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# WHO DRUG

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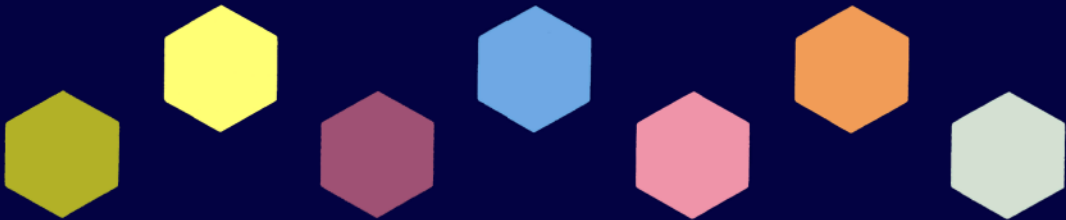
# INFORMATION

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RECOMMENDED INN LIST 43  
INTERNATIONAL NONPROPRIETARY NAMES  
FOR PHARMACEUTICAL SUBSTANCES



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WORLD HEALTH ORGANIZATION · GENEVA

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# General Policy Issues

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## The benefits and risks of self-medication\*

It is widely accepted that self-medication has an important role to play in health care and, with the continued improvement in people's education, general knowledge and socio-economic status, self-medication has been successfully integrated into many health care systems throughout the world.

Self-medication products are those not requiring a medical prescription and which are produced, distributed and sold to consumers for use on their own initiative. Responsible self-medication can be used to prevent and treat symptoms and ailments that do not need medical consultation or oversight. This reduces pressure on medical services, especially when these are limited. For those populations living in rural or remote areas where access to medical services may be difficult, patients are able to control their own conditions to a greater extent. Only if the condition fails to respond, persists, or becomes more severe will the patient need to seek professional medical care.

Other factors have also contributed to prescription drugs being deregulated to over-the-counter (OTC) sale and new drugs with specific pharmacological action have been successfully reclassified from prescription to non-prescription status in many countries. For example, in the United States of America, products containing over 80 active ingredients of different therapeutic groups were switched from prescription-only to OTC status between 1976 and 2000. In many cases, restrictions imposed on reimbursement of prescription drugs have provided the impetus for authorities to evaluate and deregulate self-medication products to OTC status.

Although many countries categorize medicines as either OTC or prescription-only, research data indicate that sale of self-prescription products (i.e. buying prescription-only drugs without a prescrip-

tion) is far more common than sale of OTC drugs. It is a reality that medical personnel are in very short supply in many parts of the world and legislation is lacking. Also, the cost and time of visiting a licensed medical practitioner may seem prohibitive for many patients if they do not consider the illness or condition serious enough.

According to a consumer interview study carried out in six Latin American countries, only 34% of dispensed medicines were classified as OTC (1). It was concluded that a relatively high percentage of drugs were being dispensed without medical prescription or follow-up and this was attributed to lack of access to medical care. Of equal concern is the fact that, in many countries, although OTC medicines are provided with a patient information leaflet the self-prescriber does not receive any information whatsoever on how to use a prescription medicine.

Interestingly, it is the increase in competitive promotion of self-medication products which has enhanced consumer and patient awareness of the availability of products. Worldwide promotion and cross-border sale of medical products via the Internet is another factor affecting consumer behaviour which is set to boost demand. Already, the Internet offers a considerable amount of websites promoting mail order pharmacies (as of 7 May 2000, a count using the search engine Yahoo identified 16 966 and WebCrawler identified 244 546). Many of these sites are not secure in terms of guaranteeing the safety and quality of the products. However, there is no doubt that in the future self-prescription product sales through the Internet will increase enormously. This could create additional demand to switch prescription products to OTC status.

However, there are several critical issues that must be explored before promoting the potential benefits of self-medication. Any self-medication product should be safe for use. This implies the availability of appropriate consumer information and avoidance of any delay in diagnosis and treatment of diseases not suitable for self-medication. Furthermore, self-medication drugs are known to interact with many prescription-only drugs, alcohol and foods. How can interactions be avoided in the event of self-medication? Unfortunately, before making out a prescription, many doctors do not enquire whether patients

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\*Based on a presentation given by Dr Lembit Rägo, Coordinator, Quality Assurance and Safety: Medicines, World Health Organization, Geneva, to the First Latin American World Self-Medication Industry (WSMI) Conference: "Recognizing and Developing the Vital Role of Responsible Self-medication in Latin America", 29-31 March 2000.

are also using self-medication products. Additionally, promotional messages through the media and the Internet tend to convey a feeling of confidence in the safety of the product and often give the impression that self-medication products are just another consumer article. In other cases, excessive or non-medical use may be a problem. Reports have been received of OTC medicines being misused by drug addicts (2) and, according to a recent study in Northern Ireland, pharmacists admit that OTC drugs may be used in this way (3).

There are several critical issues involved before deciding if drugs should be authorized for self-medication. First and foremost, is the principle that no drug is absolutely safe — prescription drugs remain potent medications. Self-medication is, in the majority of cases, applied without medical supervision and, to a certain extent, is an uncharted area with regard to interactions, pregnancy, lactation, use in children and the elderly, driving, working conditions, alcohol, or food compared to the more controlled prescription-only environment. In many countries, the possibility of reporting adverse drug reactions (ADR) to self-medication products is not available since many conventional ADR reporting schemes operate through health care professionals. Only in a small number of countries with highly developed ADR systems are patients and consumers able to report ADRs directly to the authorities or through pharmacies. Moreover, clinical trial data for prescription use may not necessarily be valid for self-medication. This situation is beginning to improve within some countries that now demand OTC-environment studies to be undertaken before registration.

Special mention should be made of the heavy reliance placed on OTC analgesics. These have long been associated with chronic renal failure. Many earlier reports implicated phenacetin-containing analgesics as the risk factor. Since the early 1980s, several case-control studies have reported associations between chronic renal failure and use of other forms of analgesics, including paracetamol, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs). Although findings from these studies should be interpreted with caution, the use of OTC analgesics is widespread and the potential impact of these drugs on the development of chronic renal failure may be significant (4). Furthermore, the consumer may be unaware that several products with different brand names and for different indications may contain the same active ingredient.

Consumers need independent information to ensure the safe, effective and rational use of drugs in

self-medication. Advice to the consumer/patient should include a description of how to use the product without medical supervision and the circumstances in which referral for medical advice is necessary. In many cases, self-medication products are also understood to mean alternative medicines, food supplements, vitamins, herbs or other substances contained in commercially available products. Many are also sold in pharmacies or health food stores and have not been clinically tested and do not have a scientific basis for their recommended medicinal use. Moreover, certain products can cause severe safety problems. In highly regulated markets, pharmacists and other health care providers that recommend alternative medicines expose themselves to malpractice and liability claims if a patient is either injured or has treatment inappropriately delayed as a result of recommending such products.

In conclusion, self-medication can facilitate access to medicines and reduce health care costs. But more specific studies are needed to evaluate the impact and role of self-medication in the diversity of settings of different health care sectors. The combined efforts of industry and regulators must meet the expectations of consumers by providing products which are safe, effective, good value for money, and accompanied by complete and relevant information. High ethical standards should be applied to the provision of information, promotional practices and advertising. The content and quality of such information and its mode of communication remains a key element in educating consumers in responsible self-medication.

An abridged version of WHO's Guideline for the Regulatory Assessment of Medicinal Products for Use in Self-Medication is included on pages 18–26 of this journal.

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# Personal Perspectives

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## **Tobacco product regulation: what can be achieved?**

*T. Yoshida, Quality and Safety of Medicines, World Health Organization, Geneva*

Few people would question the evidence now available that smoking tobacco is both addictive and harmful to health. Ample proof has been provided to support the linkage between smoking and increased incidence of serious health problems, notably lung cancer and cardiovascular diseases (1). Tobacco now kills over 4 million people annually. By 2030, it will kill 10 million people, out of which 7 in 10 will be in developing countries.

This public recognition has led many governments to implement legal and/or administrative measures to reduce tobacco smoking. Some countries have already achieved tangible results in reduction of both smoking rates and associated health problems. However, there is still an ongoing debate among countries concerning the interpretation of the harmfulness of tobacco smoking and the measures needed for effective reduction of smoking.

Faced with this situation, public health administrators of WHO Member States have urged governments to intensify their efforts to reduce tobacco smoking. Concerted international action will be needed to help governments achieve this objective and the World Health Assembly has resolved that WHO should develop a Framework Convention on Tobacco Control (FCTC) (2). WHO has already begun a formal process of intergovernmental negotiations for this purpose.

The FCTC will be supplemented by several protocols, each containing specific control measures related to a particular field. As a package, it is expected to provide a legal instrument for a comprehensive set of tobacco control measures to be implemented globally in a stepwise manner. The flexibility required for implementation is provided through the accession procedure which allows governments to ratify the FCTC and different protocols separately at different times depending on progress made.

Against this background, tobacco product regulation is increasingly viewed as one of the potential areas for international control under the FCTC. Needless to say, product regulation is applied widely in the pharmaceuticals sector. The topic therefore attracted the attention of many drug regulators in April 1999, and the Ninth International Conference of Drug Regulatory Authorities (ICDRA) devoted one plenary session to discussion of this issue.

More recently, tobacco product regulation was discussed at two WHO meetings — the Conference on the Regulation of Tobacco and Tobacco Dependence Treatment Products, held in Helsinki, 18–19 October 1999 and the International Conference on Advancing Knowledge on Regulating Tobacco Products, held in Oslo, 9–11 February 2000. In addition, the European Commission (EC) has announced a proposal to update a directive calling for the harmonization of the laws and regulations of its Member States regarding the manufacture, presentation and sale of tobacco products. Although formal reports of the WHO conferences mentioned above are not published yet, highlights of these events are discussed below.

### **Public health goals of tobacco regulation**

The public health goal of tobacco product regulation should be to reduce the health risks due to smoking. However, it is not immediately clear how action to reduce the amount of risk to an individual smoker would justify action taken on behalf of the community as a whole. If there is a difference between the two, it may be necessary to evaluate the risk to the entire population rather than the risk to individual smokers. This was the consensus reached after some debate at the Oslo Conference, which agreed that the objective of tobacco product regulation should be to prevent the initiation of tobacco use and thereafter aim for a substantial and sustained reduction in tobacco-related morbidity and mortality among smokers.

Harm reduction is not a well-defined concept. In the context of discussions on illegal drug problems surrounding heroin and cocaine abuse, the ambiguous use of the expression "harm reduction" has created much confusion leading to confrontational

debates. The controversy has mainly been a consequence of the implicit acceptance of illegal drug use. For this reason, the United Nations Commission on Narcotic Drugs, the international policy-making body for drug abuse control, did not accept "harm reduction" as a substitute for demand reduction. Since tobacco is not an internationally agreed illegal drug, such a controversy was not anticipated in the discussion of "harm reduction" concerning tobacco smoking.

Contrary to expectations, there were numerous debates on the question of whether "safer cigarettes" are a good thing from a public health point of view or not. The answer is not so simple as one may think. Firstly, the meaning of "safe cigarettes" would have to be clarified.

With regard to the harm to individual smokers, there is broad consensus that most of the health risks associated with tobacco smoking are due to the intake of a large number of chemical substances resulting from the combustion and heat decomposition of tobacco constituents and additives as well as the paper used to roll cigarettes. Nicotine itself is not regarded as the main culprit but is responsible for addiction (dependence-producing capacity). Tar and the nonvolatile constituents of tobacco smoke contain most of the harmful chemical substances in the smoke, particularly those associated with lung cancer. Carbon monoxide is considered to be responsible for cardiovascular disease as well as low-birth-weight babies and foetal abnormalities. Based on these facts, it has been concluded that the health risks associated with tobacco smoking can be reduced by decreasing tar levels, nicotine contents and carbon monoxide yields in cigarettes. The proposed European Union (EU) directive is a direct translation of this concept into a concrete EU-wide anti-smoking policy.

### **EU directive on tobacco product regulation**

Past EU directives were progressively aimed at reducing the permissible tar yield of cigarettes, and the current ceiling is set at 12 mg/cigarette. The new directive proposed by the Commission of the European Communities in 1999 (3), if adopted, will lower this limit to 10 mg/cigarette. Likewise, it would set the ceiling on the nicotine yield in cigarettes at 1 mg/cigarette. The limit of carbon monoxide yield would be 10 mg/cigarette. The effective date of the directive will be 31 December 2003 (or 3 years from the date of adoption). The measurement systems proposed for each of these ceilings are

those set down by the International Standards Organization (ISO). With regard to labelling, the existing provisions require that yields of tar and nicotine be shown on cigarette packaging and that warning messages to alert consumers be printed on all tobacco product packaging. The proposed directive would additionally require that the carbon monoxide yield be indicated on cigarette packaging, in addition to improved clarity and presentation of warning messages (e.g. "Smoking kills"). The use of terms which convey the impression that a particular product is less harmful than others (e.g. "low tar") will be prohibited, unless expressly approved by the national authorities.

With regard to non-tobacco ingredients, including additives, manufacturers or importers of tobacco products would be required to submit to the authorities not only the list of such ingredients and the reasons for their inclusion but any toxicity data they may have to demonstrate their safety when used as intended in their tobacco products. The directive also requires a ban on the marketing of tobacco for oral use in the EU except in Sweden, where its use is traditionally allowed.

### **Reduction in tar yield**

Questions have been raised concerning the usefulness of the reduction in tar level per cigarette. Doubts exist concerning the linkage between the tar yield as measured by the ISO method and the amount of tar actually absorbed by the body of the smoker.

However, it was noted that the ISO methods currently in use, which employ a smoking machine, were not designed to measure the biological impact of tobacco products. Unlike the smoking machine, smokers can and do modify the way they smoke in order to change the subjective effects of smoking. This practice has been shown to have a significant influence on the amount and composition of tar taken into the lungs of the smoker. Therefore, there is no assurance that the amount of tar per cigarette measured by the ISO method will demonstrate the amount of toxic substances absorbed by the biological system of the smoker when smoking a cigarette. Secondly, experts have pointed out that so-called "low tar" or "light" cigarettes did not actually lead to any significant reduction in the incidence of health problems associated with smoking (4). This is due to the "compensation mechanism", which is the tendency of nicotine-dependent smokers to adjust their smoking patterns according to the quantity of nicotine actually absorbed into the body.

Thus, if the "low tar" cigarette also contains less nicotine, the smoker might simply smoke more cigarettes so that there may be no real reduction in the total amount of the tar that has entered the body. The question would be equally valid for the yield of carbon monoxide. Furthermore, it was pointed out that the perception of "low tar" or increased safety may reduce the motivation to quit smoking.

#### **Reduction in nicotine level**

The question raised about the usefulness of reducing the nicotine content per cigarette is related again to the "compensation mechanism". If nicotine-dependent smokers smoke more cigarettes to compensate for the reduced nicotine, the total intake of tar will increase. On the other hand, experimental and casual smokers who are not dependent on nicotine yet would have a smaller risk of developing nicotine dependence. In theory, therefore, there is likely to be a turning point below which the reduction in the risk of developing nicotine dependence in non-dependent smokers would outweigh the increase in the risk of tar intake in nicotine-dependent smokers.

Unfortunately, no studies are available to enable an estimation of where this break-off nicotine level in cigarettes would be. Although some studies and industry reports have addressed "threshold levels" of nicotine the authors have studied "the lowest addictive level of nicotine" rather than the turning point level in terms of public health risk-benefit ratio (5). If it were close to the level specified by the EU directive (1 mg/cigarette), any further reduction would be a public health gain. Should it be much lower than this level, a gradual reduction in nicotine levels per cigarette would increase the overall public health problems associated with smoking.

#### **Recommendations and discussion**

What is recommended? In general, both the Helsinki and Oslo Conferences were supportive of the EU policy outlined in the new directive, with the exception of the two questions mentioned above. On these contentious issues, the Oslo Conference adopted the following recommendations:

1. Discontinue harm reduction strategies based on naive interpretation of tar and nicotine yield measurements.

This means abandoning the strategy of seeking lower nominal tar yields and instead finding approaches that genuinely reduce harm to nicotine users.

2. Remove tar and nicotine measures derived from ISO methods from packages.

From a public health point of view, it will be valuable to see how the policy-makers of the European Union respond to these recommendations.

Other recommendations adopted by the Oslo Conference but not mentioned in the EU directive, include the proposal that product regulation should be applied to all forms of tobacco and nicotine products. This would require a unified regulatory framework for nicotine delivery products, including tobacco products, products for treating tobacco dependence, and novel nicotine delivery devices, whether or not these are based on tobacco products.

A required condition for the successful implementation of this recommendation would be the existence of a national agency mandated to regulate the marketing of all nicotine-containing products, regardless of their usage. Currently, it is common to find diverse laws, often implemented by various governmental agencies, which regulate the marketing of different consumer products containing the same chemical substance. However, the idea of having a single agency regulating all nicotine-containing products did receive some international attention at the Ninth ICDRA held in Berlin in April 1999, when the representative of the US Food and Drug Administration (FDA) presented the FDA tobacco regulations, promulgated on the basis of the agency's legal interpretation that nicotine in tobacco is a "drug" as defined by the US Food, Drug and Cosmetic Act. This focus on such a solution seems to have lost support as a result of a Supreme Court ruling, in March 2000, that the FDA did not have such authority.

Setting legal questions aside, it is clear that several key questions remain unanswered. It was therefore important for the Oslo Conference to urge further research, listing the following as priority areas.

- Research to evaluate the benefits and/or hazards of reducing nicotine and other possible addictive constituents in tobacco products over time. Particular attention should be given in research to determining whether a threshold exists for addiction.
- Research to develop better measures, including biomarkers, to assess the health impact of the use of "less harmful" tobacco products in order to drive

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future regulatory action. For exposure, a composite measure of toxicity is needed. In addition, the unintended consequences of consuming such products should be investigated.

- Expand behavioural research on how “cigarettes affect smokers” and how the population (of smokers and nonsmokers) responds to claims about new products and to new packaging rules.
- Research to determine whether regulators should encourage the development of substantially less harmful nicotine delivery devices.
- Research to determine whether countries should forbid addition of all new additives and explicitly address the possibility of reducing the use of additives that make tobacco products more attractive and/or taste better.
- Research to evaluate how regulatory approaches developed for cigarettes could be adapted to cover all forms of tobacco use.

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## Reports on Individual Drugs

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### Spread of quinolone-resistant salmonella

Food-borne salmonella infections have become a major problem in many industrialized countries (1, 2). *Salmonella enterica* serotype typhimurium (DT104) is now resistant to five drugs: ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An increasing proportion of DT104 isolates also have reduced susceptibility to fluoroquinolones. The concomitant use of these and other antimicrobial agents at sub-therapeutic concentrations to enhance growth in animals and for farming purposes is causing obvious concern and national and international recommendations on the use of antimicrobials for disease control in humans and animals have been proposed (3, 4).

A recent study in Denmark has demonstrated the spread of an unusually resistant strain of typhimurium, through the food chain, from food-producing animals to humans (5). The surveillance of salmonella in farms in Denmark covers nearly all commercial food-producing animal facilities and slaughterhouses. In 1998, the first community outbreak of quinolone-resistant salmonella occurred. The outbreak included 25 culture-confirmed cases which were difficult to treat: eleven patients were hospitalized and two died. The investigators succeeded in tracing the source of infection in most of the 25 cases. During microbiological investigation, an unusual resistance pattern was found in isolates from all patients, the slaughterhouse, two samples of pork originating from food inspection agencies and two swine herds. Nine patients had eaten pork originating from a slaughterhouse where two herds tested positive for multidrug-resistant salmonella. The molecular epidemiological data from patients confirmed that the primary source of all cases was a Danish swine herd.

Fluoroquinolones were licensed in Denmark for veterinary use in 1993 and by 1998 accounted for 400 kg of a total of 57 300 kg of antimicrobial agents consumed by food-producing animals. No indication of fluoroquinolone use was found in the implicated herds. It is therefore suggested that resistant salmonella may have originated as a result of use of fluoroquinolones prior to 1998 or

through introduction from pigs not bred in Denmark, and thereafter spread through wild animals or equipment.

A further case of ceftriaxone resistant salmonella infection acquired by a child from cattle has also been reported from the United States (6). The ceftriaxone-resistant isolate from the child was indistinguishable from one of the isolates from cattle, which was also resistant to ceftriaxone. Furthermore, both isolates were resistant to 13 antimicrobial agents; all but one of the resistance determinants were on a conjugative plasmid of 160 kb that encoded the functional group 1 beta-lactamase CMY-2. This study provides additional evidence that antibiotic-resistant strains of salmonella evolve primarily in livestock. Resistance to ceftriaxone is a concern, especially with respect to children, since fluoroquinolones are not approved for use in children in the United States.

Fluoroquinolones remain the empirical treatment for suspected intestinal salmonella infection. They are crucial for the treatment of severe concomitant diseases and health conditions. The increased presence of quinolone-resistant salmonella strains in food producing animals is therefore of public health concern. Fluoroquinolones should not be used in food-producing animals to enhance growth or for other purposes. They should be used in veterinary practice for therapeutic indications only when other options are not possible.

Antimicrobial resistance was the topic of a conference of Health Ministers from the European Union countries in 1998 (4, 7). The majority of participants considered the use of antimicrobials as growth promoters in animals unjustified and recommended that safer alternatives such as improved farming practices should be developed. The follow-up of these recommendations is increasingly important.

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## Evidence for the role of zinc in childhood survival

Although the theoretical basis for a potential role of zinc has been postulated for quite some time, convincing evidence for its importance in child health has come only recently from randomized controlled trials of zinc supplementation. Episodes of childhood diarrhoea that last 14 days or more are associated with increased morbidity and growth retardation. Children who experience such episodes are more likely to have other serious infections and to die (1).

Zinc is essential for many cellular functions, including transcription of DNA and cell division (2) and is required for normal immune function (3). It has been shown to hasten mucosal recovery after diarrhoea. Zinc deficiency, as indicated by low plasma zinc concentrations, is associated with both an increased risk of diarrhoeal episodes and greater severity of these illnesses (4, 5).

The data from 10 trials evaluating preventive effects of zinc supplementation; three trials evaluating the therapeutic effects on acute diarrhoea; and four trials in therapy of persistent diarrhoea have now been subjected to a pooled analysis (6). This evaluation assessed studies carried out on the effects of zinc supplementation in the prevention of diarrhoea and pneumonia. Trials included those that provided oral supplements containing at least one half of the United States Recommended Daily Allowance of zinc in children under 5 years of age and evaluated the prevention of serious infectious morbidity. The effects of supplements on diarrhoea

and pneumonia were analysed overall and in subgroups, defined by age, baseline plasma zinc concentration, nutritional status, and sex. The analysis used random effects hierarchical models to calculate odds ratios and confidence interval.

