosis (14). Some support the routine use of cysticidal drugs in all patients with active disease (15–19). Some consider that these drugs should be used only in carefully selected patients with active disease who are not at particular risk of an acute rise in intracranial pressure (20–22), and some maintain that parenchymal cysts carry a good prognosis regardless of therapy and that cysticidal drugs should be reserved for exceptional cases (23). Large randomized comparative trials, it is now recognized, would help to resolve fundamental uncertainties (24, 25) such as the extent to which anti-epilepsy drugs alone control seizures, and the extent to which cysticidal therapy improves control of seizures in the longer term.

Two recent studies suggest that even meticulously executed comparative studies may not provide information that is of broad general relevance. An open study involving 40 patients in South America has indicated that, even when treatment with albendazole is followed by complete radiological clearance of the lesions, clinical relapse is frequent within the first 12 months of withdrawal of anti-epilepsy drugs (26). In contrast, it is reported that single cystic lesions in Indian patients, many of which were confirmed serologically to be cysticercal, resolved as rapidly among patients treated with placebo as with albendazole, and sometimes within as little as three months (27).

Marked variations in the presentation, localization and natural history of parenchymal cysticercosis seem to preclude broad generalizations about optimal forms of treatment. Firmer diagnostic criteria may be needed. Apparent variations in the natural history of the lesions as well as their

response to treatment need more systematic investigation. In the present state of knowledge, use of cysticidal drugs seems best guided by local experience and by the presentation and progress of individual patients.

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Influenza: the rationale for routine vaccination of the elderly

Firm evidence that immunization of the elderly against influenza is a beneficial and cost-effective intervention has been slow to emerge. Observational studies and case-control comparisons have often provided inconclusive results because they have been too small to detect a significant advantage with reasonable confidence, or because the results have been confounded by the vaccine being selectively offered to high-risk patients with chronic cardiac and pulmonary conditions (1).

The problem of scale was recently overcome in two large observational studies undertaken in the United States (2, 3). One of these involved some 25 000 persons aged 65 years or more and was sustained for three years (2). Over this period non-vaccinated persons were almost twice as likely as vaccinees to be admitted to hospital with influenza, pneumonia and and other chronic respiratory conditions. In the light of these findings, one of the largest US health insurance organizations decided to add influenza vaccination to its list of reimbursable services for the elderly (2). However, given the current widespread political commitment to trim the costs of public-sector health care, provision of routine immunization against influenza is unlikely to become readily accepted for as long as doubts are sustained about its protective value in the elderly population at large (4, 5).

The public health rationale for supporting routine immunization has become more persuasive following publication of the first prospective, randomized, double-blind, placebo-controlled trial undertaken to assess the efficacy of influenza vaccination in elderly patients (6). The opportunity to conduct such a study arose in the Netherlands in 1991. It resulted from a recommendation of the National Health Council that influenza vaccine be reserved for patients with chronic illnesses rendering them vulnerable to the complications of infection (7). This created a setting in which a comparison of vaccination and placebo in elderly volunteers in relatively good general health became feasible.

Over 1800 patients aged 60 years or older, not known to belong to a high-risk group, were admitted to the study. Half were randomly allocated in advance of the influenza season to a vaccine that conformed with WHO's recommended specification. The other subjects received a matching placebo. Within the next 5 months serologically-confirmed clinical influenza was diagnosed in 2.1% of the vaccinated subjects and in 5.5% of those who received placebo (relative risk 0.42; 95% confidence interval 0.23–0.75).

On this assessment, vaccination reduces by about one half the risk of clinical influenza within the age group in which 95% of influenza-related deaths occur (8). The results also suggest that vaccination is less effective in protecting against asymptomatic infection; that previously vaccinated subjects are best protected; and, conversely, that the protective effect may decrease in patients older than 70 years. However, numbers of subjects were too small either to enable these trends to be confirmed with confidence or to demonstrate a possible reduction in severe complications or mortality.

The investigators do not rule out the possibility that the protective effect may have been maximized, both by a good match between the vaccine and the epidemic strains and by the proximity of vaccination to the influenza season. But they offer no reason to believe that this match differed essentially from that of other seasons. In fact, this trial demonstrated a degree of protection comparable to that reported earlier in young healthy volunteers (9–11). The results are also compatible with retrospective studies that have consistently demonstrated rates of protection within institutionalized elderly populations in the range of 60 to 90% for pneumonia, hospitalization and death (5, 12–14).

Estimates made within the past 5 years in the United States suggest that only about one-third of the population older than 65 years is vaccinated against influenza (15, 16). Each year, it is estimated that between 10 000 and 40 000 US citizens die from influenza and its complications (17), and that the total cost of these epidemics to the country can exceed US$ 12 billion annually (4). The accumulated clinical evidence, it has been suggested, "boils down to the simplest of all expressions of cost and benefit: influenza vaccine works, it's inexpensive, and it saves money (18)."

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Vitamin A supplementation and measles vaccination

Even in moderate degree, vitamin A deficiency has been shown to increase the vulnerability of malnourished children to intercurrent infections. Measles and diarrhoeal diseases, in particular, take greater toll of life wherever this deficiency is endemic (1, 2). The status of these children is rapidly improved by vitamin A (INN = retinol) supplements (3–5) which are now widely provided to infants in communities at greatest risk (6), usually as single high-dose capsules each containing 100 000 IU vitamin A. These have been supplied most economically when they have been delivered and administered to infants (7) at the time that they are vaccinated against measles at 6 to 9 months of age (8).

Until recently, the safety and value of linking these two interventions had not been closely examined. However, evidence that vitamin A status influences immune mechanisms (9–11) has created an impetus to assess whether co-administration of vitamin A influences the immunogenic response to measles vaccine. The results of the first such investigation, which was undertaken in Indonesia, have recently been published (12). In all, 336 infants aged six months were randomized to receive either 100 000 units of vitamin A or placebo on the occasion that they were immunized with standard-titre Schwarz measles vaccine.

Overall, the seroconversion rate among these infants was high: 82% developed a protective antibody titre to measles of 120 or more (13). However, failures to immunize were not distributed evenly throughout the cohort:

- the failure rate was significantly higher among girls than among boys (odds ratio 0.34; 95% confidence interval 0.15-0.76). The authors were not able to offer an explanation for this finding, but they recall that, coincidentally, unexplained excess mortality and immune abnormalities have been reported selectively among girls within a cohort of infants who had been inoculated with high-titre measles vaccine two to four years earlier (14).
- failure to seroconvert occurred some 50% more frequently among infants who had received vitamin A supplements than among those who had received placebo (OR 0.40; CI 0.19-0.88). Most vulnerable to failure were some 200 infants who still retained demonstrable titres of maternal antibody to measles: within this subgroup failure to convert occurred in 33.7% of infants who received vitamin A and in only 20.7% of those who received placebo. Moreover, after 6 months, the proportions with less than threshold protective levels of antibodies had risen to 38.2% in the vitamin A group and 22.8% in the placebo group.

The expectation at the outset of the study was that vitamin A would enhance the protection provided by immunization. The fact that the converse occurred places current policy into question, since the results are plausible in biological terms, and because the reduced antibody response associated with vitamin A supplementation seems likely to have adverse consequences for long-term immunity against the disease.

All currently-available preparations of measles vaccine contain attenuated live virus. Immunization, to be effective, induces a subclinical infection which results in an antibody response that determines seroconversion. The results of this study suggest that vitamin A supplements tend to suppress measles infection (caused either by wild virus or by attenuated vaccine strains) by a mechanism that is independent of antibody production, and possibly by limiting virus replication. Residual maternal measles antibody operates independently to inactivate invading virus. This effect, it seems, acts synergistically with maternal antibody to inhibit seroconversion.

It is possible, in nine-month-old infants with considerably lower levels of maternal antibodies, that vitamin A supplementation would have little, if any, attenuating effect on the response to measles immunization. The authors, however, caution against any policy that involves deferral of measles vaccination on the grounds that, at six months old, almost one-third of the infants admitted to their trial had no detectable levels of maternal antibody. They were consequently already highly vulnerable to measles infection at an age at which case-fatality rates have approached 15% (15).

In the light of these results, the uncontested benefits of improving vitamin A status in the very young need to be weighed against the possible negative effect on measles immunization. In the last analysis, observational studies may need to be carried out in different settings to monitor measles morbidity and mortality in children treated in accordance with prevailing policies. Consideration will also need to be given, as the authors point out, to possible untoward interactions between vitamin A supplementation and vaccination with other live attenuated virus vaccines including, most importantly, oral poliovirus vaccine.

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Vitamin A status: is dietary replacement practicable?

Correction of even moderate deficiencies of vitamin A among children in less developed countries has been shown to reduce both morbidity and mortality (1, 2). Dietary adjustment is widely favoured to correct these deficiencies on the grounds that it is sustainable and provides other essential nutrients. In many developing countries, fruit and green vegetables are the main source of provitamin A carotenoids (3). Adequate intake of these foods is essential to avoid vitamin A deficiency. It has recently been questioned, however, whether dietary adjustment alone is sufficient to rectify established vitamin A deficiency (4).

Demonstrable increases in serum vitamin A concentrations have been described after massive consumption of mangoes (5). However, in a recent controlled study undertaken in rural Java, sustained daily supplements of dark green leafy vegetables were found to be ineffective when compared with beta carotene supplements in raising serum vitamin A levels among anaemic women (4).

It is important to stress that these results were obtained in adults, few of whom were deficient in vitamin A, The authors conclude that the bioavailability of beta carotene in plant tissues is less than has been widely presumed. However, there is no basis, other than speculation, for extrapolating these results to vitamin A deficient children. Nor are there grounds to overturn current policy which emphasizes the need for dietary adjustment wherever vitamin A deficiency is endemic.

Vitamin A supplements offer the most reliable and rapid means of correcting established, severe deficiency, but this does not detract from the need to assure adequate dietary sources of vitamin A for children everywhere.

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Ophthalmia neonatorum: opportunity for improved prophylaxis

Clinical features and treatment

Conjunctivitis of the newborn (or ophthalmia neonatorum) is defined by convention as any conjunctival infection with discharge that occurs during the first four weeks of life (1). Included are many infections due to staphylococci and Gram-negative bacteria that are acquired after birth. However, the conditions most likely to damage the eye are gonococcal and chlamydial infections transmitted from the mother's genital tract during delivery.

Untreated, gonococcal ophthalmia progresses with alarming rapidity (2). Corneal involvement commonly results in blindness and sometimes perforation of the eye. Chlamydial infection is generally less severe, but signs of conjunctivitis may persist for several weeks during which vision may be impaired as a result of corneal scarring, vascularization and pseudomembrane formation (3, 4).

Notwithstanding widespread reports of gonococci resistant to tetracycline (5–7), it is current practice to treat all cases of neonatal ophthalmia with frequent applications of 1% tetracycline eye ointment, initially at hourly intervals decreasing progressively after several days to 4 times daily (1). It is vital, however, that infants with gonococcal infection — which is readily diagnosed by examining a conjunctival smear for Gram-negative intracellular diplococci (8) — additionally receive effective antigonococcal therapy. This is most conveniently administered as a single intramuscular injection of spectinomycin, kanamycin, or a cefalosporin such as cefotaxime which has pronounced activity against Gram-negative organisms (9). The diagnosis of chlamydial disease is often established on a presumptive basis when gonococci cannot be detected, since laboratory confirmation demands cell culture or testing for specific antigens. It is less responsive to antibiotics, and a two week course of erythromycin (50 mg/kg daily in 4 divided doses) is widely used (9).

The essential need for protection

Estimates of the prevalence of neonatal ophthalmia in less developed countries range as high as 4% of live births for gonococcal infection and 8% for chlamydial infection (10). The prevalence of gonorrhoeal and chlamydial infections among pregnant women in many of these countries is far higher, and in some surveys it has exceeded 20% (1, 2). These grim statistics press home the urgent need to better protect the sight of infants throughout the less developed world by more effective treatment of sexually transmitted diseases in pregnant women, and more effective chemoprophylaxis of infants at birth. Meanwhile, considerable effort and expenditure is directed to an often despairing effort to treat cases of neonatal ophthalmia that could readily have been prevented.

Opportunity may now be at hand to protect a greater proportion of infants in developing countries. Case-management of sexually transmitted diseases is improving in many countries as a result of the HIV pandemic. Recently generated evidence suggests that this effort and related educational programmes can reduce the prevalence of these infections both in mothers and in babies (11, 12). These improvements, however, can do no more than supplement the need for routine prophylaxis at the time of delivery. Since silver nitrate was first instilled into the eyes of newborn infants as a protection against infection over 100 years ago, this intervention has been the mainstay in the management of neonatal ophthalmia. Once the practice had become widely accepted the incidence of blindness in children in nineteenth-century Europe was reduced 20 to 30-fold (13). Precisely the same technique — or some comparably effective form of prophylaxis — remains a statutory requirement in many highly developed countries. Yet, through lack of resources, prophylaxis is failing in the least developed countries, where it is most needed.

Erythromycin and tetracycline preparations are some 20-fold less expensive than silver nitrate and have been preferred in some centres on the basis of claims that they are more effective against *Chlamydia trachomatis* and less likely to cause severe toxic conjunctivitis (14,15). However, it seems that the protective efficacy of topical erythromycin may have been overstated (16–19): in one recent study it did not significantly reduce the overall incidence of ophthalmia (17); failure rates as high as 10 to 20% are quoted for chlamydial conjunctivitis (18); and outbreaks of erythromycin-resistant staphylococcal conjunctivitis have been reported following its use (19).

Tetracycline was found to be significantly superior to silver nitrate in protecting against both gonococcal and chlamydial infection in one large controlled trial undertaken in Kenya (20). However, concerns about the global prevalence of tetracycline-resistant gonococci (5–7) have accentuated the need for a new approach to prophylaxis.

Experience with povidone-iodine

One highly-promising candidate prophylactic substance is the non-organic broad-spectrum antimicrobial compound, povidone (INN = polyvidone) -iodine. A 2.5% ophthalmic solution can be prepared at a cost estimated to be 70-fold less than that of 1% silver nitrate and 3-fold less than tetracycline ointment (9). *In vitro*, it is active against a wide spectrum of microorganisms and no evidence of bacterial resistance has yet been reported (21). Sensitive organisms include not only gonococci and chlamydia but also the herpes simplex virus (22), an occasional yet serious cause of an insidious form of keratoconjunctivitis (23).

Instilled prophylactically before ocular surgery, a 5% solution has been shown in adults to be well tolerated and effective in reducing the bacterial flora and to significantly decrease the incidence of post-operative endophthalmitis (24, 25).

In a preliminary trial of povidone-iodine among newborn infants, a 2.5% solution was used to decrease risk of conjunctival hyperaemia. Even at this lower concentration, povidone-iodine was more potent in inhibiting bacterial growth and less irritating than silver nitrate (26). This finding has now been confirmed in a masked prospective trial (27) involving over 3000 newborn infants in an area of Kenya where the incidence of ophthalmia has been reported to exceed 20% (10). Each child received an instillation of either 2.5% povidone-iodine, 1% silver nitrate, or 0.5% erythromycin ointment. Within these treatment groups, the incidence of infective conjunctivitis was respectively, 13%, 17.5% and 15%, and of conjunctival hyperaemia, 10%, 14% and 13%. In both respects, the advantage associated with povidone-iodine was statistically significant.

The authors conclude that povidone-iodine provides more secure protection than silver nitrate, is less likely to cause allergic or inflammatory reactions, and is less costly to administer. But there is need for caution: the incidence of ophthalmitis resulting from gonococcal infection was 0.8% among the children who received povidone-iodine, but only 0.4% among those who received silver nitrate. This difference, which was determined within a total of only 13 cases, does not attain significance, but the trend is disquieting. An independent commentator emphasizes the need to determine the efficacy of povidone-iodine more precisely in gonococcal and other specific infections and to monitor possible adverse effects in a considerably larger cohort.

It is important to resolve these residual issues efficiently and promptly: on the available evidence, any one of these treatments offers manifest advantage to the considerable numbers of infants in less developed countries that remain perilously devoid of protection.

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Ivermectin: an effective acaricide

As a result of generous and free supplies by the Merck pharmaceutical company through the Mectizan Donation Programme, ivermectin has become indivisibly associated with the control of onchocerciasis. However, its value is now also established in lymphatic filariasis (see page 132) and interest is emerging in its broader antiparasitic properties.

Ivermectin is a chemically-modified form of a member of a class of macrocyclic compounds called avermectins that are apparently unique to a strain of actinomycetes called *Streptomyces avermitilis* which was isolated during large-scale screening of samples of Japanese soil in the 1970s (1). Although it is structurally similar to the macrocyclic lactone antibiotics, ivermectin has no antibacterial activity. It is exceptional, however, in that it is highly active against a wide range of parasites that infect animals and man, including nematode worms, mites (acarines), and insects (2).

Among the uses for which ivermectin is already established in veterinary medicine is the treatment of sarcoptic mange, a mite infection in domesticated animals. Early attempts to use it in the treatment of human scabies — which is also caused by a variety of the same organism, *Sarcoptes scabiei* — provided inconsistent and sometimes disappointing results. In the Pacific islands a single oral dose of ivermectin (100 µg/kg) cured 70% of the treated patients — a substantially higher proportion than were cured by a standard course of benzyl benzoate applications (3). Similar results were reported from a trial conducted in Mexico in which patients were treated with ivermectin, 200 µg/kg (4). In India, however, a dose of 100 µg/kg has been reported to be inadequate (5), while in West Africa a single oral dose of either 100 or 200 µg/kg was considered to be no more effective than placebo (6).

In the light of these findings, the results of a recent open uncontrolled study — which involved otherwise healthy individuals and immunodeficient patients with HIV infection — are reassuring (7). Scabies was parasitologically confirmed in all 22 patients admitted to the study and each received a single oral dose of ivermectin, 200 mcg/kg. After 4 weeks, no sign of scabies was detected in any of 11 otherwise healthy patients. Scabies was also apparently eradicated in all but one of 11 patients with HIV infection (although two of these patients received a second dose of ivermectin 2 weeks after the first). The remaining patient, who was seriously ill with advanced AIDS and tuberculosis, was eventually cured of extensive, heavily crusted scabies after a third dose of ivermectin and total body treatment with 5% permethrin cream applied under supervision.

