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# WHO DRUG

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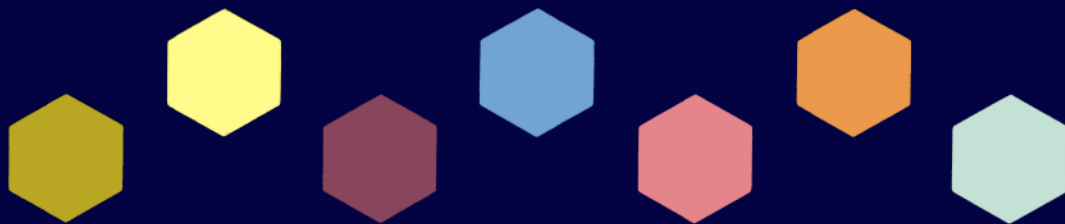
# INFORMATION

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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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## Generic drugs: the hidden issues of quality and cost

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As we move into the new century, a widening economic gap separating rich and poor countries confronts the public health sector. The challenge lies in providing an acceptable level of health care at a reasonable cost for populations in the developing world — including the ever growing number of displaced communities — who are left behind in the economic race. Although the manufacture of generic essential drugs offers a practical way of achieving this aim, the quality of these products tends to be jeopardized by overriding considerations of cost. Assuring the quality and safety of essential drugs is paramount to achieving effective implementation of national drug policies, pharmaceutical programmes and humanitarian relief operations (1).

Quality assurance of medicines is a feature of all procedures and processes employed throughout the production chain: whether development, manufacture, monitoring, distribution or final use. Unfortunately, it is not possible to evaluate the quality of products merely through the provision of a compliance certificate for good manufacturing practices (GMP) or from the results of a quality control test. The specific criteria of quality control each confirm the validity of different stages of manufacture and process control points. Quality thus has to be built in at each critical stage of the production process, the end result of which is the production of a medicinal product fit for its purpose and use (2).

Regulatory information reflecting the manufacturing status and provenance of imported medicines, such as that provided through the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, is essential but will only be of use if the drugs are approved for

marketing in the country of origin. Developing countries should also evaluate their own particular needs and standards in relation to the national and international situation. International open tenders may seem to offer the advantage of favouring competition and increasing the possibility of access to essential drugs by lowering the price, but the principal drawback to this option is that quality is not always given the priority it deserves over cost considerations.

The WHO Model List of Essential Drugs and the underpinning concept were developed in the 1970s to stimulate the rational availability of medicines in developing countries. Essential drugs are those that meet the health needs of the majority of the population; they should be available at all times in adequate amounts and in appropriate dosage forms. The WHO Model List of Essential Drugs enables countries to identify priorities and make their own drug selection.

The term generic drug has been legally defined in France as "a copy of an original medicinal drug whereby production and marketing are made possible by the expiry of the patent covering the innovator product" (3). It is further described in the Public Health Code as "a specialty which is essentially similar and presents the same qualitative and quantitative composition of active ingredients, the same dosage form, and bioequivalence as the original product" (4).

In the manufacture of generic drugs, the three concepts of quality, safety and efficacy apply to generics in the same way as they do to the innovator product. Regulatory authorities should require that documentation supporting a generic pharmaceutical product meets the following criteria:

- manufacture (GMP) and quality control;
- product characteristics and labelling; and
- therapeutic equivalence.

Reasonable assurance must be provided that the generic drug is clinically interchangeable with the nominally equivalent marketed product (5). When the therapeutic activity of the active ingredient is known and correctly reproduced, clinical studies are unnecessary although bioequivalence data will be required. Safety data are provided through refer-

ence to the literature, and can be supported by a profile listing impurities and degradation products and stability studies. It is clear that such principles will be meaningless if quality raw materials are not used: whether as active ingredients, excipients, accessory materials, manufacturing intermediaries or primary packaging.

For a generic drug, the quality of the active ingredient takes on great importance. Almost 90% of essential drugs contained in the WHO Model List are off-patent and available in generic form. Raw materials can also be generic, and their cost can vary considerably depending on labour costs, quality of the facilities, reputation of the supplier, quality and purity processes applied to the material. Professional judgement must be exercised in the purchase of such materials because compliance with pharmacopoeial specifications may not necessarily indicate good quality. The price of the raw material often represents more than 50% of the industrial cost price of a generic, which may lead manufacturers to target a lower quality raw material in their efforts to offer competitively attractive prices.

### **The quality of raw materials**

The quality of the raw material is unfortunately a parameter that is rarely taken into account in granting export permits for generics if they are not licensed for sale on the domestic market, and rarely is this parameter considered important by international purchasers.

Equally, the method of drug synthesis is an important consideration which will enhance the quality of the drug. Pharmacopoeial monographs are based on the latest synthesis procedures where impurities, related substances and subproducts of degradation are well defined. A change in the method of synthesis must therefore be followed by a suitable adaptation to the process control, which is not always the case. The purchaser of generic drugs should be aware that conducting analyses which rely solely on pharmacopoeial monographs may not necessarily indicate the risk of toxicity from degradation products or impurities in the event that the method of synthesis has been changed (1).

The raw material market is extensive and a great choice of products is available worldwide. The following quality problems may be encountered when suppliers are located in different parts of the world:

- Geographical distance makes it difficult to locate or get information on the actual suppliers. The practice of using brokers or commercial intermediaries to facilitate administration and communication tends to break the bond between supplier-client. Additionally, a broker may be dealing with several manufacturers who are providing different components of one finished product.
- It may be difficult to locate the manufacturer of the raw material and obtain details of the synthesis procedure (profile of impurities and degradation products).
- Even when the manufacturer is known, distances make it both difficult and costly to audit.
- Production may be held up if suppliers are changed, if a source is suddenly cut or if the raw material is of a different standard and requires adjustments to the product formula.

Greater vigilance is therefore needed to assure quality when suppliers are situated at great distances. None the less, some countries have good systems and testing facilities in place.

### **Excipients**

Since excipients often make up the bulk of a formulation, the same requirements and quality criteria should apply. The great diversity and use of excipients throughout other industries makes it of paramount importance to establish their purity and chemical and pharmaceutical quality. Tests should include a rheological study, solubility and kinetics of dissolution, determination of specific surface, establishment of a granulometric curve and shredding.

Any change in the excipient may cause variations in bioavailability and produce toxic phenomena or allergies. Several examples of such variations have been encountered with fatal consequences for the patient. Recommendations on the control and safe trade in starting materials for pharmaceuticals have been published by WHO (6). Certificates of analysis and vendor qualification should comply with guidelines of the International Pharmaceuticals Excipient Council (IPEC) (7).

### **Packaging/containers**

It must be remembered that the container will also come into direct contact with the pharmaceutical product. Careful consideration should therefore be given to the material and composition of the container. The manufacturer must clearly communi-

cate medical grade specifications because the supplier of the container does not necessarily know the level of quality requirements.

In tropical countries, plastic containers, for example, may not be recommended due to interactions between container/content or between powders and container walls. Adsorption of plastic materials will also modify the stability of the product. Intolerance reactions or toxic phenomena can result from the stability modifications of the product following a shift in content constituents and adherence to the sides of the container.

### Stability studies

The stability of a drug is evaluated through its ability to maintain chemical, physical, microbiological and biopharmaceutical properties within specified limits during the entire extent of its validity. There are two types of stability studies (i) accelerated degradation studies meant to increase the speed of physical or chemical degradation of a drug by subjecting it to extreme storage conditions and (ii) stability studies in real time. This would be an experimental study of the chemical, physical, biological and microbiological characteristics of a drug during its period of validity, foreseen use and beyond, under real storage conditions as encountered in the market for which it is intended.

Tests for high humidity conditions are particularly important because the risk of degradation of semi-permeable packaging is much higher. Evidence of stability studies is one of the most important parameters to be considered for supplies because:

- climatic conditions in many developing countries are very different to those in temperate climates which serve as a reference for studies.
- poor stability may lead to drugs becoming toxic or increasingly inactive.
- stability cannot be evaluated through quality control of the delivered final product.

### Bioequivalence

Bioequivalence refers to the speed and absorption by the body of the pharmaceutical, the active principle or its therapeutic fraction. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and if the rate and extent of availability after administration in the same molar dose is essentially the same. Different methods may be used to demonstrate this:

- comparative bioavailability studies in humans consisting of titration of the active ingredient or one or several of its metabolites in an accessible biological liquid such as plasma, blood or urine;
- comparative pharmacodynamic studies in humans;
- comparative clinical trials; and
- in vitro dissolution tests.

### Means available to evaluate drugs

In many developing countries, central purchasing depots have been created and rely on a system of open tendering. However, if this allows drugs to be obtained at a very low price, it does not address the need for quality products. Further shortcomings to this kind of method include:

- numbers of suppliers in all countries worldwide will respond to open tenders.
- there is a lack of quality control laboratories in developing countries. Where these are present, they suffer from underresourcing in staff, material and finances.
- a large proportion of drugs on open tender do not have a marketing authorization in the country of manufacture.
- even if drugs do have a marketing authorization, the requirements for authorization may differ between countries. Furthermore, a product may be marketed in packaging which will change when supplied in bulk to developing countries or humanitarian aid programmes. For example, products which are supplied in 28-day patient packs with information leaflets are supplied in bulk packs of maybe 1000 tablets.
- export certificates may not conform to the requirements of the importer and verification of the file with the actual practices of the manufacturer are almost always precluded.

Three approaches are available for the evaluation of drugs:

1. Proof of quality control at various stages, i.e. receipt of raw material, in-production process, and finished product.

2. Audit of the manufacturer to include process validation of manufacturing and quality assurance.

3. Registration of the drug in the country of manufacture and in the importing country. Where a product is not for local use, the registration authority must ensure that the same laws and regulations which apply to the manufacture and sale of products on the local market also apply to products to be exported/imported.

An association of these approaches will strengthen the objectives of providing quality drugs at the lowest price.

#### **Hidden cost**

Most buyers of healthcare and medicinal products will be aware of the usual implicit hidden costs such as freight costs. Experience will urge them to ask for a quotation of these costs to be included with the goods to be purchased. These basic costs should be included as part of budgeting and forecasting of need.

One ambivalent hidden cost is that of purchasing poor quality medicinal products. Suppliers offering the lowest prices often win the tender, particularly where the country is self-financing, or is directly controlling donated funds. Although there is always a desire to stretch the funds to cover as wide a need as possible, this should not compel buyers to forego the important issue of product quality. Poor performance of procured drugs is not just costly in financial terms, but in the number of patients who may be affected by consuming poor quality or ineffective products. It is important that buyers are aware of the wider implications of their function: that of saving human lives and not just saving money. If goods are purchased from suppliers and manufacturers with a validated track record, this would guarantee safeguards which low-cost suppliers are unable to provide.

#### **Proposed strategy**

The first step should be to avoid calls for open tenders, even where stringent guidelines are in operation, and to prefer limited calls for tenders from a restricted list of prequalified suppliers (1). In this event quality assurance factors would apply equally to distributors and manufacturers.