This analysis indicated that there is significant homogeneity in the results across the studies conducted throughout 10 developing countries. Zinc supplementation in these children in developing countries is associated with substantial reductions in the rates of diarrhoea and pneumonia, the two leading causes of death in these settings. These studies also provide by far the best evidence of widespread prevalence of zinc deficiency among preschool children.

However, although the available evidence is promising, it is still insufficient to formulate public health policies. Extrapolation of mortality impact from morbidity trial data is fraught with problems of both underestimating and overestimating the impact. Therefore, given its substantial potential to become a powerful intervention to promote child survival, the World Health Organization, in collaboration with UNICEF backed by funding from the United Nations Foundation, has initiated two large studies to determine whether zinc supplementation truly has an important role in decreasing child mortality and morbidity. These studies should provide conclusive new evidence on which to base interventions within the next 30 months and allow recommendations concerning the benefit of zinc supplementation in young children to be made.

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### Increased risk of gastrointestinal bleeding: SSRIs and NSAIDs

Antidepressants with selective serotonin re-uptake inhibitory action such as fluoxetine, fluvoxamine, paroxetine and sertraline have been associated with bleeding disorders including purpura, ecchymose, epistaxis, prolonged bleeding time, thrombocytopenia, platelet dysfunction, and haemorrhage (1–3). Serotonin released from platelets has an important role in regulating the haemostatic response to vascular injury. Selective serotonin re-uptake inhibitors (SSRIs) diminish transportation of serotonin from circulation to platelets creating a haemostatic defect with increased risk of bleeding. New data show that concurrent use of SSRIs with nonsteroidal anti-inflammatory drugs (NSAIDs) greatly increases the risk of upper gastrointestinal bleeding.

A population-based case-control study has been carried out using the United Kingdom General Practice Research Data Base (1). The study identified 1651 cases of upper gastrointestinal bleeding against 10 000 controls. Current exposure to SSRIs was found in 3.1% of patients with upper gastrointestinal bleeding and only 1% in controls. The estimated absolute risk of upper gastrointestinal bleeding was 1 case in 8000 prescriptions which was similar to that of low-dose ibuprofen, a commonly used NSAID.

In contrast, the nonselective serotonin re-uptake inhibitors such as amitriptyline, imipramine, lofepramine and doxepin showed only a small trend toward gastrointestinal bleeding with a ratio of 1.4. No increased risk was shown with nortriptyline, protriptyline, desimipramine or mianserin. The concomitant use of SSRIs with NSAIDs increased significantly the risk of upper gastrointestinal bleeding to a ratio of 15.6 which was beyond the sum of their independent effects.

These data show that the SSRIs have an increased risk of gastrointestinal bleeding but the older antide-

pressants with no action on serotonin mechanisms lack this risk. Moreover, there is clinically relevant interaction between SSRIs and anti-inflammatory drugs. Their concurrent use significantly increases the risk of upper gastrointestinal bleeding. Since many of these drugs such as acetylsalicylic acid, ibuprofen and ketoprofen are available over-the-counter it is important to warn patients using SSRIs of this risk.

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### Clozapine and venous thromboembolism

Data from the Swedish Adverse Drug Reaction Committee suggest that use of clozapine is associated with venous thromboembolic complications. Until now, use of clozapine, an atypical antipsychotic agent, has been limited by agranulocytosis, and the existence of other potentially fatal adverse effects such as myocarditis and thromboembolism has also been suggested.

Between April 1989 and March 2000, six cases of pulmonary embolism and six of venous thrombosis were reported. In all cases, the diagnosis of the adverse drug reaction was supported by clinical findings. In eight patients, symptoms occurred in the first 3 months of treatment. Massive pulmonary embolism was confirmed in the five patients who died, and in three of these patients no other factors contributed to death.

The mechanism by which clozapine can induce thromboembolism remains to be established. The assumed risk would be at least one per 2000–6000 treated patients and could be higher because of under-reporting. This potentially fatal effect seems to occur mainly during the first 3 months of clozapine treatment and the drug should not be used in any patient in whom this reaction may be suspected.

**Reference:** Hägg, S., Spigset, O., Söderström, T.G. Association of venous thromboembolism and clozapine. *Lancet*, **355**: 1155–1156 (2000).

## ACE inhibitors improve cardiovascular outcome

Angiotensin converting enzyme (ACE) inhibitors have been shown to improve outcome among patients with left ventricular dysfunction, whether or not they have heart failure. ACE inhibitors block the activation of the renin-angiotensin system and may retard the progression of both heart failure and atherosclerosis. In a meta-analysis of three studies (1–3) that included more than 9000 patients with low ejection fractions, treatment with ACE inhibitors reduced the risk of myocardial infarction by 23% suggesting that ACE inhibitors may have a role in preventing myocardial infarction in a wide range of patients. ACE inhibitors may also reduce the risk of stroke by lowering blood pressure and may prevent complications related to diabetes (4).

A recently reported (5) trial has now evaluated the role of ramipril, an ACE inhibitor, in patients at high risk for cardiovascular events not having left ventricular dysfunction or heart failure.

The Heart Outcomes Prevention Evaluation (HOPE) study was carried out in centres in Argentina, Brazil, Canada, Mexico, USA and western Europe. A total of 9297 high-risk patients of 55 years of age or older who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor were randomly assigned to receive ramipril or matching placebo and vitamin E for a mean of five years. A substudy compared low-dose ramipril (2.5 mg daily) with a full dose (10 mg daily). A total of 3578 patients in the study had diabetes, and 8160 had cardiovascular disease. The event rate in this group for those receiving placebo was about half that in patients with cardiovascular disease receiving placebo.

The magnitude of the benefit of treatment with ramipril was at least as large as that observed with other proven secondary prevention measures. Treatment with ramipril significantly reduced rates of death from cardiovascular causes, myocardial infarction, stroke, death from any cause, revascularization procedures, cardiac arrest heart failure, and complications related to diabetes.

The study concluded that ramipril is beneficial in a broad range of patients without evidence of left

ventricular systolic dysfunction or heart failure who are at high risk for cardiovascular events.

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## Ticlopidine and thrombotic thrombocytopenic purpura

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has recently received its first report of thrombotic thrombocytopenic purpura (TTP) in association with ticlopidine (Ticlid®).

TTP is a life-threatening syndrome of thrombocytopenia and microangiopathic haemolytic anaemia commonly associated with fluctuating neurological abnormalities, renal dysfunction, and fever. A central feature is widely disseminated platelet aggregates, which have been observed in the adrenal glands, brain, heart, kidneys, and pancreas.

The association of TTP with ticlopidine has been the subject of two recent publications (1, 2). In the report to ADRAC (3), a 56-year-old female was admitted to hospital with spontaneous bruising on the arms, chest and legs after about 3 weeks use of ticlopidine for coronary stenting. Laboratory investigations showed thrombocytopenia (platelets  $9 \times 10^9$  /L [reference range: 150–400  $\times 10^9$  /L]) and declining haemoglobin (haemoglobin 88 g/L [refer-

ence range: 115–165 g/L). Microangiopathic red cells consistent with TTP were present on full blood examination. The patient's highest recorded temperature was 38 °C and involved haematuria in addition to spontaneous bruising. Neurological signs and symptoms included severe headaches and neck stiffness. Recovery was achieved after aggressive treatment which included plasmapheresis. TTP is a rare and often fatal disorder with an estimated incidence of 3.7 cases per million people (0.0004%).

Since mortality exceeds 20%, this complication needs to be recognized promptly and treatment commenced rapidly.

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### Miltefosine: effectiveness in visceral leishmaniasis explored

There is currently no effective orally administered medication against visceral leishmaniasis, a parasitic disease affecting 500 000 people a year and occurring mainly in India, Brazil and Sudan. Symptoms of infected patients are hepatosplenomegaly and pancytopenia, while the disease is usually fatal if left untreated.

Traditionally, four weeks of injections of pentavalent antimonial agents has been the mainstay of treatment. In 1997, liposomal amphotericin B was licensed for visceral leishmaniasis but because of its high cost and need for parenteral administration it has not been successfully deployed in the developing world.

Miltefosine, originally developed as an antitumour compound, has now shown promise in use against visceral leishmaniasis and successful reports have been received following a phase II trial conducted in India.

The study was an open-label, multicentre trial in which four 30-person cohorts received 50 mg, 100 mg or 150 mg of miltefosine per day for four or six weeks. The 120 patients, who ranged in age from 12 to 50 years, had anorexia, fever and splenomegaly as a result of confirmed leishmania infection. Parasitological cure was defined by the absence of parasites in a splenic aspirate obtained two weeks after completion of treatment.

In all 120 patients there was an initial parasitological cure. Six patients had clinical and parasitological relapse, but the remaining 114 had not relapsed by six months follow up. This represents a cure rate of 95%. The regimen of 100 mg per day produced the best cure rate. Gastrointestinal side effects were frequent (62%) but mild to moderate in severity and no patient discontinued therapy. A phase III trial is under way in adults in India.

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# Current Topics

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## HIV treatment guidelines for adults and adolescents

An updated version of the Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents has been posted on the HIV/AIDS Treatment Information Service (ATIS) website (1, 2). The new Guidelines are based on the latest research findings and provide recommendations on how to make optimal use of the many antiretroviral medications and sophisticated laboratory tests now available.

The increased number and availability of treatment options for HIV-infected individuals and the rapid evolution of new information has introduced extraordinary complexity into the treatment of HIV. In 1996, the Department of Health and Human Services and the Henry J. Kaiser Family Foundation convened a Panel on Clinical Practices for the Treatment of HIV to develop guidelines for the clinical management of HIV-infected adults and adolescents.

The latest Guidelines include recommendations for the use in clinical practice of recently developed tests to help determine if the virus a patient is carrying has developed resistance to one or more antiretroviral drugs. The likelihood of reducing viral load to undetectable levels is significantly increased when results of resistance testing are available.

The Guidelines also discuss other primary goals of antiretroviral therapy including:

- restoring or preserving the patient's immunologic function;
- improvement in quality of life;
- reduction of HIV-related illness and death.

The Guideline proposes that care should ideally be supervised by an expert, and makes recommendations for laboratory monitoring including plasma HIV RNA, CD4+ T cell counts and HIV drug resistance testing. Guidelines are also provided for antiretroviral therapy, including when to start treatment, what drugs to initiate, when to change therapy and

therapeutic options when doing this. Special considerations are provided for adolescents and pregnant women. As with treatment of other chronic conditions, therapeutic decisions require a mutual understanding between the patient and the health care provider regarding the benefits and risks of treatment.

Antiretroviral regimens are complex, have major side effects, pose difficulty with compliance, and carry serious potential consequences as a result of development of viral resistance due to non-adherence to the drug regimen or suboptimal levels of antiretroviral agents. Patient education and involvement in therapeutic decisions is important for all medical conditions, but is considered especially critical for HIV infection and its treatment.

With regard to specific recommendations, treatment should be offered to all patients with the acute HIV syndrome, those within six months of HIV seroconversion, and all patients with symptoms ascribed to HIV infection. Recommendations for offering antiretroviral therapy in asymptomatic patients depend on virologic and immunologic factors. In general, treatment should be offered to individuals with fewer than 500 CD4+ T cells/mm<sup>3</sup> or plasma HIV RNA levels exceeding 10 000 copies/mL (branched DNA assay) or 20 000 copies/mL (RT-PCR assay). The strength of the recommendation to treat asymptomatic patients should be based on the patient's willingness to accept therapy, the probability of adherence to the prescribed regimen, and the prognosis in terms of time to an AIDS-defining complication as predicted by plasma HIV RNA levels and CD4+ T cell counts, which independently help to predict prognosis.

Once the decision has been made to initiate antiretroviral therapy, the goals should be maximal and durable suppression of viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Results of therapy are evaluated primarily with plasma HIV RNA levels; these are expected to show a one-log (10-fold) decrease at eight weeks and no detectable virus (<50 copies/mL) at 4–6 months after initiation of treatment. Failure of therapy (i.e., plasma HIV RNA levels

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exceeding 50 copies/mL) at 4–6 months may be ascribed to non-adherence, inadequate potency of drugs or suboptimal levels of antiretroviral agents, viral resistance, and other factors that are poorly understood.

Patients whose therapy fails in spite of a high level of adherence to the regimen should have their regimen changed; this change should be guided by a thorough drug treatment history and the results of drug resistance testing. Optimal changes in therapy may be especially difficult to achieve for patients for whom the preferred regimen has failed due to limitations in the available alternative antiretroviral regimens that have documented efficacy; these decisions are further confounded by problems with adherence, toxicity, and resistance. In some set-

tings it may be preferable to participate in a clinical trial with or without access to new drugs or to use a regimen that may not achieve complete suppression of viral replication. It is emphasized that concepts relevant to HIV management evolve rapidly.

The Panel has a mechanism to update recommendations on a regular basis, and the most recent information will be posted on the HIV/AIDS Treatment Information Service (ATIS) website (2).

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# Vaccines and biomedicines

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## Immunization safety: a global priority

Immunization is undoubtedly one of the most effective health interventions. Nevertheless, implementation of immunization programmes faces many challenges. One such challenge is immunization safety – monitoring of adverse events following immunization, as well as all other aspects of immunization such as vaccine quality, storage and handling, administration and disposal of sharps (1).

It is accepted that adverse events may follow the administration of vaccines. Such events may be mild or severe, at the site of injection or systemic. It has also been recognized that while some of these events are indeed due to the vaccine, many are coincidental and arise because of other medical conditions. The vast number of doses of vaccines administered creates conditions that are auspicious for the occurrence of post-vaccination events which may lead to undue concerns and allegations.

In the past, the initial focus after an adverse event or a series of events was the quality of the vaccine. Because of the need to assure and improve vaccine quality, WHO and national regulatory authorities worldwide have devoted much energy and resources to working with vaccine manufacturers to enhance their compliance with good manufacturing practices.

The availability of vaccines of good quality, however, is not sufficient. It is known, for example, that up to one-third of vaccination injections are not carried out in a way that guarantees sterility, and infectious diseases have actually been transmitted by immunization. In addition, errors occur and individuals involved in immunization may be badly prepared to deal with adverse events. Vaccination is expected to be a safe medical intervention that will not lead to harm. This expectation arises because vaccines are given to healthy children and pregnant women. This situation is in contrast to therapeutic drugs, which are taken to cure or alleviate disease.

Paradoxically, the very success of global immunization programmes in decreasing the incidence of

long-dreaded scourges such as poliomyelitis, diphtheria and measles, as well as in eradicating smallpox in the late 1970s, can actually lead to public complacency. If there is no discernible risk from the infectious disease, why be vaccinated against it?

It is therefore not surprising that immunization safety ranks high on WHO's priority list, resulting in the creation of the Immunization Safety Priority Project (ISPP). Countries are the primary focus of this project, whose main target is to establish by the year 2003 a comprehensive system to ensure the safety of all immunizations given in national immunization programmes. It requires an overall awareness of the importance of safety and need for prevention, early detection, and quick response to adverse events following immunization, to lessen their negative impact on health and on immunization programmes equally (2).

The ISPP partners include UNICEF, the World Bank, Program for Appropriate Technologies for Health (PATH), the Bill and Melinda Gates Children's Vaccine Program, vaccine manufacturers, and professional organizations. Several development or technical agencies such as the Canadian International Development Agency (CIDA), the Japanese International Cooperation Agency (JICA), the U.S. Agency for International Development (USAID), and the Centers for Disease Control and Prevention (CDC) are also key participants. WHO is the coordinating agency which acts as Secretariat.

The objectives of the project are to:

- ensure vaccine safety, throughout clinical trials and distribution to point of use;
- strengthen research and development of safer and simpler delivery systems;
- establish efficient mechanisms that detect potentially serious adverse events following immunization and enable prompt and effective response; and
- broaden access to safer and more efficient systems for vaccine delivery and sharps waste management.

The latter activity is an area of concerted action with the Safe Injection Global Network (SIGN), whose mission is to achieve safe and appropriate use of all injections worldwide.

Recent ISPP activities include the establishment of a Global Advisory Committee on Vaccine Safety to provide a reliable and independent scientific assessment of vaccine safety issues; the development of training materials and activities on post-marketing surveillance and managing/monitoring of adverse events following immunization; partnerships with the media; and a WHO/UNICEF/UNFPA statement on safe injections and use of auto-disposable syringes.

A Steering Committee on Immunization Safety has been set up to provide technical and scientific advice to the ISPP. Meeting for the first time in October 1999, members stressed the importance of delivering safe vaccines of high quality and of focusing on preventive and safety assurance. Also highlighted was the value of prompt management of adverse events following immunization, strengthening national regulatory authorities and of collaboration between regulatory authorities and immunization programme managers. The following recommendations were proposed.

- Strategies must be developed to assure advocacy for vaccine safety and target appropriate levels of government and the health care delivery system.
- The overall concept of "cost of a safely immunized child" should be promoted. Complete budgeting for safe delivery of vaccines, including the disposal of residual waste, should be an integral part of financing strategies.
- Immunization safety should be emphasized as a core function of immunization systems during health care reform.
- The capacity at all levels to assess/manage immunization safety concerns should be enhanced.
- WHO/UNICEF and their Member States should expand access to training as a core element of immunization safety. This should include monitoring adverse events following immunization, risk communication/media training, injection safety, and national regulatory authorities functions. The ability to train should be addressed at an early stage in the development of new technologies or programmes, with emphasis on pre-service training.
- National immunization plans should include policies towards safety and waste management, and these policies should be implemented. Early detection, proper response and timely management of vaccine safety concerns, in particular to correct programmatic errors, should be instigated.

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### Cost effectiveness of influenza vaccination in healthy infants

Influenza is the only respiratory virus for which there is a vaccine. Vaccination is generally recommended for use in adults over 65 years of age, high risk persons 6 months of age or older, and those who might transmit the virus to persons at high risk (1, 2). Despite high annual rates of influenza in children and the increased risk of serious complications from influenza leading to otitis media, sinusitis, pneumonia and other bacterial infections, influenza vaccination has not yet been considered for inclusion in immunization schedules for children. Quantifying the risk of influenza virus alone among infants and children has been complicated because young children are more susceptible than older children to respiratory viruses, particularly syncytial virus infections which occur in winter and coincide with influenza virus infections.

Two recent studies measured the disease burden of influenza in healthy children under 18 years of age (3, 4). Healthy children younger than one year of age were hospitalized for illness attributable to influenza at rates similar to those in adults for whom an influenza virus vaccine is recommended (3). The rate of hospitalization decreased markedly with age. The rates were 12 times higher in children younger than two years compared with rates in children who were from 5 to 17 years of age (4). Children of all ages were more likely to receive outpatient medical care and antibiotic prescriptions during the winter when influenza virus was circulating. However, both studies leave considerable uncertainty about whether influenza alone was responsible for all, or even most, of the excess morbidity that is attributed to it. The second study



was more likely to exclude the effect of respiratory syncytial virus infection and some 20% of excess numbers of hospitalizations were attributed to influenza virus infection. These studies raise the question of whether influenza vaccine would be advantageously used in infants and toddlers (4, 5) who are increasingly placed in day care where transmission is a matter of concern.

Many issues remain to be considered before a vaccination policy is formulated. The potential benefits of such a policy should be weighed against risk and cost. Furthermore, inactivated influenza vaccines are currently not approved for use in infants under 6 months of age. Two doses of vaccine are required in children to assure efficacy, which increases the number of injections received routinely in childhood. The degree of protection in children under three years of age has not been sufficiently documented through clinical trials. Adding influenza vaccination to the immunization schedule would be logistically challenging, particularly in countries with limited resources and a weak health care infrastructure.

None the less, the two studies do raise interesting points for discussion as they both clearly suggest that routine influenza vaccination in young children has many potential benefits to offer. Hopefully, these studies will inspire international multicentre trials on the safety, effectiveness and cost benefit of influenza virus vaccination in children.

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## Diphtheria and tetanus vaccines: harmonization of testing in sight?

Diphtheria is a bacterial infection transmitted from person to person through close physical and respiratory contact. It can cause infection of the throat that may lead to fatal obstruction of breathing. Like other respiratory infections, transmission is increased in overcrowded and poor socio-economic conditions. Large epidemics occurred in Europe in the 1940s involving over one million cases and 50 000 deaths.

Tetanus is the only vaccine-preventable disease that is acquired through environmental exposure. The disease is caused by a potent neurotoxin produced during anaerobic bacterial growth in necrosed tissues, such as dirty wounds. Clinical symptoms of tetanus are muscle spasms which may be fatal unless treatment is rapidly initiated. Neonatal tetanus is the most common form of the disease in developing countries and is caused by contamination of the umbilical stump with spores following childbirth.

Diphtheria and tetanus vaccines are amongst the most successfully used worldwide and are considered an essential component of the Expanded Programme on Immunization (EPI) schedule. Their use has resulted in a significant decrease in the incidence of these diseases in developed and developing countries.

The quality control of vaccines has always relied on three components: control of the starting materials; control of the production process; and control of the final product. For traditional vaccines such as tetanus and diphtheria toxoids, there is a vast production experience and a long history of use. In this case, considerable emphasis is placed on a bioassay for potency testing of the final product in animals.

However, fundamental problems still exist in the standardization and control of the potencies of these toxoids globally, even when international standards are used, since different potency tests are being used in different regions of the world. Until a universally accepted method is developed, problems will continue to be encountered in the international movement and licensing of diphtheria and tetanus vaccines. In recent years, efforts have been made to simplify the current tests and reduce the number of animals used in control testing.

The standard design of the D- and T-potency test developed by WHO and the European Pharmacopoeia involves titrating the test vaccine in groups of animals and comparing the dose response curves in a probit analysis to calculate the potency of the test vaccine in international units against the reference.

However, problems observed with this system include:

- the use of large numbers of experimental animals;
- potencies estimated in one species of animal may differ from those obtained in another;
- inconsistent data are available on the predictive value of the potency test for efficacy in the target population;
- The reference and test vaccine cannot be considered as unknown dilutions of each other;
- Dilution of the vaccine results in a dilution of the D- and T-toxoid, as well as other components present in the vaccine. This may alter the effect of the vaccine;
- the testing of booster injections is not covered; and
- the probit analysis is not sensitive enough to demonstrate small differences in immunological characteristics of test and reference vaccine.

Another common approach is that used by the United States Food and Drug Administration, where

the test vaccine is injected into a small group of guinea-pigs and the induced antibody titer in serum determined in a prescribed toxin neutralization assay *in vivo* against equine hyperimmune reference serum. The problem with this system is that no reference vaccine is included in the assay and no statistical analysis of the data is possible because the toxin neutralization titer is estimated in pooled sera. External factors may also influence the antibody titer.