The authors conclude that a single oral dose of ivermectin will cure most cases of scabies, but that crusted or other stubborn cases may require additional treatment. They stress the need, however, for community treatment since, within two

months of administration, ivermectin may have no residual activity against scabies. Reinfection, they suggest, may explain many of the apparent treatment failures reported in other studies.

As yet, application for formal approval of ivermectin in the treatment of human scabies has not been sought (8), but prospective clinical trials are now planned in several centres. If, as seems likely, ivermectin is confirmed to be both effective and acceptably safe in this indication, it will offer substantial advantages over topical treatments. Administration will be greatly simplified; treatment may be readily arranged on a community basis which will greatly reduce the risk of reinfection; and many of the intestinal parasites endemic where scabies is most prevalent will be incidentally but effectively controlled (9–11).

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Hepatitis B vaccination in infancy: evidence of long-term efficacy

Hepatitis B virus infection in infancy commonly results in chronic carriage of the virus (1) and, eventually, in a high risk of chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma (2). Infection is hyperendemic in large areas of sub-Saharan Africa and south-east Asia. Most infections in Africa are spread from sibling to sibling within the first few years of life (3), while, in Asia, perinatal infections predominate that are acquired from mothers who are carrying the HBVe antigen (4).

These patterns of transmission suggest that, in Africa, infection might be effectively controlled by mass vaccination during infancy, whereas, in Asia, very early vaccination — and, ideally, passive immunization — would be required. Even short-term immunity would be of considerable value since it seems that the chronic carrier state rarely develops in children older than 4 years (5). Results already obtained among preschool children in the African Sahel with hepatitis B vaccine have been highly promising. Protective efficacy over a six-year period has been estimated to be between 80% and 90% (6), while regimens involving 2 or 3 booster doses given over a period of several months have been highly efficient in protecting children against persistent infection (7).

The only long-sustained programme of vaccination against hepatitis B infection in west Africa was started in The Gambia in 1986 (8). At that time, all non-immune children under the age of 5 years in two Gambian villages were vaccinated. Since then, all children born in these villages have been vaccinated in infancy. After 4 years, the efficacy of vaccination in protecting children against chronic carriage of the virus was 97.3%, and the choice of different schedules of vaccination involving different timings, doses, and routes of administration (intradermal or intramuscular) was found to have little influence on this outcome (7).

As breakthrough infections continue to occur, overall vaccine efficiency must be expected to fall. By 1993 it had dropped among children vaccinated between 1984 and 1989 to 89.8% (95% confidence interval: 86.0-92.9), and antibody concentrations

had fallen to a geometric mean of 4.8% (3.6–6.4) of the peak value (8). However, examination of the temporal pattern of infection within a cohort of children drawn from this group indicates that the incidence of breakthrough infection (when adjusted for duration of exposure and antibody concentrations) is falling to a highly significant extent: in the second of two successive 4-year periods there were fewer than half the expected number of infections.

This is a most encouraging finding. It suggests that not only has the vaccination programme had an immediate impact on transmission by reducing the prevalence of acutely-infected and highly-infectious children; it has also greatly reduced the risk of children becoming chronic carriers of the disease. Meanwhile, in accordance with expectation (9), existing carriers — formerly the principle source of infection within families — are becoming less infectious with the passage of time.

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General Information

"Natural" medicines: a Pandora's box

After 100 years of unprecedented scientific achievement society is beset with apprehension about the pervasive and ominous effects of technological innovation on the quality of the environment. An antipathy has emerged among some consumers to highly-processed commodities. Backed by forceful advertising exploiting the flawed principle that what is natural is safe and wholesome, a flourishing market has developed in nutritional supplements, herbal preparations, tonics and home remedies that often escape regulation. Even more questionable is the panoply of unproven systems of unorthodox medicine offered to despairing patients sceptical of the value of conventional terminal cancer care (1–6).

The extent to which such products are controlled under national drug legislation varies considerably. Even where product licences are required, the criteria on which they are issued are far from uniform. Most frequently, whether or not a product qualifies for control is decided by the claims on the label. This is a broadly encompassing criterion, but it is also arbitrary: herbal products sold as teas or food supplements may escape controls applied to the same substances promoted with a medicinal claim. Even when controls are applicable, the need to provide documented proof of efficacy and safety may be waived for products accepted to have been in prolonged "traditional" use (see also page 152).

Within the context of its new MedWatch programme — and in the wake of the US epidemic of eosinophilia-myalgia syndrome which was attributed to food products containing L-tryptophan, possibly derived from a contaminated bulk product (7), and reports of deaths attributed to the inclusion of germanium salts in similar products in the United Kingdom (8) — the US Food and Drug Administration has requested doctors to provide reports of suspected adverse reactions to dietary supplements (9). However, many herbal products, now central to a thriving trade in alternative, or unconventional medicines, remain unregulated and largely undocumented (10).

Many of these products are likely to be innocuous, but herbal preparations and products derived from them are far from innocuous as a class. The range and importance of the toxic effects attributed to them is reflected in the following restrictive decisions taken by national drug regulatory authorities and documented by WHO over the past two decades (11):

- in 1977 the US Food and Drug Administration denounced the promotion of Laetrile or "vitamin B17", a preparation derived from crushed apricot pips. The major component was amygdalin, a glycoside that yields hydrogen cyanide when hydrolysed. The originator claimed that hydrolyzation occurs only in cancer cells which are selectively destroyed by the product. The FDA countered that it could cause poisoning and death when taken by mouth and a subsequent clinical study has evaluated it as worthless on objective criteria (12).
- in 1979 the Singapore government prohibited the importation and sale of preparations containing berberine, an alkaloid derived from *Coptis teeta*, following reports of jaundice and haemolytic anaemia in infants with glucose-6-phosphate-dehydrogenase deficiency.
- in 1980 superheporin capsules, a traditional herbal mixture of *angelica radix*, *ligustica rhizoma*, *salviae radix*, *pteropii excrementum* and *carthamic flos*, was withdrawn from sale in Indonesia following its association with congenital malformations.
- in 1981 the Health Office of the Federal Republic of Germany withdrew from the market all proprietary medicines containing aristolochic acid including and all herbal preparations and extracts prepared from plants of the *Aristolochiaceae* family. Extracts of this plant, which was shown to have a potent carcinogenic potential in animal studies, had been traditionally used as a bitter and a wide range of therapeutic effects had been claimed.
- in 1992 the German Federal Health Office withdrew all herbal products derived from *Rubiae tinctorum radix*, including lucidine and other

derivatives of anthraquinone. These substances are partially metabolized *in vivo* to 1-hydroxy-anthraquinone which was shown in animal studies to induce tumour formation in the gastric and intestinal mucosa and in the liver.

This list is by no means exhaustive. Indeed, the range of adverse effects attributed to natural agents ranges widely across the biological spectrum. Most of those described above are due to direct dose-related toxic effects. Other substances have an allergic potential: life-threatening anaphylactic reactions have been associated in Australia with the use of health tonics containing "royal jelly", a product of honey bees, which is derived not from plant pollens, but from the secretions of their salivary glands (13). Other substances provide overdosage of a specific pharmacologically-active substrate: use of the seaweed, kelp, in herbal slimming medicines has resulted in clinical hyperthyroidism from excess of iodine (14). Yet other effects are due to activation of specific receptor mechanisms: potent oxytocic properties have been reported in a slimming preparation prepared from broom (*Cytisus scoparius*) which contains high concentrations of sparteine (15).

Lengthening the list are the photosensitivity reactions caused by herbal preparations containing high concentrations of psoralens (16) and the veno-occlusive hepatic disease and cirrhosis caused by the pyrrolizidine alkaloids contained in plants used in the preparation of "bush teas" in Africa and South-East Asia (17–19).

The wide variety of herbal preparations implicated in cases of clinically-evident liver toxicity has become the foremost concern among commentators who are calling for increased oversight of the safety of these products (20–22). The plants that have been cited include germander (*Teucrium* species), comfrey, coltsfoot (*Tussilago* sp.), mistletoe, pennyroyal oil, skullcap (*Scutellaria* sp.), valerian (*Valeriana* sp.) margosa oil, and some Chinese herbal products (23–31).

Concern has been heightened by reports in the United States of four cases of subacute and fulminant liver failure attributed to a preparation of chaparral (23–25), an evergreen desert shrub that contains a potent antioxidant, nordihydroguaiaretic acid, which has been shown to inhibit vital mechanisms of hepatic metabolism (32). In the past, cases of fulminant liver failure have mostly been attributed to viral infection (33). Now, it seems, infection may have been overdiagnosed. Newly available techniques, including the highly sensitive polymerase chain reaction (PCR), have shown no trace of any nucleic acid of known hepatic viruses in some 50% of these patients (34–36).

The extent to which cases of fulminating hepatitis, as well as the 5% of cases of presumed viral hepatitis which are not confirmed on serological testing (37), may be due to herbal toxicity remains an open question. This is a possibility that doctors should keep in mind and record when questioning patients with acute hepatic disease.

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Homoeopathy put to the test

Over the years, assessment of homoeopathic practice has been determined more by conviction than by hard evidence. This is now changing. Two double-blind, randomized trials have recently been published in the *Lancet* in which the effect of homoeopathic treatments have been compared with placebo under controlled conditions.

The first of these trials (1), which involved only 24 patients, compared homoeopathic immunotherapy with placebo in asthmatic patients who continued to receive their normal treatment. The allergen used for desensitization was selected by a homoeopathic physician on the basis of the patient's history of exposure and a conventional skin test.

Daily digital symptom scores (severity of night-time and daytime attacks, morning tightness and cough) provided no evidence of significant differences between the two treatment groups. However, 9 of

11 patients receiving the homoeopathic treatment and only 5 of 13 receiving the placebo registered improvement on a visual analogue scale. This trend in favour of the homoeopathic treatment was also evident in some measurements of lung function (forced vital capacity and forced expiratory volume in one second).

A similar pattern of results has subsequently been reported in a double-blind randomized trial of individually prescribed homoeopathic medicines against placebo in preschool children with frequently-recurrent upper respiratory tract infections (2). Over one year of follow-up, mean daily symptom scores tended to be somewhat lower in the treated group, and the same trend was reflected in the use of antibiotics and the proportion of children undergoing adenoidectomy.

In both trials the differences were small but consistent. One group concludes: "Our results lead us to conclude that homoeopathy differs from placebo in an inexplicable but reproducible way". The clinical relevance of the effect, however, remains undetermined.

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Medical records and medical research

Occasional reports released from official archives describing questionable biomedical research undertaken on unknowing subjects during time of war continue to remind both the public at large as well as the medical profession that society must respect the rights of the individual. This is the philosophy of the Declaration of Helsinki which was drafted and adopted in its initial form during the 18th World Medical Assembly in 1964. Not only does the text emphasize that medical progress is based on research which ultimately must rest in part on experimentation involving human subjects; it states categorically that most diagnostic, therapeutic or prophylactic procedures involve hazards, and that this applies *a fortiori* to biomedical research. An inevitable corollary to this statement is that every reasonable effort should be made to assess the safety and efficacy of innovative interventions within the shortest possible time frame and that every respect be accorded to the welfare and human rights of every individual who participates in these assessments.

The safeguards to the individual that are set out in the Declaration of Helsinki are based on two requirements: that biomedical research involving human subjects should be undertaken only after the protocol has been cleared through a process of independent peer review; and that no subject should be involved in such research without having provided freely-elicited informed consent. Some of the problems involved in extending the concept of informed consent to vulnerable minorities still evoke discussion (see page 151), but these debates underscore and refine the basic principles of the Declaration.

More contentious are proposals now under consideration in some countries to extend the application of these principles to the use for research purposes of preexisting medical records. That sensitive personal information generated for medical reasons needs to be held in confidence and must not be used administratively for other purposes is not in dispute. Concern centres on the fact that, collectively, patients' medical records constitute an important resource for research, and that denial of their use for this purpose would constitute a major setback for public health, and frustrate a longstanding practice by doctors in every branch of the profession.

In particular, it has been argued, to withdraw this resource or to impede it through impracticable constraints will jeopardize the vital observational research needed to identify adverse effects of drugs, the safety of medical procedures, and the environmental effects of toxic substances (1). Not only do these records provide the sole means of identifying or confirming the existence of such hazards, they also provide the reassurance needed before new techniques or new products can become established in routine practice.

Doctors everywhere are subject to a code of collective confidentiality in their routine management of patients. Once this strict sense of duty in sharing personal medical information within the profession is accepted, it is argued that whether the knowledge obtained is required for the care of the individual patient or for the wellbeing of the collectivity of similar patients becomes irrelevant.

In the United Kingdom, a working group formed under the aegis of the Royal College of Physicians has published a report (2) that explores ways in which medical records can continue to be used for research purposes within a setting that assures appropriate confidentiality. The group proposes that the following guidelines should be applied:

"Research involving access to medical records, registers, or existing biological samples only, without direct patient involvement, is not considered to require individual patient consent or independent ethical approval provided that:

"1. explicit consent to access a person's records is obtained either from the official custodian of the records or from the patients clinician: the decision to access personal medical information should not be left to the sole discretion of the investigator.

"2. the recipient of the information is a senior professional person (e.g. a consultant medical practitioner or a principal in general practice) who may be disciplined by his or her professional body over any breach of confidentiality.

"3. confidentiality is assured through exercising professional codes of conduct.

"4. anonymity is assured in any report or publication."

Nowhere more than in medicine is progress determined by individual experience. Unless a manifestly practicable way can be found to continue to access medical records for research purposes a resource will be lost that is of profound importance to the wellbeing and protection of society as a whole.

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Malaria: practicable approaches to prevention remain elusive

Within the Gambia, as elsewhere in equatorial Africa, malaria remains one of the foremost causes of death among young children. At least 1000 children less than 5 years of age — or more than 1 in 200 within this age group — die from the disease each year (1).

Prevention of infection remains a high public health priority, but neither vector control nor routine chemoprophylaxis alone offers a practicable solution within a national context. One possible approach is to encourage sustained use of insecticide-impregnated bed nets. Results of a large-scale controlled trial conducted within the Gambia to test the feasibility of this option provided promising results. Sleeping under nets, combined with a short period of chemoprophylaxis during the season of maximum transmission, more than halved overall mortality from the disease among young children (2-4).

Progress in a subsequent programme aimed to introduce this form of protection in all large villages within the Gambia over a 2–3-year period has recently been evaluated (5). Within 5 selected areas of the country comprising a total of 104 villages and some 100 000 persons, a 25% reduction in mortality from all causes among children aged between 1 and 9 years was recorded during the first year of the programme. In one area alone, the programme was unsuccessful, particularly among children aged 1 and 2 years. When this area was excluded from evaluation the reduction in mortality rose to 38% (rate ratio 0.62; 95% confidence interval 0.46–0.83. p=0.04). Decreases were also reported in the prevalence of parasitaemia and high-density parasitaemia, and a corresponding increase was recorded in mean packed cell volume.

These results were less encouraging than those presented in the preliminary controlled study. Overall, it was estimated that only some 70% of children aged 1 to 4 years slept regularly under bed nets in these sentinal villages (6), whereas in the controlled study compliance was estimated at 96%. Similarly, only about 80% of the nets were brought to local centres for impregnation, whereas a much higher rate was achieved in the controlled trial (4). Particularly low rates of usage and high transmission were reported from the area in which the intervention was unsuccessful.

On balance, the authors conclude, in a country where nets are widely used and which has a good primary health care system the use of impregnated bed nets can substantially reduce child mortality. As yet, however, this cannot be done at a cost that the

Gambia can afford. It is estimated that the cost of running the national programme throughout the first year was about US$ 92 000. Almost two-thirds of this represented the cost of insecticide — 40 ml of 20% permethrin was needed to treat each net. On this basis, the annual cost of insecticide needed to treat all bednets in the Gambia would be about US$ 150 000. This sum is beyond the means of the Gambian Ministry of Health, and a pilot cost-recovery programme in which families were asked to pay the equivalent of US$ 0.5 for each treated bednet resulted in a dramatic drop in coverage and a return of child mortality rates to their pre-intervention levels.

The average cost of saving one life within the context of this programme has been estimated at US$ 600. Few can disagree with the authors that "finding new ways of financing such programmes is now a matter of priority."

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Traditional eye medicines: a note of concern

For many families living in rural Africa the nearest health clinic or hospital may be a day's journey distant. Most villages, however, have at least one traditional healer. It is clearly a sound investment to train and encourage healers to contribute to those elements of basic modern community care that are within their compass. It is equally important to discourage them from engaging in practices found to be unhelpful or positively harmful.

A recent leading article in the *Lancet* has drawn attention to the dangers of traditional eye medicines (1). It cites estimates from three studies undertaken in rural sub-Saharan Africa over the past 20 years to suggest that about one-quarter of corneal ulcers and cases of blindness in children result from the instillation of traditional medicines into the eye (2–4). A further recent study has confirmed these findings: not only had as many as one in three patients with corneal disease received eye medicines from traditional healers, they also took four times longer than other patients to report to health centres and had three times the rate of blindness in the affected eye (5).

In some hospitals in rural Africa it seems that as many as half the patients have consulted a traditional practitioner prior to admission. It is suggested that this does not simply reflect a stark lack of facilities and trained medical personnel: minor illness often has an important psychosomatic component, and for a patient to understand from a powerful and respected member of the local community why such symptoms have occurred, within the context of local beliefs and customs, is comforting to the individual and stabilizing to society. Moreover, since cure of the condition is not regarded as the prime function of the healer, when patients eventually "come for help to hospitals ... it is seldom with the sense that the local man has failed" (1).