#### **Safety and quality assurance**

A systematic audit of the manufacturer should be made through documentary evaluation via the site

master file or effective auditing according to GMP. This must stress process validation and competence to manufacture products fit for their intended purpose.

#### **Registration in the country of origin**

Any manufacturer not applying for a marketing authorization in the country of origin should nonetheless provide sufficient elements of the master file to complete an evaluation. The importing country should evaluate this file in line with its own criteria for bioequivalence, expected uses, medical information, labelling and sampling.

The exporting country should be able to assure drug quality through an evaluation of the information contained in the master file and be able to inspect the manufacturer on that basis. Furthermore, it should be the responsibility of the relevant authorities to ensure that there is a clear and qualitative difference between a manufacturing licence for medicines and healthcare products and the licence for non-medical products.

#### **Mutual recognition of inspections**

Inspections should be promoted to ensure conformity with the reference data. Developing countries should be encouraged to adhere to the Pharmaceutical Inspections Convention (PIC) treaty.

In conclusion, quality assurance is an important tool in the control and evaluation of drugs. This is the only approach that can currently provide assurance that the product is safe for human use. However, this approach has a price and competition for supplies needs to take place among suppliers known to apply quality assurance procedures. Furthermore, manufacturers must collaborate more fully with drug regulatory authorities to ensure quality when drugs are exported. This will ensure that drug quality in developing countries will be more standardized and rational.

If it is important to ensure that the demands made on manufacturers and suppliers of quality medicinal products are met, it is equally important that the authorities demanding the drugs accept the costs implied in assuring quality. It is a fallacy to believe that quality production and assurance can be achieved at no great investment. The following factors need to be understood in the drug procurement process:

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- Quality has a cost;
  - Procurement from non-validated suppliers carries a health risk for the patient;
  - Cheap medical products also carry a health risk;
  - Procurement should be restricted to selected suppliers, not through open tender;
  - Suppliers should be validated according to a country's defined quality supply standards
  - In the absence of local standards, use those promoted by WHO.
  - Conformity with international standards, as promoted by WHO, should be demanded.

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# Personal Perspectives

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## Pharmaceutical policies and regulatory control

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In an ideal world, all countries would have abundant medicines which are safe, effective and of good quality and regulated by a competent national drug regulatory authority respected for its expertise, professionalism, efficiency, independence, and integrity. Policy would be made confidently on the basis of scientific criteria by the national drug regulatory authority, as would the decisions taken by any government-based authority responsible for considering and negotiating the costs of medicines.

Cost controls would be firm but at the same time respectful of the rights, including intellectual property rights, of the pharmaceutical industry. Of the total national expenditure on health — which itself would be competently controlled — a fixed 6–10% would be spent on pharmaceuticals. The health budget would be a little greater than 5% of the gross national product. The development of local industry would be encouraged and appropriately supported, and the national drug regulatory authority would actively encourage and stimulate local enterprise in the production of essential drugs with emphasis on appropriate standards.

There would be a strong focus on the manufacture and rational use of generic medicines, particularly those that are included in the national or WHO Model List of Essential Drugs. There would also be uninterrupted supply and access to essential medicines, including vaccines and birth control measures. New drug development, where it is relevant to the health of the country, would be served by the conduct of clinical trials, approved in advance by the national drug regulatory authority as well as by the institutional review board at those sites where studies are conducted. The health professionals and the general public would be well informed about the medicines they take, and they would

have access to independent and authoritative information should they require it. As a result, the public would have confidence in the medicines available to them and, by extension, would be supportive of the health system.

Such an apparently straightforward and reasonable set of circumstances would seem necessary. However, this situation scarcely exists anywhere and certainly not in the developing world. It may be time for an objective evaluation of the reality.

### The current situation

World Bank health reports published in 1993 and 1994 covering sub-Saharan Africa showed that more than 85% of funding allocated to acquisition of pharmaceuticals in the region was lost through waste and inefficiency. The reports found that at every level — whether in procurement, distribution, rational and informed use, or patient compliance — any real value which is targeted to advantage the patients themselves is eroded before it reaches the consumer. Donors are working at cross-purposes: and in so doing undermining their own programmes as well as those of others; national policies fail to consider important principles necessary for the conduct of a sound national pharmaceuticals policy; and important partners — including the pharmaceutical industry — work in disharmony.

Following an analysis of the report, it was concluded that a sound pharmaceuticals policy is achievable only if:

- The issues are adequately understood and there is political will to address them.
- International organizations, The World Bank, UNICEF, WHO, and nongovernmental organizations accept a shared responsibility and recognise their considerable potential to contribute to sound drug policies in the countries that they support.
- The national drug regulatory authority is fully supported and is acknowledged as being crucial to the success of these policies.

### **The role of the national drug regulatory authority**

A description has already been provided of the expected role of the national drug regulatory authority. Words such as sound, independent, competent, reasonable, professional and efficient reflect their required characteristics. A budget should be available of 1 US dollar per 1000 dollars of national turnover in pharmaceuticals. The activities of the authority should be independent of any cost control initiatives, but the national drug regulatory authority decisions and advice should inform the latter. All decisions and contributions to policy should be underpinned by good science and a thorough and first-hand appreciation of clinical medicine. The national drug regulatory authority needs to act independently of government and industry in its decision-taking to ensure that the drugs available and the way they are used are suitable for local conditions and are appropriate. It should be supported by adequate yet simple systems of postmarketing surveillance, adverse drug event monitoring, and independent drug information. It should be thoroughly underpinned by a sound and appropriate legal system while consistent with national and regional policy and legislation. All its actions should be directed to promoting public health, and should be readily and openly explicable as such.

### **The national drug regulatory authority's contribution to research**

A research agenda should be developed taking into consideration the following issues:

- Definition of the role of a national drug regulatory authority in the developing world, and of the international drug regulatory environment, with special reference to new drug development, research, access, and affordability of essential medicines for important and common diseases.
- The special case of tropical disease policies in endemic areas of the world, with particular reference to research, development and deployment of drugs, the nature of policy implementation, impediments to progress, and the costs of therapy and prevention.
- Consolidation of the respective roles of the pharmaceutical industry, United Nations agencies, nongovernmental organizations, bilateral agreements, ministries of health, and the communities themselves in providing essential medicines for important and common diseases which affect the country or region. This includes research and

development of novel medicines for diseases such as malaria, viral infections, and tuberculosis.

- A developing world perspective of scientific, ethical and intellectual property issues pertaining to the use of traditional medicines and herbal preparations.
- An examination of alternatives to conventional industry-based approaches to new drug development and marketing.

### **Promoting essential standards for new drug development**

An important role exists for the national drug regulatory authority to support and promote standards for new drug development to combat diseases such as malaria and tuberculosis and to support the manufacture of essential generic medicines. The following points will need consideration.

- There can be no compromise on basic standards of quality, safety and efficacy. After all, unsafe and ineffective medicines are costly and dangerous. The same applies to poor quality medicines.
- Fast track approval of important new products should not compromise any of these standards. Marketing of needed medicines can further be expedited by processes of mutual recognition between regulatory agencies and acceptance of decisions taken by other trusted agencies.

To meet these expectations, an expanded role and vision for key national drug regulatory authorities is beginning to emerge. This is evidenced by the recent WHO initiative to develop rectal artesunate for malaria in children. The US Food and Drug Administration, the UK Medicines Control Agency and the Swiss Intercantonal Office for the Control of Medicines have each agreed to deliver accelerated marketing approval in the interests of public health — a perspective which goes well beyond national responsibilities.

The establishment of the International Conference on Harmonization (ICH) presents a challenge to international public health objectives. The declared structure and purpose of ICH — which is made up of representatives of drug regulatory authorities of the European Union, Japan and USA and the pharmaceutical industry — does not take particular account of the special needs of the developing world. Standards have been set through ICH guidelines which, although excellent and helpful in devel-



oping innovative new medicinal products, have been interpreted as rules. Beyond an observer status, WHO and countries not included in the ICH are effectively excluded. In a sense, ICH is counter-productive to approaches for development of critically required new drugs by groups such as WHO and the non-ICH countries.

It is a further challenge to this new public health perspective that national drug regulatory authorities must also foster the development of local industry in a manner that promotes public confidence, supports excellent essential standards and is free of special arrangements between government and industry.

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## Reports on Individual Drugs

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### New use for artemether in schistosomiasis

Evidence suggests that artemether could have a major impact on the control of schistosomiasis. Since the early 1990s, evidence has been accumulating to support the prophylactic use of the artemesinins (artesunate and artemether) against *Schistosoma japonicum* infections. In addition to their well-known effect against the malaria parasite, these drugs also kill juvenile (schistosomula) forms of schistosomes. The artemesinins have now been shown to be effective against *S. mansoni* in animals and humans (1–3) while laboratory work on *S. haematobium* has been completed and field studies are under way with support from The WHO/World Bank/UNDP Special Programme for Research and Training in Tropical Diseases. Since these species are responsible for the majority of schistosome infections and are predominant in Africa, the outcome could be a major impact on control of schistosomiasis.

In a study on the use of artemether in *S. mansoni* infections in hamsters and mice, very few animals developed schistosomiasis when treated during the first month after infection and the parasite was particularly susceptible between weeks 3 and 4 (2). Single treatment with artemether gave cure rates of up to 82%, while follow-up therapy raised this to almost 100%. In animals with repeated infection, representing more closely the situation in nature, there was almost complete protection. Previous studies using *S. mansoni* had shown no effect of artemether, but had concentrated on the adult parasite, not the schistosomula. A clinical trial in Côte d'Ivoire has confirmed this potential of artemether to significantly reduce *S. mansoni* infection (3).

Artemether is already in use as an antimalarial and has a good safety profile. Praziquantel is a drug that has been used against schistosomiasis for more than two decades. It is safe and effective but has to be given repeatedly due to rapid reinfection. Combined treatment with the two drugs has been studied in rabbits infected with *S. japonicum* parasites at different developmental stages, represent-

ing the natural situation in areas where infection occurs throughout the year. Using this animal model, combined treatment significantly increased the single effects of the individual drugs (4).

Praziquantel and artemether affect schistosomes at different developmental stages and work surprisingly well together in this respect. Praziquantel affects the adult parasites, but also the very young stage during the first day in the host: times at which artemether has no effect. Conversely, artemether affects the juvenile stages except immediately after infection, thereby blocking the development of the adult stages.

Whether the two drugs can actually be administered at the same time and whether there is any pharmacological interaction remains to be investigated. Since artemether blocks the development of adult worms, even a limited period of treatment with this drug could theoretically eliminate parasite transmission in certain areas. Praziquantel on the other hand, cannot stop the infection, but remains the cornerstone of control since it retards the development of morbidity. The different species of parasite are sensitive to artemether for slightly different lengths of time. *S. japonicum* is susceptible up to 21 days of age, while *S. mansoni* responds to the drug for up to 42 days, and *S. haematobium*, due to the longer time it takes to develop into the adult, has an even longer period of sensitivity.