A working group has now been set up by WHO to work towards the harmonization of potency measurements of these vaccines. The group met at the Rijksinstituut voor Volksgezondheid en Milieu-Hygiene (RIVM), Netherlands, in 1999, and agreed that WHO should continue to evaluate the value and limits of the current potency assays and explore alternative approaches. As a result, a small group of experts was established to coordinate the development of a simple, robust and standardized assay suitable for demonstrating consistency of immunological characteristics for batch release. Also, the relevance of the minimum potency expressed in an international unit (IU) of toxoid determined in animals to human immune responses should be re-evaluated based on clinical efficacy and safety data. In addition, the working group also urged WHO to develop guidelines on the antigen content and quality control of diphtheria and tetanus vaccines used as boosters in adults and adolescents.

Further discussion of these activities will take place at the forthcoming International Symposium on Tetanus Vaccine for Human Use to be held in Strasbourg, France, from 22–23 June 2000. The meeting is organized by the European Directorate for the Quality of Medicine in collaboration with WHO.

# General Information

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## WHO Guidelines for the regulatory assessment of medicinal products for use in self-medication\*

Self-care can be defined as a primary public health resource in the health care system. It concerns the health activities and health decisions of individuals and includes self-medication, self-treatment, social support in illness, and first aid in everyday life.

The decision to allow products to be used in self-medication through over-the-counter (OTC) sale is currently of great interest in many countries. Drug regulatory and health authorities have to consider the types of medicinal products for which marketing is appropriate, safe and rational in the interests of public health. The following guidelines have been devised by WHO for the use of regulatory authorities and other interested parties and are available from: Quality and Safety of Medicines, Essential Drugs and Medicines Policy (EDM), World Health Organization, 1211 Geneva 27, Switzerland. <http://www.who.int>

It has become widely accepted that self-medication has an important role to play in the health care system. Recognition of the responsibility of individuals for their own health, and awareness that professional care for minor ailments is often unnecessary have contributed to this view. Improvements in people's general knowledge, level of education and socioeconomic status in many countries form a reasonable basis for successful self-medication.

New drugs with specific pharmacological action, such as histamine H<sub>2</sub>-receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAID) and nicotine preparations for cessation of smoking, have been successfully reclassified from prescription to non-prescription status in many countries. Regulatory assessment of a change from prescription to non-prescription status should be based on medical and scientific data, on safety and efficacy of the compound, and on rationality in terms of public health.

The present guidelines propose criteria and methods which drug regulatory authorities can employ in determining the suitability of medicinal products for use in self-medication. The term "assessment" is used rather than "clinical evaluation", since in many cases the process will involve a review of existing data and experience and not the performance of new clinical trials or investigations, though the latter may occasionally be necessary. The guidelines are also intended for use by marketing authorization holders applying for the classification of a prescription medicinal product to be switched to non-prescription sale. Lastly, they provide guidance on documentation to accompany applications for marketing authorization of new active substances which have not been marketed as prescription medicines but for self-medication.

The initiative for the review of prescription products or any new product that might reasonably be released for self-medication has generally been taken by the pharmaceutical industry in the form of documented proposals to national drug regulatory authorities. Occasionally, such authorities have themselves taken steps to reclassify medicinal products and make them available for self-medication. In some cases, moreover, products have been changed back from self-medication to prescription drug status because new safety issues have arisen. This underlines the fact that it is of crucial importance to carefully monitor the use of medicinal

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\* The text of the Guidelines was endorsed at a consultation on 15–16 April 1999. Participants included: Dr D. Bown, United States of America, Mr G. Kisuule, Uganda, Dr H. Ogasawara, Japan, Dr Ch. Siregar, Indonesia, Mrs G. Williams, United Kingdom, and included representatives from the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and the World Self Medication Industry (WSMI).

products and post-marketing data on adverse effects and respond adequately and quickly to possible harmful developments.

### **Scope of the guidelines**

These guidelines address the criteria for regulatory assessment of safety and efficacy of self-medication products, including new active substances that have not been marketed as prescription medicines, drugs that have hitherto been available only on prescription, and those for which new information requires the re-evaluation of safety. These guidelines do not address homoeopathic medicines, *in vitro* diagnostic products or other medicinal preparations such as vitamin and mineral supplements, and some medicines of plant origin that are not well characterized.

### **Definition of medicinal products for self-medication**

Medicinal products for self-medication may be defined as those not requiring a medical prescription and produced, distributed and sold primarily to consumers for use on their own initiative and responsibility when they consider such use appropriate. The term "over-the-counter (OTC) medicines" is widely used to describe this class of product. The packing, package size, labelling and product information (package insert, leaflet, directions folder or other accompanying text) will generally be designed and written to ensure appropriate self-medication.

The distinction between self-medication products and prescription medicines is not a sharp one and differences in dosage and/or in indications can lead to differences in classification. For example, ibuprofen is sold only on prescription at high dose for treatment of arthritis and over-the-counter at low doses for treatment of headaches and other minor pain. It is often the practice to provide self-medication in smaller packages.

### **Basic criteria for a self-medication product**

A self-medication product should fulfil at least the following three criteria:

- (1) **Active ingredient:** The active ingredient at the intended dose should have low inherent toxicity (e.g. no reproductive toxicity, genotoxic or carcinogenic properties relevant to human use, unless such hazard can be appropriately addressed by labelling).
- (2) **Intended use:** The intended use should be appropriate for self-medication. Use of the

product should not unduly delay diagnosis and treatment of a condition requiring medical attention.

- (3) **Product properties:** The product should not have properties that make it undesirable. For example, it should not have an unfavourable adverse event profile, require a physician's supervision for monitoring during therapy, represent a significant risk of dependence or abuse, or display other limiting characteristics such as interaction with commonly used medicines or foods that may result in serious adverse reactions.

If a new chemical entity or a prescription product meets the three basic criteria, the following additional criteria may favour change of status to non-prescription sale:

- (1) The use of the product has been sufficiently extensive or in high enough volume.
- (2) The product has been marketed on prescription for at least five years. The time considered appropriate for a product to have been on prescription varies widely, e.g. no time specified in the European Union, three years in New Zealand, six years in Japan, and up to 10 years in the Philippines.
- (3) Its adverse events give no cause for concern, and their frequency has not increased unduly during the marketing period.

The reason for requiring five years prescription marketing is that withdrawals from the market for adverse events or for major changes in product information have usually occurred during the first three to five years after marketing in those countries with effective safety monitoring systems. A high level of use permits detection of relatively rare but serious adverse effects and sometimes the detection of an increased frequency of a particular adverse event. High use is also likely to mean that the drug has been used in a broad range of people with a wide variety of concomitant diseases, concomitant drugs and risk factors for adverse events. It should be noted that the period of use may vary in countries with well-developed pharmacovigilance systems.

The criteria outlined above are based on the normal stepwise widening of exposed patients in three consecutive stages of drug development:

- (1) Investigational use prior to marketing authorization with limited controlled exposure of a relatively small group of people in clinical trials who are monitored closely for adverse effects.
- (2) Prescription marketing entailing exposure of potentially large numbers of people, though limited to those who go to a physician and for whom the physician considers the drug has a positive risk/benefit balance in the treatment of a disease.
- (3) Marketing and commercial promotion for self-medication – involving the increasing exposure of potentially enormous numbers of people – when concomitant diseases and other medications used may vary, and other risk factors such as pregnancy, lactation, working conditions, driving, sport, alcohol use, and potential interaction with climate, sun or food may be present. It should be noted that systems to monitor adverse reactions to self-medication products may not always exist.

Only for a few drugs will information from clinical trials prior to use be enough to support general availability in self-medication form, because such trials are conducted in selected populations monitored intensively for efficacy and safety. However, experience from marketing elsewhere in the world may provide suitably detailed data on exposure under conditions of use that are sufficiently similar to the situation in a particular country. Additional clinical studies may sometimes be necessary in the target consumer population where the product is expected to be used.

Consumers may believe that a medicinal product not subject to a medical prescription is less harmful than the same product under medical prescription. Labelling directed to the consumer should clearly communicate both the benefits and the risks of using the product for self-medication.

### Characteristics of self-medication

Self-medication involves the use of medicinal products by the consumer to treat self-recognized disorders or symptoms, or the intermittent or continued use of a medication prescribed by a physician for chronic or recurring diseases or symptoms. In practice, it also includes use of the medication for family members, especially where the treatment of children or the elderly is involved.

In order to use a non-prescription product safely and effectively, the consumer must accurately

recognize symptoms, set therapeutic objectives, select a product, and determine both an appropriate dosage and schedule, taking into account the person's medical history, contraindications, concomitant diseases and concurrent medications and monitoring of the response to the treatment and adverse effects.

In the case of non-prescription medicinal products, all of the information required to permit safe and effective use must come from the labelling material, patient information texts, the individual's previous personal experience, various sources of information in the media, advertising, and advice given by health care professionals. Pharmacists play a key role in giving advice to consumers on the proper and safe use of medicinal products intended for self-medication. It is important that this role is included in training and practice.

The rapid development of new technology, the Internet, and related communication systems has opened up new possibilities for seeking information and offers important new channels for the dissemination of knowledge on medicinal product characteristics and proper use in self-medication. It should be emphasized, however, that there are marked differences in opportunities to obtain access to this information between people with different socioeconomic and educational backgrounds and in different countries. Well-tested labelling designed for a particular cultural environment can help to reduce these differences. However, it should not be used in a way that would limit the availability of the OTC product.

### Potential benefits

The benefit of self-medication is that it is voluntarily chosen by consumers for conditions when it is preferable to them. It will usually be selected for use in symptoms and conditions which the user regards as sufficiently troublesome to need medicinal treatment but not to justify consulting a physician. If the condition fails to respond, persists or becomes more severe, professional medical help should be sought. Accordingly, good self-medication should offer the individual consumer:

- Efficacy, whereby the product does what it is claimed to do;
- Reliability and safety: the individual will often choose a product which experience has shown to be suitable. The scope and duration of self-medication can be kept within safe limits by

appropriate selection of approved indications, labelling texts, dosage strengths and forms, and package sizes;

- Product safety when used as recommended by the instructions;
- Acceptable risk, even when used for a longer duration, at a higher dose, or somewhat differently than recommended in the instructions;
- Wider availability of medicines;
- Greater choice of treatment;
- Direct, rapid access to treatment;
- An active role in his or her own health care;
- Self-reliance in preventing or relieving minor symptoms or conditions;
- Educational opportunities on specific health issues (i.e. stop-smoking aids and products to treat heartburn);
- Convenience;
- Economy, particularly since medical consultations will be reduced or avoided.

At the community level, good self-medication can also provide benefits such as saving scarce medical resources from being wasted on minor conditions, lowering the costs of community-funded health care programmes (including prescription reimbursement systems), and reducing absenteeism from work due to minor symptoms.

#### *Potential risks*

Self-medication has a number of potential risks. In particular, the ordinary user will usually have no specialized knowledge of the principles of pharmacology or therapy, or of the specific characteristics of the medicinal product used. This results in certain potential risks for the individual consumer:

- Incorrect self-diagnosis;
- Failure to seek appropriate medical advice promptly;
- Incorrect choice of therapy;

- Failure to recognize special pharmacological risks;
- Rare but severe adverse effects;
- Failure to recognize or self-diagnose contraindications, interactions, warnings and precautions;
- Failure to recognize that the same active substance is already being taken under a different name (products with different trademarks may have the same active ingredient);
- Failure to report current self-medication to the prescribing physician (risk of double medication or harmful interaction);
- Failure to recognize or report adverse drug reactions;
- Incorrect route or manner of administration;
- Inadequate or excessive dosage;
- Excessively prolonged use;
- Risk of dependence and abuse;
- Risks at work or in sport;
- Food and drug interactions;
- Storage in incorrect conditions or beyond the recommended shelf-life.

At the community level, improper self-medication could result in an increase in drug-induced disease and in wasteful public expenditure.

It is important to realize that many of these risks are not unique to self-medication: they can also occur in prescription-only medication, particularly if the patient consults several physicians for the illness or lacks counselling during therapy.

In selecting the types of medicinal products that can be used for self-medication, the aim should be to exploit the benefits listed above and to minimize the risks.

#### *Acceptable degrees of risk*

Safeguards need to be provided to make self-medication as safe and effective as possible. Self-medication is a valid part of health care provided

that the medicinal products used have been shown to be safe and effective for their intended purpose, are sold with explicit directions for their use, and are manufactured to high quality according to the principles of good manufacturing practice (GMP). Safeguards relate largely to the selection of the most suitable and safe substances, doses and dosage forms and may involve the provision of special information or public education, the control of advertising and package texts, or the limitation of distribution channels.

In accepting the principle of self-medication, the community makes a positive judgement on the risk/benefit ratio of self-medication as a whole. It cannot reasonably be assumed that benefit will always be assured or the risk will be entirely eliminated. Since the risk factors listed above vary in degree from one individual to another and one situation to another, there may be patients who will suffer inconvenience or harm. However, if the degree and incidence of such harm are not disproportionate to the benefits offered, the risk will be acceptable.

Only long-term exposure of the population can uncover rare or delayed adverse events. Consequently, there continues to be a need to revise product information, or even to withdraw medicinal products aimed at self-medication when necessary.

#### *Adaptation to the community*

Any assessment of suitability of a medicinal product for use in self-medication should take into account the situation and population in which it is proposed. Clearly, in a region where endemic disease occurs in large areas without adequate medical services, the potential benefit of certain medicinal products may outweigh risks that would not be acceptable elsewhere; policies also need to reflect the degree of literacy and general education of the population concerned.

#### **General basis for regulatory assessment**

Basic criteria for a self-medication product are set out above and include the following.

#### *Established properties*

The pharmacokinetics, pharmacodynamics, indications, safety and efficacy, and toxic or allergic potential of a medicinal product should have been reasonably well established and documented in humans before its eligibility for use in self-medication can be assessed.

Where a new active pharmaceutical substance that has not been marketed as a prescription medicine is being considered for use in self-medication, the previous studies will have been conducted largely in animals. The clinical trials and investigations with such a substance should reflect the self-medication situation, and subsequent collections of post-marketing data on long-term safety and efficacy may be necessary. These data must be sufficient to meet the criteria for self-medication.

When the release for self-medication of a medicinal product hitherto used only on prescription is being considered, it should first have been properly investigated and then employed for a number of years on a considerable scale in prescription medicine. The older the original product, however, the more likely it is that the original studies will prove to fall short of present-day investigational standards, and the more necessary it will be to rely on subsequent evidence from incidental studies, adverse reaction reporting and general experience in the field.

Similarly, where the future status is being considered of a product already in use for a long time for self-medication, there is commonly a lack of formal prospective clinical studies matching present-day standards. Again it will often be necessary to draw conclusions from practical and circumstantial data, but if the medicinal product has been used on a large scale this may be possible.

Where the suitability of a fixed-combination product for use in self-medication is being considered, the basic principle will apply that the combination should be therapeutically rational, including only ingredients necessary for the treatment and containing no active ingredients that are superfluous to the treatment of the conditions in which efficacy for self-medication is to be claimed.

#### *Approaches to regulatory assessment and supervision*

In the assessment of a medicinal product's suitability for use in self-medication, the following complementary aspects need to be considered:

- (1) The active substance and the rationality of its indications;
- (2) One or more specific routes of administration, dosage forms and formulations;
- (3) Other specific safeguards;

- (4) Suitability for self-medication status; and  
 (5) Labelling and package inserts and other information forming a basis for advertising and promotion.

Other aspects may require more specific additional consideration in the light of the pharmacological properties of the medicinal product, the intended indication, type of use, adverse effects or other characteristics, such as those relating to social and environmental circumstances.

*Consideration of the active substance and its indications*

This will involve deciding whether the active compound itself is suitable and rational for self-medication. It should include the following aspects:

- The purpose for which the product is indicated, i.e. whether this can be regarded as appropriate for self-diagnosis, self-medication and self-monitoring. Generally, such indications are for widely experienced symptoms or disorders that are readily recognizable by ordinary consumers, or that are initially diagnosed by a doctor and are often self-limiting in nature;
- Provision of reliable and consistent relief of symptoms;
- Favourable risk/benefit ratio of the product; if the indications are minor, as they generally will be in self-medication, the benefit will be quickly outweighed by potential adverse effects that are other than minor;
- The general toxicity, reproduction toxicity, genotoxicity and carcinogenicity of the compound with regard to its use in self-medication. In general, the drug must have a wide margin of safety, even if used incorrectly;
- Its potential risks in comparison with prescription drugs that are commonly used in the same patient group;
- Its mode of action and pharmacokinetics. In particular, the absorption, metabolism and excretion of the compound should not be affected by other commonly used drugs or display marked fluctuations between individuals because of concomitant diseases, interactions with food, or genetic or environmental factors (working conditions, climate, and so forth);

- Low and well-documented risks in specific patient groups, for example in elderly people, during pregnancy and lactation, and in patients with impaired liver or kidney function;
- The potential impact of widespread use on the levels of microbial resistance to antimicrobial medicines in the general population;
- Low risk of masking symptoms of underlying serious disease, resulting in delays in proper diagnosis and treatment;
- Acceptable level of risk from inappropriate use;
- Low or well-characterized incidence of adverse effects or side-effects, and contraindications for which advice or counselling is easily available;
- Drug dependence and abuse potential of the drug;
- The existence of other dosage forms of the same active ingredient that have already been approved for OTC sale.

*Specific routes of administration, dosage forms and formulations*

Since no active therapeutic substance is likely to be ideal in every way, it will be necessary to consider which specific presentations or formulations might be best suited to self-medication, since these can affect the medicinal product's safety, efficacy and suitability. For example, only preparations that can be administered in a manner not requiring technical expertise, assistance or patient training can be considered suitable for self-medication. Thus, oral or topical preparations will generally be suitable, but injections will usually not. It may be desirable to avoid certain types of excipient, where they are known to affect certain patient groups adversely.

**Consideration of other specific safeguards**

The suitability of a substance for use in self-medication can be further affected by the feasibility of providing other specific safeguards related to:

- (1) **Dosage**: Restricting the maximum single dose or maximum daily dose may protect against danger when the medicinal product is used either correctly or incorrectly. However, it is necessary to confirm that the dose retains the necessary efficacy.



- (2) **Dosage strength:** For children, specific dosage strengths suitable for paediatric use are preferable. For the adult population, consideration should be given to the need for several strengths, bearing in mind different uses and characteristics, though this should be balanced against any problem that may be encountered in selecting the proper dose.
- (3) **Dosage schedule:** The recommended duration of treatment should prevent unnecessarily prolonged use. If the symptoms fail to respond adequately or persist, medical attention/consultation is necessary.
- (4) **Package size:** The package size should be limited to a reasonable number of doses in relation to the recommended duration of the treatment. This is necessary to safeguard against misuse, particularly overdose or undue delay in seeking medical attention. There may occasionally be a need for larger packages as an option in specific, designated situations or for prolonged use.
- (5) **Packing material and form:** Medicinal products should have a container which as far as possible prevents children gaining access to the medicine if they get hold of the container.

#### *Suitability for self-medication status*

The potential risk/benefit characteristics of the medicinal product in self-medication should be set against its risk/benefit characteristics as a prescription product since it cannot be assumed that prescription status necessarily provides a greater guarantee of safety than non-prescription status. Where prescription status has been considered preferable because a physician can perform certain diagnostic or sensitivity tests before selecting the product, ensure good patient compliance, or take steps to avoid adverse effects or interactions, it is important to know whether physicians can and do perform these tasks. If they do not, the self-medication form with appropriate warning instructions may provide a measure of safety for the user.

Similarly, in some countries a large number of medicinal products originally intended for use under medical supervision are in fact widely sold without prescription. In such instances, recognition of the real self-medication situation and the introduction of appropriate safeguards may be more in the public health interest than maintenance of a theoretical prescription status. The possibility of considering the reclassification of products to non-prescription

status on the basis of experience in other countries should be considered.

#### **Labelling and package inserts**

Adequate information on appropriate use should always accompany the product. Further guidance on self-medication can be provided by health care professionals. Accompanying texts (information, advice and warnings) should be sufficiently clear and complete to enable the consumer to use the product safely, effectively and in a rational way.

When package inserts or leaflets are required by governments, they should reflect only the information that has been approved by the country's drug regulatory authority. If package inserts or leaflets are used for promotional purposes, they should comply with the *WHO Ethical Criteria for Medicinal Drug Promotion* (1).

In addition to approved package inserts and leaflets, the preparation and distribution of booklets and other informational material for patients and consumers should be encouraged. If such material is promotional, it should also comply with the *WHO Ethical Criteria for Medicinal Drug Promotion* (1).

Information for the consumer should be easily understandable and in accordance with national legislation. For self-medication products it is particularly important that the written text is easily understandable. In general, sufficient information should appear on the outer packaging to allow consumers to make a decision about suitability of the product before purchase. This is of particular importance where advice from health care professionals is not readily accessible. The following aspects of labelling and package inserts should be considered:

- Consumer information which is simple and not confusing;
- Indication of the item as a medicinal product;
- Composition of the product including international nonproprietary name (INN)/generic name of the active substance;
- Uses for which the product is intended;
- Mode of use, including route of administration (systemic or local), maximum single dose, maximum daily dose and duration of treatment;

- Who the product is intended for (children or adults);
- Presentation of the most important precautions, contraindications and adverse effects clearly stated in easily understandable language;
- Specific warnings and information for use during pregnancy, lactation, by the elderly, or in patients with renal or hepatic failure;
- When medical advice should be sought;
- Duration of use;
- Information on storage conditions and shelf-life;
- Other measures the patient should take to control symptoms;
- Inactive ingredients listed;
- Expected benefit when the drug is used properly;
- The use of pictograms.

#### *Advertising and promotion*

Approval of product information relating to a medicine is an important part of product assessment. Advertising and promotion should always be consistent with this approved information. However, compliance of advertising with product information can only be judged after product approval. Advertising should comply with the *WHO Ethical Criteria for Medicinal Drug Promotion*(1).

#### **Collection and regulatory assessment of evidence**

When drug regulatory authorities assess applications for marketing authorization, three types of situation need to be distinguished:

- (1) Assessment of new active substances, not marketed as prescription medicines and designed specifically for use in self-medication.
- (2) Assessment for self-medication of medicinal products hitherto available only on prescription.
- (3) Assessment of existing self-medication products that have not previously been evaluated.

#### *New active substances for use in self-medication*

Data for submission to the regulatory authority for review should comprise pharmaceutical, pharmacological (preclinical and general pharmacological characterization of the compound), toxicological, clinical pharmacological (clinical trials) and long-term therapeutic data (efficacy and safety) obtained through appropriate experimental studies in animals and humans. Clinical studies must address the specific issue of use in a representative self-medication population. Sufficient clinical experience of a new active substance must be gained before marketing authorization can be granted.