The article concludes that it is vital not to devalue traditional practice. The local system of medicine provides the best and only relief for the overwhelming numbers of patients who are neurotic, depressed or mentally handicapped, as well as those who are afflicted with AIDS and other essentially untreatable conditions. Traditional

healers require education to recognize illnesses that they cannot and should not treat, but at the same time they require encouragement to provide safe treatment for conditions that they are in a position to manage effectively. Dialogue is needed, but it must be based on attitudes of mutual understanding and respect.

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Regulatory Matters

Informed consent in emergency situations

United States of America — Freely elicited informed consent and independent peer review are the dual safeguards applied to protect the interests of subjects involved in biomedical research. The limited application of the informed consent procedure, and its vulnerability to abuse, render it inadequate as an exclusive means of protecting the human rights and welfare of research subjects, and it fails most decisively when the population from which the subjects are drawn are most vulnerable. Not least, this limitation applies to research conducted in emergency circumstances.

Patients with such conditions as traumatic brain injury, occlusive stroke, cardiac arrest, life-threatening arrhythmias, myocardial infarction, haemorrhagic shock, pulmonary embolism, status epilepticus and poisoning are acutely and gravely ill and face severe disability or death. Nearly always they are cognitively and physically unable to consent to participate in a research programme and it is often not feasible to obtain proxy consent from a responsible relative within practicable time limits. It has been contended that, as a result of varying interpretations of the existing regulations, some important research proposals have been substantially delayed. In some cases institutional review boards (or ethics review committees) have delayed or disapproved protocols calling for a waiver of informed consent on the basis of their interpretation of Federal regulations. In other cases these bodies have approved protocols only to be instructed by a Federal agency that the protocols do not comply with the requirements of the regulations.

A public forum, co-sponsored by the Food and Drug Administration and the National Institutes of Health, was consequently held in January 1995 to explore the ethical, legal, and operational aspects of obtaining informed consent in research conducted in emergency circumstances (1, 2). All the participants agreed that regulations need to be developed that accommodate the possibility of conducting research in emergency circumstances, while at the same time securely protecting the interests of the subjects. Some felt that current regulations overemphasize the principle of autonomy for the subject at the expense of the principles of beneficence and justice. They argued that when the expected outcome of standard therapy is dismal, the principle of beneficence — that is, seeking what is best for the target population of subjects — should outweigh the principle of autonomy.

Considerable weight was accorded to a consensus statement prepared in October 1994 by US investigators active in this field (3), which contends that "the risk of not doing emergency research is denying promising new treatments to individual patients with conditions that currently have no effective therapy, or to future patients with the same devastating conditions." The public forum considered that serious consideration should be given by Federal Agencies to the recommendations in the consensus statement which are set out in full below:

1. Federal regulations must be developed that explicitly address the investigation of emergency therapies for patients unable to give informed consent. This population of patients should be identified as a vulnerable population and specific safeguards should be implemented to protect them from research risks without excluding them from research benefits.

2. The Federal regulations that are developed should be complete and compatible. Institutional review boards (IRB) should receive clear guidance from the regulatory agencies to allow consistent interpretation and application of the new regulations.

3. A new category, termed "Appropriate Incremental Risk" should be defined for studies that propose to forgo consent in emergency research. Incremental risk is defined as the increased risk of participating in the research protocol relative to the natural consequences of the medical condition, or the increased risk of receiving the experimental intervention relative to receiving the standard treatment for the medical condition. Appropriate incremental risk is an amount of incremental risk that is acceptable to the vast majority of potential patients.

4. Federal regulations that are developed to provide for the emergency studies that forgo informed consent should include the following elements. Emergency research protocols which propose to forgo informed consent should also include these elements:

a. the potential subject enters into the clinical condition under study unexpectedly and suddenly;

b. once the clinical condition develops the potential subject cannot give consent as a result of the condition;

c. the legally-authorized representative is not available to give proxy permission;

d. to be effective, the intervention under study must be administered before consent from the legally authorized representative is feasible;

e. the experimental intervention poses no more than Appropriate Incremental Risk;

f. the research could not practicably be carried out without forgoing consent;

g. the research hypothesis is based on a foundation of valid scientific studies that support a realistic possibility of a benefit over standard care;

h. the state of knowledge has reached the point where necessary answers can be best obtained through human trials; and

i. when possible, and at the earliest reasonable opportunity, the patient or his/her legally authorized representative will be informed of the patient's inclusion in the study. Informed consent should be obtained for continuation in the protocol and for subsequent examinations or tests related to the study. The patient or representative should also be informed that the patient may withdraw from the study at any time: upon withdrawal, the patient will receive only non-investigational treatment.

5. The interests, rights and welfare of potential subjects in emergency research trials, as a vulnerable population, must be protected by special safeguards applied by IRBs. These safeguards may include:

a. additional scientific, medical, or ethical consultation;

b. consultation with former or potential patients or community groups;

c. specialized monitoring procedures to be followed by Data Safety and Monitoring Boards;

d. careful review of how subjects are selected, including extraneous incentives to enroll patients in the study;

e. careful review of the relative risks and benefits of participation; and

f. careful consideration of the usefulness of the research.

6. IRB members should receive formal continuing education about the regulations applying to studies which propose to forgo consent, and the ethical principles upon which these regulations are based.

7. Because local IRBs have good insight into local practice, the local patient population, and the capabilities of local researchers, institutions and resources, they should be the monitoring bodies primarily responsible for maintaining vigilant oversight of clinical trials of emergency research.

Sources

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2. *Report on the public forum on informed consent in clinical research conducted in emergency circumstances.* Food and Drug Administration/National Institutes of Health, Washington, USA. May 1995.

3. *Informed consent in emergency research.* Consensus from the Coalition Conference of Acute Resuscitation and Critical Care Researchers. 25 October, 1994.

Natural remedies: requirements for registration

Sweden — From July 1996 natural remedies will be regarded as medicinal products. The approval of the Medical Products Agency will be required for their production and wholesale distribution. They are described as products that:

- contain active ingredients that consist of naturally-occurring vegetable, animal or mineral matter, bacterial cultures, a salt or salt solution and which are not processed "too highly" by chemical, biotechnical or other methods;

- are intended for general sale (not restricted to pharmacies); and
- are suitable for self-medication in accordance with "tested national tradition or tradition in countries close to Sweden with respect to drug usage."

Homoeopathic products and preparations intended for injection are subject to other regulations and are excluded from these requirements.

Applications will be assessed by the Medical Products Agency having regard to quality, efficacy and safety, while general rules regarding claims that can be made in advertising and other forms of product information will be determined by the Swedish Board for Consumer Policies.

Manufacturers will be required to satisfy the Agency that they comply in all respects with Good Manufacturing Practice (GMP). This will be determined by an inspection of the manufacturing facilities and a review of documentation to determine whether the application provides sufficient chemical, microbiological and pharmaceutical data to ensure the product in question can be produced to a consistently high production standard. The preparation of dried plants, extracts and tinctures will be required to conform to currently existing guidelines.

The assessment of safety will be determined primarily on whether or not safety in use has been established by traditional use. If this evidence is not available, harmlessness must be established by submission of relevant pharmacological, toxicological and clinical data, as necessary.

Natural remedies may be marketed only for conditions that can be appropriately treated by self-medication. Reliable bibliographic data may suffice to establish the efficacy of well-documented traditional products. In other cases evidence of efficacy will need to be generated in accordance with existing guidelines.

Source: Medical Products Agency, Sweden. Press release, July 1995.

Starting materials: proposals for a regulatory framework

European Community — In the light of recommendations from its technical advisory bodies, the European Commission has issued a concept paper that marks a decisive departure from the existing philosophy that the manufacturer of a finished pharmaceutical product should assume sole responsibility for the quality of its ingredients. The paper sets out a framework for the adoption of a licensing, inspection and certification scheme for starting materials.

At present — with the exception of biological products which are excluded from consideration within this paper — the legislative framework now operative within the European Union does not apply to the manufacture of starting materials. Although an inventory is still to be carried out, it is estimated that there are some 250 producers of pharmaceutical active substances within the countries of the Union and around 400 manufacturing sites. No authorization is currently required at Community level to manufacture starting materials — which are defined in the concept paper to include not only active substances, but also precursors, excipients and packaging materials — and in most member states there is no compulsory inspection scheme nor even the possibility to establish GMP certificates. Instead, routine tests, which must be defined in the marketing authorization for the finished product, are required to be carried out on each batch of starting material.

The testing of samples is no longer considered sufficient to ensure the quality of production batches of starting materials. It is emphasized that lack of consistency in the chemical or physical properties of the starting material, or impurities and contaminants not detected by routine analytical methods, could adversely affect the finished product. Controlling starting materials only at the end of the manufacturing process, it is concluded, is not consonant with the general principle of quality assurance: that quality should be "built into" a product throughout **all** the stages of manufacture.

The additional costs and administrative requirements involved in introducing the proposed scheme are acknowledged. It is noted, however, that some Member States (notably, Austria, Finland and Italy) have been inspecting producers of starting materials for years, that France and Germany are developing this capacity, and that some other Member States inspect these facilities on a voluntary basis when this is required as a condition of export. Moreover, it is noted that the United States Food and Drug Administration is working on standards for bulk pharmaceutical products (active ingredients) and has expressed its concern about foreign bulk manufacturing sites.

Several benefits are identified that would derive from the proposed common framework:

- an important shortcoming in the compilation of European Drug Master Files would be resolved. At present, active ingredient manufacturers contribute relevant data, but these data cannot be checked nor can manufacturing operations be inspected on premises that are not registered;
- the enactment of legal provisions to inspect companies submitting data to the European Pharmacopoeia (EP) would resolve a similar shortcoming in the system of certification of pharmacopoeial monographs;
- the exportation of starting materials from Member States would be facilitated — since manufacturers are often requested to submit GMP certificates — and the quality of imports would be better controlled; and
- the expensive and burdensome number of foreign inspections within the Member States of the Union would be reduced, since the proposed system would improve confidence in and use of the European Drug Master Files and the EP certification procedures.

It is proposed that the framework should initially be applied exclusively to active ingredients, although the need to extend the framework to other classes of starting materials should be established at the outset. The following aspects should be considered in the development of the framework:

- a system by which Member States grant manufacturing licences;
- a requirement for producers to observe appropriate GMP;
- adoption by the Commission, in consultation with Member States, of Community GMP for starting materials;
- provision for routine inspection of producers by the supervisory authorities at a frequency to be determined and for inspection reports to be drafted after each inspection;
- provision for additional targeted inspections, for example, when a new application for a marketing application is submitted;
- provision for supervisory authorities to inspect in third countries and for reciprocal agreements between the Community and third countries;
- provision to link the inspection services with both the European Drug Master File scheme and the EP certification scheme;
- a need to refer to the WHO certification scheme where appropriate;
- a need to set up and maintain a Community data base of manufacturers of active ingredients, and ultimately, all starting materials;
- if appropriate, a provision for the cost of inspections to be charged to the industry; and
- a requirement that manufacturers operating within the Community purchase only active ingredients manufactured in inspected and approved production facilities.

Interested parties are invited to offer comments, particularly on the proposed regulatory framework by 1 December 1995.

Source: European Commission (DG III/E-3 Pharmaceuticals, RP11 4/50). *Community regulatory framework on good manufacturing practice and certification of starting materials for the manufacture of medicinal products.* Concept paper addressed to the Pharmaceutical Committee and the Working Party on Control of Medicinal Products and Inspections. Brussels, 28 July 1995.

Medication errors: a new reporting initiative

United States of America — The Food and Drug Administration is encouraging the medical community to report serious medication errors that result, or could have resulted, in fatalities, disability, or hospitalization. If warranted, the agency will take appropriate action to change the design, name or packaging of a product. One manufacturer has already agreed to change the proprietary name of a prescription drug to avoid potential and serious confusion with a totally different product. The agency recommends, particularly when a possibility of confusion of names is known to exist, that prescriptions for drugs be printed or typed and that, whenever possible, the condition to be treated be entered on the prescription.

Within the same programme, the agency is collaborating with the Association for the Advancement of Medical Instrumentation to develop standard enteral feeding set connectors that are different in gauge and design from connectors and devices (such as intravenous lines and syringes)

used for parenteral administration. The FDA has received numerous reports of fatalities and serious injuries resulting from administration through an intravenous line of liquid medicines and enteral solutions intended for a gastric tube. It has been recommended during this interim period that the distal end of every catheter be clearly labelled to decrease the possibility of confusion.

Source: *FDA Medical Bulletin*, **25**: 6 (1995).

Aminosalicylates and blood dyscrasias

United Kingdom — The Committee on Safety of Medicines has advised doctors that all marketed aminosalicylates share a potential to cause blood dyscrasias (1). Sulfasalazine, which is widely used in the management of rheumatoid arthritis and ulcerative colitis, is metabolised in the large bowel to mesalazine (5-amino-salicylic acid) and sulfapyridiine.It has been assumed that the sulfonamide moiety, which has been claimed to be responsible for the beneficial effects of sulfasalazine in rheumatoid arthritis, is solely responsible for the blood dyscarias associated with its use.

The other component, mesalazine, has been marketed as a single-component anti-inflammatory substance for the management of inflammatory bowel disease while, more recently, olsalazine — which consists of two mesalazine molecules linked by a diazo bond which is cleaved in the gut — has also become available. An initial review of adverse reaction reports provided no clear indication that these substances carried any risk of blood dyscrasias (2). This is no longer the case. The UK Medicines Control Agency has now received a total of 49 haematological reactions associated with mesalazine therapy, 3 of which were fatal. These include 5 patients with aplastic anaemia, 11 with leukopenia, 17 with thrombocytopenia and one with agranulocytosis. A further four reports associate olsalazine with such events.

The Committee notes that the reporting rates for blood dyscrasias associated with sulfasalazine, mesalazine and olsalazine are of similar order. It suggests, however, that events related to use of sulfasalazine are less likely to be reported because its adverse effects on the bone marrow are well recognized.

This expectation is consonant with results obtained in a comparative post-marketing study involving some 14 000 patients. In patients with inflammatory bowel disease, both sulfasalazine and mesalazine were associated with a risk of blood dyscrasias of less than 1:1000 users: in fact, no cases were associated with mesalazine within a sample of 4000 patients. In contrast, among patients with rheumatoid arthritis, the incidence of blood dyscrasias associated with sulfasalazine was some ten-fold higher at 6.1:1000 users. This relatively high incidence possibly reflects an intrinsic sensitivity among patients with this disease.

The Committee recommends that patients receiving an aminosalicylate drug should be advised to report any unexplained bleeding, bruising, purpura, sore-throat, fever or malaise that occurs during treatment. A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

Sources

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Antimicrobial susceptibility tests: unreliable performance

United States of America — The Food and Drug Administration has notified users that some commercial antimicrobial susceptibility tests may not reliably detect resistance in some pathogens, notably pneumococci and enterococci. These bacteria are slow-growing, whereas the systems in question — which were developed before the emergence of resistance in these pathogens — were designed for testing rapidly-growing bacterial isolates.

The FDA stresses the vital need for these tests to be reliable. The results that they offer determine not only the therapeutic management of individual patients, but also the strategies to be employed in surveillance and prevention.

The unreliability of penicillin (and other beta-lactam) disk diffusion systems for screening susceptibility in pneumococci has led the National Committee for Clinical Laboratory Standards (NCCLS) to recommend an oxacillin disk screen for this purpose. If this screen suggests resistance, a standardized minimum inhibitory concentration(MIC) test method is recommended to detect resistance to penicillin and other individual beta-lactam drugs.

To detect vancomycin-resistant enterococci, NCCLS recommends agar or broth microdilution, MIC, or disk diffusion testing allowing incubation for a full 24 hours, or a vancomycin agar test screen. For detection of penicillin/ampicillin resistance, agar or broth dilution tests and a nitrocefin-based beta-lactamase test are recommended.

Source: *FDA Medical Bulletin*, **25**: 2 (1995).

Coumarin: a strong association with hepatotoxicity

Australia — The benzopyrone, coumarin, which is used in the control of lymphoedema and other high protein oedemas, was introduced in Australia in mid-1993. Over a period of little more than one year the regulatory authority received a total of 10 adverse reaction reports citing the drug (1). Six of these describe jaundice — which in one case progressed to fatal hepatic necrosis — occurring in women aged 49 years or more. The one liver biopsy that has been obtained showed periportal and lobular necrosis. Each of the women had been taking coumarin in a daily oral dose of 400 mg for periods ranging from one to four months, and in no case was any other cause of jaundice apparent. In all but one instance coumarin was the only suspected causal agent, the 5 surviving patients recovered after coumarin was withdrawn, and in one of these jaundice recurred on rechallenge.

No restriction on the availability of coumarin has been announced, but these cases suggest that the frequency of hepatotoxicity among treated patients is at least 34 :10 000. This is considerably higher than has been demonstrated for flucloxacillin — which has recently been associated in Australia with cholestatic jaundice (2) — and other generally-available hepatotoxic compounds.

Sources

1. *Australian Adverse Drug Reactions Bulletin*, **14**: 11 (1995).

2. Jick, H., Derby, L., Dean, A., Henry, D. Flucloxacillin and cholestatic hepatitis. *Medical Journal of Australia*, **160**: 525 (1994).

Clomifene and ovarian cancer

United Kingdom — In the light of published evidence associating prolonged use of clomifene for infertility with a small increase in absolute risk of ovarian cancer (1), the Committee on Safety of Medicines has recommended that treatment should not normally be extended beyond six cycles (2). Within this limit there is no evidence of increased carcinogenic risk.

The Committee considers that further studies are needed to investigate the possible association between clomifene and ovarian cancer. For women aged between 20 and 30 years, the overall incidence of this cancer in non-users is around 2 cases per 100 000 women per year. The risk increases tenfold during the fifth decade and is greater in nulliparous women.

Sources

1. Rossing, M., Daling, J.R., Weiss, N.S. et al. Ovarian tumors in a cohort of infertile women. *New England Journal of Medicine*, **331**: 771-776 (1994).

2. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, **No. 21** (1995).