In areas that are endemic for both malaria and schistosomiasis, the use of artemether is precluded because of the possibility that its regular use might contribute to the development of resistance of the malaria parasite. On the other hand, the drug could safely be recommended for use in schistosomiasis in areas where there is no regular malaria transmission (e.g. in China, southern Brazil, countries north of the Sahara, parts of the Middle East). Of particular interest are those areas where human schistosomiasis has been very much reduced, but final eradication has proved difficult such as Saudi Arabia or Morocco and where artemether could contribute to breaking its transmission. It could also play an important role in the control of schistosomiasis in Egypt.

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## Clopidogrel and thrombotic thrombocytopenic purpura

The antiplatelet drug clopidogrel is a new thienopyridine derivative with a mechanism of action and chemical structure similar to ticlopidine. The estimated incidence of ticlopidine-associated thrombotic thrombocytopenic purpura is 1 per 1600 to 5000 patients treated (1–4). Thrombotic thrombocytopenic purpura is a life-threatening, multisystem disease characterized by thrombocytopenia, microangiopathic haemolytic anaemia, fever, neurologic changes and renal abnormalities. It can result in multiorgan dysfunction or death (5, 6).

During phase III clinical trials of clopidogrel carried out in 20 000 subjects, no cases of thrombotic thrombocytopenic purpura, neutropenia, adverse skin or gastrointestinal effects were observed. As a result, this more favourable safety profile led to clopidogrel replacing ticlopidine in clinical practice for the prevention of stroke and thrombosis in patients who have received coronary-artery stents and in patients with peripheral vascular disease or acute cardiac ischaemia (7, 8). However, two postmarketing reports of cases of thrombotic thrombocytopenic purpura have been received by the Food and Drug Administration (FDA). A recent report has now been published which has set out to determine the clinical characteristics, interval between treatment and onset of disease, response to treatment, outcomes and laboratory findings related to these cases (9).

Between 1998 and 2000, through active surveillance, eleven cases of thrombotic thrombocytopenic purpura were identified in patients treated with clopidogrel. The 11 patients ranged in age from 35 to 70 years and 6 patients were women. Platelet counts were less than 20 000 per cubic millimetre in 10 patients and haematocrit values were less than 27% in 8 patients. Seven patients had neurological changes, including disorientation, slurred speech, confusion, aphasia, and coma. Four patients had renal insufficiency and two patients had evidence of acute liver injury. All patients underwent plasma exchange, with resolution of symptoms and laboratory abnormalities occurring after a median of 8 plasma exchanges. One patient died.

The features of thrombotic thrombocytopenic purpura in patients who had received ticlopidine can be contrasted with those who had received clopidogrel, despite marked differences in the methods used to ascertain cases. For example, 95% of cases reported among ticlopidine-treated patients occurred after 2 to 12 weeks of treatment, whereas all but one of the cases among clopidogrel-treated patients occurred within 2 weeks of initiation. Although the study was unable to ascertain the frequency of thrombotic thrombocytopenic purpura in patients receiving clopidogrel, physicians should be made aware of the possibility of this syndrome when initiating treatment. The possibility that cholesterol-lowering drugs, which were taken concomitantly by 5 patients, may have adverse pharmacological interactions in some patients deserves further study.

For all new drugs, a comprehensive assessment of safety requires postmarketing surveillance. Ticlopidine-associated thrombotic thrombocytopenic purpura was not widely recognized until 7 years after the drug was approved by the FDA despite its use in several million patients (1–4). In the United States, the occurrence of adverse effects is monitored by the FDA. However, only 1 to 10% of all adverse effects are reported, and the majority of these come from drug companies.

A more aggressive approach is called for in post marketing surveillance of new drugs, particularly if there is a reason — as in the similarity between ticlopidine and clopidogrel — to suspect that there may be adverse effects. A means of funding an evaluation of a drug's safety after it is approved and marketed needs to be developed that is independent of the FDA and drug manufacturers (10).

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### Statins: benefit in cardiovascular disease extended to bone fracture

Two recent reports have shown that 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) might substantially reduce the risk of bone fractures in addition to reducing blood cholesterol levels and risk of cardiovascular disease (1, 2). According to the studies, statins predominantly seem to increase bone formation.

Two population-based, case-control studies were carried out to determine the risk of fractures and risk of hip fractures in elderly patients following exposure to lipid-lowering drugs. The results showed that women and men taking any kind of statins had a lower risk of fractures than those who were not. The reductions were statistically significant: 45% lower risk of all types of fractures and 88% lower risk of hip fractures were achieved in the first study and a 71% reduction in risk of hip fracture in the second. Both studies showed that use of nonstatin cholesterol-lowering drugs was not associated with a reduction in risk of fractures.

The first trial, to demonstrate whether exposure to statins, fibrates or other lipid-lowering drugs is associated with reduced bone fracture risk was carried out in a base population of 91 611 individuals aged at least 50 years (1). Nested case-control analysis identified 3940 case patients who had a bone fracture and 23 379 controls. After controlling for body mass index, smoking, number of physician visits, and corticosteroid and estrogen use, current use of statins was associated with a significantly reduced fracture risk (adjusted odds ratio, 0.55; 95% confidence interval, 0.44–0.69) compared with non-use of lipid-lowering drugs. Current use of fibrates or other lipid-lowering drugs was not related to a significantly decreased bone fracture risk (adjusted OR, 0.87; 95% CI, 0.70–1.08 and adjusted OR 0.76; 95% CI, 0.41–1.39 respectively).

The second trial, a case-controlled study to determine whether the use of statins is associated with reduced hip fracture risk in elderly patients (2), was carried out in a total of 6110 US residents aged at least 65 years. Case patients underwent surgical repair of a hip fracture in 1994. Control patients were identified at a ratio of 4:1 and frequency matched to case patients for age and sex. Use of statins in either the prior 180 days or prior 3 years was associated with a significant reduction in the risk of hip fracture, even after controlling for variables such as race, insurance status, psycho-active medications, estrogen and thiazide use, ischaemic heart disease, cancer and diabetes mellitus. Clear relationships were observed between the degree of reduction in hip fracture risk and the extent of statin use; there was no such relationships with nonstatin lipid-lowering agents. After adjusting for extent of statin use in the prior 3 years, current use was associated with a 71% reduction in risk (adjusted OR, 0.29; 95% CI, 0.10–0.81).

However, statins that are currently approved for lowering cholesterol and reducing the risk of cardiovascular disease may not be the most effective drugs for increasing bone mass. These agents preferentially affect HMG-CoA reductase in the liver, not bone, and they have been selected and developed for their effects on circulating cholesterol concentrations. Perhaps intermittent use of high doses will stimulate bone formation more effectively than daily use of a standard dose. Research is needed to find formulations, doses, and routes of administration that optimize the effects of statins on bone without diminishing their cardiovascular benefits (3).

Because of the potential public health impact, it is important to demonstrate the effectiveness and safety of drugs that may be widely used. Even though statins seem to be quite safe (4) recommendations about prescription of statins to prevent fractures must await the results of rigorous trials to confirm the present findings. In the meantime, patients with osteoporosis should continue to be treated with agents that have been proven to reduce the risk of fractures, such as bisphosphonates.

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## Cholera: can rehydration therapy be improved?

Diarrhoeal diseases rank high among the leading causes of mortality in African, Eastern Mediterranean and South-East Asian countries causing annually more than 2.5 million deaths (1). It is estimated that at least 4 billion episodes of diarrhoea occur each year. At present, oral rehydration therapy provides the mainstay of effective interventions, preventing from one to two million deaths each year, mainly in children.

Cholera is a killer disease with pandemic potential. It is endemic in Asia and recent epidemics have been reported in Africa and Latin America. Sporadic cases have occurred even in industrialized countries (2). A new type of vibrio cholera, 0139 Bengal, has a potential for global resurgence and continued vigilance is necessary.

Recently, a modified oral rehydration solution composed of amylase-resistant starch extracted from maize has been tested in India (3). Randomly assigned patients with cholera received one of three therapies: a glucose-based oral rehydration solution (WHO formula B), the same solution with 50 g of rice flour per litre, or the same solution with 50 g of high-amylose maize starch per litre.

Amylose-resistant starch which is indigestible, moves through the small intestine unchanged and enters the colon where the bacteria metabolize starch into short-chain fatty acids which facilitate the absorption of salt and water. Starch also provides a source of energy, increases the synthesis of proteins and improves the use of oxygen by the colonic mucosa (4).

However, the small size of this study makes it difficult to interpret the results. The reported benefit of amylase-resistant starch occurred in the second 24 hours of treatment whereas rice-based oral rehydration solution reduces stool output throughout treatment. This finding suggests that the beneficial effect of amylase-resistant starch is delayed (5). Furthermore, this effect is likely to be considerably reduced when effective antimicrobial therapy is given at the outset, as is universally recommended. Such treatment routinely reduces stool output during the second 24 hours by about 65%, as compared with no antibiotic treatment, and causes diarrhoea to end within 48 hours (6).

Oral rehydration solution containing amylase-resistant starch deserves further study as a treatment in adults with cholera. To determine whether amylase-resistant starch is effective and can increase the efficacy of rice-based oral rehydration solution, an appropriately designed study might compare three formulations: conventional rice-based oral rehydration solution, oral rehydration solution containing amylase-resistant starch as the only organic solute, and oral rehydration solution containing both rice and amylase-resistant starch with all patients receiving immediate treatment with an effective antimicrobial agent. Such a study should be performed before extending this research to include the treatment of children with acute

diarrhoea from causes other than cholera, in whom rice-based oral rehydration solution has no advantage over the standard glucose oral rehydration solution (5).

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### Antibiotics, *E. coli* and haemolytic-uraemic syndrome

The pathogenesis of the haemolytic-uraemic syndrome that is associated with infection with enterohaemorrhagic *Escherichia coli* is not well understood. The organisms apparently colonize the intestine after being ingested in contaminated food or transmitted by person-to-person contact (1). These organisms have at least three different virulence properties: they produce intimin, a protein necessary for their attachment to the intestinal wall, haemolysin, a protein that affects the growth of other bacteria and may also haemolyze human cells, and they release a toxin known as Shiga toxin (verotoxin or Shiga-like toxin). This toxin can initiate apoptosis in endothelial and epithelial cells in animals. The syndrome in these animals does not completely resemble the haemolytic-uraemic syndrome in children, but in baboons, parenteral administration of Shiga toxin results in endothelial and epithelial damage in the intestine that is similar to the damage that occurs in patients with the haemolytic-uraemic syndrome (2).

In an experiment in 1986, trimethoprim-sulfamethoxazole was added to cultures of *E. coli* O157:H7 and found to increase the release of Shiga toxin by the bacteria. The findings have since been extended to other enterohaemorrhagic strains of *E. coli* and to 13 other antibiotics (3). These findings have also raised the possibility that antibiotic treatment of *E. coli* infections might actually increase the risk of the haemolytic-uraemic syndrome, although the response of *E. coli* O157 isolates to subinhibitory concentrations of antibiotics seems to be highly dependent on the nature of the strain involved (3–4).