#### *Self-medication products previously available on prescription-only*

Evidence for or against the proposed use of a self-medication product previously available on prescription only may be obtained from many sources worldwide and may not be analysed in the same depth as the innovative prescription-only pharmaceutical product. Selected evidence should comprise:

##### **(1) The original regulatory data**

This will be relevant only if the product is in all respects identical to the original product. Human data will weigh much more heavily than animal data. If any of the original animal investigations suggested severe risks (e.g. carcinogenicity), the risks should be reassessed in the light of subsequent experience in humans.

##### **(2) Clinical data obtained post-marketing**

Trials performed according to the latest standards and relating closely to proposed use in self-medication should be accorded the greatest weight.

##### **(3) Data on drug utilization and consumption**

These can be helpful in determining the way in which the product has been employed by physicians (volume of use, major indications in practice, precautions normally taken), and particularly in interpreting alleged risks.

##### **(4) Reported adverse reactions or interactions**

The profile, frequency and severity of adverse events, reactions or drug interactions should be examined. Situations in which the evidence is critically assessed such as well-controlled clinical or epidemiological studies, are preferable to unevaluated observations of adverse reactions. Data from sources that have collected adverse drug

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reaction data from different countries for long periods of time may be useful, in particular, information from the WHO International Drug Monitoring Programme (2).

#### **(5) Current scientific data**

The pharmaceutical form and packaging should be considered; any available clinical studies, field data and market-related studies on consumer use of the product for self-medication should be examined.

#### *Self-medication products not previously evaluated*

In reassessing the status of an existing self-medication product, the following steps should be considered:

- (1) Review of justification for the product (single active ingredient or combination), its efficacy, adverse effects, patterns of use, and labelling, particularly for consumer use.
- (2) Assessment of the risk/benefit of the product.
- (3) Action to be taken to deal with emerging problems. When steps have been taken (e.g. publication of warnings or imposition of limitations on package size or distribution) the effect of these measures should be assessed.

#### *Assessment of new strengths, formulations, doses, indications or combinations*

Careful assessment is also necessary when it is proposed to make the medicinal product available without prescription in a new strength, in a new formulation, at a new dose, using a new route of administration, for a new age group or for a new indication, particularly if the indication has not previously been approved without a medical prescription. In addition to an assessment of the rationality of such a proposal, the safety and risk/benefit of a medicinal product in the new circumstances should be evaluated.

A medicinal product containing a new combination of two or more active substances, which are available in two separate products, neither of which is subject to a medical prescription, will not automatically be classified as a non-prescription product. The applicant needs to demonstrate that the combination offers an advantage over the separate active substances, and that the risk is acceptable.

#### **Reference:**

1. *Ethical Criteria for Medicinal Drug Promotion*. World Health Organization, Geneva, 1988. ISBN 92 4 154239 X.

# Regulatory and Safety Matters

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## Troglitazone withdrawn

**United States of America** — The Food and Drug Administration has requested Parke-Davis/Warner-Lambert, the manufacturer of troglitazone (Rezulin®) to remove the product from the market. This action has been taken subsequent to a review of safety data which compared the risk benefit of troglitazone with rosiglitazone (Avandia®, Smith-Kline Beecham) and pioglitazone (Actos®, Takeda/Eli Lilly).

Troglitazone was indicated for the treatment of type 2 diabetes mellitus. When considered as a whole, the pre-marketing clinical data and post-marketing safety data from troglitazone indicated that continued use of troglitazone poses an unacceptable risk to patients as compared to similar alternative diabetes drugs.

Patients using troglitazone should not discontinue taking troglitazone but are urged to contact their physicians for information on alternative treatments.

**Reference:** *HHS News*, P00-8. 21 March 2000.

## Cisapride and cardiac effects

**United States of America** — The manufacturer of cisapride has announced that it will stop marketing the product (Propulsid®: Janssen) in the USA with effect 14 July 2000. This effective date is intended to provide adequate time for patients and physicians to decide on treatment alternatives. Cisapride is a prescription drug indicated for severe night-time heartburn in patients with gastro-oesophageal reflux disease who do not adequately respond to other therapies.

Patients who already take the drug are encouraged to consult their doctors about other treatment options. The company will continue to make the drug available only to patients who meet specific clinical eligibility criteria under a limited-access protocol.

Continuing reports of heart rhythm disorders and deaths have been associated with cisapride in

people taking certain other medications or with underlying conditions known to be risk factors. A recent analysis of 270 cases of adverse events (including 70 fatalities) revealed that approximately 85% of these cases occurred in patients with identifiable risks.

**Reference:** *FDA Talk Paper*, T00-14, 23 March 2000.

## Cisapride: changes to labelling

**United States of America** — Prior to the subsequent withdrawal of cisapride (Propulsid®) from the US market referred to above, the manufacturer had announced changes to the labelling and patient medication guide following reports of serious cardiac arrhythmias including ventricular fibrillation, torsades de pointes, and QT prolongation.

Between July 1993 and May 1999 more than 270 cases were reported, with 70 fatalities. Approximately 85% of these cases occurred in patients with known risk factors including the administration of other drugs which cause QT prolongation, inhibited liver enzyme metabolism or depleted serum electrolytes.

Cisapride is contraindicated in patients taking certain macrolide antibiotics, antifungals, and protease inhibitors, anti-arrhythmics, antidepressants and other agents such as grapefruit juice. The revised package insert contains full prescribing information.

**Reference:** Dear Doctor letter dated 24 January 2000 from Janssen Pharmaceutica Research Foundation.

## Cisapride: updated warning issued

**New Zealand** — Strict controls are in place on the use of cisapride, which is indicated for severe gastro-intestinal conditions. In New Zealand, cisapride can only be prescribed by a physician on a specialist's recommendation, thereby minimizing the possibility of the drug being prescribed to people most at risk of known side effects. However, an updated warning has been circulated to physicians giving information on the reports received in the USA.

The National Centre for Adverse Reactions Monitoring has received 19 reports of adverse effects since 1991. None of these were fatal and only one case involved cardiac disturbance.

**Reference:** *Medsafe Media Release*, 24 March 2000.

### St John's wort: recommendations for use

**France** — Following the recent publication of several papers describing significant interactions between St John's wort (*Hypericum perforatum*) and digoxin, theophylline, indinavir, ciclosporin, certain oral anticoagulants, antidepressants and oral contraceptives, the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSPS) has made the following recommendations:

#### 1. Patients not yet taking St John's wort:

- patients being treated with antiretroviral agents, and particularly indinavir (Crixivan®), for HIV infection should not take St John's wort in view of the risk of decreased efficacy of the treatment.
- patients being treated with antidepressants should not take St John's wort concomitantly because of the risk of adverse reactions (restlessness, nausea, gastric disturbance).
- women taking oral contraceptives should not take St John's wort concomitantly because of the risk of a diminution in the contraceptive effect.
- in general, St John's wort should not be taken concomitantly with any other medicinal treatment in view of the risk of a drug interaction which could result in a reduction in the efficacy of the medicines.

#### 2. Patients under treatment must not discontinue taking St John's wort without medical advice.

Although St John's wort has been promoted as a treatment for mood disorders and is available as a food supplement, it is not approved as a medicine in France.

**Reference:** Communiqué from the Agence Française de Sécurité Sanitaire des Produits de Santé, 1 March 2000.

### Northern hemisphere influenza vaccine

**World Health Organization** — The composition of the vaccine for the November 2000–April 2001 influenza season in the Northern hemisphere has been determined and communicated to vaccine manufacturers.

- an A/Moscow/10/99(H3N2)-like virus
- an A/New Caledonia/20/99(H1N1)-like virus
- a B/Beijing/184/93-like virus+

WHO strongly recommends the use of vaccine as an effective preventive measure against this potentially fatal disease. Even in those cases when the vaccine does not fully protect against the disease, severity of illness and frequency of serious complications are reduced.

Specific vaccine viruses used in each country should be approved by the national control authorities. National public health authorities are responsible for recommendations regarding use of vaccines. All WHO recommendations are published and communicated to public health authorities, national control authorities and influenza vaccine manufacturers. Updated epidemiological information is available on <http://www.who.ch/emc/flu/index.htm> and the geographical information system, Flunet, at <http://oms.b3e.juu.fr/flunet>.

**Reference:** Recommended composition of influenza virus vaccines for use in the 2000–2001 season. *Weekly Epidemiological Record*, **75**: 61–65 (2000).

### Nicotine replacement therapy

**New Zealand** — The Government has announced measures to improve access to nicotine replacement therapies. These may now be sold through smoking cessation clinics run by medical practitioners, nurses, pharmacists or psychologists. Previously, they could only be obtained from pharmacies or on a doctor's prescription.

The Government has taken a strong stance on smoke-free policies and improving access to smoking cessation therapies.

**Reference:** *Medsafe Media Release*, 15 March 2000.

## Anorectic agents: suspension of marketing authorization

**France** — As a result of recommendations made by the Committee on Proprietary Medicinal Products (CPMP), the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSPS) has announced that it will shortly suspend marketing authorization for medicinal products containing the anorectic agents amfepramone, clobenzorex, fenproporex and mefenorex. These products have been dispensed through hospital prescription since 1995 because of their implication in the occurrence of arterial pulmonary hypertension.

The Agency suspended marketing authorizations for fenfluramine and dexfenfluramine in 1997 due to the unacceptable risk of cardiac valvulopathies.

**Reference:** La Revue Prescrire Vol. 19, No. 199, October 1999.

## Insulin cartridges: leakage risk

**European Union** — The European Agency for the Evaluation of Medicinal Products (EMA) has issued a warning on the risk of leakage during use of recombinant human insulin cartridges (Insuman Infusat®; 100 IU/ml solution for injection in cartridges of 3.15 ml). Insufficient supply of insulin has led to reports of hyperglycaemia with hospitalization in four cases.

The marketing authorization holder, Aventis Pharma, recently informed the EMA of 15 reports concerning leakage of cartridges used for semi-synthetic insulin. Faulty cartridges should be returned via the pharmacy or medical pump centre.

**Reference:** EMA Public Statement on Insuman Infusat® 100 IU/ml solution for injection in cartridges of 3.15 ml (insulin human), 14 February 2000.

## Zimox®: trade name duplication and risk of errors

**Islamic Republic of Iran** — The Tehran Drug and Poison Information Centre has informed the World Health Organization that a combination product containing the anti-Parkinson drugs carbidopa and levodopa is being imported into Iran from Greece with the trade name Zimox®. Zimox® is also the name of a product well known to contain the anti-

biotic amoxicillin and is cited in reference books such as Martindale and Index Nominum.

The Centre is concerned about the potential for error that could result from this duplication of trade names. Information has been forwarded to the national drug authorities in order to avoid preventable mistakes in the dispensing of Zimox®, and an announcement has also been circulated to health professionals.

The Centre urges pharmaceutical companies to establish beforehand whether the names chosen for their products have not already been used.

**Reference:** Communication from the Tehran Drug and Poison Information Centre, 24 November 1999.

## Benzbromarone and hepatitis

**Japan** — Following reports of eight cases of fulminant hepatitis related to use of benzbromarone, the Ministry of Health and Welfare in Japan has requested all manufacturers to revise the labelling to include a warning of hepatic dysfunction and to circulate a letter to health professionals.

Benzbromarone, which is indicated for gout, is marketed as 13 products by 10 companies. As reflected in the revised labelling, liver function tests should now be performed periodically and for at least six months after the start of administration. Patients should receive an explanation of the risk of hepatic dysfunction and should consult the physician immediately in the event of anorexia or general malaise. Contraindications for this condition have also been added.

**Reference:** *Pharma Japan*, Number 1689, 20 March 2000.

## Nevirapine: severe cutaneous reactions

**France** — Nevirapine, a non-nucleoside reverse transcriptase inhibitor was first launched in Europe in 1998 for use in HIV infection. Although attention was drawn to the possibility of serious cutaneous reactions and hepatic complications through a warning notice and information to prescribers, fatal outcome reports continue to be received.

Between November 1997 and November 1999, the Agence Française de Sécurité Sanitaire des

Produits de Santé (AFSSPS) has received 16 reports of cases of Stevens-Johnson syndrome and 14 cases of Lyell syndrome, of which 5 were fatal. It was noted that in many cases the manufacturer's recommendation to initiate treatment with a half-dose had not been respected.

During the same period, 44 cases of hepatic complications were also reported. The Agency has drawn attention to the need for care and recommended that liver function tests should be carried out at two-weekly intervals during the first two months of treatment. A letter has been circulated to health care professionals giving details of warnings and contraindications.

**Reference:** *La Revue Prescrire*, Number 205, April 2000.

## FDA cannot regulate tobacco industry

**United States of America** — The Supreme Court has ruled that the Food and Drug Administration (FDA) lacks the power to regulate tobacco. In 1996, the FDA decided that it could regulate tobacco in the light of new evidence that demonstrated the industry's intention to feed consumers' nicotine habits.

In the 5 to 4 ruling, the judges said that Congress had not given the FDA the authority to regulate tobacco. The Court agreed that tobacco use, particularly among children and adolescents, poses perhaps the single most significant threat to public health in the United States. However, it said that regulations on tobacco were the responsibility of Congress.

The FDA's antismoking initiative would have required retailers to check the identification of cigarette buyers under the age of 27 and would have prohibited cigarette vending machines except in bars and other adult-only places.

**Reference:** *News. British Medical Journal*, 320: 894 (2000).

## New Internet website: information for consumers

**United States of America** — The Food and Drug Administration has announced the establishment of an Internet website to provide information on buying prescription drugs and medical products on-line.

This initiative is part of an action plan to increase public awareness of the health, economic and legal risks of on-line sales of prescription drugs and medical products.

The website is located at: <http://www.fda.gov>

Information is available on consumer protection, FDA enforcement practices, advice on identifying health fraud and general questions about Internet drug sales. Consumers who suspect that a website is illegally operating can fill in an electronic complaint form.

**Reference:** *HHS News*, P99-33 (1999).

## Cyber warnings for drug sales via the Internet

**United States of America** — In recent weeks the Food and Drug Administration has issued letters via the Internet to operators of non USA-based internet sites that offer to sell on-line prescription medicines that may be illegal. The letters inform the operators about the laws governing prescription drug sales within the USA, with an explanation of the statutory provisions that govern interstate commerce of drugs and a warning that future shipments of the products may be automatically detained and subject to refusal of entry.

**Reference:** *FDA Talk Paper*, T00-8 (2000).

## Triax®: a harmful product sold on the Internet

**United States of America** — The Food and Drug Administration has warned consumers not to purchase or consume the product Triax Metabolic Accelerator®, containing the active ingredient tiratricol.

The product is marketed as a dietary supplement for weight-loss purposes. However, the Food and Drug Administration has determined that it contains an unapproved new drug containing triiodothyroacetic acid, a potent thyroid hormone which can cause serious health problems, including heart attacks and stroke. Several individuals have reported abnormal thyroid function test results while using Triax® and have experienced severe diarrhoea, fatigue, lethargy or profound weight loss.

**Reference:** *FDA Talk Paper* T99-52 (1999).

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## Illegal products on the market

**United States of America** — The Food and Drug Administration (FDA) has taken legal action to protect consumers against unproven claims for drugs promoted as treatments for cancer and other diseases.

Such unapproved drugs include: *BeneFin*, produced from shark cartilage and promoted as a treatment for cancer; *SkinAnswer*, a glycoalkaloid skin cream advertised for treatment of skin cancer; and *MGN-3*, a rice-bran extract promoted as a treatment for cancer and HIV.

**Reference:** *FDA Talk Paper*, T99-56 (1999).

## Epoetin alfa: inappropriate practices compromise product sterility

**United States of America** — An outbreak of 21 episodes of bacteraemia or pyrogenic reactions has been reported in patients receiving epoetin alfa (Epogen®, Amgen) at a dialysis unit. A recent investigation has revealed that unused portions of epoetin alfa remaining in single dose preservative-free vials were collected and pooled into common vials for use in other patients. These practices were linked to extrinsic bacterial contamination.

Health care professionals are warned that once a syringe has entered a single-dose vial, the sterility of the product can no longer be guaranteed. Multiple entries should not therefore be made into single-dose vials and residual medication from two or more vials should not be pooled.

**Reference:** Letter from Amgen at [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

## Propylene glycol and amprenavir

**United States of America** — The manufacturer of amprenavir (Agenerase®, Glaxo Wellcome) has issued a warning concerning a potential risk associated with the amount of propylene glycol present in the oral solution formulation. Amprenavir is a protease inhibitor indicated for the treatment of HIV infection in combination with other antiretroviral agents in patients 4 years of age and older.

Propylene glycol is metabolized by an enzyme pathway which does not attain equivalent adult activity until 12 to 30 months of age. Infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole are not able to adequately metabolize and eliminate propylene glycol, leading to its accumulation.

Although no reports have been received of serious injury or death, potential safety concerns exist due to the high propylene glycol content of amprenavir. It is therefore advisable to use amprenavir capsules or other protease inhibitor formulations in preference to the oral solution in those patients at risk.

**Reference:** Letter from GlaxoWellcome Inc. at [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

## Trastuzumab: pulmonary reactions

**United States of America** — The manufacturer of trastuzumab (Herceptin®, Genentech) has warned of 62 postmarketing reports of serious adverse events related to the use of their product indicated for the treatment of breast cancer. To date, 25 000 women have been treated with trastuzumab which the FDA approved in 1998.

Adverse events include hypersensitivity reactions (anaphylaxis), infusion reactions, and pulmonary events (adult respiratory distress syndrome). A total of 15 fatal outcomes were reported. In the majority of patients the symptoms occurred with the first dose of trastuzumab or within 12 hours of infusion. Most patients with fatal outcome had significant pre-existing pulmonary compromise secondary to intrinsic lung disease and/or malignant pulmonary involvement.

Such patients should be treated with extreme caution. Any patients experiencing symptoms should be discontinued immediately and be closely monitored until complete resolution of symptoms. Patients should also be informed of the possibility of delayed severe reactions.

**Reference:** Letter from Genentech dated 3 May 2000 at [www.fda.gov/medwatch](http://www.fda.gov/medwatch)



# ATC/DDD Classification (temporary)

The following temporary anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 23 and 24 March 2000. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whocc@nmd.no, before **1 August 2000**. If no objections are received before this date, the new ATC codes and DDDs will be considered final and will be included in the January 2001 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC level	INN/common name	ATC code
<b><i>New ATC level codes (other than 5<sup>th</sup> level):</i></b>		
	Vasopeptidase inhibitors, plain	C09E
	Vasopeptidase Inhibitors, plain	C09EA
	Drugs used in alcohol dependence	N07BB
	Drugs used in opioid dependence	N07BC
<b><i>Change of level name:</i></b>		
<i>Previous:</i>		
	Antismoking agents	
<i>New:</i>		
	Drugs used in addictive disorders	N07B
<i>Previous:</i>		
	Antismoking agents	
<i>New:</i>		
	Drugs used in nicotine dependence	N07BA
<i>Previous:</i>		
	Oxytocin and derivatives	
<i>New:</i>		
	Oxytocin and analogues	H01BB
<b><i>New ATC 5th level codes:</i></b>		
	almotriptan	N02CC05
	buprenorphine	N07BC01
	carbetocin	H01BB03
	dihydroemetine	P01AX09
	diosmectite	A07BC05
	esomeprazole	A02BC05
	exemestane	L02BG06
	gatifloxacin	J01MA16
	gemifloxacin	J01MA15
	glucose, combinations	C05BB56
	hydroquinone	D11AX11
	inositol	A11HA07
	isotretinoin, combinations	D10AD54

ATC level	INN/common name	ATC code
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**New ATC 5th level codes (continued):**

leflunomide		L04AA13
macrogol		A06AD15
melanoma vaccine		L03AX12
nateglinide		A10BX03
nitisinone		A16AX04
octenidine, combinations		D08AJ57
octenidine, combinations		G01AX16
omapatrilat		C09EA01
propanofen		S01BC09
risedronic acid		M05BA07
sodium fluoride, combinations		A01AA51
technetium ( <sup>99m</sup> Tc) sulesomab		V09HA04
thiamphenicol, combinations		J01BA52
verteporfin		L01XX26

**ATC code changes:**

acamprosate	V03AA03	N07BB03
calcium carbimide	V03AA02	N07BB02
disulfiram	V03AA01	N07BB01
levacetylmethadol	N02AC06	N07BC03
methadone	N02AC02	N07BC02
naltrexone	V03AB30	N07BB04

**New DDDs:**

INN/common name	DDD	Unit	Route of Administration	ATC code
amodiaquine	0.5	g	O	P01BA06
artemether	0.28	g	O	P01BE02
artemisinin	1	g	O	P01BE01
artemimol**	0.28	g	O	P01BE05
artesunate	0.28	g	O	P01BE03
dihydroemetine	60	mg	P	P01AX09*
exemestane	25	mg	O	L02BG06*
galantamine	24	mg	O	N06DA04
halofantrine	1.5	g	O	P01BX01
ibandronic acid	4	mg	P***	M05BA06
leflunomide	15	mg	O	L04AA13*
macrogol****	10	g	O	A06AD15*
mercaptamine	2	g	O	A16AA04
pioglitazone	30	mg	O	A10BG03
risedronic acid	30	mg	O	M05BA07*
tirofiban	10	mg	P	B01AC17
trogliatone	0.4	g	O	A10BG01
valproic acid	1.5	g	R	N03AG01
zotepine	0.2	g	O	N05AX11

\* Temporary ATC code

\*\* Previously: dihydroartemisinin

\*\*\* Course dose

\*\*\*\* Refers to macrogol 4000

# ATC/DDD Classification (final)

The following final anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 27 and 28 October 1999 in Oslo. They came into force on 1 February 2000 and can be viewed on <http://www.whooc.nmd.no>. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC level	INN/common name	ATC code
<b>New ATC level codes (other than 5<sup>th</sup> level):</b>		
	Artemisinin and derivatives	P01BE
	Nitrofuran derivatives	J01XE
<b>New ATC 5<sup>th</sup> level codes:</b>		
	ancrod	B01AD09
	artemether	P01BE02
	artemether, combinations	P01BE52
	artemisinin	P01BE01
	artemotil	P01BE04
	artenimol	P01BE05
	artesunate	P01BE03
	atosiban	G02CX01
	bexarotene	L01XX25
	codeine, combinations with psycholeptics	N02AA79
	collagenase	D03BA03
	dermatan sulfate	B01AX04
	desloratadine	R06AX27
	dronabinol	A04AD10
	gentamicin	S02AA14
	<i>haemophilus influenzae</i> Band hepatitis B	J07CA08
	imidapril	C09AA16
	insulin aspart	A10AB05
	interferon alfacon-1	L03AB09
	levosimendan	C01CX08
	mitotane	L01XX23
	mometasone	D07XC03
	mometasone	R03BA07
	moxicylyte	G04BE06
	nabilone	A04AD11
	omeprazole, amoxicillin and clarithromycin	A02BD05
	palivizumab	J06BB16

ATC level	INN/common name	ATC code
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**New ATC 5th level codes (continued)**

pegaspargase		L01XX24
peginterferon alfa-2b		L03AB10
ribavirin, combinations		J05AB54
rofecoxib		M01AH02
sorbitol		A06AD18
stannous fluoride		A01AA04
tasonermin		L03AX11
technetium ( <sup>99m</sup> Tc) nanocolloid		V09EA03
tositumomab/iodine ( <sup>131</sup> I)		
tositumomab		V10XA53
zotepine		N05AX11

**ATC code changes**

cinoxacin	G04AB05	J01MB06
flumequine	G04AB06	J01MB07
mandelic acid	G04AG05	J01XX06
mefloquine	P01BA05	P01BC02
methenamine	G04AA01	J01XX05
methenamine and sulfonamides	G04AH01	J01RA02
nalidixic acid	G04AB01	J01MB02
nifurtoinol	G04AC02	J01XE02
nitrofurantoin	G04AC01	J01XE01
nitroxoline	G04AG06	J01XX07
oxolinic acid	G04AB04	J01MB05
phenazopyridine and sulfonamides	G04AH02 J01EB20	J01EC20 J01ED20*
phenyl salicylate	G04AD01	G04BX12
pipemidic acid	G04AB03	J01MB04
piromidic acid	G04AB02	J01MB03

\*products classified according to sulfonamides

**Change of level name:**

Previous:

Quinine alkaloids

New:

Methanolquinolines

P01BC

**New DDDs:**

INN/common name	DDD	Unit	Route of Administration	ATC code
abacavir	0.6	g	O	J05AF06
barnidipine	10	mg	O	C08CA12
cefprozil	1	g	O	J01DA41
cetrorelix	0.25	mg	P	H01CC02

INN/common name	DDD	Unit	Route of Administration	ATC code
chlorphenamine*	12	mg	P	R06AB04
clopidogrel	75	mg	O	B01AC04
dicycloverine	80	mg	O, P	A03AA07
efavirenz	0.6	g	O	J05AG03
fluticasone	1.5	mg	inhal.solution	R03BA05
ganirelix	0.25	mg	P	H01CC01
interferon alfacon-1	4	mcg	P	L03AB09
miocamycin	1.2	g	O	J01FA11
rofecoxib	12.5	mg	O	M01AH02
rosiglitazone	6	mg	O	A10BG02
sorbitol	10	g	O	A06AD18
tasonermin	3.5	mg	P	L03AX11

\*chlorpheniramine in previous Indexes. Name corrected to INN in 2000 Index.