Iron-containing drugs and supplements: accidental poisoning

United States of America — Since 1986 more than 110 000 reports of children who had accidentally swallowed iron tablets have been received nationwide by poisons control centres. Throughout this period, the overall frequency of these reports and the number of associated fatalities has more than doubled. During the mid-1980s, up to 5% of children's deaths reported to these centres were attributed to iron-containing drugs and supplements. This proportion has now risen to approximately 17%. In some cases death has resulted from ingestion of no more than 5 tablets.

Current regulations require any product containing a total of 250 mg or more of iron in an orally-administered form to be sold in child-resistant packaging. FDA now proposes that dosage units (tablets and capsules) containing 30 mg or more of iron should be wrapped individually, as in blister packs, and that warning statements be carried on packaging of solid oral-dosage forms of iron-containing drugs and dietary supplements. It is proposed that these statements include the message that an overdose of iron may kill or harm a child; that the product should be kept in the original container, tightly closed and out of reach of children; and that medical help should be sought

immediately if a child accidentally swallows any of the product.

Source: *FDA Medical Bulletin*, **25**: 3 (1995).

Quinolones and tendon rupture

United Kingdom — The Committee on Safety of Medicines has received a total of 21 reports of tendon damage associated with use of the quinolone antibiotics, ciprofloxacin and ofloxacin (1). In 15 of these cases — which ranged in severity from tendonitis to partial or complete tendon rupture — the Achilles' tendon was involved. Similar cases reported in other countries suggest that this is a class-effect shared by all quinolones, and that the risk increases with age or when steroids are taken concomitantly.

The Committee advises doctors that, at the first sign of pain or inflammation, patients taking quinolones should discontinue treatment and rest the affected limb until the symptoms have resolved.

Source: Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, **No. 21** (1995).

Tocolytics and pulmonary oedema

United Kingdom — The Committee on Safety of Medicines has received several reports of maternal pulmonary oedema developing during the infusion of β-receptor agonist tocolytics (ritodrine, salbutamol and terbutaline). These drugs are used in pre-term labour (24–33 weeks) to delay delivery temporarily, allowing time to administer glucocorticoids and to take other measures to improve perinatal survival.

The Committee acknowledges that several risk factors are operative in these circumstances, including multiple pregnancy, pre-existing cardiac disease and maternal infection. It emphasizes, however, that fluid overload is the single most important predisposing factor, and that this risk is substantially reduced when these drugs are diluted with 5% dextrose (rather than saline) and when the rate of infusion is accurately controlled by using a syringe pump or similar device. In all cases, the mother's state of hydration must be closely monitored and, should signs of pulmonary oedema develop, the beta-agonist should be withdrawn immediately and diuretic therapy instituted.

Source: Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, **No. 21**(1995).

Selegiline and antidepressants: risk of serious interactions

United States of America — The Food and Drug Administration has modified the labelling for selegiline hydrochloride, a selective monoamine oxidase (MAO) inhibitor which prevents dopamine breakdown in the brain, and which potentiates and prolongs the effect of levodopa in the treatment of parkinsonism. A warning will now be carried to reflect the risk of serious adverse effects when the drug is used in patients taking tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs). These effects, which are variable, are in some instances similar to the potentially fatal syndromes reported when tricyclic or SSRI-type antidepressants are prescribed together with nonselective MAO inhibitors.

Thus far, at least two deaths have been attributed to use of a combination of selegiline and tricyclic antidepressants. One of these, which was associated with use of amitriptyline, had the characteristics of the acute encephalopathy associated with concomitant use of tricyclics and nonselective MAO inhibitors: death was preceded by acute, severe central nervous toxicity and hyperpyrexia. In the other, which involved protriptyline, the patient developed tremors, became agitated and restless, and died after two weeks. Reports involving other tricyclics cite a variety of signs including hypertension, syncope, asystole, sweating, seizures, muscular rigidity and changes in behaviour.

Signs that have been reported when selegiline is combined with the selective serotonin reuptake inhibitors, fluoxetine, paroxetine and sertraline, include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations in vital signs, and behavioural changes that range from agitation to delirium and coma. Some of the reactions involving fluoxetine have resulted in death.

The FDA consequently advises that every care should be taken to avoid these potentially dangerous interactions involving selegiline. In general, at least 14 days should elapse between discontinuation of selegiline and subsequent treatment with a tricyclic antidepressant or a selective serotonin reuptake inhibitor. Conversely, selegiline should not be prescribed to any patient who has recently received these drugs. Sufficient time should elapse for the drugs to be completely metabolized or excreted. In the case of fluoxetine, which has a

particularly long half-life, this period should not be less than 5 weeks.

Source: *FDA Medical Bulletin*, **25:** 6 (1995).

Simvastatin and endocrine effects in men

Australia — Simvastatin was the first of the co-enzyme A reductase inhibitors to become available in Australia for treating hypercholesterolaemia. Since it was introduced in 1990 it has been associated with a small but appreciable number of reports of gynaecomastia and impotence.

Eleven men, all over 50 years of age, are reported to have developed gynaecomastia after having received the drug for periods ranging from 2 to 10 months. Five of these patients had not received any other drugs in the recent past, and in at least 4 of the other cases the temporal relationship and other considerations suggested that simvastatin was the most likely cause. Regression of the condition subsequent to withdrawal of treatment has been reported in only one of the patients. However, it is noted that gynaecomastia is a condition that is often slow to resolve.

The temporal relationship is less persuasive in the 28 reports of impotence reported in men aged 45 to 72 years who were taking simvastatin. Onset of the complaint occurred from 48 hours to 27 months (median about 4 weeks) after starting treatment. However, in 24 cases, simvastatin was the only drug implicated; function was restored in 12 of these patients after withdrawal of treatment; and, in 4 instances, the problem was again reported on rechallenge. A further 9 patients reported no improvement on withdrawal of treatment.

Source: *Australian Adverse Drug Reactions Bulletin*, **14:** 10 (1995).

Tacrolimus and cardiomyopathy

United Kingdom — The Committee on Safety of Medicines has advised doctors that cases of hypertrophic cardiomyopathy have developed in children undergoing organ transplants who have been treated with tacrolimus, a new immunosuppressant agent introduced in the UK late in 1994 (1).

A series of 5 such cases has recently been published (2), and a total of 29 suspected cases has now been reported worldwide. Most relate to children aged 5 years or less who have received transplants of liver, small bowel, colon or a combination of these organs. In at least some of these cases trough blood concentrations of tacrolimus exceeded the recommended maximum level of 25 ng/ml, and in most cases the myopathy regressed when the drug was withdrawn or the dosage reduced.

This finding is unanticipated and unexplained. The product information in the UK is being revised to emphasize that patients receiving tacrolimus should be monitored carefully by echocardiography for hypertrophic changes, and that the drug should be either withdrawn or reduced in dosage should these be detected.

Sources

1. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, **No. 21** (1995).

2. Atkinson, P., Joubert, G., Barron, A. Hypertrophic cardiomyopathy associated with tacrolimus in paediatric transplant patients. *Lancet*, **345**: 894-896 (1995).

Trimethoprim/sulfamethoxazole: restriction of previously-approved indications

United Kingdom — The Committee on Safety of Medicines has decided to restrict the approved indications for preparations of the combination antibiotic trimethoprim/sulfamethoxazole on the grounds that "its place in therapy has changed", and particularly because trimethoprim alone is now widely used for urinary tract and chest infections (1).

The Committee considers that the use of the combination product remains unchallenged in the treatment and prophylaxis of three opportunistic infections commonly associated with HIV infection: *Pneumocystis carinii* pneumonia, toxoplasmosis and nocardiasis.

However, the combination is now approved for use in acute exacerbations of chronic bronchitis and infections of the urinary tract only when there is bacteriological evidence of sensitivity and when there is "good reason to prefer this combination of drugs to a single antibiotic." Similarly, it is approved for use in acute otitis media in children "when there is good reason to prefer this combination."

In announcing this decision, the Committee emphasizes that it has no newly-founded concerns about the safety of the combination products. Spontaneously reported adverse reactions continue to conform to long-established patterns (2), and the profile of these reactions has been shown to be similar to that associated with trimethoprim when it is administered alone. This implies that there is no evidence that the sulfonamide component significantly augments any known risk associated with treatment.

The most serious reactions — blood dyscrasias and generalized skin disorders which occur predominantly in elderly patients — are associated with both the combination products and with trimethoprim. The Committee cites a recent large post-marketing study (3) which confirms that these reactions are very rare, and which fails to demonstrate any significant difference in the frequency with which serious hepatic, renal, blood and skin disorders are associated with the combination products and trimethoprim alone.

Sources

1. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, **No. 21** (1995).

2. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*, **No. 15** (1985).

3. Jick, H., Derby, L. Is co-trimoxazole safe? *Lancet*, **345:** 1118-1119 (1995).

Macrolide antibiotics interfere with response to warfarin

Australia — Within the past two years the Adverse Drug Reaction Advisory Committee has received over 20 reports indicating that intercurrent use of a macrolide antibiotic interferes with the therapeutic action of warfarin on coagulation factors. Half the cases were associated with use of erythromycin and half with roxithromycin.

The changes occurred in patients who had been on stable doses of warfarin for prolonged periods and within a few days of starting antibiotic therapy. In nearly all cases the prothrombin time rose considerably above the accepted therapeutic range. Spontaneous bleeding occurred in patients who received roxithromycin and three required transfusion.

The Committee concludes that a clear causal relationship exists and it stresses the need for careful monitoring when either erythromycin or roxithromycin is administered to a patient receiving warfarin. It lacks evidence to indicate whether the effect results from a direct interaction with warfarin, or from an independent effect of the antibiotic such as reduced synthesis of vitamin K resulting from changes in the gut flora. The Committee does not comment on possible reasons for the apparent clustering of these reports within the past two years, or whether, as is possible, they have resulted from a targeted screening programme undertaken in one or more hospital laboratories rather than from spontaneously-generated reports submitted by clinicians.

Source: *Australian Adverse Drug Reactions Bulletin*, **14:** 11 (1995).

Cyproterone acetate: further restrictive action

European Commission — The German health authorities have recently referred to the Committee for Proprietary Medicinal Products (CPMP) of the European Commission data suggesting that the synthetic anti-androgen, cyproterone acetate, is a genotoxic substance which may have carcinogenic potential. Concern was raised specifically about a possible association with primary hepatic cancer. Thus far, however, it seems that only one case possibly attributable to use of cyproterone acetate has been cited (1).

Although the CPMP considers that an association with hepatic cancer remains unproven, it has concluded that use of cyproterone acetate is associated with significant hepatotoxicity, particularly when it is administered at relatively high doses over extended periods of time to patients with prostatic carcinoma (2). A similar conclusion was announced by the UK Committee on Safety of Medicines early in 1995 (3, 4). Its use in this condition is still considered justified in long-term palliative treatment of prostatic cancer when surgery has failed or when LHRH analogues are ineffective, contraindicated or poorly tolerated.

Given this finding, the CPMP has advised that the approved indications for products containing cyproterone acetate should be restricted to serious conditions. It should no longer be contained, it is suggested, even at low dosage, in products promoted solely for contraception, nor should it be indicated for the treatment of precocious puberty, or

for less severe forms of acne, hirsutism and other androgen-induced changes in women.

Sources:

1 Rüdiger, T., Beckmann, J., Queisser, W. Hepatocellular carcinoma after treatment with cyproterone acetate combined with ethinyloestradiol. *Lancet*, **345**: 452 (1995).

2. Committee for Proprietary Medicinal Products, European Commission. *Pharmacovigilance opinion No. 19: cyproterone acetate*. Meeting of 13–14 December 1994.

3. Committee on Safety of Medicines. *Current Problems in Pharmacovigilance*. No. 21, 1995.

4. Cyproterone acetate and hepatic reactions. *WHO Drug Information*, **9**: 30 (1995).

Spermicide contraceptives: do they really work?

United States of America — The Food and Drug Administration has proposed that manufacturers of over-the-counter spermicidal products should generate data in prospective clinical studies to demonstrate the extent to which the final formulations are effective as contraceptives. The products at issue, nonoxinol-9 and, less commonly octoxinol-9, are polymers of substituted phenoxyethyl alcohol with surfactant properties.

The agency has evidence that some of these formulations may rapidly lose effectiveness *in situ*, and that they sometimes cause vaginal irritation which may facilitate transmission of infections. Manufacturers have been asked to collect information on the occurrence of vaginal irritation in the course of the required clinical studies.

Conversely, these products have also been shown to possess antimicrobial activity *in vitro* which may provide a tangible degree of protection in normal use against sexually transmitted diseases, including, perhaps, HIV infection. In addition to the requirements imposed by its formal proposal, the FDA is encouraging companies to evaluate this antimicrobial potential in separate clinical trials.

The marketing status of existing products will not be immediately affected by the proposed rule but, to assure continued availability of these products once the rule is adopted, the FDA is encouraging companies to conduct the required clinical studies as quickly as possible. Products that fail to meet the requirements of the final rule will be subject to regulatory action.

Source: *United States Federal Register*, 3 February 1995.

Towards one strength of insulin (IU100)

The International Diabetes Federation (IDF), representing 130 diabetes associations in 108 countries, recommends that all countries change to IU100 insulin before the end of the century. This target is proposed in the knowledge that major insulin-consuming countries of the world have either already changed to one common insulin concentration of 100 u/ml (IU100) or will do so within the next 24 months. Continuing availability of other strengths (IU40 and IU80) is claimed to be confusing, costly and potentially dangerous.

Experience in many countries over the past two decades has shown that the withdrawal of redundant strengths of insulin and injection equipment can be undertaken safely, and without arousing significant concern among persons with diabetes. However, the IDF stresses that these changes have to be carefully planned at all levels to ensure that both patients and health professionals are adequately informed of their nature and timing.

IDF has consulted with the World Health Organization and the major insulin manufacturers who agree that other strengths, including IU40 and IU80, should be removed from the market before 31 December 1999.

Source: Statement from International Diabetes Federation transmitted to WHO, dated 23 May 1995.

Recent Publications

Tropical disease research: twenty years of collaboration

The twelfth programme report of the UN inter-agency programme on Tropical Disease Research is a celebration of 20 years of productive and coordinated effort to engage science in combat against the transmissible and infectious diseases which thrive in the poverty of the developing world.

The objectives of the programme, for which WHO acts as the executive agency, are twofold: to develop new tools to control tropical diseases, and to train individuals and strengthen institutions to increase the relevant research capability of less developed tropical countries. The focus of activity is directed to six diseases — malaria, schistosomiasis, the filariases, African and American trypanosomiasis, the leishmaniases and leprosy — which were selected having regard to their impact as public health problems, the absence of satisfactory methods of control, and the scientific potential for developing such methods.

The donations generously contributed by governments, intergovernmental, and nongovernmental organizations and foundations, has enabled the secretariat in Geneva to develop a partnership with some 5000 scientists from 160 countries who collaborate in its activities. Relevant research of every nature is accommodated in the programme, from basic biomedical research — encompassing immunology, cell biology and biochemistry — to community-based field research. The current director of the programme, Dr Tore Godal, attributes the atmosphere of confidence and the track record of collaborative innovation — which are the hallmarks of the success of the programme — to four fundamental abilities:

- the ability to take risks and identify new opportunities;
- the ability to maintain research on a promising lead long enough to develop a useful product;
- the ability to invest truly in and around talented individuals;
- the ability to allow researchers to come up with their own solutions.

The last of these abilities has been fostered by inviting, though advertisement to the research community, applications to resolve problems which are often defined in very specific and narrow terms. This, experience has shown, has been of particular value in field research:

- it elicits excellent proposals from scientific groups previously unknown to have an interest in a specific area;
- it stimulates and facilitates further development of the initially proposed design, execution and analysis of the work, often within the context of a research capability strengthening exercise; and
- in the case of research focused on precise field activities, it enables the programme to inform interested governments and institutions of proposed projects before they have been funded, to obtain their approval, and to ensure their receptivity to the ultimate conclusions.

This issue of *WHO Drug Information* contains much that is of primary interest to less developed countries. Immense problems clearly remain to be tackled, but much that is encouraging is being achieved. The Tropical Disease Research Programme has been directly involved in many important aspects of the work that is reported. Where it has not been involved, its influence has had a pervasive catalytic effect in stimulating research and funding for research in those countries most in need of international support.

UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. *Tropical disease research: progress 1975-1994: highlights 1993-1994. Twelfth programme report.* WHO, Geneva, 1995. ISBN 92 4 156179 3 (NLM Classification: WC 680).