Recent data validate this concern. Children who received antibiotics for diarrhoea caused by *E. coli* had a significantly higher risk of the haemolytic-uraemic syndrome. A prospective cohort study was carried out in 71 children under 10 years of age with diarrhoea (5). The haemolytic-uraemic syndrome developed in 10 overall and 5 out of 9 children receiving antibiotics. In a multivariate analysis adjusted for the initial white cell count and the day of illness on which a stool was obtained for culture, antibiotic administration remained a risk factor for the development of the haemolytic-uraemic syndrome (relative risk, 17.3; 95% confidence interval, 2.2–137).

Since the theory is supported that antibiotics have an important role in the progression of gastrointestinal infection with *E. coli* to the haemolytic-uraemic syndrome, it would seem prudent to avoid giving antibiotics to children who have these infections and to carry out work to devise specific therapies to interrupt this progression. Particular attention should also be placed on increased efforts to avoid initial infection with these organisms.

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## Orlistat associated with hypertension

The latest drug for weight reduction, orlistat, was approved for use in Sweden in July 1998, and by September 1999 13 million defined daily doses (360 mg per defined daily dose) had been sold. Steatorrhoea and other gastrointestinal disorders were the most frequently reported adverse reactions in clinical trials (1). Adverse reactions indicating systemic effects have also been reported for orlistat including 13 cases of hypertension.

At the beginning of 1999, a 40-year-old previously healthy woman commenced orlistat treatment because of obesity. She took sporadic doses for some months and then increased the dosage to 120 mg three times daily during one week in May 1999. She experienced dizziness, peripheral oedema, and pulsating headache and stopped the treatment. On medical examination, her blood pressure was 190/100 mm Hg on three different occasions. Her heart rate was regular, at 60 beats/min. She was advised to stop taking orlistat, and a few days later her blood pressure had decreased to 160/90 mm Hg and the oedema had regressed. Laboratory tests, including measurement of thyroid hormone concentrations, were all normal.

Oral treatment with 30 mg furosemide daily was started and blood pressure decreased to 145/95 mm Hg. The patient restarted orlistat treatment in July 1999. Headache and peripheral oedema recurred, and her blood pressure increased to 170/100 mm Hg. Again, orlistat was discontinued. Her symptoms disappeared, and her blood pressure decreased to 140/90 mm Hg. After another month she experienced dizziness, and her blood pressure was 110/70 mm Hg. After cessation of diuretic treatment her blood pressure stabilised at 130/90 mm Hg, and this remained stable after three months. Orlistat was considered causal to the hypertension in this patient owing to a positive dechallenge and rechallenge. The mechanism for this reaction is not clear. Fluid retention may be a possibility.

Overall, 13 cases of hypertension associated with orlistat have been reported to the manufacturer, but information on blood pressure measurements and follow-up was limited in these cases. Although some of the patients had a history of hypertension, others, as in this case, had not.

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## Current Topics

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### The WHO-UNAIDS Care and Support Strategy

Building on the work of UNAIDS, and in collaboration with co-sponsors and partners worldwide, a new initiative is under way to enhance the health capacity of countries and increase access to HIV care and treatment. The principle objective of the United Nations Care and Support Strategy is to improve the quality of life and chances of survival of people living with HIV while reducing the devastating impact that HIV is having on developing countries. For this to be accomplished, prevention is a number one priority and care and treatment must be made available and affordable to people in need. Wherever possible, this care and support should encompass more advanced preventive and treatment options.

The delivery of HIV care and treatment requires policy and strategy decisions at global, national and community levels. Pivotal elements of the strategy are the political commitment of governments, strengthening of health infrastructures, engagement of all sectors, reliability of distribution systems and significant additional funding that is on a level with the enormous human, social and economic challenges now being imposed by the epidemic. As part of the Strategy, an **Interagency Task Team on Access to HIV-Related Drugs** was established in late 1999 to coordinate UN support to countries in expanding access to HIV-related drugs. The principal members are UNAIDS, UNDCP, UNDP, UNESCO, UNFPA, UNICEF, WHO, WIPO, and the World Bank.

### Interagency Task Team on Access to HIV-Related Drugs

Problems in assuring the availability, affordability, quality, and rational use of drugs are universal, but access to HIV-related drugs in developing countries and underprivileged communities presents particular challenges. In many cases, HIV patients are struggling to obtain even the most basic essential drugs. The Task Team on Access to HIV-related Drugs has adopted a four-part strategy and plan of action to guide and coordinate access to HIV-related drugs:

#### 1. Rational selection and use

HIV/AIDS-related drugs include established essential drugs for prevention and treatment of opportunistic infections, palliative and supportive care, treatment for sexually-transmitted diseases, "lower cost" infections such as pneumonia and tuberculosis, "high cost" opportunistic infections, HIV-related cancers, and antiretrovirals, which may be used for prevention of mother-to-child transmission, needle-stick injuries by health workers, or treatment of clinical AIDS. Use of HIV-related drugs should be

based on guidelines which have been locally adapted to achieve the greatest impact with available resources.

#### 2. Affordable prices

Affordable prices are a critical factor given the cost of some HIV-related drugs and are being pursued through a UNICEF/WHO/UNAIDS price information service, support for competitive procurement through generic tendering and therapeutic competition among different single-source drugs, dialogue with pharmaceutical companies to achieve preferential prices for lower income countries, reduction or elimination of import duties for essential drugs (including HIV-related drugs) including local taxes, local production where this results in lower prices and assures drug quality, and application of Trade Related Aspects of Intellectual Property Rights (TRIPS) safeguards as needed — prompt availability of generic drugs, compulsory licensing, and related measures.

#### 3. Sustainable financing

Sustainable financing for HIV-related drugs must be viewed in the context of overall health care financing, financing for HIV/AIDS prevention and care,



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and financing for essential drugs. Multiple sources of funding are being sought, including a call for increased public expenditure for health, advocacy for coverage of HIV-related drugs through social security schemes (where they exist), special funding facilities from the World Bank, targeted use of debt relief funds, tax incentives in high-income countries, in-kind funding in the form of drug donations, solidarity funds, and some degree of cost sharing if it can help extend access to a larger number of people.

#### **4. Reliable health care services**

Important elements to support access to HIV-related drugs include improved care and treatment services (voluntary counselling and testing, laboratory facilities, accreditation of clinicians and nurses, social support to help adherence, and strengthening of health and social services in a continuum of care), reliable supply systems (based increasingly on an effective mix of public, private, and nongovernmental organization procurement, storage, and transport services), and regulatory control (needed to assure quality, to combat counterfeits, and thereby to contain drug resistance).

#### **Tools and resources**

Members of the Task Team have developed resource materials to support countries in increasing access to HIV-related drugs. These tools are avail-

able from UNAIDS and co-sponsors and include needs assessment instruments, clinical guidelines, drug information, price information, and financing options.

The UNAIDS Drug Access Initiative was launched in 1997 and focused initially on antiretroviral therapy, but has since been a significant initiative to increase access to other HIV-related drugs. In June 2000, a technical meeting on access to drugs for HIV/AIDS within national essential drugs programmes was held in Pretoria, South Africa. This meeting involved national AIDS control programmes, essential drugs programmes, ministries of finance, and nongovernmental organizations from nine African countries.

To support African countries, UNAIDS and WHO are working to develop a network of country drug access advisors to provide policy and technical guidance to governments, nongovernmental organizations, and people living with AIDS (PLWA) groups. Drug access advisors will be able to provide direct assistance or to access external expertise in areas such as drug selection, development of local treatment guidelines, quantification of needs, identification of financing options, price information, procurement, patents, and quality assurance.

## Regulatory and Safety Matters

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### **Pneumococcal vaccine: recommendations for use**

**United States of America** — The Federal Advisory Committee on Immunization Practices has recommended administration of pneumococcal vaccine during the 2000–2001 flu season. The vaccine has a demonstrated effectiveness of almost 70% in preventing infections and can be given at the same time as influenza vaccine (1).

Infection with *Streptococcus pneumoniae* is one of the most common causes of death in the United States, mainly in the elderly. It accounts for approximately 50 000 cases of bacteraemia, 3000 cases of meningitis, up to 175 000 hospitalizations from pneumonia and 7 million cases of otitis media yearly.

The vaccine is recommended for persons aged 65 years or older; persons 2–64 years of age with chronic cardiovascular disease, pulmonary disease or diabetes, including immunocompromised individuals, those suffering from sickle cell disease or splenectomy, or ethnic groups such as Native or Alaskan Americans.

Children under 2 years of age and children up to 59 months of age who are at high risk of infection (such as those in day care, with frequent acute otitis media, etc.) should receive the pneumococcal vaccine, Prevnar® which was licensed in February 2000 (2). The vaccine is the first multivalent conjugate pneumococcal vaccine for children under 2 years of age and is administered in 4 shots. Most children over 2 years of age will only need one dose of the vaccine.

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2. *HHS News*, P00-3, 2000.

### **Valaciclovir: neuropsychiatric reactions**

**Australia** — Valaciclovir is an antiviral prodrug of aciclovir used in the treatment of herpes infections.

The Adverse Drug Reactions Advisory Committee has received 69 reports of minor reactions including headache, nausea, rash, dizziness. However, 13 more severe neuropsychiatric reactions have been reported and include hallucination, confusion, delirium, ataxia, dysarthria, convulsions, psychosis and stupor. Of these, all but one occurred in patients with chronic renal failure or age-related renal impairment. Although this is consistent with the product information physicians should be made aware of the possibility of these risks.

**Reference:** *Australian Adverse Drug Reactions Bulletin*, 19: 2 (2000).

### **Zanamivir: revisions to labelling**

The manufacturer of zanamivir (Relenza® Glaxo-Wellcome Inc.), has circulated an important warning on revisions to the safety labelling of the product, which was approved in 1999 for the treatment of uncomplicated acute illness due to influenza virus.

The warning describes reports of bronchospasm and decline in lung function in some patients and states that zanamivir is not recommended in patients having underlying airways disease, such as asthma or chronic obstruction pulmonary disease. Fatal events have been reported and information has been added on allergic-like reactions including the potential for masking of serious bacterial infections which may present as influenza-like symptoms. New animal toxicity data have also led to a change in the information on use in pregnancy.

**Reference:** Letter from Glaxo Wellcome, July 2000 available from US Food and Drug Administration on <http://www.fda.gov/medwatch/safety/2000/relenz.htm>

### **Celecoxib: adverse reaction reports**

**Australia** — Since October 1999 the Adverse Drug Reaction Advisory Committee has received 919 reports of suspected adverse reactions to celecoxib the first in the class of COX-2 inhibitors to be marketed. In 869 reports, celecoxib was the only suspected drug. Commonly, minor gastrointestinal reactions have been reported but there have also been cases of other more serious reports including gastrointestinal ulcers and bleeding.