#### Change of DDDs

INN/common name	DDD	Unit	Route of Administration	ATC code
cabergoline	3	mg	O	N04BC06
sumatriptan	50	mg	O	N02CC01

# Recent Publications and Documents

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## International Travel and Health

This annual guide issues authoritative advice on the medical and personal precautions needed to protect the health of international travellers. Information is provided on general precautions as well as recommended and legally required vaccinations. Extensive information is given on malaria including epidemiological data for endemic areas, geographical and seasonal distribution and the recommended chemoprophylactic regimen for each area.

Other chapters are dedicated to arthropod-borne, food-borne and water-borne diseases and other common health hazards. Advice is offered to travellers on how to protect themselves from the risks of contaminated food and water. Advice is also offered on immunization of HIV-infected travellers and on the risk of tuberculosis transmission during air travel.

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*International Travel and Health; Vaccination Requirements and Health Advice. Available from: Marketing and Dissemination, World Health Organization, 1211 Geneva 27, Switzerland. ISBN 92 4 158025 9 Price: Sw.fr. 17.-*

## WHO Expert Committee on Drug Dependence

The role of the WHO Expert Committee on Drug Dependence is to evaluate selected psychoactive substances and recommend an appropriate level of control under the international conventions on narcotic drugs and psychoactive substances. When making its recommendations, the Committee balances consideration of a drug's therapeutic usefulness against data on its pharmacological and toxicological properties, evidence of its dependence potential and likelihood of abuse, and provides an assessment of the corresponding risk to public health.

The Committee's Thirty-first report sets out the criteria used to review data on psychoactive substances and recommends the level of control in scheduling. In this report, the Committee also provides comments on a proposal to extend inter-

national control to the isomers, esters, ethers and pharmacological analogues of controlled substances in response to the growing problem of clandestine synthesis of psychoactive drugs.

Pre-reviews are presented of six psychoactive substances, including benzodiazepines, to determine the need for critical review. Given WHO's intention to develop an International Framework Convention for tobacco control, a critical review of tobacco was not recommended.

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*WHO Expert Committee on Drug Dependence. Thirty-first report. Technical Report Series No. 687, 1999. Available from: World Health Organization, 1211 Geneva 27, Switzerland. ISBN 92 4 120887 2 Price: Sw.fr. 14.-*

## Correct handling and distribution of propylene glycol

Starting materials used in the manufacture of pharmaceutical products often change hands many times before reaching the end user. Along the distribution, packaging and trade chain there are many opportunities for the starting material to be altered or become unsafe. Propylene glycol of pharmaceutical quality is a high purity product having various applications. Contamination or mislabelling could have serious consequences on the quality of the product and the health of the end user. Intermediate handling should therefore be subject to strict conditions.

The European Chemical Industry Council (CEFIC) has developed safe handling guidelines based on good manufacturing practices. Six major European producers of monopropylene glycol USP/EP (pharmaceutical grade) have jointly committed to enforce compliance with these guidelines in their own facilities and in downstream distribution chains by intensive auditing. CEFIC recommends that these guidelines be adopted as a code of practice by all parties involved in the distribution of propylene glycol (pharmaceutical grade). End users should also consider these guidelines for their own handling and storage purposes and impose them on their own contractors. All suppliers should operate

in compliance with this code of practice with full traceability and transparency as to the origin of materials through a certificate of origin.

The guidelines are available in English, French, German, Spanish and Italian and are posted on the CEFIC website at <http://www.cefig.org>.

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*Guidelines for Handling and Distribution of Propylene Glycol USP/EP. Available from the Propylene Oxide/ Propylene Glycols Sector Group of CEFIC, European Chemical Industry Council (CEFIC), Brussels, Belgium.*

## Reporting adverse drug reactions

Compiled at the request of the pharmaceutical industry, this book responds to the urgent need for standard international terminology that is specific to adverse reaction reporting and procedures for post-marketing surveillance. Definitions are set out for over 180 terms commonly used for the reporting of adverse drug reactions to regulatory authorities and drug manufacturers.

The book is intended to facilitate the work of drug regulatory authorities and the drug safety departments of pharmaceutical companies. The terms, definitions and criteria are the result of more than a decade of meetings and consultations involving over 160 experts.

The terms are grouped according to 21 disorders using the standard WHO Adverse Reaction Terminology (WHO-ART). These are also reproduced on a CD-ROM which accompanies the publication.

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*Reporting of Adverse Drug Reactions. Definitions of Terms and Criteria for their Use. Available from: CIOMS, 1211 Geneva 27, Switzerland. ISBN 92 9036 071 2. Price: Sw.fr. 24.50.*

## Preparing core safety information

In 1995, the Council for International Organizations of Medical Sciences (CIOMS) Working Group III report was drafted in response to the need to harmonize core drug safety information. It has been widely endorsed by pharmaceutical manufacturers as a standard for preparation of information for data sheets, package inserts and product labelling.

The complementary *Guidelines for Preparing Core Clinical-Safety Information on Drugs* include recom-

mended safety information for drugs undergoing investigation, development of core safety information to be included in investigator's brochures, and information to support product approval. Relevant information is provided to researchers on the 7-day and 15-day global reporting requirements.

A new and important proposal is set out on the threshold requirements and assessment of risk benefit of a marketed product when a significant new safety signal is identified. The Guidelines conclude with the text of the European Union *Summary of Product Characteristics* and the US Food and Drug Administration *General Requirements on Content and Format of Labelling for Human Prescription Drugs*.

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*Guidelines for Preparing Core Clinical-Safety Information on Drugs, Including New Proposals for Investigators Brochures. Report of CIOMS Working Groups III and V. Available from: CIOMS, 1211 Geneva 27, Switzerland. ISBN 92 9036 070 4 Price: Sw.fr. 15.-*

## Good pharmaceutical procurement

Improper procurement practices lead not only to high prices and poor quality, but can also result in shortages of life-saving drugs. Ideally, the most cost-effective drugs should be bought in appropriate quantities from reputable suppliers at the lowest possible cost. However, procurement can go off track when a number of different agencies are involved, making the process highly complex and vulnerable to inefficiency and waste. Other problems — such as lack of transparency — lead to higher prices and poor quality. Irregular and limited funding can greatly hinder efforts to secure timely delivery.

The Guideline on Operational Principles for Good Pharmaceutical Procurement aims to assist governments, donor agencies and other organizations involved in drug procurement to obtain lower priced, better quality essential drugs and more reliable delivery. The Interagency Pharmaceutical Coordination (IPC) Group which devised the guidelines is made up of pharmaceutical advisers from UNICEF, UNFPA, the World Bank and WHO.

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*Operational Principles for Good Pharmaceutical Procurement. WHO/EDM/PAR/99.5. Available from Department of Essential Drugs and Medicines Policy, World Health Organization, Geneva.*

# International Nonproprietary Names for Pharmaceutical Substances (INN)

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## RECOMMENDED International Nonproprietary Names (Rec. INN): List 43

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. Wild Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy. Lists of Proposed (1–73) and Recommended (1–35) International Nonproprietary Names can be found in *Cumulative List No. 9, 1996*.

## Dénominations communes internationales des Substances pharmaceutiques (DCI)

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### Dénominations communes internationales RECOMMANDÉES (DCI Rec): Liste 43

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 choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie. On trouvera d'autres listes de Dénominations communes internationales proposées (1–73) et recommandées (1–35) dans la *Liste récapitulative No. 9, 1996*.

## Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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### Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 43

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 Internacionales Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia. Las listas de Denominaciones Comunes Internacionales Propuestas (1–73) y Recomendadas (1–35) se encuentran reunidas en *Cumulative List No. 9, 1996*.



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

*atizoram, atliprofen, beclamide, bicifadine, bornelone, ciadox, cloperastine, clorexolone, cloroperone, corticotropin zinc hydroxide, cresotamide, difenidol, diosmin, divabuterol, eledoisin, eritryl tetranitrate, exepanol, fenaclon, fenoprofen, fluquazone, glutaurine, guaifylline, halazone, kebuzone, metamfepramone, meticillin, moquizone, nabilone, nonabine, norgesterone, odalprofen, oletimol, pentiapine, plauracin, sulisatin, tandamine, teoprانيتol, ticarcillin, tienocarbine, triclofos, triflocin, trimecaine, zolazepam*

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

*atizoram, atliprofène, béclamide, bicifadine, bornélonge, ciadox, clopéastine, clorexolone, cloropélonge, corticotropine hydroxyde de zinc, crésotamide, difénidol, diosmine, divabutérol, élédoisine, tétranitrate d'éritrityle, exépanol, fénaclone, fénoprofène, fluquazone, glutaurine, guaifylline, halazone, kébuzone, métamfépramone, métilicine, moquizone, nabilone, nonabine, norgestélonge, odalprofène, olétimol, pentiapine, plauracine, sulisatine, tandamine, téoprانيتol, ticarcilline, tiénocarbine, triclofos, triflocine, trimécaïne, zolazépam*

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

*atizoram, atliprofeno, beclamida, bicifadina, bornelona, ciadox, cloperastina, clorexolona, cloroperona, corticotropina hidróxido de zinc, cresotamida, difenidol, diosmina, divabuterol, eledoisina, tetranitrato de eritritilo, exepanol, fenaclón, fenoprofeno, flucuazona, glutaurina, guaifilina, halazona, kebuzona, metamfepramona, metilicina, moquizona, nabilona, nonabina, norgesterona, odalprofeno, oletimol, pentiapina, plauracina, sulisatina, tandamina, teoprانيتol, ticarcilina, tienocarbina, triclofós, triflocina, trimecaína, zolazepam*

*Proposed INN*  
(Latin, English, French, Spanish)

*Chemical name or description: Action and use: Molecular formula*  
*Chemical Abstracts Service (CAS) registry number: Graphic formula*

*DCI Proposée*

*Nom chimique ou description: Propriétés et indications: Formule brute*  
*Numéro dans le registre du CAS: Formule développée*

*DCI Propuesta*

*Nombre químico o descripción: Acción y uso: Fórmula empírica*  
*Número de registro del CAS: Fórmula desarrollada*

### abetimumum

abetimus

d(C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A)-P,5',5''',5''''',5''''''-tetraester withethylenebis(oxyethylene)bis[bis[2-[6-[2-[(6-hydroxyhexyl)thio]=acetamido]hexanamido]ethyl]carbamate], complex with d(T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G) (1:4)

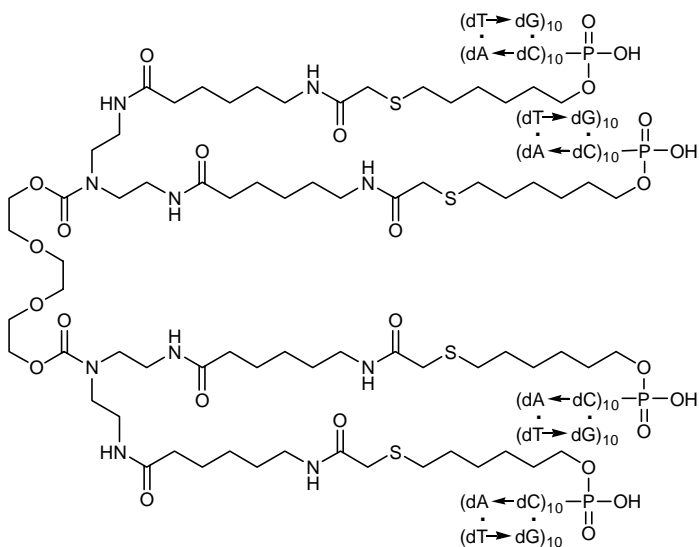
abétimus

complexe (4:1) entre l'acide désoxyribonucléique d(T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G) et le tétrakis[5'-hydrogénophosphate de l'acide désoxyribonucléique d(C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A)] de 6,6',6''',6''''-[éthylènebis[oxyéthylèneoxycarbonylnitrilobis[éthylèneimino=(6-oxohexane-6,1-diyl)imino(2-oxoéthane-2,1-diyl)sulfanediyl]]]tétrahexyle

abetimús

5',5''',5''''',5''''''-P-tetraéster del d(P-tetraéster del d(C-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A) con bis[bis[2-[6-[2-[(6hidroxihehil)tio]acetamido]=hexanamido]etil]carbamato] de etilenobis(oxietileno) de etilenobis(oxietileno), complejo con d(T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G) (1:4)

C<sub>1632</sub>H<sub>2100</sub>N<sub>610</sub>O<sub>970</sub>P<sub>156</sub>S<sub>4</sub>



**acidum caloxeticum**

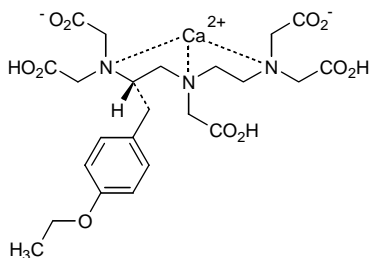
caloxetic acid

trihydrogen *N*-[(2*S*)-2-[bis(carboxymethyl)amino]-3-(*p*-ethoxyphenyl)propyl]-*N*-[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]calciate(3-)

acide caloxétique

trihydrogénéo*N*-[(2*S*)-2-[bis(carboxyméthyl)amino]-3-(4-éthoxyphényl)propyl]-*N*-[2-[bis(carboxyméthyl)amino]éthyl]glycinato(5-)]calciate(3-)

ácido caloxético

[*N*-[(2*S*)-2-[bis(carboximetil)amino]-3-(*p*-etoxifenil)propil]-*N*-[2-[bis(carboximetil)amino]etil]glicinato(5-)]calciato(3-) de trihidrógenoC<sub>23</sub>H<sub>31</sub>CaN<sub>3</sub>O<sub>11</sub>**anidulafunginum**

anidulafungin

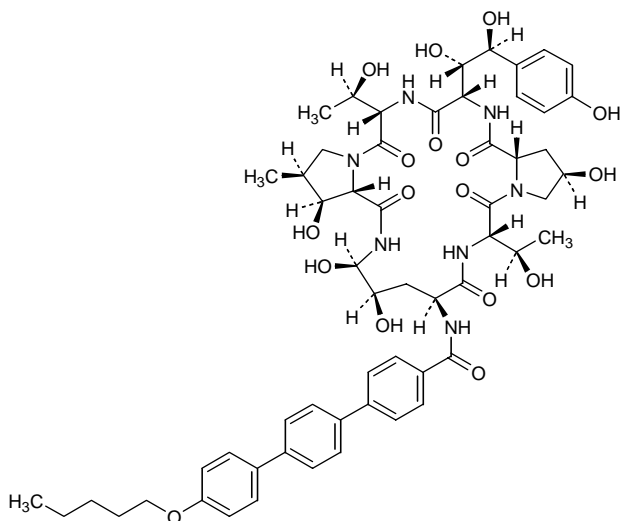
(4*R*,5*R*)-4,5-dihydroxy-*N*<sup>2</sup>-[[4''-(pentyloxy)-*p*-terphenyl-4-yl]carbonyl]-*L*-ornithyl-*L*-threonyl-*trans*-4-hydroxy-*L*-prolyl-(*S*)-4-hydroxy-4-(*p*-hydroxyphenyl)-*L*-threonyl-*L*-threonyl-(3*S*,4*S*)-3-hydroxy-4-methyl-*L*-proline cyclic (6→1)-peptide

anidulafungine

*N*-[(2*R*,6*S*,9*S*,11*R*,12*R*,14*aS*,15*S*,16*S*,20*S*,23*S*,25*aS*)-23-[(1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxyphényl)éthyl]-2,11,12,15-tétrahydroxy-6,20-bis[(1*R*)-1-hydroxyéthyl]-16-méthyl-5,8,14,19,22,25-hexaoxotétracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-*l*][1,4,7,10,13,16]hexaazacyclohénicosén-9-yl]-4''-(pentyloxy)-1,1':4',1''-terphényle-4-carboxamide

anidulafungina

péptido (6→1)-cíclico (4*R*,5*R*)-4,5-dihidroxi-*N*<sup>2</sup>-[4''-(pentiloxi)-*p*-terfenil-4-il]carbonyl]-*L*-ornitil-*L*-treonil-*trans*-4-hidroxi-*L*-proliil-(*S*)-4-hidroxi-4-(*p*-hidroxifenil)-*L*-treonil-*L*-treonil-(3*S*,4*S*)-3-hidroxi-4-metil-*L*-prolina

C<sub>58</sub>H<sub>73</sub>N<sub>7</sub>O<sub>17</sub>**artemimolum**

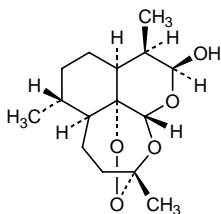
artemimol

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-decahydro-3,6,9-triméthyl-3,12-époxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxépin-10-ol

arténimol

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-3,6,9-triméthyl-décahydro-3,12-époxy-pyrano[4,3-*j*]-1,2-benzodioxépin-10-ol

artemimol

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-decahydro-3,6,9-triméthyl-3,12-époxi-12*H*-pirano[4,3-*j*]-1,2-benzodioxépin-10-olC<sub>15</sub>H<sub>24</sub>O<sub>5</sub>

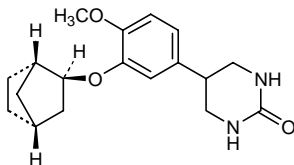
**atizoramum**

atizoram tetrahydro-5-[4-methoxy-3-[(1*S*,2*S*,4*R*)-2-norbornyloxy]phenyl]-2(1*H*)-pyrimidinone

atizoram 5-[3-[[[(1*S*,2*S*,4*R*)-bicyclo[2.2.1]hept-2-yl]oxy]-4-méthoxyphényl]=tétrahydropyrimidin-2(1*H*)-one

atizoram tetrahydro-5-[4-metoxi-3-[(1*S*,2*S*,4*R*)-2-norborniloxi]fenil]-2(1*H*)-pirimidinona

$C_{18}H_{24}N_2O_3$

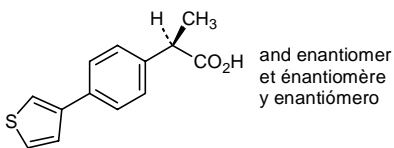
**atliprofenum**

atliprofen ( $\pm$ )-*p*-3-thienylhydratropic acid

atliprofène acide (*RS*)-2-[4-(thiophén-3-yl)phényl]propanoïque

atliprofenno ácido ( $\pm$ )-*p*-3-tienilhidratrópico

$C_{13}H_{12}O_2S$

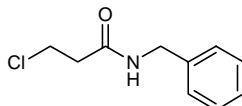
**beclamidum**

beclamide *N*-benzyl- $\beta$ -chloropropionamide

béclamide *N*-benzyl-3-chloropropanamide

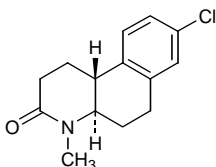
beclamida *N*-bencil- $\beta$ -cloropropionamida

$C_{10}H_{12}ClNO$

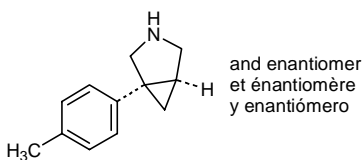


**bexlosteridum**

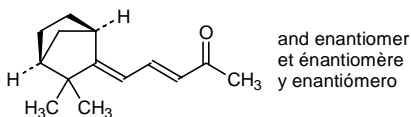
bexlosteride	(4 <i>aR</i> ,10 <i>bR</i> )-8-chloro-1,4,4 <i>a</i> ,5,6,10 <i>b</i> -hexahydro-4-methylbenzo[ <i>f</i> ]quinolin-3(2 <i>H</i> )-one
bexlostéride	(4 <i>aR</i> ,10 <i>bR</i> )-8-chloro-4-méthyl-1,4,4 <i>a</i> ,5,6,10 <i>b</i> -hexahydrobenzo[ <i>f</i> ]quinoléin-3(2 <i>H</i> )-one
bexlosterida	(4 <i>aR</i> ,10 <i>bR</i> )-8-cloro-1,4,4 <i>a</i> ,5,6,10 <i>b</i> -hexahidro-4-metilbenzo[ <i>f</i> ]quinolin-3(2 <i>H</i> )-ona
	C <sub>14</sub> H <sub>16</sub> ClNO