International Nonproprietary Names for Pharmaceutical Substances (INN)

Recommended International Nonproprietary Names (Rec. INN): List 35

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 (1–65) and Recommended (1–31) International Nonproprietary Names can be found in *Cumulative List No. 8, 1992.*

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales recommandées (DCI Rec): Liste 35

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 (1–65) et recommandées (1–31) dans la *Liste récapitulative No. 8, 1992.*

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 35

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 (1–65) y Recomendadas (1–31) se encuentran reunidas en *Cumulative List No. 8, 1992.*

Recommended INN (Latin, English, French, Spanish) *DCI Recommandée* *DCI Recomendada*	*Chemical name or description and Molecular formula* *Nom chimique ou description et Formule brute* *Nombre químico o descripción y Fórmula empírica*
acidum gadoxeticum	
gadoxetic acid	dihydrogen [*N*-[(2*S*)-2-[bis(carboxymethyl)amino]-3-(*p*-ethoxyphenyl)propyl]-*N*-[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]gadolinate(2-)
acide gadoxétique	dihydrogéno[*N*-[(2*S*)-2-[bis(carboxyméthyl)amino]-3-(4-éthoxyphényl)propyl]-*N*-[2-[bis(carboxyméthyl)amino]éthyl]glycinato(5-)]gadolinate(2-)
ácido gadoxetico	dihidrógeno [*N*-[(2*S*)-2-[bis(carboximetil)amino]-3-(*p*-etoxifenil)propil]-*N*-[2-[bis(carboximetil)amino]etil]glicinato(5-)]gadolinato(2-)
	$C_{23}H_{30}GdN_3O_{11}$
acidum ibandronicum	
ibandronic acid	[1-hydroxy-3-(methylpentylamino)propylidene]diphosphonic acid
acide ibandronique	acide [1-hydroxy-3-[méthyl(pentyl)amino]propylidène]bisphosphonique
ácido ibandrónico	ácido [1-hidroxi-3-(metilpentilamino)propilideno]difosfónico
	$C_9H_{23}NO_7P_2$
acidum olpadronicum	
olpadronic acid	[3-(dimethylamino)-1-hydroxypropylidene]diphosphonic acid
acide olpadronique	acide [3-(diméthylamino)-1-hydroxypropylidène]bisphosphonique
ácido olpadrónico	ácido [3-(dimetilamino)-1-hidroxipropilideno]difosfónico
	$C_5H_{15}NO_7P_2$
acidum zoledronicum	
zoledronic acid	(1-hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid
acide zolédronique	acide [1-hydroxy-2-(1*H*-imidazol-1-yl)éthylidène]bisphosphonique
ácido zoledrónico	ácido (1-hidroxi-2-imidazol-1-iletiliden)difosfónico
	$C_5H_{10}N_2O_7P_2$
acitazanolastum	
acitazanolast	3'-(1*H*-tetrazol-5-yl)oxanilic acid
acitazanolast	acide *N*-[3-(1*H*-tétrazol-5-yl)phényl]oxamique
acitazanolast	ácido 3'-(1*H*-tetrazol-5-il)oxanílico
	$C_9H_7N_5O_3$

adefovirum

adefovir	[[2-(6-amino-9*H*-purin-9-yl)ethoxy]methyl]phosphonic acid
adéfovir	acide [[2-(6-amino-9*H*-purin-9-yl)éthoxy]méthyl]phosphonique
adefovir	ácido [[2-(6-amino-9*H*-purin-9-il)etoxi]metil]fosfónico
	$C_8H_{12}N_5O_4P$

afelimomabum

afelimomab	immunoglobulin G 3 (mouse monoclonal LU54107 Fab' fragment γ-chain anti-human tumor necrosis factor α), disulfide with mouse monoclonal LU54107 κ-chain, dimer
afélimomab	immunoglobuline G 3 (chaîne γ du fragment Fab' de l'anticorps monoclonal de souris LU54107 anti-facteur de nécrose tumorale α humain), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris LU54107
afelimomab	inmunoglobulina G 3 (cadena γ del fragmento Fab' del anticuerpo monoclonal de ratón LU54107 anti-factor de necrosis tumoral α humano), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón LU54107

alniditanum

alniditan	2-[[3-[[(*R*)-2-chromanylmethyl]amino]propyl]amino]-1,4,5,6-tetrahydropyrimidine
alniditan	*N*-[[(2*R*)-3,4-dihydro-2*H*-chromén-2-yl]méthyl]-*N'*-(1,4,5,6-tétrahydropyrimidin-2-yl)propan-1,3-diyldiamine
alniditan	2-[[3-[[(*R*)-2-cromanilmetil]amino]propil]amino]-1,4,5,6-tetrahidropirimidina
	$C_{17}H_{26}N_4O$

anakinrum

anakinra	N^2-L-methionylinterleukin 1 receptor antagonist (human isoform x reduced)
anakinra	N^2-L-méthionylantagoniste du récepteur de l'interleukine-1 (isoforme x humaine réduite)
anakinra	N^2-L-metionil antagonista del receptor de interleukina 1 (isoforma x reducida, humana)
	$C_{759}H_{1186}N_{208}O_{232}S_{10}$

anastrozolum

anastrozole	α,α,α',α'-tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-*m*-benzenediacetonitrile
anastrozole	2,2'-diméthyl-2,2'-[5-[(1*H*-1,2,4-triazol-1-yl)méthyl]benzène-1,3-diyl]=dipropanenitrile
anastrozol	α,α,α',α'-tetrametil-5-(1*H*-1,2,4-triazol-1-ilmetil)-*m*-bencendiacetonitrilo
	$C_{17}H_{19}N_5$

apaxifyllinum

apaxifylline	(-)-(*S*)-8-(3-oxocyclopentyl)-1,3-dipropylxanthine
apaxifylline	(-)-(*S*)-8-(3-oxocyclopentyl)-1,3-dipropyl-3,7-dihydro-1*H*-purine-2,6-dione
apaxifilina	(-)-(*S*)-8-(3-oxociclopentil)-1,3-dipropilxantina
	$C_{16}H_{22}N_4O_3$

bivalirudinum

bivalirudin — D-phenylalanyl-L-prolyl-L-arginyl-L-prolylglycylglycylglycylglycyl-L-asparaginylglycyl-L-α-aspartyl-L-phenylalanyl-L-α-glutamyl-L-α-glutamyl-L-isoleucyl-L-prolyl-L-α-glutamyl-L-α-glutamyl-L-tyrosyl-L-leucine

bivalirudine — D-phénylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-glycyl-L-asparaginyl-glycyl-L-α-aspartyl-L-phénylalanyl-L-α-glutamyl-L-α-glutamyl-L-isoleucyl-L-prolyl-L-α-glutamyl-L-α-glutamyl-L-tyrosyl-L-leucine

bivalirudina — D-fenilalanil-L-prolil-L-arginil-L-prolilglicilglicilglicilglicil-L-asparraginilglicil-L-α-aspartil-L-fenilalanil-L-α-glutamil-L-α-glutamil-L-isoleucil-L-prolil-L-α-glutamil-L-α-glutamil-L-tirosil-L-leucina

$C_{98}H_{138}N_{24}O_{33}$

candesartanum

candesartan — 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylic acid

candésartan — acide 2-éthoxy-1-[4-[2-(1*H*-tétrazol-5-yl)phényl]benzyl]-1*H*-benzimidazole-7-carboxylique

candesartan — ácido 2-etoxi-1-[*p*-(*o*-1*H*-tetrazol-5-ilfenil)bencil]-7-bencimidazolcarboxílico

$C_{24}H_{20}N_6O_3$

capecitabinum

capecitabine — pentyl 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinecarbamate

capécitabine — [1-(5-désoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate de pentyle

capecitabina — 1-(5-desoxi-β-D-ribofuranosil)-5-fluoro-1,2-dihidro-2-oxo-4-pirimidincarbamato de pentilo

$C_{15}H_{22}FN_3O_6$

cartasteinum

cartasteine — (*S*)-3-[*N*-[(*R*)-2-mercaptopropionyl]glycyl]-4-thiazolidinecarboxylic acid

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

cartasteina — ácido (*S*)-3-[*N*-[(*R*)-2-mercaptopropionil]glicil]-4-tiazolidinecarboxílico

$C_9H_{14}N_2O_4S_2$

cefluprenamum

cefluprenam — (-)-[(*E*)-3-[(6*R*,7*R*)-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-en-3-yl]allyl](carbamoylmethyl)ethylmethylammonium hydroxide, inner salt, 7^2-(*Z*)-[*O*-(fluoromethyl)oxime]

céfluprénam — (-)-(2-amino-2-oxoéthyl)[(*E*)-3-[(6*R*,7*R*)-7-[[(*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(fluorométhoxy)imino]acétyl]amino]-2-carboxylato-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-én-3-yl]prop-2-ényl]éthylméthylammonium

cefluprenam — hidróxido de (-)-[(*E*)-3-[(6*R*,7*R*)-7-[2-(5-amino-1,2,4-tiadiazol-3-il)glioxilamido]-2-carboxi-8-oxo-5-tia-1-azabiciclo [4.2.0]oct-2-en-3-il]alil](carbamoilmetil)=etilmetilamonio, sal interna, 7^2-(*Z*)-[*O*-(fluorometil)oxima

$C_{20}H_{25}FN_8O_6S_2$

cefoselisum

cefoselis — (-)-5-amino-2-[[(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-(2-hydroxyethyl)= pyrazolium hydroxide, inner salt, 7^2-(*Z*)-(*O*-methyloxime)

céfosélis — (-)-5-amino-2-[[(6*R*,7*R*)-7-[[(*Z*)-2-(2-aminothiazol-4-yl)-2-(méthoxyimino)= acétyl]amino]-2-carboxylato-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-én-3-yl]= méthyl]-1-(2-hydroxyéthyl)-1*H*-pyrazolium

cefoselis — (-)-5-amino-2-{[(6*R*,7*R*)-7-[[(*Z*)-2-(2-aminotiazol-4-il)-2-(metoxiimino)acetil]= amino]-2-carboxilato-8-oxo-5-tia-1- azabiciclo[4.2.0]oct-2-en-3-il]metil]-1-(2 hidroxietil)-1*H*-pirazolio

$C_{19}H_{22}N_8O_6S_2$

cidofovirum

cidofovir — [[(*S*)-2-(4-amino-2-oxo-1(2*H*)-pyrimidinyl)-1-(hydroxymethyl)ethoxy]methyl]= phosphonic acid

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

cidofovir — ácido [[(*S*)-2-(4-amino-2-oxo-1(2*H*)-pirimidinil)-1-(hidroximetil)etoxi]metil]= fosfónico

$C_8H_{14}N_3O_6P$

cilmostimum

cilmostim — 1-223-colony-stimulating factor 1 (human clone p3ACSF-69 protein moiety reduced) dimer, cyclic (7→90), (7'→ 90'), (31→31'), (48→139), (48'→ 139'), (102→146), (102'→ 146')-heptakis(disulfide)

cilmostime — (7→90), (7'→ 90'), (31→31'), (48→139), (48'→ 139'), (102→146), (102'→ 146')-heptakis(disulfure cyclique) du dimère de 1-223-facteur 1 de stimulation des colonies (partie protéique réduite du clone humain p3ACSF-69)

cilmostim — (7→90), (7'→ 90'), (31→31'), (48→139), (48'→ 139'), (102→146), (102'→ 146')-heptakis(disulfuro cíclico) del dímero de 1- 223-factor 1 de estimulación de colonias (fracción proteica reducida del clon humano p3ACSF-69)

$C_{2198}H_{3430}N_{588}O_{704}S_{28}$

cipamfylline

cipamfylline — 8-amino-1,3-bis(cyclopropylmethyl)xanthine

cipamfylline — 8-amino-1,3-bis(cyclopropylméthyl)-3,7-dihydro-1*H*-purine-2,6-dione

cipamfilina — 8-amino-1,3-bis(ciclopropilmetil)xantina

$C_{13}H_{17}N_5O_2$

cromoglicas lisetilum

cromoglicate lisetil — diethyl 5,5'-[(2-hydroxytrimethylene)dioxy]bis[4-oxo-4*H*-1-benzopyran-2-carboxylate], ester with L-lysine

cromoglicate lisétil — (+)-5,5'-[[2-[[(2*S*)-2,6-diaminohexanoyl]oxy]propane-1,3-diyl]dioxy]bis(4-oxo-4*H*-chromène-2-carboxylate d'éthyle)

cromoglicato lisetil — 5,5'-[(2-hidroxitrimetileno)dioxi]bis[4-oxo-4*H*-1-benzopirano-2-carboxilato] de dietilo, éster con L-lisina

$C_{33}H_{36}N_2O_{12}$

dacliximabum

dacliximab	immunoglobulin G 1 (human-mouse monoclonal clone 1H4 γ-chain anti-human interleukin 2 receptor), disulfide with human-mouse monoclonal clone 1H4 light chain, dimer
dacliximab	immunoglobuline G 1 (chaîne γ de l'anticorps monoclonal du clone homme-souris 1H4 dirigé contre le récepteur de l'interleukine 2 humain), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal du clone homme-souris 1H4
dacliximab	inmunoglobulina G 1(cadena γ del anticuerpo monoclonal del clon humano-murino 1H4 anti-receptor de la interleukina 2 humano), dimero del disulfuro con la cadena ligera del anticuerpo monoclonal del clon humano-murino
	$C_{6394}H_{9888}N_{1696}O_{2012}S_{44}$

delavirdinum

delavirdine	1-[3-(isopropylamino)-2-pyridyl]-4-[(5-methanesulfonamidoindol-2-yl)= carbonyl]piperazine
délavirdine	1-[3-[(1-méthyléthyl)amino]pyridin-2-yl]-4-[[5-[(méthylsulfonyl)amino]-1*H*-indol-2-yl]carbonyl]pipérazine
delavirdina	1-[3-(isopropilamino)-2-piridil]-4-[(5-metanosulfonamidoindol-2-il)carbonil]= piperazina
	$C_{22}H_{28}N_6O_3S$

dexpemedolacum

dexpemedolac	(1*S*,4*R*)-4-benzyl-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid
dexpémédolac	acide 2-[(1*S*,4*R*)-4-benzyl-1-éthyl-1,3,4,9-tétrahydropyrano[3,4-*b*]indol-1-yl]= acétique
dexpemedolaco	ácido (1*S*,4*R*)-4-bencil-1-etil-1,3,4,9-tetrahidropirano[3,4-*b*]indol-1-acético
	$C_{22}H_{23}NO_3$

docetaxelum

docetaxel	(2*R*,3*S*)-*N*-carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate
docétaxel	(2*R*,3*S*)-3-[[(1,1-diméthyléthoxy)carbonyl]amino]-2-hydroxy-3-phénylpropanoate de 4-(acétyloxy)-2α-(benzoyloxy)-5β,20-époxy-1,7β,10β-trihydroxy-9-oxotax-11-én-13α-yle
docetaxel	(2*R*,3*S*)-*N*-carboxi-3-fenilisoserina, *N*-*terc*-butil éster, 13-éster con 5β-20-epoxi-1,2α,4,7β,10β,13α-hexahidroxitax-11-en-9-ona 4-acetato 2-benzoato
	$C_{43}H_{53}NO_{14}$

ebalzotanum

ebalzotan	(*R*)-*N*-isopropyl-3-(isopropylpropylamino)-5-chromancarboxamide
ébalzotan	(3*R*)-*N*-(1-méthyléthyl)-3-[(1-méthyléthyl)propylamino]-3,4-dihydro-2*H*-chromène-5-carboxamide
ebalzotan	(*R*)-*N*-isopropil-3-(isopropilpropilamino)-5-cromancarboxamida
	$C_{19}H_{30}N_2O_2$

efegatranum

efegatran — *N*-methyl-D-phenylalanyl-*N*-[(1*S*)-1-formyl-4-guanidinobutyl]-L-prolinamide

éfégatran — (2*S*)-*N*-[(1*S*)-1-formyl-4-guanidinobutyl]-1-[(2*R*)-2-(méthylamino)-3-phénylpropanoyl]pyrrolidine-2-carboxamide

efegatrán — *N*-metil-D-fenilalanil-*N*-[(1*S*)-1-formil-4-guanidinobutil]-L-prolinamida

$C_{21}H_{32}N_6O_3$

efletirizinum

efletirizine — [2-[4-[bis(*p*-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid

éfletirizine — acide 2-[2-[4-[bis(4-fluorophényl)méthyl]pipérazin-1-yl]éthoxy]acétique

efletirizina — ácido [2-[4-[bis(*p*-fluorofenil)metil]-1-piperazinil]etoxi]acético

$C_{21}H_{24}F_2N_2O_3$

elisartanum

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

élisartan — 2-butyl-4-chloro-1-[4-[2-(1*H*-tétrazol-5-yl)phényl]benzyl]-1*H*-imidazol-5-carboxylate de (*RS*)-1-[(éthoxycarbonyl)oxy]éthyle

elisartán — (±)-2-butil-4-cloro-1-[*p*-(*o*-1*H*-tetrazol-5-ilfenil)bencil]imidazol-5-carboxilato,etil carbonato de 1-hidroxietilo (éster)

$C_{27}H_{29}ClN_6O_5$

epoetinum epsilonum

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

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

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

$C_{809}H_{1301}N_{229}O_{240}S_5$
(for non-glycosylated protein)
(pour la protéine non glycosylée)
(fracción proteica no glicosilada)

eprosartanum

eprosartan — (*E*)-2-butyl-1-(*p*-carboxybenzyl)-α-2-thienylimidazole-5-acrylic acid

éprosartan — acide (*E*)-3-[2-butyl-1-(4-carboxybenzyl)-1*H*-imidazol-5-yl]-2-[(2-thiényl)méthyl]prop-2-énoïque

eprosartán — ácido (*E*)-2-butil-1-(*p*-carboxibencil)-α-2-tienilimidazol-5-acrílico

$C_{23}H_{24}N_2O_4S$

eptacogum alfa (activatum)

eptacog alfa (activated) — blood-coagulation factor VII (human clone λHVII2463 protein moiety)

eptacog alfa (activé) — facteur VII de coagulation sanguine (partie protéique de la substance issue du clone humain λHVII2463)

eptacog alfa (activado) — factor de coagulación VII (fracción proteica del clon humano λHVII2463)

$C_{2621}H_{4056}N_{728}O_{812}S_{36}$

ersentilidum

ersentilide — 4'-[(2*S*)-2-hydroxy-3-[[2-(*p*-imidazol-1-ylphenoxy)ethyl]amino]propoxy]= methanesulfonanilide

ersentilide — *N*-[4-[[(*S*)-2-hydroxy-3-[[2-[4-(1*H*-imidazol-1-yl)phénoxy]éthyl]amino]propyl]= oxy]phényl]méthanesulfonamide

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

$C_{21}H_{26}N_4O_5S$

examorelinum

examorelin — L-histidyl-2-methyl-D-tryptophyl-L-alanyl-L-tryptophyl-D-phenylalanyl-L-lysinamide

examoréline — L-histidyl-(2-méthyl-D-tryptophyl)-L-alanyl-L-tryptophyl-D-phénylalanyl-L-lysinamide

examorelina — L-histidil-2-metil-D-triptofil-L-alanil-L-triptofil-D-fenilalanil-L-lisinamida