There have also been 9 reports of acute renal failure or worsening of chronic renal failure. In these reports the patients were elderly or taking both an angiotensin converting enzyme (ACE) inhibitor or diuretic at the time celecoxib was started. Other types of reactions appear to be rashes/urticaria; allergy; peripheral oedema; dizziness and headache.

**Reference:** *Australian Adverse Drug Reactions Bulletin*, **19**: 2 (2000).

### Olanzapine: serious reactions

**Canada** — Olanzapine, an atypical antipsychotic, was first marketed in July 1996 for treatment of schizophrenia and related psychotic disorders. A total of 153 reports of suspected adverse drug reactions associated with olanzapine have so far been received by the Canadian Adverse Drug Reaction Monitoring Programme.

Olanzapine was reported as a suspected drug in 22 deaths including suicide, overdose, neuroleptic malignant syndrome, arrhythmia, myocardial infarction, heart failure, pneumonia, sepsis, sudden death, mesenteric thrombosis, and choking.

Eleven reports of haematological reactions described leukopenia, granulocytopenia, neutropenia, pancytopenia or anaemia. In 5 of the 11 cases, the patient had a history of similar problems when taking the chemically related drug, clozapine. A history of clozapine-induced leukopenia may be a risk factor for haematological reactions to olanzapine.

Neuroleptic malignant syndrome was reported in 11 cases of which 2 were fatal. Health care professionals should be aware of the signs and symptoms of this syndrome which includes fever, sweating, muscle rigidity, altered mental state, irregular heart rate or blood pressure or heart rhythm. Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents.

Adverse drug reactions of a similar nature have previously been reported in this journal (2).

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1. *Canadian ADR Newsletter*, **10**(3): 2 (2000)
2. *WHO Drug Information*, **13**(3):171 (1999).

### Infliximab approved for rheumatoid arthritis

**European Union** — The European Commission has granted marketing authorization for infliximab, (Remecade®) for use in combination with methotrexate in the reduction of signs and symptoms of rheumatoid arthritis in patients with active disease. The product should only be used when the response to disease-modifying antirheumatic drugs, including methotrexate alone, has been inadequate.

The ability of infliximab to neutralize tumour necrosis factor (TNF)-alpha, a proinflammatory mediator, represents a treatment advance in reducing the swelling and inflammation associated with the disease. The approval was based on findings from ATTRACT, one of the largest clinical trials to be carried out in patients with advanced rheumatoid arthritis. Results from the trial demonstrate that infliximab was generally well tolerated. The most common adverse events included upper respiratory tract infections, headache, nausea, sinusitis, rash and cough. The incidence of infusion reactions was below 5%. It is estimated that 2.5 million people in Europe are affected by rheumatoid arthritis.

Infliximab is also approved for the treatment of Crohn disease.

#### Reference:

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2. European Agency for the Evaluation of Medicinal Products. Listing of medicinal products granted a community marketing authorization under the centralized procedure, June 2000.
3. *Pharmaceutical Journal*, **265**: 10 (2000).

### Tenecteplase: the first "clot buster"

**United States of America** — The Food and Drug Administration has approved tenecteplase for the reduction of mortality associated with acute myocardial infarction. The product is a single-bolus thrombolytic agent having the potential to simplify heart attack treatment by offering physicians the fastest administration of a thrombolytic to date. It is possible to administer within five seconds and in one dose, which is evaluated in relation to the weight of the patient.

Tenecteplase works by stimulating the body's own clot-dissolving mechanism by activating plasminogen, a naturally occurring substance secreted by endothelial cells in response to injury to the artery walls. Tenecteplase activates plasminogen, which converts into plasmin and breaks down the fibrin mesh that binds the clot together. The clot is then dissolved, restoring blood flow to the heart.

As with all thrombolytics, the most significant adverse events observed in clinical trials with this product include intracranial haemorrhage and stroke. The effects of the drug are currently under investigation in four ongoing clinical trials, involving more than 9000 patients, which have been designed to evaluate various heart attack regimens in combination with other agents.

Tenecteplase (TNKase<sup>®</sup>, Genentech) is a bioengineered recombinant DNA-derived version of naturally-occurring tissue plasminogen activator (TPA). The product will be provided in a needleless injection system kit.

**Reference:** Genentech, <http://www.genentech.com> 2 June 2000.

## Bupropion: a new approach to smoking cessation

**United Kingdom** — Bupropion, (Zyban<sup>®</sup>) the first non-nicotine prescription medicine for use as an aid to smoking cessation has been launched. It acts as a dopamine and noradrenaline reuptake inhibitor to break the cycle of addiction: dopamine is implicated in craving and noradrenaline in withdrawal symptoms. Clinical trials involving 1500 patients (1) showed bupropion to be twice as effective as nicotine replacement therapy. The results also showed that 30% of subjects were not smoking after one year compared to 16% using nicotine replacement therapy patches.

It is recommended that bupropion be used alone since combining with nicotine replacement therapy may raise blood pressure. This possibility needs further investigation. Side effects to date have been mild and transient with the most common reports being insomnia, dry mouth and headache. No dependency has so far been demonstrated. A support programme is also provided by the manufacturer (2).

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2. *Pharmaceutical Journal*, 265: **9** (2000).

## Doxorubicin for ovarian cancer

**European Union/United States of America** — The Committee for Proprietary Medicinal Products (CPMP) has recommended approval of pegylated liposomal doxorubicin hydrochloride (Caelyx<sup>®</sup>) for the treatment of advanced ovarian cancer in women who have failed first-line platinum-based therapy (1). The application proposes that Caelyx<sup>®</sup> be administered intravenously once every four weeks for as long as the disease does not progress and the patient continues to tolerate treatment. The product has previously received centralized marketing authorization in the European Union for the treatment of AIDS-related Kaposi sarcoma and extensive mucocutaneous or visceral disease (2).

In the USA, doxorubicin (Doxil<sup>®</sup>) was approved in 1999 (under an accelerated review process designed to address urgent unmet needs) to treat metastatic ovarian cancer in women whose disease is refractory to paclitaxel and platinum-based chemotherapy. The product is a liposomal formulation of doxorubicin, using a novel targeted delivery system to help evade recognition and uptake by the immune system. This allows liposomes and their pharmaceutical content to circulate in the body longer (3).

Ovarian cancer is the second most common gynaecological cancer in the USA; an estimated 25 200 cases were diagnosed in 1999 and approximately 35 000 new cases are diagnosed in the European Union every year. Between 55 to 75% of women relapse within two years.

## References

1. Publication of CPMP opinions at <http://www.eudra.org/humandocs/humans/opinion.htm> June 2000.
2. Schering Plough, company news on line. <http://www.schering-plough.com> (3 July 2000).
3. Alza corporation. <http://www.alza.com> (3 July 2000).

## Linezolid: the first oxazolidone antimicrobial approved

**United States of America** — The Food and Drug Administration has approved linezolid, (Zyvox®), the first antibacterial drug of the new oxazolidinone class to treat infections associated with vancomycin-resistant *Enterococcus faecium*, including cases with bloodstream infection. Other indications are treatment of hospital-acquired pneumonia, complicated skin and skin structure infections, including cases of methicillin-resistant *Staphylococcus aureus*, community-acquired pneumonia and uncomplicated skin and skin structure infections.

Vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* infections are a particular problem in hospitalized or immunocompromised individuals. Since 1989 there has been a rapid increase in the incidence of methicillin-resistant *Staphylococcus aureus* infections. These organisms are often resistant to multiple antibiotics and limited therapeutic options are available to patients.

The most frequently reported side effects attributed to linezolid in clinical studies were headache, nausea, diarrhoea and vomiting. The most important laboratory test change was a decrease in platelet counts. Linezolid may interact with other drugs, including over-the-counter cold remedies containing pseudoephedrine or phenylpropranolamine and cause an increase in blood pressure.

Due to concerns about appropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with linezolid in an outpatient setting. The manufacturer anticipates that linezolid will be used principally in hospitals or institutional care settings.

Worldwide licensing is intended by the manufacturer, and an application has also been submitted in the United Kingdom (2).

### References

1. *FDA Talk Paper*, T00-17 (2000).
2. *Pharmaceutical Journal*, **264**: 284 (2000).

## Guidance for adverse reactions labelling

**United States of America** — The Food and Drug Administration has issued a draft guidance for the development of the adverse reactions section of labelling for human prescription drugs and biologicals. The document, which was published in June, is the first in a series of guidances for industry that are intended to make the labelling more consistent and helpful to prescribers and patients.

The draft guidelines emphasize the need to focus the adverse reactions section on drug safety information that is important to prescribing decisions, and to convey this in a format that is clear, easy to find and consistent across different drugs and drug classes. The guidance suggests that the adverse reaction section be limited to information that can be helpful in treating, monitoring and advising patients. Long and exhaustive lists of every reported adverse event, including those that are infrequent or minor, should be avoided.

*Guidance for Adverse Reactions Labeling*, Food and Drug Administration is available on: [www.fda.gov/cder/guidance/1888dft.htm](http://www.fda.gov/cder/guidance/1888dft.htm).

**Reference:** *FDA Talk Paper*, T00-30 (2000).

## Legislation adopted in Europe on orphan drugs

**European Union** — In a bid to encourage the pharmaceutical industry to invest in developing treatments for diseases which are rare or not economically viable, legislation has been adopted to stimulate new treatment options for patients. Pharmaceutical companies may now apply to the European Agency for the Evaluation of Medicinal Products (EMA) to designate orphan medicinal products. Under the new legislation, companies will be able to request reductions in fees for market authorizations and for alterations to the approval after registration. Companies whose products are granted orphan drug status will be entitled to a 10-year period of market exclusivity.

The prospect of obtaining a 10-year period of market exclusivity for orphan medicinal products in the European Union will provide a strong incentive for sponsors. Pharmaceuticals intended to treat

diseases which may have a high prevalence in developing countries, but which are classified as rare in the European Union, such as malaria, may also be designated as orphan medicinal products. A Committee, which includes representatives of patient organizations, has been created to evaluate whether a potential medicine meets the criteria of an orphan drug.

Similar legislation was adopted in the United States in 1983, where the application of tax incentives for companies proved to be effective. However, tax incentives are not possible in the European Union due to the absence of a centralized system of taxation.

**Reference:** European Commission Press Release. *Commission takes measures to help rare disease patients*. <http://www.eudra.org> 27 April 2000.

## More drug safety measures planned in Japan

**Japan** — The Ministry of Health and Welfare will propose new drug safety measures, including standardization of safety measures. The Ministry will continue to study ways to improve drugs and medical devices that are liable to be misused or confused with other products, including ways to improve postmarketing surveillance. Among these measures is the standardization of warning labels and rules for product naming. A proposal has also been submitted which will oblige manufacturers to conduct intensive monitoring of their products shortly after launching.