**bicifadinum**

bicifadine	(±)-1- <i>p</i> -tolyl-3-azabicyclo[3.1.0]hexane
bicifadine	(1 <i>RS</i> ,5 <i>SR</i> )-1-(4-méthylphényl)-3-azabicyclo[3.1.0]hexane
bicifadina	(±)-1- <i>p</i> -tolil-3-azabíciclo[3.1.0]hexano
	C <sub>12</sub> H <sub>15</sub> N

**bornelonum**

bornelone	5-(3,3-dimethyl-2-norbornylidene-3-penten-2-one
bornélonge	(3 <i>E</i> )-5-[(1 <i>RS</i> ,2 <i>E</i> ,4 <i>SR</i> )-3,3-diméthylbicyclo[2.2.1]hept-2-ylidène]pent-3-én-2-one
bornelona	5-(3,3-dimetil-2-norbornilideno-3-penten-2-ona
	C <sub>14</sub> H <sub>20</sub> O



**cadrofloxacinum**

cadrofloxacín

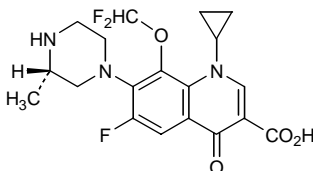
(-)-1-cyclopropyl-8-(difluoromethoxy)-6-fluoro-1,4-dihydro-7-[(S)-3-methyl-1-piperazinyl]-4-oxo-3-quinolinecarboxylic acid

cadrofloxacine

(-)-acide 1-cyclopropyl-8-(difluorométoxy)-6-fuoro-7-[(3S)-3-méthylpipérazin-1-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique

cadrofloxacino

ácido (-)-1-ciclopropil-8-(difluorometoxi)-6-fluoro-1,4-dihidro-7-[(S)-3-metil-1-piperazinil]-4-oxo-3-quinolinacarboxílico

C<sub>19</sub>H<sub>20</sub>F<sub>3</sub>N<sub>3</sub>O<sub>4</sub>**cefmatilenum**

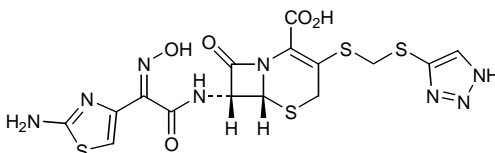
cefmatilén

(-)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[v-triazol-4-ylthio)methyl]thio]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7<sup>2</sup>-(Z)-oxime

cefmatilène

(-)-acide (6R,7R)-7-[[Z]-2-(2-aminotiazol-4-yl)-2-(hydroxyimino)acétyl]=amino]-8-oxo-3-[[[(1H-1,2,3-triazol-4-yl)sulfanyl]méthyl]sulfanyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ène-2-carboxylique

cefmatileno

7<sup>2</sup>-(Z)-oxima del ácido (-)-(6R,7R)-7-[2-(2-amino-4-tiazolil)glioxilamido]-8-oxo-3-[[v-triazol-4-iltio)metil]tio]-5-tia-1-azabicyclo[4.2.0]oct-2-eno-2-carboxílicoC<sub>15</sub>H<sub>14</sub>N<sub>8</sub>O<sub>5</sub>S<sub>4</sub>**ciadoxum**

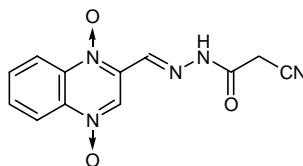
ciadox

cyanoacetic acid (2-quinoxalinylmethylene)hydrazide N<sup>1</sup>,N<sup>4</sup>-dioxide

ciadox

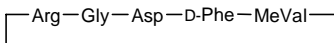
2-cyano-2'-[(E)-(quinoxalin-2-yl 1,4-dioxyde)méthylène]acétohydrazide

ciadox

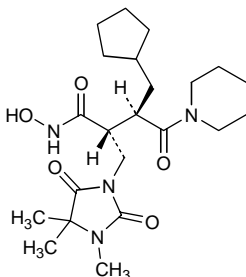
N<sup>1</sup>,N<sup>4</sup>-dióxido de la (2-quinoxalinilmetileno)hidrazida del ácido cianoacéticoC<sub>12</sub>H<sub>9</sub>N<sub>5</sub>O<sub>3</sub>

**cilengitidum**

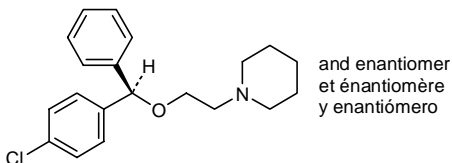
cilengitide	cyclo(L-arginylglycyl-L- $\alpha$ -aspartyl-D-phenylalanyl-N-methyl-L-valyl)
cilengitide	cyclo[L-arginyl-glycyl-L- $\alpha$ -aspartyl-D-phénylalanyl-(N-méthyl-L-valyl)]
cilengitida	ciclo(L-arginilglicil-L-a-aspartil-D-fenilalanil-N-metil-L-valil)

C<sub>27</sub>H<sub>40</sub>N<sub>8</sub>O<sub>7</sub>**cipemastatum**

cipemastat	( $\alpha R, \beta R$ )- $\beta$ -(cyclopentylmethyl)- $\gamma$ -oxo- $\alpha$ -[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-1-piperidinebutyrohydroxamic acid
cipémastat	(2 <i>R</i> ,3 <i>R</i> )-3-(cyclopentylméthyl)- <i>N</i> -hydroxy-4-oxo-4-(pipéridin-1-yl)-2-[(3,4,4-triméthyl-2,5-dioxoimidazolidin-1-yl)méthyl]butanamide
cipemastat	ácido ( $\alpha R, \beta R$ )- $\beta$ -(ciclopentilmetil)- $\gamma$ -oxo- $\alpha$ -[(3,4,4-trimetil-2,5-dioxo-1-imidazolidinil)metil]-1-piperidinabutiroidroxámico

C<sub>22</sub>H<sub>36</sub>N<sub>4</sub>O<sub>5</sub>**cloperastinum**

cloperastine	1-[2-[( <i>p</i> -chloro- $\alpha$ -phenylbenzyl)oxy]]piperidine
clopérastine	1-[2-[( <i>RS</i> )-(4-chlorophényl)phénylméthoxy]éthyl]pipéridine
cloperastina	1-[2-[(4-cloro- $\alpha$ -fenilbencil)oxi]etil]piperidina

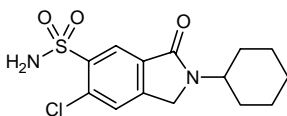
C<sub>20</sub>H<sub>24</sub>ClNO



**clorexolonum**

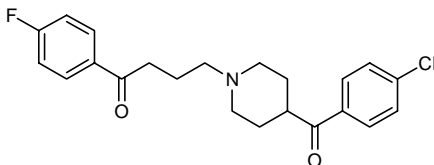
clorexolone	6-chloro-2-cyclohexyl-3-oxo-5-isoindolinesulfonamide
clorexolone	6-chloro-2-cyclohexyl-3-oxo-2,3-dihydro-1 <i>H</i> -isoindole-5-sulfonamide
clorexolona	6-cloro-2-ciclohexil-3-oxo-5-isoindolinosulfonamida

$C_{14}H_{17}ClN_2O_3S$

**cloroperonum**

cloroperone	4- [4-( <i>p</i> -chlorobenzoyl)piperidino]-4'-fluorobutyrophenone
cloropérone	4-[4-(4-chlorobenzoyl)pipéridin-1-yl]-1-(4-fluorophényl)butan-1-one
cloroperona	4- [4-( <i>p</i> -clorobenzoil)piperidino]-4'-fluorobutirofenona

$C_{22}H_{23}ClFNO_2$

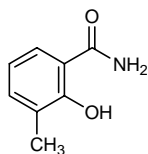
**corticotropinum zinci hydroxydum**

corticotropin zinc hydroxide	a preparation of purified corticotropin adsorbed on zinc hydroxide
corticotropine hydroxyde de zinc	préparation de corticotropine purifiée adsorbée sur l'hydroxyde de zinc
corticotropina hidróxido de zinc	preparación de corticotropina purificada adsorbida en hidróxido de zinc

**cresotamidum**

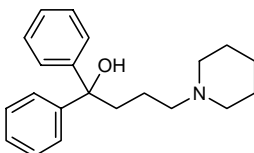
cresotamide	2,3-cresotamide
crésotamide	2-hydroxy-3-méthylbenzamide
cresotamida	2,3-cresotamida

$C_8H_9NO_2$

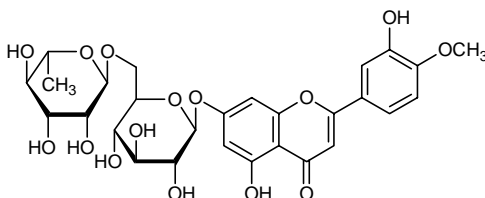


**difenidolum**

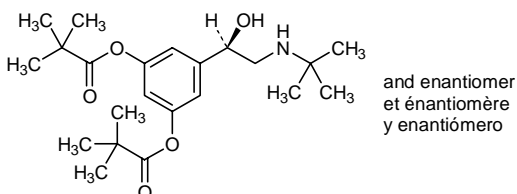
difenidol	$\alpha,\alpha$ -diphenyl-1-piperidinebutanol
difénidol	1,1-diphényl-4-(pipéridin-1-yl)butan-1-ol
difenidol	1,1-difenil-4-piperidinobutanol
	$C_{21}H_{27}NO$

**diosminum**

diosmin	3',5,7-trihydroxy-4'-methoxyflavone 7-[6-O-(6-deoxy- $\alpha$ -L-mannopyranosyl)- $\beta$ -D-glucopyranoside]
diosmine	7-[[6-O-(6-désoxy- $\alpha$ -L-mannopyranosyl)- $\beta$ -D-glucopyranosyl]oxy]-5-hydroxy-2-(3-hydroxy-4-méthoxyphényl)-4H-1-benzopyran-4-one
diosmína	7-[6-O-desoxi- $\alpha$ -L-manopiranosil]- $\beta$ -D-glucopiranosido de 3',5,7-trihydroxi-4'-metoxiflavona
	$C_{28}H_{32}O_{15}$

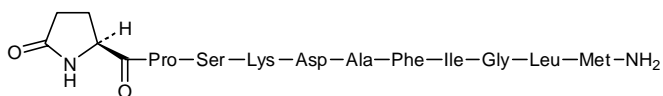
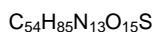
**divabuterolum**

divabuterol	(±)-5-[2-( <i>tert</i> -butylamino)-1-hydroxyethyl]- <i>m</i> -phenylene dipivalate
divabutérol	bis(2,2-diméthylpropanoate) de 5-[(1 <i>RS</i> )-2-[(1,1-diméthyléthyl)amino]-1-hydroxyéthyl]-1,3-phénylène
divabuterol	dipivalato de (±)-5-[2-( <i>terc</i> -butilamino)-1-hidroxietil]- <i>m</i> -fenileno
	$C_{22}H_{35}NO_5$

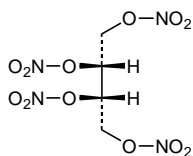
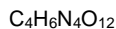


**eledoisinum**

eledoisin	5-oxo-L-prolyl-L-prolyl-L-seryl-L-lysyl-L-aspartyl-L-alanyl-L-phenylalanyl-L- isoleucylglycyl-L-leucyl-L-methioninamide
elédoïsine	(5-oxo-L-prolyl)-L-prolyl-L-seryl-L-lysyl-L-aspartyl-L-alanyl-L-phénylalanyl-L- isoleucyl-glycyl-L-leucyl-L-méthioninamide
eledoisina	5-oxo-L-prolil-L- prolil-L-seril-L-lisil-L-aspartil-L-alanil-L-fenilalanil-L- isoleucilglicil-L-leucil-L-metioninamida

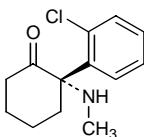
**eritryli tetranitras**

eritryl tetranitrate	erythritol tetranitrate
tétranitrate d'éritrityle	tétranitrate de (2 <i>R</i> ,3 <i>S</i> )-butane-1,2,3,4-tétryle
tetranitrato de eritritilo	tetranitrato de eritritol



**esketaminum**

esketamine	(S)-2-(o-chlorophenyl)-2-(methylamino)cyclohexanone
eskétamine	(2S)-2-(2-chlorophényl)-2-(méthylamino)cyclohexanone
esketamina	(S)-2-(o-clorofenil)-2-(metilamino)ciclohexanona

C<sub>13</sub>H<sub>16</sub>ClNO**etanerceptum**

etanercept	1-235-tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human $\gamma$ 1-chain Fc fragment), dimer
étanercept	1-235-récepteur du facteur de nécrose tumorale (humain)-236-467-immunoglobuline G1 (chaîne $\gamma$ 1 du fragment Fc humain), dimère
etanercept	dímero de la proteína de fusión del 1-235 receptor del factor de necrosis tumoral (humano) con la 236-467-immunoglobulina G1 (cadena $\gamma$ 1 del fragmento Fc humano)

C<sub>2224</sub>H<sub>3472</sub>N<sub>618</sub>O<sub>701</sub>S<sub>36</sub> (monomer)

LPAQVAFTPY	APEPGSTCRL	REYYDQTAQM	CCSKCSPGQH
AKVFCTKTS	TVCDSCEDST	YTQLWNWVPE	CLSCGSRCSS
DQVETQACTR	EQNRICTCRP	GWYCALSKQE	GCRLCAPLRK
CRPGFGVARP	GTETSDVVCK	PCAPGTFSNT	TSSTDICRPH
QICNVVAIPG	NASMDAVCTS	TSPTRSMAPG	AVHLPQPVST
RSQHTQPTPE	PSTAPSTSFL	LPMGPSPPAE	GSTGDEPKSC
DKTHTCPPCP	APELLGGPSV	FLFPPKPKDT	LMISRTPEVT
CVVVDVSHED	PEVKFNWYVD	GVEVHNAKTK	PREEQYNSTY
RVVSVLTVLH	QDWLNGKEYK	CKVSNKALPA	PIEKTISKAK
GQPREPQVYT	LPPSREEMTK	NQVSLTCLVK	GFYPSDIAVE
WESNGQPENN	YKTTTPVLDS	DGSFFLYSKL	TVDKSRWQQG
NVFSCSVMHE	ALHNHYTQKS	LSLSPGK	

2

**exatecanum**

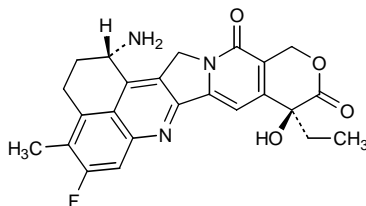
exatecan

(1*S*,9*S*)-1-amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-méthyl-10*H*,13*H*-benzo[*de*]pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-10,13-dione

exatécan

(1*S*,9*S*)-1-amino-9-éthyl-5-fluoro-9-hydroxy-4-méthyl-1,2,3,9,12,15-hexahydro-10*H*,13*H*-benzo[*de*]pyrano[3',4':6,7]indolizino[1,2-*b*]quinoléine-10,13-dione

exatecán

(1*S*,9*S*)-1-amino-9-etil-5-fluoro-1,2,3,9,12,15-hexahidro-9-hidroxi-4-metil-10*H*,13*H*-benzo[*de*]pirano[3',4':6,7]indolizino[1,2-*b*]quinolina-10,13-dionaC<sub>24</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub>**exepanolum**

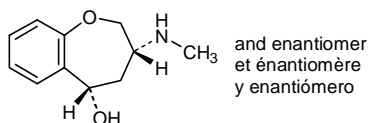
exepanol

(±)-*cis*-2,3,4,5-tetrahydro-3-(méthylamino)-1-benzoxépin-5-ol

exépanol

(3*RS*,5*SR*)-3-(méthylamino)-2,3,4,5-tétrahydro-1-benzoxépin-5-ol

exepanol

(±)-*cis*-2,3,4,5-tetrahydro-3-(metilamino)-1-benzoxépin-5-olC<sub>11</sub>H<sub>15</sub>NO<sub>2</sub>**falnidamolum**

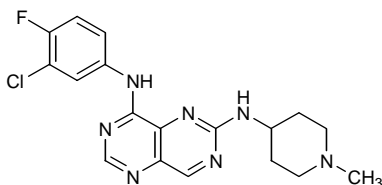
falnidamol

8-(3-chloro-4-fluoroanilino)-2-[(1-méthyl-4-piperidyl)amino]pyrimido=[5,4-*d*]pyrimidine

falnidamol

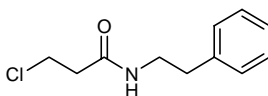
*N*<sup>β</sup>-(3-chloro-4-fluorophényl)-*N*<sup>γ</sup>-(1-méthylpipéridin-4-yl)pyrimido=[5,4-*d*]pyrimidine-2,8-diamine

falnidamol

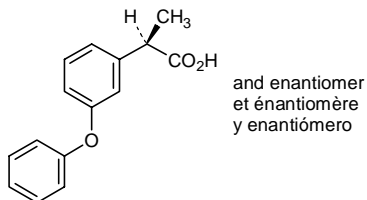
8-(3-cloro-4-fluoroanilino)-2-[(1-metil-4-piperidil)amino]pirimido=[5,4-*d*]pirimidinaC<sub>18</sub>H<sub>19</sub>ClFN<sub>7</sub>

**fenaclonum**

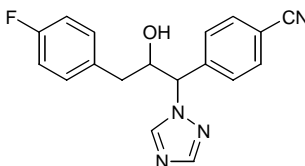
fenaclon	3-chloro- <i>N</i> -phenethylpropionamide
fénacloñe	3-chloro- <i>N</i> -(2-phényléthyl)propanamide
fenaclona	3-cloro- <i>N</i> -fenetilpropionamida
	C <sub>11</sub> H <sub>14</sub> ClNO

**fenoprofenum**

fenoprofen	(±)- <i>m</i> -phenoxyhydratropic acid
fénoprofène	acide ( <i>RS</i> )-2-(3-phénoxyphényl)propanoïque
fenoprofeno	ácido (±)- <i>m</i> -fenoxihidratrópico
	C <sub>15</sub> H <sub>14</sub> O <sub>3</sub>

**finrozolum**

finrozole	<i>p</i> -[3-( <i>p</i> -fluorophenyl)-2-hydroxy-1-(1 <i>H</i> -1,2,4-triazol-1-yl)propyl]benzonitrile
finrozole	4-[3-(4-fluorophényl)-2-hydroxy-1-(1 <i>H</i> -1,2,4-triazol-1-yl)propyl]benzonitrile
finrozol	<i>p</i> -[3-( <i>p</i> -fluorofenil)-2-hidroxi-1-(1 <i>H</i> -1,2,4-triazol-1-il)propil]benzonitrilo
	C <sub>18</sub> H <sub>15</sub> FN <sub>4</sub> O



**fluquazonum**

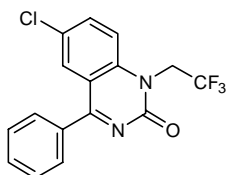
fluquazone

6-chloro-4-phenyl-1-(2,2,2-trifluoroethyl)-2(1*H*)-quinazolinone

fluquazone

6-chloro-4-phényl-1-(2,2,2-trifluoroéthyl)quinazolin-2(1*H*)-one

flucuaazona

6-cloro-4-fenil-1-(2,2,2-trifluoroetil)-2(1*H*)-quinazolinona $C_{16}H_{10}ClF_3N_2O$ **fosfructosum**

fosfructose

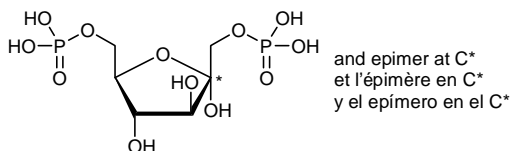
D-fructose 1,6-bis(dihydrogen phosphate)

fosfructose

1,6-bis(dihydrogénophosphate) de D-*arabino*-2-hexulofuranose

fosfructosa

1,6-bis(dihidrógenofosfato) de D-fructosa

 $C_6H_{14}O_{12}P_2$ **frakefamidum**

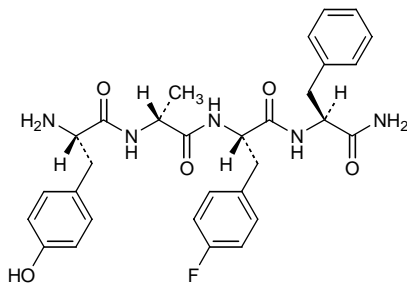
frakefamide

L-tyrosyl-D-alanyl-*p*-fluoro-L-phenylalanyl-L-phenylalaninamide

frakéfamide

L-tyrosyl-D-alanyl-(4-fluoro-L-phénylalanyl)-L-phénylalaninamide

frakefamida

L-tirosil-D-alanil-*p*-fluoro-L-fenilalanil-L-fenilalaninamida $C_{30}H_{34}FN_5O_5$ 

**ganstigminum**

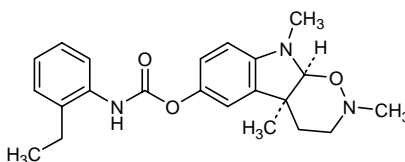
ganstigmine

(4a*S*,9a*S*)-2,3,4,4a,9,9a-hexahydro-2,4a,9-trimethyl-1,2-oxazino[6,5-*b*]indol-6-yl *o*-ethylcarbanilate

ganstigmine

(2-éthylphényl)carbamate de (4a*S*,9a*S*)-2,4a,9-triméthyl-2,3,4,4a,9,9a-hexahydro-1,2-oxazino[6,5-*b*]indol-6-yle

ganstigmina

*o*-etilcarbanilato de (4a*S*,9a*S*)-2,3,4,4a,9,9a-hexahidro-2,4a,9-trimetil-1,2-oxazino[6,5-*b*]indol-6-iloC<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>**gemifloxacinum**

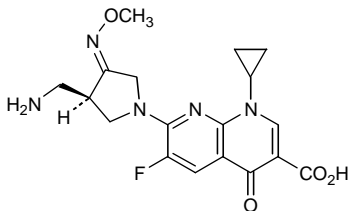
gemifloxacin

(±)-7-[3-(aminométhyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 7<sup>4</sup>-(*Z*)-(O-méthylloxime)

gémifloxacine

acide 7-[(3*RS*,4*Z*)-3-(aminométhyl)-4-(méthoxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphtyridine-3-carboxylique

gemifloxacino

7<sup>4</sup>-(*Z*)-(O-metiloxima) del ácido (±)-7-[3-(aminometil)-4-oxo-1-pirrolidinil]-1-ciclopropil-6-fluoro-1,4-dihidro-4-oxo-1,8-naftiridina-3-carboxílicoC<sub>18</sub>H<sub>20</sub>FN<sub>5</sub>O<sub>4</sub>and enantiomer  
et énantiomère  
y enantiómero