$C_{47}H_{58}N_{12}O_6$

fampridinum

fampridine — 4-aminopyridine

fampridine — pyridin-4-ylamine

fampridina — 4-aminopiridina

$C_5H_6N_2$

faropenemum

faropenem — (+)-(5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[(2*R*)-tetrahydro-2-furyl]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

faropénem — acide (+)-(5*R*,6*S*)-6-[(1*R*)-1-hydroxyéthyl]-7-oxo-3-[(2*R*)-tétrahydrofuran-2-yl]-4-thia-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique

faropenem — ácido (+)-(5*R*,6*S*)-6-[(1*R*)-1-hidroxietil]-7-oxo-3-[(2*R*)-tetrahidro-2-furil]-4-tia-1-azabiciclo[3.2.0]hept-2-en-2-carboxílico

$C_{12}H_{15}NO_5S$

fenleutonum

fenleuton — (±)-1-[3-[*m*-(*p*-fluorophenoxy)phenyl]-1-methyl-2-propynyl]-1-hydroxyurea

fenleuton — (±)-1-[(1*RS*)-3-[3-(4-fluorophénoxy)phényl]-1-méthylprop-2-ynyl]-1-hydroxyurée

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

$C_{17}H_{15}FN_2O_3$

fodipirum

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

fodipir — *N*,*N*'-éthane-1,2-diylbis[*N*-[[3-hydroxy-2-méthyl-5-[(phosphonooxy)méthyl]= pyridin-4-yl]méthyl]glycine]

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

$C_{22}H_{32}N_4O_{14}P_2$

follitropinum alfa

follitropin alfa

follicle-stimulating hormone, glycoform α
α-subunit:
chorionic gonadotropin (human α-subunit protein moiety reduced)
β-subunit:
follicle-stimulating hormone (human clone λ 15B β-subunit protein moiety reduced)

follitropine alfa

hormone folliculo-stimulante, forme glycosylée α
Sous-unité α :
gonadotropine chorionique (partie protéique réduite de la sous-unité α humaine)
Sous-unité β :
hormone folliculo-stimulante (partie protéique réduite de la sous-unité β du clone humain λ 15B)

folitropina alfa

hormona estimulante del folículo, glicoforma α
subunidad α :
gonadotropina coriónica (fracción proteica reducida de la subunidad α humana)
subunidad β :
hormona estimulante del folículo (fracción proteica reducida de la subunidad β del clon humano humane λ 15B)

α : $C_{437}H_{682}N_{122}O_{134}S_{13}$

β : $C_{538}H_{833}N_{145}O_{171}S_{13}$

fradafibanum

fradafiban

(3*S*,5*S*)-5-[[(4'-amidino-4-biphenylyl)oxy]methyl]-2-oxo-3-pyrrolidineacetic acid

fradafiban

acide 2-[(3*S*,5*S*)-5-[[(4'-amidinobiphényl-4-yl)oxy]méthyl]-2-oxopyrrolidin-3-yl]acétique

fradafibán

ácido (3*S*,5*S*)-5-[[(4'-amidino-4-bifenilil)oxi]metil]-2-oxo-3-pirrolidinacético

$C_{20}H_{21}N_3O_4$

fuladectinum

fuladectin

a mixture of components A_4 and A_3,
component A_4 (major component):
4'-[2-[[(2a*E*,4*E*,5'*S*,6*S*,6'*R*,7*R*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6'-ethyl-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy-5',6,8,19-tetramethyl-17-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2'-[2*H*]pyran]-7-yl]oxy]ethyl]-*N*-methylmethanesulfonanilide
component A_3 (minor component):
4'-[2-[[(2a*E*,4*E*,5'*S*,6*S*,6'*R*,7*R*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy-5',6,6',8,19-pentamethyl-17-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2'-[2*H*]pyran]-7-yl]oxy]ethyl]-*N*-methylmethanesulfonanilide

fuladectine

mélange des constituants A_4 et A_3,
constituant A_4 (constituant principal):
N-[4-[2-[[(2a*E*,4*E*,8*E*)-(2'*R*,5'*S*,6*S*,6'*R*,7*R*,11*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6'-éthyl-20,20b-dihydroxy-5',6,8,19-tétraméthyl-7-oxo-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tétradécahydrospiro[11,15-méthano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadécène-13,2'-[2*H*]pyran]-7-yl]oxy]éthyl]phényl]-*N*-méthylméthanesulfonamide
constituant A_3 (constituant secondaire):
N-[4-[2-[[(2a*E*,4*E*,8*E*)-(2'*R*,5'*S*,6*S*,6'*R*,7*R*,11*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-20,20b-dihydroxy-5',6,6',8,19-pentaméthyl-7-oxo-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tétradécahydrospiro[11,15-méthano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadécène-13,2'-[2*H*]pyran]-7-yl]oxy]éthyl]phényl]-*N*-méthylméthanesulfonamide

fuladectina

mezcla de los componentes A_4 y A_3,
componente A_4 (constituyente principal):
4'-[2-[[(2a*E*,4*E*,5'*S*,6*S*,6'*R*,7*R*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6'-etil-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahidro-20,20b-dihidroxi-5',6,8,19-tetrametil-17-oxospiro[11,15-metano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxaciclooctadecin-13,2'-[2*H*]piran]-7-il]oxi]etil]-*N*-metilmetanesulfonanilida
componente A_3 (constituyente segundario):
4'-[2-[[(2a*E*,4*E*,5'*S*,6*S*,6'*R*,7*R*,8*E*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahidro-20,20b-dihidroxi-5',6,6',8,19-pentametil-17-oxospiro[11,15-metano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxaciclooctadecin-13,2'-[2*H*]piran]-7-il]oxi]etil]-*N*-metilmetanesulfonanilida

A_4 : $C_{42}H_{59}NO_{10}S$ + A_3 : $C_{41}H_{57}NO_{10}S$

gadoversetamidum

gadoversetamide

[*N*,*N*-bis[2-[[(carboxymethyl)[(2-methoxyethyl)carbamoyl]methyl]amino]ethyl]=glycinato(3-)]gadolinium

gadoversétamide

[*N*,*N*-bis[2-[(carboxyméthyl)[2-[(2-méthoxyéthyl)amino]-2-oxoéthyl]amino]=éthyl]glycinato(3-)]gadolinium

gadoversetamida

[*N*,*N*-bis[2-[[(carboximetil)[(2-metoxietil)carbamoil]metil]amino]etil]=glicinato(3-)]gadolinio

$C_{20}H_{34}GdN_5O_{10}$

galdansetronum

galdansetron

(+)-(3*R*)-2,3-dihydro-9-methyl-3-[(5-methylimidazol-4-yl)methyl]carbazol-4(1*H*)-one

galdansétron

(+)-(3*R*)-9-méthyl-3-[(5-méthyl-1*H*-imidazol-4-yl)méthyl]-1,2,3,9-tétrahydro-4*H*-carbazol-4-one

galdansetron

(+)-(3*R*)-2,3-dihidro-9-metil-3-[(5-metilimidazol- 4-il)metil]carbazol-4(1*H*)-ona

$C_{18}H_{19}N_3O$

goralatidum

goralatide

1-[N^2-[*N*-(*N*-acetyl-L-seryl)-L-α-aspartyl]-L-lysyl]-L-proline

goralatide

(*N*-acétyl-L-séryl)-L-α-aspartyl-L-lysyl-L-proline

goralatida

1-[N^2-[*N*-(*N*-acetil-L-seril)-L-α-aspartil]-L-lisil]-L-prolina

$C_{20}H_{33}N_5O_9$

idramantonum

idramantone — 5-hydroxy-2-adamantanone

idramantone — 5-hydroxytricyclo[3.3.1.1^{3,7}]décan-2-one

idramantona — 5-hidroxi-2-adamantanona

$C_{10}H_{14}O_2$

ifetrobanum

ifetroban — *o*-[[(1*S*,2*R*,3*S*,4*R*)-3-[4-(pentylcarbamoyl)-2-oxazolyl]-7-oxabicyclo=[2.2.1]hept-2-yl]methyl]hydrocinnamic acid

ifétroban — acide 3-[2-[[(1*S*,2*R*,3*S*,4*R*)-3-[4-[(pentylamino)carbonyl]oxazol-2-yl]-7-oxa=bicyclo[2.2.1]hept-2-yl]méthyl]phényl]propanoïque

ifetroban — ácido *o*-[[(1*S*,2*R*,3*S*,4*R*)-3-[4-(pentilcarbamoil)-2-oxazolil]-7-oxabiciclo=[2.2.1]hept-2-il]metil]hidrocinámico

$C_{25}H_{32}N_2O_5$

imidaprilatum

imidaprilat — (4*S*)-3-[(2*S*)-*N*-[(1*S*)-1-carboxy-3-phenylpropyl]alanyl]-1-methyl-2-oxo-4-imidazolidinecarboxylic acid

imidaprilate — acide (*S*)-3-[(*S*)-2-[[(*S*)-1-carboxy-3-phénylpropyl]amino]propanoyl]-1-méthyl-2-oxo-imidazolidine-4-carboxylique

imidaprilat — ácido (4*S*)-3-[(2*S*)-*N*-[(1*S*)-1-carboxi-3-fenilpropil]alanil]-1-metil-2-oxo-4-imidazolidincarboxílico

$C_{18}H_{23}N_3O_6$

imiglucerasum

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

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

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

$C_{2532}H_{3843}N_{671}O_{711}S_{16}$

inogatranum

inogatran — *N*-[(1*R*)-2-cyclohexyl-1-[[(2*S*)-2-[(3-guanidinopropyl)carbamoyl]piperidino]=carbonyl]ethyl]glycine

inogatran — acide 2-[[(1*R*)-1-(cyclohexylméthyl)-2-[(2*S*)-2-[[(3-guanidinopropyl)amino]=carbonyl]pipéridin-1-yl]-2-oxoéthyl]amino]acétique

inogatran — *N*-[(1*R*)-2-ciclohexil-1-[[(2*S*)-2-[(3-guanidinopropil)carbamoil]piperidino]=carbonil]etil]glicina

$C_{21}H_{38}N_6O_4$

inolimomabum

inolimomab — immunoglobulin G 1 (mouse monoclonal B-B10 γ-chain anti-human interleukin-2 receptor α-chain), disulfide with mouse monoclonal B-B10 κ-chain, dimer

inolimomab — immunoglobuline G 1 (chaîne γ de l'anticorps monoclonal de souris B-B10 dirigé contre la chaîne α du récepteur de l'interleukine-2 humain), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris B-B10

inolimomab	inmunoglobulina G 1 (cadena γ del anticuerpo monoclonal de ratón B-B10 anti-cadena α del receptor de interleukina-2 humana), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón B-B10
insulinum lisprum	
insulin lispro	28^{B}-L-lysine-29^{B}-L-prolineinsulin (human)
insuline lispro	[28^{B}-L-lysine-29^{B}-L-proline]insuline humaine
insulina lispro	28^{B}-L-lisina-29^{B}-L-prolinainsulina (humana)
	$C_{257}H_{383}N_{65}O_{77}S_6$
ipenoxazonum	
ipenoxazone	(+)-(4*S*,5*R*)-3-[3-(hexahydro-1*H*-azepin-1-yl)propyl]-4-isobutyl-5-phenyl-2-oxazolidinone
ipénoxazone	(+)-(4*S*,5*R*)-3-[3-(hexahydro-1*H*-azépin-1-yl)propyl]-4-(2-méthylpropyl)-5-phényloxazolidin-2-one
ipenoxazona	(+)-(4*S*,5*R*)-3-[3-(hexahidro-1*H*-azepin-1-il)propil]-4-isobutil-5-fenil-2-oxazolidinona
	$C_{22}H_{34}N_2O_2$
irbesartanum	
irbesartan	2-butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one
irbésartan	2-butyl-3-[4-[2-(1*H*-tétrazol-5-yl)phényl]benzyl]-1,3-diazaspiro[4.4]non-1-én-4-one
irbesartan	2-butil-3-[*p*-(*o*-1*H*-tetrazol-5-ilfenil)bencil]-1,3-diazaspiro[4.4]non-1-en-4-ona
	$C_{25}H_{28}N_6O$
itamelinum	
itameline	*p*-chlorophenyl 3-formyl-5,6-dihydro-1(2*H*)-pyridinecarboxylate, *O*-methyloxime
itaméline	(*E*)-3-[(méthoxyimino)méthyl]-5,6-dihydropyridine-1(2*H*)-carboxylate de 4-chlorophényle
itamelina	*p*-clorofenil 3-formil-5,6-dihidro-1(2*H*)-piridinacarboxilato, *O*-metiloxima
	$C_{14}H_{15}ClN_2O_3$
lamifibanum	
lamifiban	[[1-[*N*-(*p*-amidinobenzoyl)-L-tyrosyl]-4-piperidyl]oxy]acetic acid
lamifiban	acide 2-[[1-[(2*S*)-2-[(4-amidinobenzoyl)amino]-3-(4-hydroxyphényl)-propanoyl]pipéridin-4-yl]oxy]acétique
lamifiban	ácido[[1-[*N*-(*p*-amidinobenzoil)-L-tirosil]-4-piperidil]oxi] acético
	$C_{24}H_{28}N_4O_6$
lanperisonum	
lanperisone	(-)-(*R*)-2-methyl-3-(1-pyrrolidinyl)-4'-(trifluoromethyl)propiophenone
lanpérisone	(-)-(2*R*)-2-méthyl-3-(pyrrolidin-1-yl)-1-[4-(trifluorométhyl)phényl]propan-1-one
lanperisona	(-)-(*R*)-2-metil-3-(1-pirrolidinil)-4'-(trifluorometil)propiofenona
	$C_{15}H_{18}F_3NO$

Ianprostonum

Ianproston (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-2-[(*E*)-2-[2-[(*m*-chlorophenoxy)methyl]-1,3-dioxolan-2-yl]vinyl]-3,5-dihydroxycyclopentyl]-5-heptenoic acid

Ianprostone acide (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*E*)-2-[2-[(3-chlorophénoxy)méthyl]-1,3-dioxolan-2-yl]éthényl]-3,5-dihydroxycyclopentyl]hept-5-énoïque

Ianproston àcido (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*E*)-2-[2-[(*m*-clorofenoxi)metil]-1,3-dioxolan-2-il]vinil]-3,5-dihidroxiciclopentil]-5-heptenoico

$C_{24}H_{31}ClO_7$

Ienerceptum

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

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

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

$C_{1993}H_{3112}N_{562}O_{624}S_{34}$

Ievosemotiadilum

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

Iévosémotiadil (-)-(2*S*)-2-[2-[[3-[[2-(1,3-benzodioxol-5-yloxy)éthyl]méthylamino]propyl]oxy]-5-méthoxyphényl]-4-méthyl-2*H*-1,4-benzothiazin-3(4*H*)-one

Ievosemotiadil (-)-(*S*)-2-[5-metoxi-2-[3-[metil[2-[3,4-(metilenodioxi)fenoxi]etil]=amino]propoxi]fenil]-4-metil-2*H*-1,4-benzotiazin-3(4*H*)-ona

$C_{29}H_{32}N_2O_6S$

Iexacalcitolum

Iexacalcitol (5*Z*,7*E*,20*R*)-20-[(4-ethyl-4-hydroxyhexyl)oxy]-9,10-secopregna-5,7,10(19)-triene-1α,3β-diol

Iexacalcitol (5*Z*,7*E*)-(20*R*)-20-[(4-éthyl-4-hydroxyhexyl)oxy]-9,10-sécoprégna-5,7,10(19)-triène-1α,3β-diol

Iexacalcitol (5*Z*,7*E*,20*R*)-20-[(4-etil-4-hidroxihexil)oxi]-9,10-secopregna-5,7,10(19)-trieno-1α,3β-diol

$C_{29}H_{48}O_4$

Iirequinilum

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

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

Iirequinilo (3*S*)-1-[(10-cloro-6,7-dihidro-4-oxo-3-fenil-4*H*-benzo[*a*]quinolizin-1-il)=carbonil]-3-etoxipirrolidina

$C_{26}H_{25}ClN_2O_3$

lisofylline

lisofylline	1-[(*R*)-5-hydroxyhexyl]theobromine
lisofylline	1-[(5*R*)-5-hydroxyhexyl]-3,7-diméthyl-3,7-dihydro-1*H*-purin-2,6-dione
lisofilina	1-[(*R*)-5-hidroxihexil]teobromina
	$C_{13}H_{20}N_4O_3$

lobucavirum

lobucavir	9-[(1*R*,2*R*,3*S*)-2,3-bis(hydroxymethyl)cyclobutyl]guanine
lobucavir	2-amino-9-[(1*R*,2*R*,3*S*)-2,3-bis(hydroxyméthyl)cyclobutyl]-1,9-dihydro-6*H*-purin-6-one
lobucavir	9-[(1*R*,2*R*,3*S*)-2,3-bis(hidroximetil)ciclobutil]guanina
	$C_{11}H_{15}N_5O_3$

lutropinum alfa

lutropin alfa	luteinizing hormone (human α-subunit reduced complex human β-subunit reduced), glycoform α α-subunit: chorionic gonadotropin (human α-subunit protein moiety reduced) β-subunit: luteinizing homone (human β-subunit protein moiety reduced)
lutropine alfa	hormone lutéinisante (complexe de sous-unités α humaine réduite et de sous-unité β humaine réduite), forme glycosylée α Sous-unité α : gonadotropine chorionique (partie protéique réduite de la sous-unité α humaine) Sous-unité β : hormone lutéinisante (partie protéique réduite de la sous-unité β humaine)
lutropina alfa	hormona luteinizante (complejo de los subunidadas α humana reducida y β humana reducida), glicoforma α subunidad α : gonadotropina coriónica (fracción proteica reducida de la subunidad α humana) subunidad β : hormona luteinizante (fracción proteica reducida de la subunidad β humana)
	α : $C_{437}H_{682}N_{122}O_{134}S_{13}$ + β : $C_{577}H_{929}N_{165}O_{161}S_{14}$

mangafodipirum

mangafodipir	hexahydrogen (*OC*-6-13)-[[*N*,*N*'-ethylenebis[*N*-[[3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl]methyl]glycine] 5,5'-bis(phosphato)](8-)] manganate(6-)
mangafodipir	(*OC*-6-13)-hexahydrogéno[[*N*,*N*'-ethane-1,2-diylbis[*N*-[[3-hydroxy-2-méthyl-5-[(phosphonooxy)méthyl]pyridin-4-yl]méthyl]glycinato](8-)]manganate(6-)]
mangafodipir	hexahidrógeno (*OC*-6-13)-[*N*,*N*'-etilenbis[*N*-[[3-hidroxi-5-(hidroximetil)-2-metil-4-piridil]metil]glicina] 5,5'-bis(fosfato)](8-)]manganato(6-)
	$C_{22}H_{30}MnN_4O_{14}P_2$

mapinastinum

mapinastine — 1-(2-ethoxyethyl)-2-[[4-(4-pyrazol-1-ylbutyl)-1-piperazinyl]methyl]= benzimidazole

mapinastine — 1-(2-éthoxyéthyl)-2-[[4-[4-(1*H*-pyrazol-1-yl)butyl]pipérazin-1-yl]méthyl]-1*H*-benzimidazole

mapinastina — 1-(2-etoxietil)-2-[[4-(4-pirazol-1-ilbutil)-1-piperazinil]metil]bencimidazol