**Reference:** *Pharma Japan*, 1704: 11 (2000).

## "Street drug alternatives" are not dietary supplements

**United States of America** — The Food and Drug Administration has made a review of 140 reports of adverse drug reactions linked to the use of dietary supplements containing ephedrine alkaloids. The FDA has called for additional information before proposing limits to the dosing level and duration of use (1).

In addition to these actions, the Agency has issued a *Guidance for Industry on Street Drug Alternatives* in response to the proliferation of various products promoted as alternatives to illicit street drugs. These products, which are intended to affect psy-

chological states are generally labelled as containing herbals, vitamins, minerals or amino acids. Given their intended use, the FDA does not consider street drug alternatives to be dietary supplements. Street drug alternatives are therefore considered as unapproved and misbranded drugs that are subject to regulatory action, including seizure and injunction (2).

## References

1. US Food and Drug Administration. *Dietary supplements containing ephedrine alkaloids: docket update, availability*. <http://www.fda.gov/OHRMS/DOCKETS/98fr> 31 March 2000.
2. US Food and Drug Administration. *Guidance for Industry on Street Drug Alternatives*. <http://www.fda.gov/OHRMS/DOCKETS/98fr.040300d.txt> 31 March 2000.

## Tamsulosin: syncope now reported

**Japan** — Tamsulosin was marketed in 1993 for dysuria due to prostatic hypertrophy. Based on reports received during the first phase of postmarketing surveillance, hypotension was added to the precautions section of the labelling in 1994. Cases of syncope/unconsciousness were also cited with reference to case reports from other countries.

Five cases of syncope/unconsciousness due to orthostatic hypotension associated with the use of tamsulosin have since been reported in Japan.

**Reference:** *Pharmaceuticals and Medical Devices Safety Information*, 159, 22 March 2000.

## Dapsone hypersensitivity syndrome

**Singapore** — A 22-year-old serviceman on an overseas training exercise in Brunei, received 100 mg dapsone and 12.5 mg pyrimethamine (Maloprim®) weekly as antimalarial chemoprophylaxis.

Two weeks later, he developed fever which was resolved by taking paracetamol but was followed by sudden onset of pruritus on both hands. Pruritic papular rash appeared on hands and feet and progressed to the trunk. Fever returned with chills, left cervical and right inguinal lymphadenopathy and hepatosplenomegaly. Maloprim® was discontinued. On admission to hospital he was afebrile and had bilateral periorbital swelling. The arms, legs and trunk were covered by an erythematous

papular rash and petechiae on the feet. The skin had begun to exfoliate. After four days' treatment with oral prednisolone and hydroxyzine he recovered.

**Reference:** *Singapore Adverse Drug Reaction News*, Volume 2 (1), March 2000.

## Kava extract linked to hepatitis

**Switzerland** — The Intercantonal Office for the Control of Medicines has received information on a case of hepatitis following administration of Kava extract (*Piper methysticum*). Physicians and pharmacists are reminded that symptoms such as fatigue, loss of appetite or nausea indicate hepatic reactions and a need to stop taking Kava extract. Patients should be warned to watch for such signs and consult a physician if they appear (1).

Since 1998, six Kava products have been marketed in Switzerland for the treatment of anxiety and nervousness. Several other cases of adverse reactions have been reported and include 9 spontaneous reports of hepatic reactions (8 women and one man). One report (2), on an ethanolic Kava extract describes severe hepatitis after 6 months intake of 60 mg Kava-lactones, while rechallenge induced recurrence of symptoms 14 days later. This represents one case in 170 000 treatment regimens of an average duration of 30 days. Delay of symptoms varies between 3 weeks and 4 months, although one case was reported two years later.

In three cases, clinical symptoms of hepatitis included icterus denoting a decrease in prothrombin time. In four cases where a biopsy was practised, cellular necrosis, inflammatory reaction and eosinophilia were observed, denoting an immunological reaction.

### References

1. Communications de l'OICM. *Bulletin des médecins suisses*, 1335–1338 (2000).
2. Strahl, R. *Deutsche Medizinische Wochenschrift*, **123**: 1410–1414 (1998).

## Gene therapy and patient protection

**United States of America** — The Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have announced two initiatives to

strengthen safeguards for individuals enrolled in clinical studies involving gene therapy.

### **The Gene Therapy Clinical Trial Monitoring Plan**

will require that sponsors of gene therapy trials routinely submit monitoring plans to the FDA. These plans will be reviewed and modifications sought if warranted. Surveillance and inspections of clinical trials will be carried out to assess whether the plans are being followed and if monitoring is adequate to identify problems. The experience and training of the monitors will also be addressed. Conferences will be convened for investigators in order to enhance the conduct of gene therapy trials.

A series of **Gene Transfer Safety Symposia** will be organized quarterly by the NIH and FDA to enhance patient safety through the sharing and analysis of medical and scientific data from gene transfer research. The symposia will include topics such as: monitoring of safety data, cardiovascular complications of vector administration, good clinical practice in research, cell and gene therapy guidance for product development, quality control and assurance, entry criteria and informed consent for participants.

The FDA is requesting manufacturers to provide additional information on cell banks, viral banks and other products for use in clinical studies. Quality control data will also need to be produced on each lot of products either produced by the manufacturer or used by them in clinical trials.

Action has also been taken to achieve greater adherence by researchers to existing requirements. These include:

- a series of site visits to NIH-funded institutions to review institutional compliance with a range of NIH rules, regulations and guidelines relevant to gene transfer research, conflict of interest and invention reporting.
- a review of institutional policies and procedures to ensure compliance with NIH guidelines. NIH is also contacting investigators to ensure they have reported all serious adverse events to the NIH.

A website and database will be created to provide public access to data on gene transfer research as of October 2000.

**Reference:** *HHS News*. New initiatives to protect participants in gene therapy trials, 7 March 2000.

# Essential Drugs

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## WHO Model Prescribing Information

### Streptococcal pharyngitis and prevention of rheumatic fever

Rheumatic fever and rheumatic heart disease are the delayed consequence of an untreated group A beta-haemolytic streptococcal infection of the upper respiratory tract. The disease can cause serious, debilitating damage to the heart and involve other tissues. Those people who have already suffered a rheumatic fever attack are extremely susceptible to a recurrence if they are again infected with group A streptococci.

Group A streptococcal infections are universally endemic. There is no available vaccine for group A infections, and preventive measures remain dependent upon accurate clinical diagnosis and appropriate antibiotic treatment. Although epidemics in nurseries and infection in younger children are reported, the majority of streptococcal infections occur in school-age children between 5 and 15 years of age. Adult infections are most frequently observed in establishments, military bases or residential facilities.

Group A streptococcal upper respiratory tract infection is spread by droplets, thus accounting for its high transmission rate where crowding is frequent. Most outbreaks are associated with this kind of transmission, but food-borne transmission has also been reported. In contrast to other infectious agents, there are approximately 100 recognized serotypes of group A streptococci. Therefore, although infection with a given serotype is thought to confer long lasting type-specific immunity, the abundance of serotypes makes the threat of new infections a continuous worldwide public health problem.

#### Diagnosis, treatment and management

Young children, school-age children, and adults may present with significantly different clinical manifestations. An accurate clinical diagnosis of group A streptococcal upper respiratory tract infec-

tion can be very difficult and laboratory confirmation of the infection should be sought whenever possible. The classical signs and symptoms — high fever, severe pain on swallowing often accompanied by abdominal pain, nausea and vomiting — may not always be present, especially in endemic situations. Likewise, in young children under three years of age the presentation of streptococcal upper respiratory tract infection varies.

As difficult as it may be to clinically establish a diagnosis of acute streptococcal tonsillitis or pharyngitis, the signs and symptoms of this bacterial infection typically are quite different from those associated with viral upper respiratory tract infections. Culture using throat swabs continues to be the most useful method for determining the presence of group A streptococci in the upper respiratory tract although prior administration of antibiotics may result in a false-negative test-result.

Rapid antigen detection tests are available which allow the detection from the throat swab. Although antibody tests such as antistreptolysin O (ASO) and anti-deoxyribonuclease-B (anti-DNase B) are very useful in confirming diagnosis of rheumatic fever or acute glomerulonephritis, they are not indicated for the diagnosis of patients with acute group A streptococcal pharyngitis.

#### 1. Primary prevention of rheumatic fever

In general, once the condition has been diagnosed, antibiotic therapy is indicated.

##### *Penicillins*

Penicillin remains the treatment of choice for group A streptococcal upper respiratory tract infections, since it is the only antibiotic that has been evaluated in controlled studies. A single injection of intramuscular benzathine benzylpenicillin is the most effective treatment in eradicating group A streptococci, probably due to its long duration of action. It can also be used for mass prophylaxis.

Oral phenoxymethylpenicillin administration for streptococcal pharyngitis must be continued for 10 days. Other orally administered penicillins include ampicillin, amoxicillin and the semisynthetic penicillins.



*Macrolides*

For penicillin-allergic patients, treatment with oral erythromycin for 10 days is often used. Newer macrolides are reported to be associated with fewer adverse effects but are generally more expensive. Short-course therapy with these newer macrolides is effective, but more definitive data are required before use in primary prevention is recommended.

*Cefalosporins*

First and second generation cefalosporins have been used to treat group A streptococcal infections. As a rule, cefalosporins are more expensive than penicillin. Short-course therapy (less than 10 days) with some cefalosporins is also under evaluation.

*Resistance*

No clinical isolate of group A streptococci has shown resistance to penicillin but resistance to macrolide antibiotics (e.g. erythromycin) is increasing in some countries. None the less, group A streptococcal resistance to the macrolides remains at less than five percent. Clinical use of macrolides should be made in relation to local resistance rates. Resistance to sulfonamides and tetracyclines is known to occur.

*Recommended antibiotics*

Table 1 shows commonly recommended antibiotics for the treatment of acute streptococcal pharyngitis for primary prevention of rheumatic fever. Sulfonamides or tetracyclines are not acceptable therapy for group A streptococcal pharyngitis.

If individuals remain symptomatic following a complete course of antibiotic therapy in which compliance was assured, a second course may be indicated. In these relatively rare instances, laboratory confirmation of the organism is advisable.

**2. Secondary prophylaxis of rheumatic fever**

For all individuals who have had an initial attack of rheumatic fever, whether or not they have rheumatic heart disease, continuous administration of an antibiotic is mandatory to prevent acquisition and infection of the upper respiratory tract by group A streptococci. Secondary prophylaxis reduces the risk of recurrent attacks with their attendant morbidity and mortality.

Antibiotic regimens for secondary prophylaxis differ. The regular intramuscular injection of benzathine benzylpenicillin is the most effective available treatment. Although usually given every four weeks, recent data indicate that 1 200 000 units of benzylbenzathine penicillin given every three weeks may be more effective in preventing recurrences of rheumatic fever, especially in high-risk patients. Commonly recommended antibiotics are set out in Table 2.