**glutaurinum**

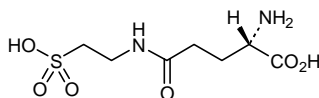
glutaurine

*N*-(2-sulfoethyl)-L-glutamine

glutaurine

acide (2*S*)-2-amino-5-oxo-5-[(2-sulfoéthyl)amino]pentanoïque

glutaurina

*N*-(2-sulfoetil)-L-glutaminaC<sub>7</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>S**guaifyllinum**

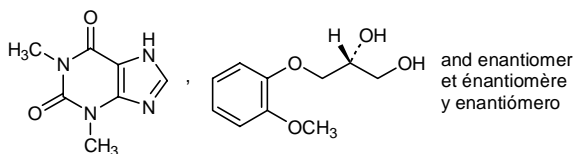
guaifylline

3-(*o*-methoxyphenoxy)-1,2 propanediol compound with theophylline

guaïfylline

composé équimoléculaire de 1,3-diméthyl-3,7-dihydro-1*H*-purine-2,6-dione et de (2*RS*)-3-(2-méthoxyphénoxy)propane-1,2-diol

guaifilina

3-(*o*-metoxifenoxi)-1,2 propanodiol compuesto con teofilinaC<sub>7</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>.C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>**halazonum**

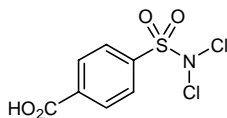
halazone

*p*-(dichlorosulfamoyl)benzoic acid

halazone

acide 4-(dichlorosulfamoyl)benzoïque

halazona

ácido-*p*-(diclorosulfamoil)benzoicoC<sub>7</sub>H<sub>5</sub>Cl<sub>2</sub>NO<sub>4</sub>S

**ibritumomabum tiuxetanum**

ibritumomab tiuxetan

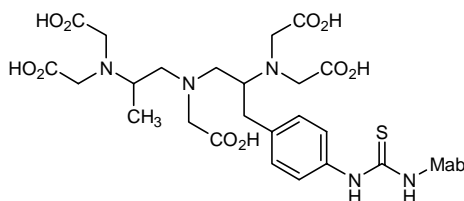
immunoglobulin G1, anti-(human CD20 (antigen)) (mouse monoclonal IDEC-Y2B8  $\gamma$ 1-chain), disulfide with mouse monoclonal IDEC-Y2B8  $\kappa$ -chain, dimer, *N*-[2-[bis(carboxymethyl)amino]-3-(4-isothiocyanatophenyl)propyl]-*N*-[2-[bis(carboxymethyl)amino]propyl]glycine conjugate

ibritumomab tiuxétan

produit de la réaction entre l'immunoglobuline G1, anti-(antigène CD20 humain) (chaîne  $\gamma$ 1 de l'anticorps monoclonal de souris IDEC-Y2B8), dimère du disulfure avec la chaîne  $\kappa$  de l'anticorps monoclonal de souris IDEC-Y2B8 et la *N*-[2-[bis(carboxyméthyl)amino]-3-(4-isothiocyanatophényl)propyl]-*N*-[2-[bis(carboxyméthyl)amino]propyl]glycine

ibritumomab tiuxetán

*N*-[[4-[(2*S*)-2-[bis(carboximéthil)amino]-3-[[[(2*R**S*)-2-[bis(carboximéthil)amino]propil](carboximéthil)amino]propil]fénil]tiocarbamoil]= immunoglobulina G1, anti-(antígeno CD20 humano) (cadena  $\gamma$ 1 del anticuerpo monoclonal quimérico hombre-ratón IDEC-Y2B8), dímero del disulfuro con la cadena  $\kappa$  del anticuerpo monoclonal quimérico hombre-ratón IDEC-Y2B8

**idremcinalum**

idremcinal

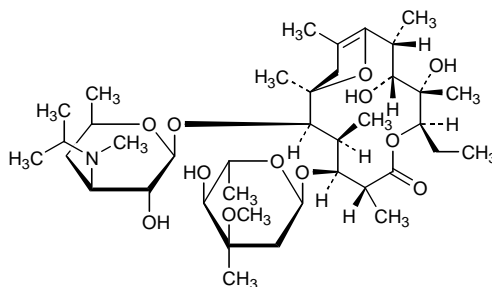
8,9-didehydro-*N*-demethyl-9-deoxo-6-deoxy-6,9-epoxy-*N*-isopropylerythromycin

idremcinal

(2*R*,3*R*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-5-éthyl-3,4-dihydroxy-2,4,8,10,12,14-hexaméthyl-9-[(3-*C*-méthyl-3-*O*-méthyl-2,6-didésoxy- $\alpha$ -*L*-ribo-hexopyranosyl)oxy]-11-[3-[méthyl(1-méthyléthyl)amino]-3,4,6-tridésoxy- $\beta$ -*D*-xylo-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-én-7-one

idremcinal

8,9-dideshidro-*N*-desmetil-9-desoxo-6-desoxi-6,9-epoxi-*N*-isopropileritromicina

C<sub>39</sub>H<sub>69</sub>NO<sub>12</sub>

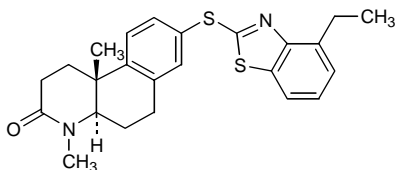
**ilodecakinum**

ilodecakin	interleukin 10 (human clone pH15C)
ilodécakine	interleukine 10 (clone humain pH15C)
ilodecakina	interleuquina 10 (clon humano pH15C)

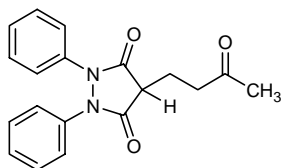
SPGQGTQSEN	SCTHFPGNLP	NMLRDLRDAF	SRVKTFQMK
DQLDNLLLKE	SLLEDFKGYL	GCQALSEMIQ	FYLEEVMPQA
ENQDPDIKAH	VNSLGENLKT	LRLRLRRCHR	FLPCENSKA
VEQVKNAFNK	LQEKGIYKAM	SEFDIFINYI	EAYMTMKIRN

**izonsteridum**

izonsteride	(4 <i>aR</i> ,10 <i>bR</i> )-8-[(4-ethyl-2-benzothiazolyl)thio]-1,4,4 <i>a</i> ,5,6,10 <i>b</i> -hexahydro-4,10 <i>b</i> -dimethylbenzo[ <i>f</i> ]quinolin-3(2 <i>H</i> )-one
izonstéride	(4 <i>aR</i> ,10 <i>bR</i> )-8-[(4-éthylbenzothiazol-2-yl)sulfanyl]-4,10 <i>b</i> -diméthyl-1,4,4 <i>a</i> ,5,6,10 <i>b</i> -hexahydrobenzo[ <i>f</i> ]quinoléin-3(2 <i>H</i> )-one
izonsterida	(4 <i>aR</i> ,10 <i>bR</i> )-8-[(4-etil-2-benzotiazolil)tio]-1,4,4 <i>a</i> ,5,6,10 <i>b</i> -hexahidro-4,10 <i>b</i> -dimetilbenzo[ <i>f</i> ]quinolin-3(2 <i>H</i> )-ona

C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>OS<sub>2</sub>**kebuzonum**

kebuzone	4-(3-oxobutyl)-1,2-diphenyl-3,5-pyrazolidinedione
kébuzone	4-(3-oxobutyl)-1,2-diphénylpyrazolidine-3,5-dione
kebuzona	4-(3-oxobutil)-1,2-difenil-3,5-pirazolidinadiona

C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>

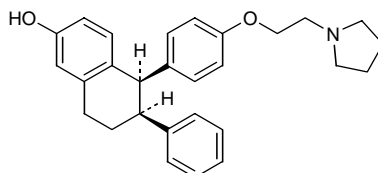
**lasofoxifenum**

lasofoxifene (-)-*cis*-5,6,7,8-tetrahydro-6-phenyl-5-[*p*-[2-(1-pyrrolidinyl)ethoxy]phenyl]-2-naphthol

lasofoxifène (-)-(5*RS*,6*SR*)-6-phényl-5-[4-[2-(pyrrolidin-1-yl)éthoxy]phényl]-5,6,7,8-tétrahydronaphtalén-2-ol

lasofoxifeno (-)-*cis*-5,6,7,8-tetrahydro-6-fenil-5-[*p*-[2-(1-pirrolidinil)etoxi]fenil]-2-naftol

$C_{28}H_{31}NO_2$



or enantiomer  
ou énantiomère  
o enantiómero

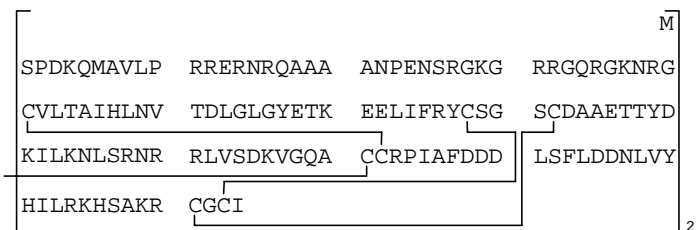
**liaterminum**

liatermin *N*-methionylneurotrophic factor (human glial-derived), dimer

liatermine *N*-méthionylfacteur neurotrophique (humain, dérivé de la glia), dimère

liatermina dímero del factor *N*-metionilneurotrófico (humano derivado de la glia)

$C_{1290}H_{2110}N_{420}O_{394}S_{18}$

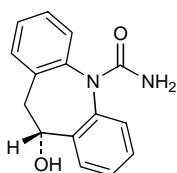
**licarbazepinum**

licarbazepine 10,11-dihydro-10-hydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide

licarbazépine (10*RS*)-10-hydroxy-10,11-dihydro-5*H*-dibenzo[*b,f*]azépine-5-carboxamide

licarbazepina 10,11-dihidro-10-hidroxi-5*H*-dibenz[*b,f*]azepina-5-carboxamida

$C_{15}H_{14}N_2O_2$



and enantiomer  
et énantiomère  
y enantiómero

**mepolizumabum**

mepolizumab immunoglobulin G1, anti-(human interleukin 5) (human-mouse monoclonal SB-240563  $\gamma$ 1-chain), disulfide with human-mouse monoclonal SB-240563  $\kappa$ -chain, dimer

mépolizumab immunoglobuline G1, anti-(interleukine 5 humaine) (chaîne  $\gamma$ 1 de l'anticorps monoclonal de souris SB-240563 humanisé), dimère du disulfure avec la chaîne  $\kappa$  de l'anticorps monoclonal de souris SB-240563 humanisé

mepolizumab inmunoglobulina G1, anti-(interleukina 5 humana) (cadena  $\gamma$ 1 del anticuerpo monoclonal de ratón SB-240563 humanizado), dímero del disulfuro con la cadena  $\kappa$  del anticuerpo monoclonal de ratón SB-240563 humanizado

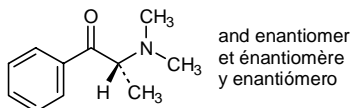
**metamfepramonum**

metamfepramone 2-(dimethylamino)propiofenone

métamfépramone (2*RS*)-2-(diméthylamino)-1-phénylpropan-1-one

metanfepramona 2-(dimetilamino)propiofenona

$C_{11}H_{15}NO$

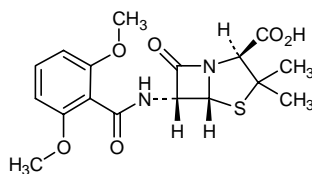
**meticillinum**

meticillin 6-(2,6 dimethoxybenzamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

méticilline acide (2*S*,5*R*,6*R*)-6-[(2,6-diméthoxybenzoyl)amino]-3,3-diméthyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylique

meticilina ácido 6-(2,6-dimetoxibenzamido)-3,3-dimetil-7-oxo-4-tia-1-azabicyclo-[3.2.0]heptano-2-carboxílico

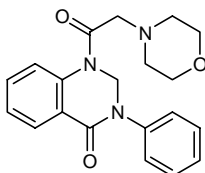
$C_{17}H_{20}N_2O_6S$

**moquizonum**

moquizone 2,3-dihydro-1-(morpholinoacetyl)-3-phenyl-4(1*H*)-quinazolinone

moquizone 1-(morpholin-4-ylacétyl)-3-phényl-2,3-dihydroquinazolin-4(1*H*)-one

moquizona 1-(2-morfolinoacetil)-3-fenil-2,3-dihidro-4-(1*H*)-quinazolinona

$C_{20}H_{21}N_3O_3$ **nabilonum**

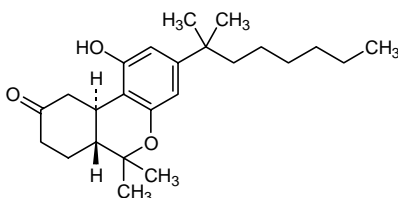
nabilone

 $(\pm)$ -*trans*-3-(1,1-diméthylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-diméthyl-9*H*-dibenzo[*b,d*]pyran-9-one

nabilone

(6*aRS*,10*aRS*)-3-(1,1-diméthylheptyl)-1-hydroxy-6,6-diméthyl-6,6a,7,8,10,10a-hexahydro-9*H*-dibenzo[*b,d*]pyran-9-one

nabilona

 $(\pm)$ -*trans*-3-(1,1-diméthilheptil)-6,6a,7,8,10,10a-hexahidro-1-hidroxi-6,6-diméthil-9*H*-dibenzo[*b,d*]piran-9-ona $C_{24}H_{36}O_3$ and enantiomer  
et énantiomère  
y enantiómero**nonabinum**

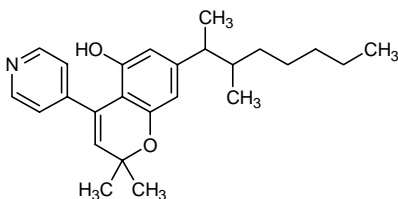
nonabine

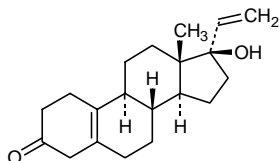
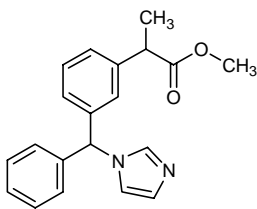
7-(1,2-diméthylheptyl)-2,2-diméthyl-4-(4-pyridyl)-2*H*-1-benzopyran-5-ol

nonabine

7-(1,2-diméthylheptyl)-2,2-diméthyl-4-(pyridin-4-yl)-2*H*-1-benzopyran-5-ol

nonabina

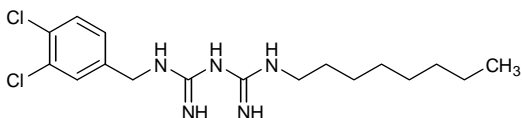
7-(1,2-diméthilheptil)-2,2-diméthil-4-(4-piridil)-2*H*-1-benzopiran-5-ol $C_{25}H_{33}NO_2$ 

**norgesteronum**norgesterone 17-hydroxy-19-nor-17 $\alpha$ -pregna-5(10),20-dien-3-onenorgestérone 17-hydroxy-19-nor-17 $\alpha$ -prégna-5(10),20-dién-3-onenorgesterona 17-hidroxi-19-nor-17 $\alpha$ -pregna-5(10),20-dieno-3-onaC<sub>20</sub>H<sub>28</sub>O<sub>2</sub>**odalprofenum**odalprofen methyl ( $\pm$ )-*m*-( $\alpha$ -imidazol-1-ylbenzyl)hydratropateodalprofène mélange d'isomères du 2-[3-[(1*H*-imidazol-1-yl)phénylméthyl]phényl]propanoate de méthyleodalprofeno ( $\pm$ )-*m*-( $\alpha$ -imidazol-1-ilbencil)hidratropato de metiloC<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>**olanexidinum**

olanexidine 1-(3,4-dichlorobenzyl)-5-octylbiguanide

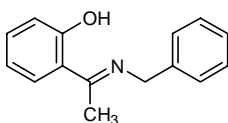
olanexidine 1-(3,4-dichlorobenzyl)-5-octylbiguanide

olanexidina 1-(3,4-diclorobencil)-5-octilbiguanida

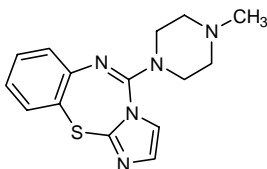
C<sub>17</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>5</sub>

**oletimolum**

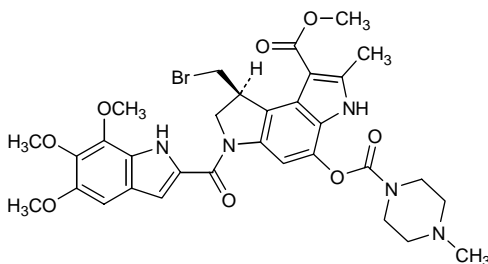
oletimol	<i>o</i> -( <i>N</i> -benzylacetimidoyl)phenol
olétimol	2-[( <i>E</i> )-1-(benzylimino)éthyl]phénol
oletimol	<i>o</i> -( <i>N</i> -bencilacetimidoil)fenol

C<sub>15</sub>H<sub>15</sub>NO**pentiapinum**

pentiapine	5-(4-methyl-1-piperazinyl)imidazo[2,1- <i>b</i> ][1,3,5]benzothiadiazepine
pentiapine	5-(4-méthylpipérazin-1-yl)imidazo[2,1- <i>b</i> ][1,3,5]benzothiadiazépine
pentiapina	5-(4-metil-1-piperazinil)imidazo[2,1- <i>b</i> ][1,3,5]benzotiadiazepina

C<sub>15</sub>H<sub>17</sub>N<sub>5</sub>S**pibrozelesinum**

pibrozelesin	methyl ( <i>S</i> )-8-(bromomethyl)-3,6,7,8-tetrahydro-4-hydroxy-2-methyl-6-[(5,6,7-trimethoxyindol-2-yl)carbonyl]benzo[1,2- <i>b</i> :4,3- <i>b'</i> ]dipyrrole-1-carboxylate, 4-methyl-1-piperazinecarboxylate (ester)
pibrozélésine	(8 <i>S</i> )-8-(bromométhyl)-2-méthyl-4-[[[4-méthylpipérazin-1-yl]carbonyl]oxy]-6-[(5,6,7-triméthoxy-1 <i>H</i> -indol-2-yl)carbonyl]-3,6,7,8-tétrahydrobenzo=[1,2- <i>b</i> :4,3- <i>b'</i> ]dipyrrole-1-carboxylate de méthyle
pibrozelesina	(8 <i>S</i> )-(bromometil)-3,6,7,8-tetrahidro-2-metil-4-[[[4-metil-1-piperazinil]=carbonil]oxi]-6-[(5,6,7-trimetoxi-1 <i>H</i> -indol-2-il)carbonil]benzo=[1,2- <i>b</i> :4,3- <i>b'</i> ]dipirrol-1-carboxilato de metilo

C<sub>32</sub>H<sub>36</sub>BrN<sub>5</sub>O<sub>8</sub>



**pimecrolimusum**

pimecrolimus

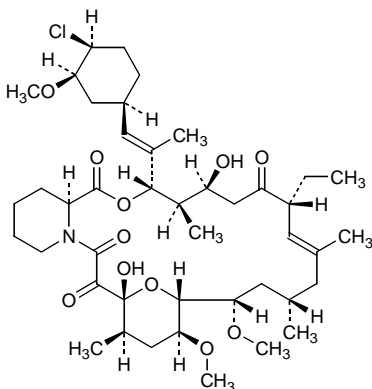
(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-3-[(*E*)-2-[(1*R*,3*R*,4*S*)-4-chloro-3-methoxycyclohexyl]-1-methylvinyl]-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-*c*] [1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone

pimécrolimus

(18*E*)-[(1*R*,9*S*,12*S*,13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*)-12-[(*E*)-2-[(1*R*,3*R*,4*S*)-4-chloro-3-méthoxycyclohexyl]-1-méthyléthényl]-17-éthyl-1,14-dihydroxy-23,25-diméthoxy-13,19,21,27-tétraméthyl-11,28-dioxa-4-azatricyclo[22.3.1.0<sup>4,9</sup>]octacos-18-ène-2,3,10,16-tétrone

pimecrolimús

(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-3-[(*E*)-2-[(1*R*,3*R*,4*S*)-4-cloro-3-metoxiciclohexil]-1-metilvinil]-8-etil-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-hexadecahidro-5,19-dihidroxi-14,16-dimetoxi-4,10,12,18-tetrametil-15,19-epoxi-3*H*-pirido[2,1-*c*] [1,4]oxaazaciclotricosina-1,7,20,21(4*H*,23*H*)-tetrona

C<sub>43</sub>H<sub>68</sub>ClNO<sub>11</sub>**plauracinum**

plauracin

an antibiotic complex obtained from cultures of *Actinoplanes auranticolor* ATCC 31011

plauracine

antibiotique extrait de cultures d'*Actinoplanes auranticolor* (ATCC 31011) composé principalement d'une lactone macrocyclique et d'un depsipeptide

plauracina

antibiótico complejo, mezcla de dos componentes principales, obtenido a partir de cultivos de *Actinoplanes auranticolor* ATCC 31011

**prazarelixum**

prazarelix

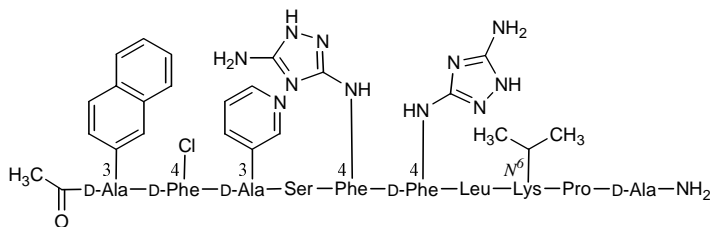
*N*-acetyl-3-(2-naphthyl)-D-alanyl-*p*-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-*p*-[(5-amino-*s*-triazol-3-yl)amino]-L-phenylalanyl-*p*-[(5-amino-*s*-triazol-3-yl)amino]-D-phenylalanyl-L-leucyl-*N*<sup>6</sup>-isopropyl-L-lysyl-L-prolyl-D-alaninamide

prazarélix

[*N*-acétyl-3-(naphthalén-2-yl)-D-alanyl]--(4-chloro-D-phénylalanyl)-[3-(pyridin-3-yl)-D-alanyl]-L-séryl-[4-[(5-amino-1*H*-1,2,4-triazol-3-yl)amino]-L-phénylalanyl]-[4-[(5-amino-1*H*-1,2,4-triazol-3-yl)amino]-D-phénylalanyl]-L-leucyl-[*N*<sup>6</sup>-(1-méthyléthyl)-L-lysyl]-L-prolyl-D-alaninamide

prazarelix

*N*-acetil-3-(2-naftil)-D-alanil-*p*-cloro-D-fenilalanil-3-(3-piridil)-D-alanil-L-seril-*p*-[(5-amino-*s*-triazol-3-il)amino]-L-fenilalanil-*p*-[(5-amino-*s*-triazol-3-il)amino]-D-fenilalanil-L-leucil-*N*<sup>6</sup>-isopropil-L-lisil-L-prolil-D-alaninamida