$C_{23}H_{34}N_6O$

mazapertinum

mazapertine — 1-[α-[4-(*o*-isopropoxyphenyl)-1-piperazinyl]-*m*-toluoyl]piperidine

mazapertine — 1-[3-[[4-[2-(1-méthyléthoxy)phényl]pipérazin-1-yl]méthyl]benzoyl]pipéridine

mazapertina — 1-[α-[4-(*o*-isopropoxifenil)-1-piperazinil]-*m*-toluoil]piperidina

$C_{26}H_{35}N_3O_2$

mibefradilum

mibefradil — (1*S*,2*S*)-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1- isopropyl-2-naphthyl methoxyacetate

mibéfradil — 2-méthoxyacétate de (1*S*,2*S*)-2-[2-[[3-(1*H*-benzimidazol-2-yl)propyl]méthyl= amino]éthyl]-6-fluoro-1-(1-méthyléthyl)-1,2,3,4-tétrahydronaphtalén-2-yle

mibefradil — (1*S*,2*S*)-2-[2-[[3-(2-bencimidazolil)propil]metilamino]etil]-6-fluoro-1,2,3,4-tetrahidro-1-isopropil-2-naftil metoxiacetato

$C_{29}H_{38}FN_3O_3$

mirisetronum

mirisetron — 1-cyclohexyl-1,4-dihydro-4-oxo-*N*-1α*H*,5α*H*-tropan-3α-yl-3-quinoline= carboxamide

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

mirisetron — 1-ciclohexil-1,4-dihidro-4-oxo-*N*-1αH,5αH-tropan-3α-il-3-quinolina= carboxamida

$C_{24}H_{31}N_3O_2$

mobenakinum

mobenakin — 71-L-serineinterleukin 1β (human clone pIL-1-14 reduced)

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

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

$C_{773}H_{1219}N_{201}O_{238}S_7$

monteplasum

monteplase — 84-L-serineplasminogen activator (human tissue-type 2-chain form), cyclic (6→36), (32'→48'), (34→43), (40'→109'), (51→73), (56→62), (75→83), (92→173), (113→155), (120'→ 264), (134'→209'), (144→168), (166'→182'), (180→261), (199'→227'), (201→243), (232→256)-heptadecakis(disulfide)

montéplase — (6→36), (32'→48'), (34→43), (40'→109'), (51→73), (56→62), (75→83), (92→173), (113→155), (120'→ 264), (134'→209'), (144→168), (166'→182'), (180→261), (199'→227'), (201→243), (232→256)-heptadécakis(disulfure cyclique) du 84-L-sérine(activateur du plasminogène, humain, de type tissulaire, constitué de deux châines)

monteplasa — 84-L-serina activador del plasminógeno (tipo tisular humano forma bicatenaria), (6→36), (32'→48'), (34→43), (40'→109'), (51→73), (56→62), (75→83), (92→173), (113→155), (120'→ 264), (134'→209'), (144→168), (166'→182'), (180→261), (199'→227'), (201→243), (232→256)-heptadecakis(disulfuro cíclico)

$C_{2569}H_{3896}N_{746}O_{783}S_{39}$

moroctocogum alfa

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

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

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

$C_{3953}H_{6020}N_{1040}O_{1158}S_{29}$ + $C_{3553}H_{5412}N_{956}O_{1028}S_{33}$

muplestimum

muplestim — interleukin 3 (human protein moiety reduced)

muplestim — interleukine 3 (partie protéique humaine réduite)

muplestim — interleukina 3 (fracción proteica reducida humana)

$C_{670}H_{1076}N_{186}O_{199}S_5$

nacolomabum tafenatoxum

nacolomab tafenatox — 20-244-immunoglobulin G 1 (mouse monoclonal r-C242Fab-SEA clone pKP941 Fab fragment γ-chain anti-human colorectal tumor antigen C242) (244→ 1')-protein with enterotoxin A (*Staphyloccoccus aureus*), disulfide with mouse monoclonal r-C242Fab-SEA clone pKP941 κ-chain

nacolomab taténatox — 20-244-immunoglobuline G1 (chaine γ du fragment Fab de l'anticorps monoclonal de souris r-C242Fab-SEA, clone pKP941, anti-antigène C242 de tumeur colorectale humaine) (244→ 1')-protéine avec l'entérotoxine A (*Staphylococcus aureus*), disulfure avec la chaîne κ de l'anticorps monoclonal de souris r-C242Fab-SEA, clone pKP941

nacolomab tafenatox — 20-244-inmunoglobulina G 1 (cadena γ del fragmento Fab del anticuerpo monoclonal de ratón r-C242Fab-SEA, clon pKP941, antiantígeno C 242 de tumor colorrectal humano) (244→1)-proteina con la enterotoxina A (*Staphyloccoccus aureus*), disulfuro con la cadena κ del anticuerpo monoclonal de ratón r-C242Fab-SEA, clon pKP941

napsagatranum

napsagatran — *N*-[*N*^{4}-[[(3*S*)-1-amidino-3-piperidyl]methyl]-*N*^{2}-(2-naphthylsulfonyl)-L-asparaginyl]-*N*-cyclopropylglycine

napsagatran — acide 2-[[(2*S*)-4-[[[(3*S*)-1-amidinopipéridin-3-yl]méthyl]amino]-2-[[(naphtalén-2-yl)sulfonyl]amino]-4-oxobutanoyl](cyclopropyl)amino]acétique

napsagatran — *N*-[*N*^{4}-[[(3*S*)-1-amidino-3-piperidil]metil]-*N*^{2}-(2-naftilsulfonil)-L-asparraginil]-*N*-ciclopropilglicina

$C_{26}H_{34}N_6O_6S$

nemorubicinum

nemorubicin — (1*S*,3*S*)-3-glycoloyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl 2,3,6-trideoxy-3-[(*S*)-2-methoxymorpholino]-α-L-*lyxo*-hexopyranoside

némorubicine — (8*S*,10*S*)-6,8,11-trihydroxy-8-(2-hydroxyacétyl)-1-méthoxy-10-[[3-[(2*S*)-2-méthoxymorpholin-4-yl]-2,3,6-tridésoxy-α-L-*lyxo*-hexopyranosyl]oxy]-7,8,9,10-tétrahydronaphtacène-5,12-dione

nemorubicina — (1*S*,3*S*)-3-glicoloil-1,2,3,4,6,11-hexahidro-3,5,12-trihidroxi-10-metoxi-6,11-dioxo-1-naftacenil 2,3,6-tridesoxi-3-[(*S*)-2-metoximorfolino]-α-L-*lixo*-hexopiranósido

$C_{32}H_{37}NO_{13}$

netivudinum

netivudine — 1-β-D-arabinofuranosyl-5-(1-propynyl)uracil

nétivudine — 1-(β-D-arabinofuranosyl)-5-(prop-1-ynyl)pyrimidine-2,4(1*H*,3*H*)-dione

netivudina — 1-β-D-arabinofuranosil-5-(1-propinil)uracilo

$C_{12}H_{14}N_2O_6$

nicanartinum

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

nicanartine — 2,6-bis(1,1-diméthyléthyl)-4-[3-[(pyridin-3-yl)méthoxy]propyl]phénol

nicanartina — 2,6-di-*terc*-butil-4-[3-(3-piridilmetoxi)propil]fenol

$C_{23}H_{33}NO_2$

ocinaplonum

ocinaplon — 2-pyridyl 7-(4-pyridyl)pyrazolo[1,5-*a*]pyrimidin-3-yl ketone

ocinaplone — (pyridin-2-yl)[7-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidin-3-yl]méthanone

ocinaplon — 2-piridil 7-(4-piridil)pirazolo[1,5-*a*]pirimidin-3-il cetona

$C_{17}H_{11}N_5O$

olopatadinum

olopatadine — 11-[(*Z*)-3-(dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acid

olopatadine — acide 2-[11-[(1*Z*)-3-(diméthylamino)propylidène]-6,11-dihydrodibenzo=[*b*,*e*]oxépin-2-yl]acétique

olopatadina — ácido 11-[(*Z*)-3-(dimetilamino)propiliden]-6,11-dihidrodibenz[*b*,*e*]oxepin-2-acético

$C_{21}H_{23}NO_3$

ontazolastum

ontazolast — 2-[[(*S*)-2-cyclohexyl-1-(2-pyridyl)ethyl]amino]-5-methylbenzoxazole

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

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

$C_{21}H_{25}N_3O$

orientiparcinum

orientiparcin — a mixture of orienticine A and orienticine D,
orienticine A (major component):
(-)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-22-[(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)oxy]-44-[[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-3-(carbamoylmethyl)-19-chloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,28,30,32-tetrahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)valeramido-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiaza=cyclotetracosine-26-carboxylic acid
orienticine D (minor component):
(-)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-22-[(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)oxy]-44-[[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-3-(carbamoylmethyl)-19-chloro-6-[(2*R*)-2-(dimethylamino)-4-methylvaleramido]-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,28,30,32-tetrahydroxy-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiaza=cyclotetracosine-26-carboxylic acid

orientiparcine — mélange d'orienticine A et d'orienticine D,
orienticine A (constituant principal):
acide (3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-22-[(3-amino-3-*C*-méthyl-2,3,6-tridésoxy-α-L-*arabino*-hexopyranosyl)oxy]-44-[[2-*O*-(3-amino-3-*C*-méthyl-2,3,6-tridésoxy-α-L-*arabino*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-3-(carbamoylméthyl)-19-chloro-7,28,30,32-tétrahydroxy-6-[[(*R*)-4-méthyl-2-(méthylamino)pentanoyl]amino]-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tétradécahydro-8,11:18,21-diéthéno-23,36-(iminométhano)-22*H*-13,16:31,35-diméthéno-1*H*,13*H*-[1,6,9]oxadiazacyclohexadécino[4,5-*m*][10,2,16]benzoxadiaza=cyclotétracosène-26-carboxylique
orienticine D (constituant secondaire):
acide (3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-22-[(3-amino-3-*C*-méthyl-2,3,6-tridésoxy-α-L-*arabino*-hexopyranosyl)oxy]-44-[[2-*O*-(3-amino-3-*C*-méthyl-2,3,6-tridésoxy-α-L-*arabino*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-3-(carbamoylméthyl)-19-chloro-7,28,30,32-tétrahydroxy-6-[[(*R*)-2-(diméthylamino)-4-méthylpentanoyl]amino]-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tétradécahydro-8,11:18,21-diéthéno-23,36-(iminométhano)-22*H*-13,16:31,35-diméthéno-1*H*,13*H*-[1,6,9]oxadiazacyclohexadécino[4,5-*m*][10,2,16]benzoxadiaza=cyclotétracosène-26-carboxylique

orientiparcina

mezcla de orienticina A y de orienticina D,
orienticina A (constituyente principal):
ácido (3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-22-[(3-amino-3-*C*-metil-2,3,6-tridesoxi-α-L-*arabino*-hexopiranosil)oxi]-44-[[2-*O*-(3-amino-3-*C*-metil-2,3,6-tridesoxi-α-L-*arabino*-hexopiranosil)-β-D-glucopiranosil]oxi]-3-(carbamoilmetil)-19-cloro-7,28,30,32-tetrahidroxi-6-[[(*R*)-4-metil-2-(metilamino)pentanoil]amino]-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahidro-8,11:18,21-dieteno-23,36-(iminometano)-22*H*-13,16:31,35-dimeteno-1*H*,13*H*-[1,6,9]oxadiazaciclohexadecino[4,5-*m*][10,2,16]=benzoxadiazaciclotetracoseno-26-carboxílico
orienticina D (constituyente secundario):
ácido (3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-22-[(3-amino-3-*C*-metil-2,3,6-tridesoxi-α-L-*arabino*-hexopiranosil)oxi]-44-[[2-*O*-(3-amino-3-*C*-metil-2,3,6-tridesoxi-α-L-*arabino*-hexopiranosil)-β-D-glucopiranosil]oxi]-3-(carbamoilmetil)-19-cloro-7,28,30,32-tetrahidroxi-6-[[(*R*)-2-(dimetilamino)-4-metilpentanoil]amino]-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahidro-8,11:18,21-dieteno-23,36-(iminometano)-22*H*-13,16:31,35-dimeteno-1*H*,13*H*-[1,6,9]oxadiaza=ciclohexadecino[4,5-*m*][10,2,16]benzoxadiazaciclotetracoseno-26-carboxílico

A: $C_{73}H_{89}ClN_{10}O_{26}$ + D: $C_{74}H_{91}ClN_{10}O_{26}$

paclitaxelum

paclitaxel

(2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5-one 6,12b-diacetate, 12-benzoate, 9-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine

paclitaxel

(2*R*,3*S*)-3-(benzoylamino)-2-hydroxy-3-phénylpropanoate de (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6,12b-bis(acétyloxy)-12-(benzoyloxy)-4,11-dihydroxy-4a,8,13,13-tétraméthyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodécahydro-7,11-méthano-1*H*-cyclodéca[3,4]benzo[1,2-*b*]oxét-9-yle

paclitaxel

(2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-dodecahidro-4,6,9,11,12,12b-hexahidroxi-4a,8,13,13-tetrametil-7,11-metano-5*H*-ciclodeca[3,4]benz[1,2-*b*]oxet-5-ona 6,12b-diacetato, 12-benzoato, 9-ester con (2*R*,3*S*)-*N*-benzoil-3-fenilisoserina

$C_{47}H_{51}NO_{14}$

pazufloxacinum

pazufloxacin

(-)-(3*S*)-10-(1-aminocyclopropyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid

pazufloxacine

acide (-)-(3*S*)-10-(1-aminocyclopropyl)-9-fluoro-3-méthyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylique

pazufloxacino

ácido (-)-(3*S*)-10-(1-aminociclopropil)-9-fluoro-2,3-dihidro-3-metil-7-oxo-7*H*-pirido[1,2,3-*de*]-1,4-benzoxazina-6-carboxílico

$C_{16}H_{15}FN_2O_4$

pegorgoteinum

pegorgotein — superoxide dismutase, reaction product with succinic anhydride, esters with polyethylene glycol monomethyl ether

pégorgotéine — esters du produit de réaction de l'anhydride succinique sur la superoxyde dismutase et de monoéther méthylique de polyéthylèneglycol

pegorgotein — esteres del producto de reacción del anhidrido succínico con la superoxido dismutasa y del monoeter metílico del polietilenglicol

perospironum

perospirone — *cis*-*N*-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]-1,2-cyclohexane= dicarboximide

pérospirone — *cis*-2-[4-[4-(1,2-benzisothiazol-3-yl)pipérazin-1-yl]butyl]hexahydro-2*H*-isoindole-1,3-dione

perospirona — *cis*-*N*-[4-[4-(1,2-bencisotiazol-3-il)-1-piperazinil]butil]-1,2-ciclohexano= dicarboximida

$C_{23}H_{30}N_4O_2S$

pimilprostum

pimilprost — (+)-methyl [2-[(2*R*,3a*S*,4*R*,5*R*,6a*S*)-octahydro-5-hydroxy-4-[(1*E*,3*S*,5*S*)-3-hydroxy-5-methyl-1-nonenyl]-2-pentalenyl]ethoxy]acetate

pimilprost — (+)-2-[2-[(2*R*,3a*S*,4*R*,5*R*,6a*S*)-5-hydroxy-4-[(*E*)-(3*S*,5*S*)-3-hydroxy-5-méthylnon-1-ényl]octahydropentalén-2-yl]éthoxy]acétate de méthyle

pimilprost — (+)-2-[2-[(2*R*,3a*S*,4*R*,5*R*,6a*S*)-5-hidroxi-4-[(*E*)-(3*S*,5*S*)-3-hidroxi-5-metilnon-1-enil]octahidropentalen-2-il]etoxi]acetato de metilo

$C_{23}H_{40}O_5$

premafloxacinum

premafloxacin — 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(3*R*)-3-[(1*S*)-1-(methylamino)ethyl]-1-pyrrolidinyl]-4-oxo-3-quinolinecarboxylic acid

prémafloxacine — acide 1-cyclopropyl-6-fluoro-8-méthoxy-7-[(3*R*)-3-[(1*S*)-1-(méthylamino)= éthyl]pyrrolidin-1-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique

premafloxacino — ácido 1-ciclopropil-6-fluoro-1,4-dihidro-8-metoxi-7-[(3R)-3-[(1S)-1-(metilamino)etil]-1-pirrolidinil]-4-oxo-3-quinolincarboxílico

$C_{21}H_{26}FN_3O_4$

priliximabum

priliximab — immunoglobulin G 1 (human-mouse monoclonal cm-T412 anti-human antigen CD 4), disulfide with human-mouse monoclonal cm-T412 κ-chain, dimer