Several technical factors related to the benzathine benzylpenicillin injection can affect its bioavailability. It is recommended that health workers are trained in the technique of giving injections. The injection should be made deep into the muscle as

**Table 1: Treatment of Group A streptococcal pharyngitis (primary prevention of rheumatic fever)**

Antibiotic	Route	Dose	Duration
<b>For non-penicillin allergic patients:</b>			
Benzathine benzylpenicillin	IM	<30 kg: 600 000 IU >30 kg: 1 200 000 IU	single injection
Phenoxyethylpenicillin	oral	<30 kg: 250 mg 2 or 3 times daily >30 kg: 500 mg 2 or 3 times daily	10 days
<b>For penicillin allergic patients:</b>			
Erythromycin ethylsuccinate	oral	40 mg/kg/day (max. 1.5 g/day) 3 times daily	10 days
Erythromycin estolate	oral	20–40 mg/kg/day (max. 1.5 g/day) 3 times daily	10 days

Antibiotic	Route	Dose
<b>For non-penicillin allergic patients:</b>		
Benzathine benzylpenicillin	IM	<30 kg: 600 000 IU every 3–4 weeks >30 kg: 1 200 000 IU every 3–4 weeks
Phenoxymethylpenicillin	oral	250 mg twice daily
<b>For penicillin allergic patients:</b>		
Sulfonamide (sulfadiazine,* sulfadoxine, or equivalent)	oral	<30 kg: 500 mg daily >30 kg: 1 g daily
Erythromycin	oral	250 mg twice daily
* Contraindicated in late pregnancy		

recommended. Superficial injections lead to the benzathine benzylpenicillin remaining in the subcutaneous tissue, resulting in decreased absorption and lower serum levels. Care should be taken that the entire content of the vial is injected.

For patients who are not able to receive injections of benzathine benzylpenicillin, a less effective method is oral phenoxymethylpenicillin daily. The potential problems with oral prophylaxis are adherence and rheumatic fever recurrence rates, which have been shown to be higher with this regimen than with intramuscular benzathine benzylpenicillin.

For patients known to be allergic to penicillin, an oral sulfonamide is recommended for secondary prophylaxis. However, it is not effective for treating established group A streptococcal infection. For individuals who cannot take either penicillin or sulfadiazine, erythromycin in a dose of 250 mg twice daily may be used, although resistance to erythromycin has been reported.

#### *Duration of secondary prophylaxis*

There are several variables that affect the likelihood of recurrences of rheumatic fever, including the time since the most recent attack, the age of the patient and the risk posed by the environment. The duration of secondary prophylaxis should be adapted to the individual patient but some general principles can be stated. Patients without carditis in a previous attack should continue prophylaxis for a

minimum of five years after the last attack, and at least until age 18 and often longer if risk factors are high. Patients with cardiac involvement in the initial attack should continue prophylaxis at least until the age of 25 years, and longer if environmental conditions or other risk factors are present.

The general principles for secondary prophylaxis are :

Patient	Duration
No carditis/rheumatic heart disease	To 18 years of age and at least 5 years after last attack
Documented carditis	At least to 25 years of age and often longer
Chronic carditis	For life
+ Artificial valves	For life

For patients with chronic valvular rheumatic heart disease, secondary prophylaxis for prolonged periods, even for life, has sometimes been recommended. Antibiotic prophylaxis for secondary rheumatic fever should be continued through pregnancy. However, sulfonamides present a risk to the fetus and an alternative antibiotic (penicillin or erythromycin) should be substituted.

**BENZATHINE BENZYL PENICILLIN**

*Powder for injection 1.44 g (2.4 million IU) in 5-ml vial*

Benzylpenicillin is a natural substance derived from *Penicillium notatum*. It is a bactericidal agent against *streptococci*, *neisseriae*, many anaerobes and spirochaetes.

After intramuscular injection, peak plasma concentrations are usually reached within 12–24 hours and are usually detectable for 1–4 weeks. It is widely distributed throughout the body and excreted mainly in the urine.

**Uses:** Streptococcal pharyngitis. Primary and secondary prophylaxis of rheumatic fever.

**Dosage and administration:****Primary prophylaxis**

*Children <30 kg:* 600,000 IU, in a single injection.  
*Children >30 kg and adults:* 1,200,000 IU, in a single injection.

**Secondary prophylaxis**

*Children <30 kg:* 600,000 IU, every 3–4 weeks.  
*Children >30 kg and adults:* 1 200 000 IU, every 3–4 weeks.

The contents of the vial should be diluted in sterile water to obtain a homogeneous suspension in order to avoid obstruction of the needle. A needle gauge of #19 or #20 is preferred. The injection should be deep into the gluteus maximus muscle. Superficial injections leave the benzathine benzylpenicillin in the subcutaneous tissue leading to decreased absorption and lower serum levels. Care should be taken that the entire content of the vial is injected.

**Contraindications:** Known hypersensitivity to penicillin or cephalosporins.

**Precautions:** Facilities should be available for treating anaphylaxis whenever penicillin is used. A full patient history should be obtained with regard to previous allergic reactions. If skin rashes develop, another antimicrobial should be given.

The overall incidence of hypersensitivity reactions reported with penicillin is from 2 to 5%. Anaphylaxis occurs in approximately 1 in 10 000 injections. Death has been reported in approximately 1 in 30–50 000 injections. Many anaphylactic reactions occur in severely ill rheumatic heart disease pa-

tients at risk of life-threatening arrhythmias where an arrhythmia associated with shock mimics anaphylaxis.

**Use in pregnancy:** There is no evidence of teratogenicity with benzathine benzylpenicillin.

**Adverse reactions:** The most common adverse effects are hypersensitivity reactions ranging in severity from skin rashes to immediate anaphylaxis.

Pain and sterile inflammation can occur at the site of intramuscular injection.

Accidental injection into a peripheral nerve will cause pain and dysfunction.

Nephropathy manifested as interstitial nephritis has been reported.

Neutropenia and thrombocytopenia have occurred rarely.

**Storage:** Powder for injection should be stored at temperatures between 2 °C and 8 °C and protected from moisture.

**PHENOXYMETHYL PENICILLIN**

*Tablet, 250 mg, 500 mg (as potassium)  
Powder for oral suspension, 250 mg, 125 mg (as potassium salt)/5 ml*

Phenoxyethylpenicillin is a semisynthetic derivative of penicillin for oral use. It is active against a wide variety of Gram-positive and Gram-negative cocci. Most strains of streptococci remain susceptible.

It is well absorbed from the gastrointestinal tract and distributed widely in tissues. It crosses the placenta, is excreted in the urine and in breast milk.

**Uses:** Treatment of streptococcal pharyngitis. Secondary prophylaxis of rheumatic fever.

**Dosage and administration:**

*Children <30 kg:* 250 mg, 2 or 3 times daily  
*Adults and children >30 kg:* 500 mg, 2 or 3 times daily.

**Contraindications:** Known hypersensitivity to penicillin or cephalosporins.

**Precautions:** Facilities should be available for treating anaphylaxis whenever penicillin is used for the first time.

A full patient history should be obtained with regard to previous allergic reactions.

If skin rashes develop, the patient should be given another antimicrobial.

**Use in pregnancy:** Phenoxyethylpenicillin can be used in pregnancy.

**Adverse reactions:** The most common adverse effects are hypersensitivity reactions that range in severity from skin rashes to immediate anaphylaxis. Mild diarrhoea may also occur.

**Storage:** Should be stored in tightly closed containers.

## ERYTHROMYCIN

*Enteric coated tablets, 250 mg (as stearate or ethylsuccinate)*

*Oral suspension, 125 mg (as stearate or ethylsuccinate)/5 ml*

Erythromycin is a macrolide antimicrobial produced by *Streptomyces erythreus*. It has selective bacteriostatic activity against both streptococci and staphylococci and some Gram-positive bacilli. Because it is inactivated by gastric juices, oral formulations are enteric-coated. It diffuses rapidly into all tissues except the brain and cerebrospinal fluid, and readily crosses the placental barrier. The plasma half life is approximately 90 minutes. It is partially demethylated in the liver and excreted largely via the bile and faeces.

**Uses:** Streptococcal pharyngitis in penicillin-allergic patients.

### **Dosage:**

#### **Primary prophylaxis of rheumatic fever**

*Adults:* 40 mg/kg/day (max. 1.5 g/day), 3 times daily.

*Children:* 20–40 mg/kg/day (max. 1.0 g/day) 3 times daily.

#### **Secondary prophylaxis of rheumatic fever**

250 mg twice daily.

**Contraindications:** Known hypersensitivity to erythromycin.

**Precautions:** Hepatic function should be monitored in patients with a previous history of liver disease.

**Adverse effects:** Erythromycin is well tolerated by most patients at the dosages suggested. Large oral doses may produce nausea, vomiting and diarrhoea.

Cholestatic hepatitis, which may present with symptoms suggestive of acute cholecystitis, occasionally complicates prolonged courses of treatment. Symptoms resolve rapidly when the drug is withdrawn.

Anaphylaxis and other hypersensitivity reactions are rare.

**Drug interactions:** Erythromycin, chloramphenicol, and clindamycin have a similar bacteriostatic action and may be antagonistic when administered together. Erythromycin decreases the rate of metabolism of carbamazepine and warfarin in the liver to a degree that can warrant readjustment of dosage.

**Storage:** Capsules and tablets should be stored in tightly closed containers.

## SULFADIAZINE or SULFISOXAZOLE

*Tablet, 500 mg*

*Injection, 250 mg (sodium salt)*

Sulfadiazine and sulfisoxazole are intermediate-acting sulfonamides with broad spectrum activity against a wide range of Gram-positive and Gram-negative organisms. They are readily absorbed from the gastrointestinal tract and widely distributed in the body. The serum half-life is 10–12 hours. After partial acetylation in the liver they are excreted in the urine.

### **Uses:**

Secondary prevention of rheumatic fever.

### **Dosage:**

*Adults:* 1 g daily in 2 divided doses.

*Children:* 150 mg/kg/day in 2 divided doses.

**Contraindications:** Hypersensitivity to sulfonamides; severe renal or hepatic function impairment; porphyria; first trimester pregnancy.

**Precautions:** The red blood cell count should be monitored regularly throughout therapy to detect signs of bone-marrow depression. Any patient suspected of being sensitive to sulfonamides should never receive them again. Presumptive signs include skin rashes and evidence of haemolysis such as dark urine and purpura.

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Sulfadiazine is less soluble in urine than many other sulfonamides. High urinary output must be maintained and patients should be advised to drink 1.0–1.5 litres of alkaline water daily.

**Use in pregnancy:** Sulfadiazine is contraindicated during the first trimester. Administration of sulfonamides can induce severe hypersensitivity reactions in the mother. Their action in displacing bilirubin from protein-binding sites has given rise to concern. Based on data derived from premature neonates, sulfonamides may promote kernicterus. Although they readily cross the placental barrier there is no conclusive evidence that the fetus is at risk.

**Adverse effects:** Nausea, vomiting, diarrhoea and headache sometimes occur.

Sulfonamide-induced hypersensitivity reactions, although uncommon, may be severe. They include rare life-threatening cutaneous reactions such as erythema multiform (Stevens–Johnson syndrome)

and toxic epidermal necrolysis. Crystalluria may result in dysuria, renal colic, haematuria and acute renal obstruction.