C<sub>80</sub>H<sub>102</sub>ClN<sub>23</sub>O<sub>12</sub>**ranpirnasum**

ranpirnase

ribonuclease (*Rana pipiens*)

ranpirnase

ribonucléase (*Rana pipiens*)

ranpirnasa

ribonucleasa (*Rana pipiens*)C<sub>520</sub>H<sub>812</sub>N<sub>142</sub>O<sub>156</sub>S<sub>9</sub>

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EDWLTQKHH  ITNTRDVDCD  NIMSTNLFHC  KDKNTFIYSR
PEPVKAICKG  IIASKNVLTT  SEFYLSDCNV  TSRPCKYKLK
KSTNKFCVTC  ENQAPVHFGV  VGSC

```

**rasburicasum**

rasburicase

urate oxydase (tetramer of the *N*-acetylpolypeptide of 301 amino acids)

rasburicase

urate oxydase (tétramère du *N*-acétylpolypeptide de 301 amino-acides)

rasburicasa

urato oxidasa (tétramero del *N*-acetilpolipeptido de 301 amino-ácidos)

C<sub>1523</sub>H<sub>2383</sub>N<sub>417</sub>O<sub>462</sub>S<sub>7</sub> (monomer)

Ac

SAVKAARYGK	DNVRVYKVHK	DEKTVGQTVY	EMTVCVLLLEG
EIETSYTKAD	NSVIVATDSI	KNTIYITAKQ	NPVTPPELFG
SILGTHFIEK	YNHIHAAHVN	IVCHRWRTRMD	IDGKPPHPSF
IRDSEEKRVN	QVDVVEGKGI	DIKSSLSGLT	VLKSTNSQFW
GFLRDEYTTL	KETWDRILST	DVDATWQWKN	FSGLQEVRSR
VPKFDATWAT	AREVTLKTFA	EDNSASVQAT	MYKMAEQILA
RQQLIETVEY	SLPNKHIFEI	DLSWHKGLQN	TGKNAEVFAP
QSDPNGLIKC	TVGRSSLKSK	L	

**rovelizumabum**

rovelizumab

immunoglobulin G4, anti-(human CD11 (antigen)/integrin β<sub>2</sub>) (human-mouse monoclonal Hu23F2G γ4-chain), disulfide with human-mouse monoclonal Hu23F2G κ-chain, dimer

rovélizumab

immunoglobuline G4, anti-(antigène CD11 humain ou intégrine β<sub>2</sub>) (chaîne γ4 de l'anticorps monoclonal de souris Hu23F2G, humanisé), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris Hu23F2G, humanisé

rovelizumab

inmunoglobulina G4, anti-(antígeno CD11 humano o integrina β<sub>2</sub>) (cadena γ4 del anticuerpo monoclonal de ratón Hu23F2G, humanizado), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón Hu23F2G, humanizado

**sarakalimum**

sarakalim

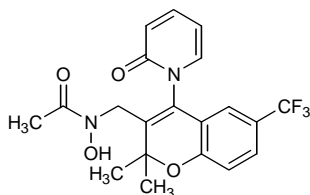
*N*-[[2,2-dimethyl-4-(2-oxo-1(2*H*)-pyridyl)-6-(trifluoromethyl)-2*H*-1-benzopyran-3-yl]methyl]acetohydroxamic acid

sarakalim

*N*-[[2,2-diméthyl-4-(2-oxopyridin-1(2*H*)-yl)-6-(trifluorométhyl)-2*H*-chromén-3-yl]méthyl]-*N*-hydroxyacétamide

sarakalim

ácido *N*-[[2,2-dimetil-4-(2-oxo-1(2*H*)-piridil)-6-(trifluorometil)-2*H*-1-benzopiran-3-il]metil]acetohidroxiácido

C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>

**selamectinum**

selamectin

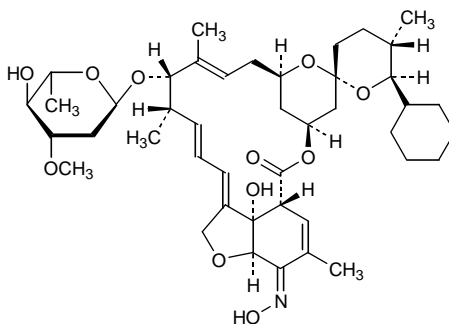
(2aE,4E,5'S,6S,6'S,7S,8E,11R,13R,15S,17aR,20aR,20bS)-6'-cyclohexyl-7-[(2,6-dideoxy-3-O-methyl- $\alpha$ -L-arabino-hexopyranosyl)oxy]-3',4',5',6,6',7,10,11,14,15,20a,20b-dodecahydro-20b-hydroxy-5',6,8,19-tetramethylspiro[11,15-methano-2H,13H,17H-furo[4,3,2-pq][2,6]=benzodioxacyclooctadecin-13,2'-[2H]pyran]-17,20(17aH)-dione 20-oxime

sélemectine

(2aE,4E,5'S,6S,6'S,7S,8E,11R,13R,15S,17aR,20aR,20bS)-6'-cyclohexyl-20b-hydroxy-5',6,8,19-tétraméthyl-7-[(3-O-méthyl-2,6-didésoxy- $\alpha$ -L-arabino-hexopyranosyl)oxy]-3',4',5',6,6',7,10,11,14,15,20a,20b-dodécahydrospiro[11,15-méthano-2H,13H,17H-furo[4,3,2-pq][2,6]benzodioxacyclooctadécène-13,2'-[2H]pyrane]-17,20(17aH)-dione (Z)-20-oxime

selamectina

20-oxima de (2aE,4E,5'S,6S,6'S,7S,8E,11R,13R,15S,17aR,20aR,20bS)-6'-ciclohexil-7-[(2,6-dideoxi-3-O-metil- $\alpha$ -L-arabino-hexopiranosil)oxil]-3',4',5',6,6',7,10,11,14,15,20a,20b-dodecahidro-20b-hidroxi-5',6,8,19-tetrametilespiro[11,15-metano-2H,13H,17H-furo[4,3,2-pq][2,6]=benzodioxacyclooctadecin-13,2'-[2H]piran]-17,20(17aH)-diona

C<sub>43</sub>H<sub>63</sub>NO<sub>11</sub>**sibrotuzumabum**

sibrotuzumab

immunoglobulin G1, anti-(human FAP (fibroblast activation protein)) (human-mouse monoclonal BIBH1  $\gamma$ 1-chain), disulfide with human-mouse monoclonal BIBH1  $\kappa$ -chain, dimer

sibrotuzumab

immunoglobuline G1, anti-(FAP (protéine activant le fibroblaste) humaine) (chaîne  $\gamma$ 1 de l'anticorps monoclonal de souris BIBH1, humanisé), dimère du disulfure avec la chaîne  $\kappa$  de l'anticorps monoclonal de souris BIBH1, humanisé

sibrotuzumab

inmunoglobulina G1, anti-(FAP humano (proteína de activación de los fibroblastos)) (cadena  $\gamma$ 1 del anticuerpo monoclonal de ratón BIBH1), dímero del disulfuro con la cadena  $\kappa$  del anticuerpo monoclonal de ratón BIBH1

**siramesinum**

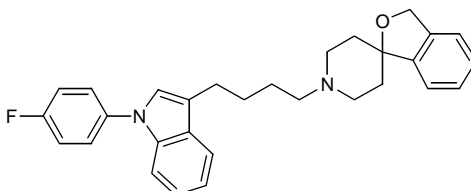
siramesine

1'-[4-[1-(*p*-fluorophenyl)indol-3-yl]butyl]spiro[phtalan-1,4'-piperidine]

siramésine

1'-[4-[1-(4-fluorophényl)-1*H*-indol-3-yl]butyl]spiro[isobenzofurane-1(3*H*),4'-pipéridine]

siramesina

1'-[4-[1-(*p*-fluorofenil)indol-3-il]butil]espiro[ftalan-1,4'-piperidina]C<sub>30</sub>H<sub>31</sub>FN<sub>2</sub>O**sulisatinum**

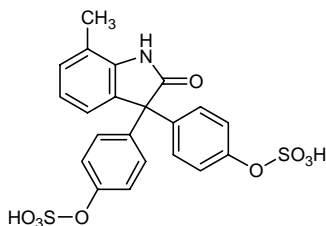
sulisatin

3,3-bis(*p*-hydroxyphenyl)-7-methyl-2-indolinone bis(hydrogen sulfate) (ester)

sulisatine

bis(hydrogénosulfate) de 4,4'-(7-méthyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidène)diphénylyle

sulisatina

bis(hidrogenosulfato) (éster) de 3,3-bis(*p*-hidroxifenil)-7-metil-2-indolinonaC<sub>21</sub>H<sub>17</sub>NO<sub>9</sub>S<sub>2</sub>**talnetantum**

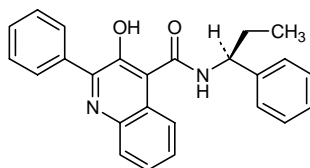
talnetant

*N*-[(*S*)- $\alpha$ -ethylbenzyl]-3-hydroxy-2-phenylcinchoninamide

talnétant

3-hydroxy-2-phényl-*N*-[(1*S*)-1-phénylpropyl]quinoléine-4-carboxamide

talnetant

*N*-[(*S*)- $\alpha$ -etilbencil]-3-hidroxi-2-fenilcinconinamidaC<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>

**tandaminum**

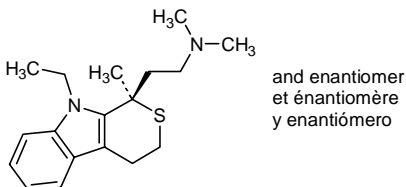
tandamine

1-[2-(diméthylamino)éthyl]-9-éthyl-1,3,4,9-tétrahydro-1-méthylthiopyrano[3,4-*b*]indole

tandamine

2-[(1*RS*)-9-éthyl-1-méthyl-1,3,4,9-tétrahydrothiopyrano[3,4-*b*]indol-1-yl]-*N,N*-diméthyléthylamine

tandamina

1-[2-(diméthylamino)éthyl]-9-éthyl-1,3,4,9-tétrahydro-1-méthylthiopyrano[3,4-*b*]indol $C_{18}H_{26}N_2S$ **teopranitolum**

teopranitol

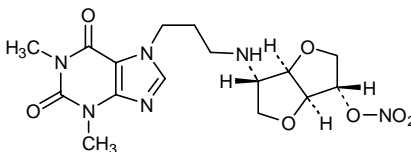
1,4:3,6-dianhydro-2-deoxy-2-[[3-(1,2,3,6-tétrahydro-1,3-diméthyl-2,6-dioxopurin-7-yl)propyl]amino]-L-idoitol 5-nitrate

téopranitol

nitrate de (3*S*,3*aS*,6*S*,6*aR*)-6-[[3-(1,3-diméthyl-2,6-dioxo-1,2,3,6-tétrahydro-7*H*-purin-7-yl)propyl]amino]hexahydrofuro[3,2-*b*]furan-3-yle

teopranitol

5-nitrato de 1,4:3,6-dianhydro-2-desoxi-2-[[3-(1,2,3,6-tétrahydro- 1,3-diméthyl-2,6-dioxopurin-7-il)propil]amino]-L-idoitol

 $C_{16}H_{22}N_6O_7$ **tesmilifenum**

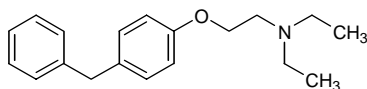
tesmilifène

2-[( $\alpha$ -phényl-*p*-tolyl)oxy]triéthylamine

tesmilifène

2-(4-benzylphénoxy)-*N,N*-diéthyléthylamine

tesmilifeno

2-[( $\alpha$ -fenil-*p*-tolil)oxi]triéthylamina $C_{19}H_{25}NO$ 

**tezosentanum**

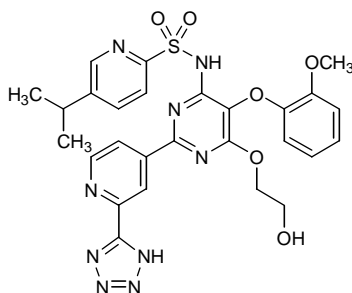
tezosentan

*N*-[6-(2-hydroxyethoxy)-5-(*o*-methoxyphenoxy)-2-[2-(1*H*-tetrazol-5-yl)-4-pyridyl]-4-pyrimidinyl]-5-isopropyl-2-pyridinesulfonamide

tézosentan

*N*-[6-(2-hydroxyéthoxy)-5-(2-méthoxyphénoxy)-2-[2-(1*H*-tétrazol-5-yl)pyridin-4-yl]pyrimidin-4-yl]-5-(1-méthyléthyl)pyridine-2-sulfonamide

tezosentano

*N*-[6-(2-hidroxietoxi)-5-(*o*-metoxifenoxi)-2-[2-(1*H*-tetrazol-5-il)-4-piridil]-4-pirimidinil]-5-isopropil-2-piridinasulfonamidaC<sub>27</sub>H<sub>27</sub>N<sub>9</sub>O<sub>6</sub>S**ticarcillinum**

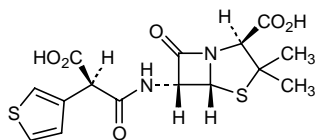
ticarcillin

*N*-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-6-yl)-3-thiophenemalonamic acid

ticarcilline

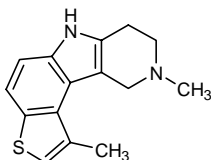
acide (2*S*,5*R*,6*R*)-6-[[2(*R*)-carboxy(thiophén-3-yl)acétyl]amino]-3,3-diméthyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylique

ticarcilina

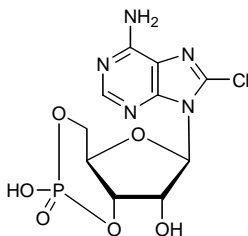
ácido *N*-(2-carboxi-3,3-dimetil-7-oxo-4-tia-1-azabicyclo[3.2.0]hept-6-il)-3-tiofenomalonámicoC<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>

**tienocarbium**

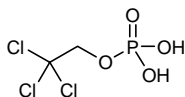
tienocarbine	7,8,9,10-tetrahydro-1,9-dimethyl-6 <i>H</i> -pyrido[4,3- <i>b</i> ]thieno[3,2- <i>e</i> ]indole
tiénocarbine	1,9-diméthyl-7,8,9,10-tétrahydro-6 <i>H</i> -pyrido[4,3- <i>b</i> ]thiéno[3,2- <i>e</i> ]indole
tienocarbina	7,8,9,10-tetrahydro-1,9-dimetil-6 <i>H</i> -pirido[4,3- <i>b</i> ]tieno[3,2- <i>e</i> ]indol
	$C_{15}H_{16}N_2S$

**tocladesinum**

tocladesine	8-chloroadenosine 3',5'-cyclic phosphate
tocladésine	3',5'-hydrogénophosphate cyclique de 8-chloroadénosine
tocladesina	3',5'-hidrógenofosfato cíclico de 8-cloroadenosina
	$C_{10}H_{11}ClN_5O_6P$

**triclofosum**

triclofos	2,2,2-trichloroethyl dihydrogen phosphate
triclofos	dihrogénophosphate de 2,2,2-trichloroéthyle
triclofós	dihidrógenofosfato de 2,2,2-tricloroetilo
	$C_2H_4Cl_3O_4P$





**triflocinum**

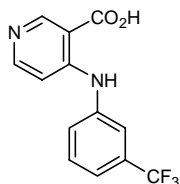
triflocin

4-( $\alpha,\alpha,\alpha$ -trifluoro-*m*-toluidino)nicotinic acid

triflocine

acide 4-[[3-(trifluorométhyl)phényl]amino]pyridine-3-carboxylique

triflocina

ácido 4-( $\alpha,\alpha,\alpha$ -trifluoro-*m*-toluidino)nicotínico $C_{13}H_9F_3N_2O_2$ **trimecainum**

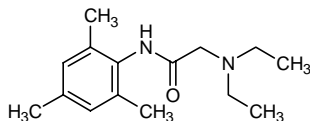
trimecaine

*N*-( $\alpha$ -diethylaminoacetyl)-2,4,6-trimethylaniline

trimécaïne

2-(diéthylamino)-*N*-(2,4,6-triméthylphényl)acétamide

trimecaína

*N*-( $\alpha$ -diétilaminoacetil)-2,4,6-trimetilanilina $C_{15}H_{24}N_2O$ **troxacitabinum**

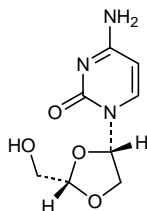
troxacitabine

(-)-1-[(2*S*,4*S*)-2-(hydroxyméthyl)-1,3-dioxolan-4-yl]cytosine

troxacitabine

(-)-4-amino-1-[(2*S*,4*S*)-2-(hydroxyméthyl)-1,3-dioxolan-4-yl]pyrimidin-2(1*H*)-one

troxacitabina

(-)-1-[(2*S*,4*S*)-2-(hidroximetil)-1,3-dioxolan-4-il]citosina $C_8H_{11}N_3O_4$ 

**zolazepamum**

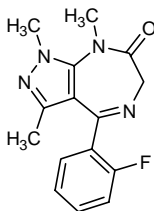
zolazepam

4-(*o*-fluorophenyl)-6,8-dihydro-1,3,8-trimethylpirazole[3,4-*e*][1,4]diazepin-7(1*H*)-one

zolazépam

4-(2-fluorophényl)-1,3,8-triméthyl-6,8-dihydropyrazolo[3,4-*e*][1,4]diazépin-7(1*H*)-one

zolazepam

4-(*o*-fluorofenil)-6,8-dihidro-1,3,8-trimetilpirazolo[3,4-*e*][1,4]diazepin-7(1*H*)-onaC<sub>15</sub>H<sub>15</sub>FN<sub>4</sub>O

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

**Recommended International Nonproprietary Names (Rec. INN): List 38**

**Dénominations communes internationales recommandées (DCI Rec.): Liste 38**

**Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 38**

*(WHO Drug Information, Vol. 11, No. 3, 1997)*

p. 166 **faralimomabum**

faralimomab

*replace the description by the following:*

immunoglobulin G1, anti-(human interferon type I receptor) (mouse monoclonal 64G12  $\gamma$ 1-chain), disulfide with mouse monoclonal 64G12 light chain, dimer

faralimomab

*remplacer la description par la suivante:*

immunoglobuline G1, anti-(récepteur humain des interférons de type I) (chaîne  $\gamma$ 1 de l'anticorps monoclonal de souris 64G12), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris 64G12

faralimomab

*sustitúyase la descripción por la siguiente:*

inmunoglobulina G1, anti-(receptor humano de los interferones del tipo I) (cadena  $\gamma$ 1 del anticuerpo monoclonal de ratón 64G12), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón 64G12

p. 169 **keliximab**

keliximab

*replace the description by the following:*

immunoglobulin G1, anti-(human CD4 (antigen)) (human-macaca monoclonal CE9.1  $\gamma$ 1-chain), disulfide with human-macaca monoclonal CE9.1  $\lambda$ -chain, dimer

kéliximab

*remplacer la description par la suivante:*

immunoglobuline G1, anti-(antigène CD4 humain) (chaîne  $\gamma$ 1 de l'anticorps monoclonal chimérique homme-macaque CE9.1), dimère du disulfure avec la chaîne  $\lambda$  de l'anticorps monoclonal chimérique homme-macaque CE9.1

keliximab

*sustituyase la descripción por la siguiente:*

inmunoglobulina G1, anti-(antígeno CD4 humano) (cadena  $\gamma$ 1 del anticuerpo monoclonal hombre-macaco CE9.1), dímero del disulfuro con la cadena  $\lambda$  del anticuerpo monoclonal quimérico hombre-macaco CE9.1

p. 172 **lintuzumabum**

lintuzumab	<i>replace the description by the following:</i> immunoglobulin G1, anti-(human CD33 (antigen)) (human-mouse monoclonal HuM195 $\gamma$ 1-chain), disulfide with human-mouse monoclonal HuM195 $\kappa$ -chain, dimer
lintuzumab	<i>remplacer la description par la suivante:</i> immunoglobuline G1, anti-(antigène CD33 humain) (chaîne $\gamma$ 1 de l'anticorps monoclonal de souris HuM195, humanisé), dimère du disulfure avec la chaîne $\kappa$ de l'anticorps monoclonal de souris HuM195, humanisé
lintuzumab	<i>sustituyase la descripción por la siguiente:</i> inmunoglobulina G1, anti-(antígeno CD33 humano) (cadena $\gamma$ 1 del anticuerpo monoclonal hombre-ratón HuM195), dímero del disulfuro con la cadena $\kappa$ del anticuerpo monoclonal hombre-ratón HuM195

**Recommended International Nonproprietary Names (Rec. INN): List 41****Dénominations communes internationales recommandées (DCI Rec.): Liste 41****Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 41***(WHO Drug Information, Vol. 13, No. 1, 1999)*p. 53 **satumomabum**

satumomab	<i>replace the description by the following:</i> immunoglobulin G1, anti-(human tumor-associated glycoprotein 72) (mouse monoclonal B72.3 $\gamma$ 1- chain), disulfide with mouse monoclonal B72.3 light chain, dimer
satumomab	<i>remplacer la description par la suivante:</i> immunoglobuline G1, anti-(glycoprotéine 72 humaine associée aux tumeurs) (chaîne $\gamma$ 1 de l'anticorps monoclonal de souris B72.3), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris B72.3
satumomab	<i>sustitúyase la descripción por la siguiente:</i> inmunoglobulina G1, anti-(glicoproteína 72 humana asociada a los tumores) (cadena $\gamma$ 1 del anticuerpo monoclonal de ratón B72.3), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón B72.3

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

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

Les textes de la *Procédure à suivre en vue de choix de dénominations communes internationales recommandées pour les substances pharmaceutiques* et des *Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques* ont été publiés avec la liste 81 des DCI proposées et seront, à nouveau, publiés avec la prochaine liste des DCI proposées.

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