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

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

prulifloxacinum

prulifloxacin (±)-7-[4-[(*Z*)-2,3-dihydroxy-2-butenyl]-1-piperazinyl]-6-fluoro-1-methyl-4-oxo-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid, cyclic carbonate

prulifloxacine acide (±)-(1*RS*)-6-fluoro-1-méthyl-7-[4-[(5-méthyl-2-oxo-1,3-dioxol-4-yl)=méthyl]pipérazin-1-yl]-4-oxo-4*H*-[1,3]thiazéto[3,2-*a*]quinoléine-3-carboxylique

prulifloxacino ácido (±)-7-[4-[(*Z*)-2,3-dihidroxi-2-butenil]-1-piperazinil]-6-fluoro-1-metil-4-oxo-1*H*,4*H*-[1,3]tiazeto[3,2-*a*]quinolina-3-carboxílico, carbonato cíclico

$C_{21}H_{20}FN_3O_6S$

quiflaponum

quiflapon 3-(*tert*-butylthio)-1-(*p*-chlorobenzyl)-α,α-dimethyl-5-(2-quinolylmethoxy)=indole-2-propionic acid

quiflapon acide 3-[1-(4-chlorobenzyl)-3-[(1,1-diméthyléthyl)thio]-5-[(quinoléin-2-yl)=méthoxy]-1*H*-indol-2-yl]-2,2-diméthylpropanoïque

quiflapon àcido 3-(*terc*-butiltio)-1-(*p*-clorobencil)-α,α-dimetil-5-(2-quinolilmetoxi)indol-2-propiónico

$C_{34}H_{35}ClN_2O_3S$

regavirumabum

regavirumab immunoglobulin G 1 (human monoclonal γ-chain anti-human cytomegalovirus glycoprotein B), disulfide with human monoclonal κ-chain, dimer

régavirumab immunoglobuline G1 (chaîne γ de l'anticorps monoclonal humain anti-glycoprotéine B de cytomégalovirus humain), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal humain

regavirumab inmunoglobulina G 1 (cadena γ del anticuerpo monoclonal humano antiglicoproteina B de Citomegalovirus humano), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humano

rocepafantum

rocepafant 6-(*o*-chlorophenyl)-7,10-dihydro-1-methylthio-4*H*-pyrido[4',3':4,5]thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine-9(8*H*)-carboxy-*p*-anisidide

rocépafant 6-(2-chlorophényl)-*N*-(4-méthoxyphényl)-1-méthyl-7,10-dihydro-4*H*-pyrido=[4',3':4,5]thiéno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazépine-9(8*H*)-carbothioamide

rocepafant 6-(*o*-clorofenil)-7,10-dihidro-1-metiltio-4*H*-pirido[4',3' :4,5]tieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepina-9(8*H*)-carboxi-*p*-anisidida

$C_{26}H_{23}ClN_6OS_2$

rofleponidum

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

rofléponide 16α,17-[(1*R*)-butylidènedioxy]-6α,9-difluoro-11β,21-dihydroxyprég-4-ène-3,20-dione

rofleponida 6α,9-difluoro-11β,16α,17,21-tetrahidroxipregn-4-eno-3,20-diona,(*R*)-16,17-acetal cíclico con butiraldehído

$C_{25}H_{34}F_2O_6$

ruzadolanum
ruzadolane 3-[[2-[4-(2,4-difluorophenyl)-1-piperazinyl]ethyl] thio]-*s*-triazolo[4,3-*a*]pyridine

ruzadolane 3-[[2-[4-(2,4-difluorophényl)pipérazin-1-yl]éthyl]thio]-1,2,4-triazolo[4,3-*a*]pyridine

ruzadolano 3-[[2-[4-(2,4-difluorofenil)-1-piperazinil]etil]tio]-*s*-triazolo[4,3-*a*]piridina

$C_{18}H_{19}F_2N_5S$

samixogrelum
samixogrel (*E*)-6-[*p*-[2-(*p*-chlorobenzenesulfonamido)ethyl]phenyl]-6-(3-pyridyl)-5-hexenoic acid

samixogrel acide (5*E*)-6-[4-[2-[[(4-chlorophényl)sulfonyl]amino]éthyl]phényl]-6-(pyridin-3-yl)hex-5-énoïque

samixogrel ácido(*E*)-6-[*p*-[2-(*p*-clorobencensulfonamido)etil]fenil]-6-(3-piridil)-5-hexenoico

$C_{25}H_{25}ClN_2O_4S$

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

sanfétrinem acide (1*S*,5*S*,8a*S*,8b*R*)-1-[(1*R*)-1-hydroxyéthyl]-5-méthoxy-2-oxo-1,2,5,6,7,8,8a,8b-octahydroazéto[2,1-*a*]iso-indole-4-carboxylique

sanfetrinem ácido(1*S*,5*S*,8a*S*,8b*R*)-1,2,5,6,7,8,8a,8b-octahidro-1-[(*R*)-1-hidroxietil]-5-metoxi-2-oxoazeto[2,1-*a*]isoindol-4-carboxílico

$C_{14}H_{19}NO_5$

saprisartanum
saprisartan 1-[[3-bromo-2-[*o*-(1,1,1-trifluoromethanesulfonamido)phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethylimidazole-5-carboxamide

saprisartan 1-[[3-bromo-2-[2-[[(trifluorométhyl)sulfonyl]amino]phényl]benzofuran-5-yl]méthyl]-4-cyclopropyl-2-éthyl-1*H*-imidazole-5-carboxamide

saprisartan 1-[[3-bromo-2-[*o*-(1,1,1-trifluorometansulfonamido)fenil]-5-benzofuranil]metil]-4-ciclopropil-2-etilimidazol-5-carboxamida

$C_{25}H_{22}BrF_3N_4O_4S$

seprilosum
seprilose 3-*O*-heptyl-1,2-*O*-isopropylidene-α-D-glucofuranose

séprilose 3-*O*-heptyl-1,2-*O*-(1-méthyléthylidène)-α-D-glucofuranose

seprilosa 3-*O*-heptil-1,2-*O*-isopropiliden-α-D-glucofuranosa

$C_{16}H_{30}O_6$

setipafantum
setipafant 6-(*o*-chlorophenyl)-7,10-dihydro-1-methyl-4*H*-pyrido[4',3':4,5]thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine-9(8*H*)-carbox-*p*-anisidide

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

setipafant 6-(*o*-clorofenil)-7,10-dihidro-1-metil-4*H*-pirido[4',3':4,5]tieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepina-9(8*H*)-carboxi-*p*-anisidida

$C_{26}H_{23}ClN_6O_2S$

tagorizinum

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

tagorizine (2*E*)-*N*-[4-[4-(diphénylméthyl)pipérazin-1-yl]butyl]-3-(6-méthylpyridin-3-yl)prop-2-énamide

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

$C_{30}H_{36}N_4O$

talsaclidinum

talsaclidine (3*R*)-3-(2-propynyloxy)quinuclidine

talsaclidine (3*R*)-3-(prop-2-ynyloxy)-1-azabicyclo[2.2.2]octane

talsaclidina (3*R*)-3-(2-propiniloxi)quinuclidina

$C_{10}H_{15}NO$

tasosartanum

tasosartan 5,8-dihydro-2,4-dimethyl-8-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]pyrido= [2,3-*d*]pyrimidin-7(6*H*)-one

tasosartan 2,4-diméthyl-8-[4-[2-(1*H*-tétrazol-5-yl)phényl]benzyl]-5,8-dihydro= pyrido[2,3-*d*]pyrimidin-7(6*H*)-one

tasosartan 5,8-dihidro-2,4-dimetil-8-[*p*-(*o*-1*H*-tetrazol-5-ilfenil)bencil]pirido= [2,3-*d*]pirimidin-7(6*H*)-ona

$C_{23}H_{21}N_7O$

tazarotenum

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

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

tazaroteno 6-[(4,4-dimetiltiocroman-6-il)etinil]nicotinato de etilo

$C_{21}H_{21}NO_2S$

teverelixum

teverelix *N*-acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-L-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-L-tyrosyl-N^6-carbamoyl-D-lysyl-L-leucyl-N^6-isopropyl-L-lysyl-L-prolyl-D-alaninamide

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

teverelix [*N*-acetil-3-(naftalen-2-il)-D-alanil]-(4-cloro-L-fenilalanil)-[3-(piridin-3-il)-D-alanil]-L-seril-L-tirosil-[N^6-(aminocarbonil)-D-lisil]-L-leucil-[N^6-(1-metiletil)-L-lisil]-L-prolil-D-alaninamida

$C_{74}H_{100}ClN_{15}O_{14}$

toborinonum

toborinone (±)-6-[2-hydroxy-3-(veratrylamino)propoxy]carbostyril

toborinone (±)-6-[[(2*RS*)-3-[(3,4-diméthoxybenzyl)amino]-2-hydroxypropyl]oxy]quinoléin-2(1*H*)-one

toborinona (±)-6-[2-hidroxi-3-(veratrilamino)propoxi]carbostiril

$C_{21}H_{24}N_2O_5$

vedaprofenum

vedaprofen (±)-4-cyclohexyl-α-methyl-1-naphthaleneacetic acid

védaprofène acide (*RS*)-2-(4-cyclohexylnaphtalén-1-yl)propanoïque

vedaprofeno àcido (±)-4-ciclohexil-α-metil-1-naftalenacético

$C_{19}H_{22}O_2$

versetamidum

versetamide *N,N*-bis[2-[[(carboxymethyl)[(2-methoxyethyl)carbamoyl]methyl]amino]ethyl]= glycine

versétamide *N,N*-bis[2-[(carboxyméthyl)[2-[(2-méthoxyéthyl)amino]-2-oxoéthyl]amino]= éthyl]glycine

versetamida *N,N*-bis[2-[[(carboximetil)[(2-metoxietil)carbamoil]metil]amino]etil]glicina

$C_{20}H_{37}N_5O_{10}$

verteporfinum

verteporfin a mixture (50:50) of : (±)-*trans*-3,4-dicarboxy-4,4a-dihydro-4a,8,14,19-tetramethyl-18-vinyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropionic acid, 3,4,9-trimethyl ester and (±)-*trans*-3,4-dicarboxy-4,4a-dihydro-4a,8,14,19-tetramethyl-18-vinyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropionic acid, 3,4,13-trimethyl ester

vertéporfine mélange sensiblement équimoléculaire : d'acide 3-[(±)-*trans*-18-éthényl-3,4-bis(méthoxycarbonyl)-13-[2-(méthoxycarbonyl)éthyl]-4a,8,14,19-tétraméthyl-4,4a-dihydro-23*H*,25*H*-benzo[*b*]porphyrin-9-yl]propanoïque et d'acide 3-[(±)-*trans*-18-éthényl-3,4-bis(méthoxycarbonyl)-9-[2-(méthoxycarbonyl)éthyl]-4a,8,14,19-tétraméthyl-4,4a-dihydro-23*H*,25*H*-benzo[*b*]porphyrin-13-yl]propanoïque

verteporfina mezcla (50:50) del : 3,4,9-trimetil ester del ácido (±)-*trans*-3,4-dicarboxi-4,4a-dihidro-4a,8,14,19-tetrametil-18-vinil-23*H*,25*H*-benzo[*b*]porfina-9,13-dipropiónico, con el 3,4,13-trimetil ester del ácido (±)-*trans*-3,4-dicarboxi-4,4a-dihidro-4a,8,14,19-tetrametil-18-vinil-23*H*,25*H*-benzo[*b*]porfina-9,13-dipropiónico

$C_{41}H_{42}N_4O_8$

zafirlukastum

zafirlukast cyclopentyl 3-[2-methoxy-4-[(*o*-tolylsulfonyl) carbamoyl]benzyl]-1-methylindole-5-carbamate

zafirlukast [3-[2-méthoxy-4-[[[(2-méthylphényl)sulfonyl]amino]carbonyl]benzyl]-1-méthyl-1*H*-indol-5-yl]carbamate de cyclopentyle

zafirlukast ciclopentil 3-[2-metoxi-4-[(*o*-tolilsulfonil)carbamoil]bencil]-1-metilindol-5-carbamato

$C_{31}H_{33}N_3O_6S$

zaleplonum

zaleplon 3'-(3-cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*-ethylacetanilide

zaléplone *N*-[3-(3-cyanopyrazolo[1,5-*a*]pyrimidin-7-y)phényl]-*N*-éthylacétamide

zaleplon 3'-(3-cianopirazolo[1,5-*a*]pirimidin-7-il)-*N*-etilacetanilida

$C_{17}H_{15}N_5O$

zifrosilonum

zifrosilone	2,2,2-trifluoro-3'-(trimethylsilyl)acetophenone
zifrosilone	2,2,2-trifluoro-1-[3-(triméthylsilyl)phényl]éthanone
zifrosilona	2,2,2-trifluoro-3'-(trimetilsilil)acetofenona
	$C_{11}H_{13}F_3OSi$

ziprasidonum

ziprasidone	5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-2-indolinone
ziprasidone	5-[2-[4-(1,2-benzisothiazol-3-yl)pipérazin-1-yl]éthyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one
ziprasidona	5-[2-[4-(1,2-bencisotiazol-3-il)-1-piperazinil]etil]-6-cloro-2-indolinona
	$C_{21}H_{21}ClN_4OS$

zucapsaicinum

zucapsaicin	(*Z*)-8-methyl-*N*-vanillyl-6-nonenamide
zucapsaïcine	(*Z*)-*N*-(4-hydroxy-3-méthoxybenzyl)-8-méthylnon-6-énamide
zucapsaicina	(*Z*)-8-metil-*N*-vanilil-6-nonenamida
	$C_{18}H_{27}NO_3$

AMENDMENTS TO PREVIOUS LISTS

WHO Drug Information, Vol. 1, No. 4, 1987

Recommended International Nonproprietary Names (Rec. INN): List 27

p. 4	ebrotidinum	*replace the chemical name by the following:*
	ebrotidine	*p*-bromo-*N*-[(*E*)-[[2-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]≈ thio]ethyl]amino]methylene]benzenesulfonamide

WHO Drug Information, Vol. 3, No. 3, 1989

Recommended International Nonproprietary Names (Rec. INN): List 29

p. 2	alteplasum	*replace the description and the molecular formula by the following:*
	alteplase	plasminogen activator (human tissue-type protein moiety), glycoform α $C_{2569}H_{3894}N_{746}O_{761}S_{40}$

WHO Drug Information, Vol. 4, No. 3, 1990

Recommended International Nonproprietary Names (Rec. INN): List 30

p. 8	nebivololum	*replace the chemical name by the following:*
	nebivolol	[2*R*[*R**[*R**(*S**)]]]-α,α'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol]

MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES

Informations pharmaceutiques OMS, Vol. 1, No. 4, 1987

Dénominations communes internationales recommandées (DCI Rec.): Liste 27

p. 4 ebrotidinum
ébrotidine

remplacer le nom chimique par:
4-bromo-*N*-[(*E*)-[[2-[[[2-[(diaminométhylène)amino]thiazol-4-yl]méthyl]=sulfanyl]éthyl]amino]méthylène]benzènesulfonamide

Informations pharmaceutiques OMS, Vol. 3, No. 3, 1989

Dénominations communes internationales recommandées (DCI Rec.): Liste 29

p. 2 alteplasum
altéplase

remplacer la description et la formule brute par:
activateur du plasminogène (type tissulaire humain, partie protéique), forme glycosylée α
$C_{2569}H_{3894}N_{746}O_{781}S_{40}$

Informations pharmaceutiques OMS, Vol. 4, No. 3, 1990

Dénominations communes internationales recommandées (DCI Rec.): Liste 30

p. 9 nebivololum
nébivolol

remplacer le nom chimique par:
(1*RS*, 1'*RS*)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-chromén-2-yl)]-2,2'-iminodiéthanol

MODIFICACIONES A LAS LISTAS ANTERIORES

Información Farmacéutica, de la OMS, Vol. 1, No. 4, 1987

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 27

p. 4 ebrotidinum
ebrotidina

sustituyase el nombre químico por lo siguiente:
p-bromo-*N*-[(*E*)-[[2-[[[2-[(diaminometileno)amino]-4-tiazolil]metil]tio]etil]=amino]metileno]bencenosulfonamida

Información Farmacéutica, de la OMS, Vol. 3, No. 3, 1989

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 29

p. 2 alteplasum
alteplasa

sustituyanse la descripción y la fórmula molecular por las siguientes:
activador del plasminógeno (tipo tisular humano, fracción proteica), forma glicosilada α
$C_{2569}H_{3894}N_{746}O_{781}S_{40}$

Información Farmacéutica, de la OMS, Vol. 4, No. 3, 1990

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 30

p. 8 nebivololum
nebivolol

sustituyase el nombre químico por lo siguiente:
[2*R**[*R**[*R**(*S**)]]]-α,α'-[iminobis(metilen)]bis[6-fluoro-3,4-dihidro-2*H*-1-benzopiran-2-metanol]

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

	Price (Sw. fr.)*
The use of essential drugs Sixth report of the WHO Expert Committee WHO Technical Report Series, No. 850 1995 (138 pages)	21.–
WHO model prescribing information: drugs used in anaesthesia 1989 (53 pages)	11.–
WHO model prescribing information: drugs used in parasitic diseases, second edition 1995 (146 pages)	35.–
WHO model prescribing information: drugs used in mycobacterial diseases 1991 (40 pages)	9.–
The International Pharmacopoeia, third edition	
Volume 1: general methods of analysis. 1979 (223 pages)	24.–
Volume 2: quality specifications. 1981 (342 pages)	36.–
Volume 3: quality specifications. 1988 (407 pages)	64.–
Volume 4: tests, methods and general requirements. 1994 (360 pages)	85.–
Basic tests for pharmaceutical substances 1986 (vi + 204 pages)	34.–
Basic tests for pharmaceutical dosage forms 1991 (v + 129 pages)	24.–
International Nonproprietary Names (INN) for Pharmaceutical Substances, Cumulative List No. 8 1992 (xlvi + 692 pages)	140.–

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

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