Other infrequent reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase.

**Drug Interactions:** Concomitant administration of other drugs that interfere with folic acid metabolism (other than pyrimethamine) should be avoided whenever possible.

**Overdosage:** Continuous forced diuresis may be beneficial and an alkaline urine should be maintained. Treatment is otherwise symptomatic.

**Storage:** Preparations should be stored protected from light.

# Recent Publications and Sources of Information

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## Emergency contraception

Emergency contraception will only have an impact on reducing unwanted pregnancies if women are provided with information and access to the methods available before they are needed. *Emergency Contraception: A Guide for Service Delivery* sets out to propose how emergency contraception can be integrated into the community and family planning care facilities through service outlets as a first contact point. Emergency contraception is considered to be one component of the long-term strategy to improve overall reproductive health care.

In spite of the effectiveness of modern contraceptives, unwanted pregnancies occur in large numbers throughout the world and many women seek termination. It is estimated that 40 to 60 million abortions are performed each year; approximately 20 million of which are carried out under unsafe and dangerous conditions. If emergency contraceptive methods were easily available, millions of unwanted pregnancies and abortions could be averted. These methods include increased doses of combined oral contraceptives, high doses of progestogen-only pills containing levonorgestrel and copper-releasing intrauterine devices.

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*Emergency Contraception: A Guide for Service Delivery. Family and Reproductive Health, World Health Organization, Geneva, WHO/FRH/FPP 98.19.*

## UN Consolidated List: restrictions in use and availability

An update of the pharmaceutical section of the Sixth Issue of the United Nations *Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments* has now been compiled.

The document *Pharmaceuticals: restrictions in use and availability* presents information on new national regulatory decisions and voluntary withdrawal of products by manufacturers on grounds of safety.

This information has been reported between 1993–1999. Criteria for inclusion of the products in the UN Consolidated List were developed in 1985 and revised subsequently. Although interpretation of the criteria continues to vary widely, leading to disharmony in reporting, the list is still useful to drug regulatory authorities and the pharmaceutical industry to give an indication of the status of products. More detailed information on action taken by the regulatory authorities or the manufacturers should be confirmed directly at source.

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*Pharmaceuticals: restrictions in use and availability. Essential Drugs and Medicines, World Health Organization, Geneva, WHO/EDM/QSM/99.2.*

## New antituberculosis drug development

Only one new antituberculosis drug has come to the market in the last 28 years despite nearly 2 million deaths from the disease occurring each year. A new report from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) – Incentives and Disincentives for New Antituberculosis Drug Development – looks at the reasons for the lack of interest in antituberculosis drugs by the pharmaceutical industry and how to stimulate research and development of new drugs. The report contains a brief description of the current situation and major findings of the evaluation. Lack of interest by pharmaceutical companies is attributed to:

- The cost of drug development: which varies between US \$300 to 500 million, and company concern that the commercial return would be insufficient from patients in developing countries.
- Risk of patent violations.
- The perception that new drugs would not be responding to an unmet medical need given the cost-effectiveness of the directly-observed short-course treatment (DOTS) regimen for TB which is currently available. This would also tend to force down the price of any new drugs.

In conclusion, the report proposes broad recommendations which include the need for public sector efforts to build relationships with industry and other stakeholders, provide discussion and drive forward the process of antituberculosis drug development by helping to build, define and protect markets for new drugs. Governments should also be encouraged to strengthen their health infrastructure, lower the barriers to development and build financing mechanisms for the private sector.

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*Incentives and Disincentives for New Antituberculosis Drug Development. World Health Organization, Geneva, WHO/TDR/PRD/TB/00.1 (2000) or <http://www.who.tdr/publications/antituberculosis.htm>*

## **Carcinogenic risks from antiviral and antineoplastic drugs**

The Seventy-Sixth volume of the International Agency for Research on Cancer (IARC) Monographs comprises evaluations of pharmaceutical agents which include antivirals (aciclovir, zidovudine, zalcitabine and didanosine), some DNA topoisomerase II inhibitors (teniposide, etoposide, mitoxantrone and amsacrine) and others (hydroxyurea, phenolphthalein and vitamin K substances) which have not been reviewed previously. The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

The term carcinogenic risk in the IARC Monograph series is taken to mean the probability that exposure to an agent will lead to cancer in humans. Inclusion of an agent in the Monographs does not imply that it is a carcinogen, only that published data have been examined. Equally, the fact that an agent has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

Two chemicals were tested for carcinogenicity in genetically engineered mice which are particularly susceptible to induction of tumours at certain sites through specific mechanisms. Some of these transgenic, knockout, models can be considered the laboratory counterparts of certain rare human genetic syndromes, and the models may be particularly useful for testing drugs to be administered to individuals with such syndromes.

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Some antiviral and Antineoplastic Drugs, and Other Pharmaceutical Agents. Volume 76, International Agency for Research on Cancer. World Health Organization, Geneva, ISBN 92 832 1276 2*

## **HIV preventive vaccine research: ethical considerations**

The HIV pandemic is characterized by unique biological, social and geographical factors that affect the balance of risks and benefits for individuals and communities who participate in HIV vaccine development activities. These factors may require that additional efforts are needed to address the protection and welfare of participating individuals and communities in order to fulfil their rights as full and equal participants.

The need for an HIV vaccine is becoming more urgent, and over twenty vaccine candidates are at various stages of development. The successful development of effective HIV preventive vaccines is likely to require studies in different populations around the world involving the collaboration of various partners in government, agencies, research institutions and industry.

The UNAIDS secretariat has developed a guidance document on the ethical considerations in HIV preventive vaccine research which is directed to use by research participants, investigators, community members, governments, pharmaceutical companies, and ethical and scientific review committees. It suggests standards, but can equally be used as a frame of reference from which to conduct discussion and reach decisions. Consultation has taken place among lawyers, activists, social scientists, ethicists, research scientists, epidemiologists, nongovernmental organizations and public health officials and has included people from 33 countries.

The guidance document sets out to highlight some of the critical elements to be considered in ensuring availability, capacity building, development of research protocols, identification of study populations, community participation, ethical review and monitoring.

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*Ethical Considerations in HIV Preventive Vaccine Research. UNAIDS Guidance Document 00/07E/2000. UNAIDS, Geneva, Switzerland. <http://www.unaids.org>*





# International Nonproprietary Names for Pharmaceutical Substances (INN)

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

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

## Dénominations communes internationales des Substances pharmaceutiques (DCI)

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

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

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

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–73) y Recomendadas (1–35) se encuentran reunidas en *Cumulative List No. 9, 1996*. Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.

## Proposed International Nonproprietary Names: List 83

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for **List 83 Proposed INN not later than 31 January 2001**.

## Dénominations communes internationales proposées: Liste 83

Des observations ou des objections formelles à l'égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l'Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans *WHO Drug Information*, c'est à dire pour la **Liste 83 de DCI Proposées le 31 janvier 2001 au plus tard**.

## Denominaciones Comunes Internacionales Propuestas: Lista 83

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en *WHO Drug Information*, es decir, para la **Lista 83 de DCI Propuestas el 31 de enero de 2001 a más tardar**.

<i>Proposed INN</i> (Latin, English, French, Spanish)	<i>Chemical name or description: Action and use: Molecular formula</i> <i>Chemical Abstracts Service (CAS) registry number: Graphic formula</i>
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<i>DCI Proposée</i>	<i>Nom chimique ou description: Propriétés et indications: Formule brute</i> <i>Numéro dans le registre du CAS: Formule développée</i>
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<i>DCI Propuesta</i>	<i>Nombre químico o descripción: Acción y uso: Fórmula empírica</i> <i>Número de registro del CAS: Fórmula desarrollada</i>
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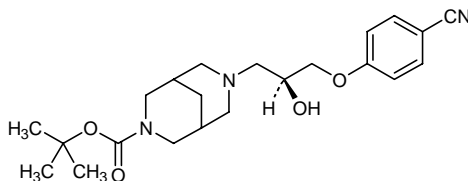
### adekalantum

adekalant	<i>tert-butyl 7-[(S)-3-(p-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo</i> <i>[3.3.1] nonane-3-carboxylate</i> <i>potassium channel blocker</i>
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adékalant	<i>7-[(2S)-3-(4-cyanophénoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]</i> <i>nonane-3-carboxylate de 1,1-diméthyléthyle</i> <i>antagoniste des canaux potassiques</i>
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adekalant	<i>7-[(S)-3-(p-cianofenoxi)-2-hidroxiopropil]-3,7-diazabicio[3.3.1]nonano-3-</i> <i>carboxilato de terc-butilo</i> <i>bloqueante de los canales de potasio</i>
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$C_{22}H_{31}N_3O_4$	227940-00-3
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**alemtuzumabum**

alemtuzumab

immunoglobulin G 1 (human-rat monoclonal CAMPATH-1H  $\gamma$ 1-chain anti-human antigen CD52), disulfide with human-rat monoclonal CAMPATH-1H light chain, dimer  
*immunomodulator*

alemtuzumab

immunoglobuline G1 anti-(antigène CD52 humain) (chaîne  $\gamma$ 1 de l'anticorps monoclonal de rat CAMPATH-1H humanisé), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de rat CAMPATH-1H humanisé  
*immunomodulateur*

alemtuzumab

inmunoglobulina G 1 anti-(antígeno humano CD52) (cadena  $\gamma$ 1 del anticuerpo monoclonal hombre-rata CAMPATH-1H), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal hombre-rata CAMPATH-1H  
*inmunomodulador*

216503-57-0

**aliskirenum**

aliskiren

(2S,4S,5S,7S)-5-amino-N-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonanamide  
*renin inhibitor*

aliskirène

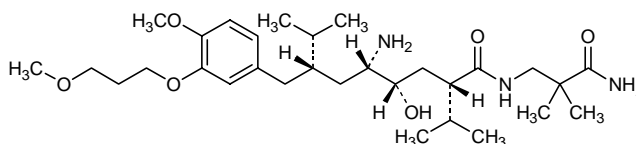
(2S,4S,5S,7S)-5-amino-N-(3-amino-2,2-diméthyl-3-oxopropyl)-4-hydroxy-7-[4-méthoxy-3-(3-méthoxypropoxy)benzyl]-8-méthyl-2-(1-méthyléthyl)nonanamide  
*inhibiteur de la rénine*

aliskiren

(2S,4S,5S,7S)-5-amino-N-(2-carbamoyl-2-metilpropil)-4-hidroxi-2-isopropil-7-[4-metoxi-3-(3-metoxipropoxi)encil]-8-metilnonanamida  
*inhibidor de la renina*

C<sub>30</sub>H<sub>53</sub>N<sub>3</sub>O<sub>6</sub>

173334-57-1

**amiloxatum**

amiloxate

isopentyl *p*-methoxycinnamate  
*sunscreen*

amiloxate

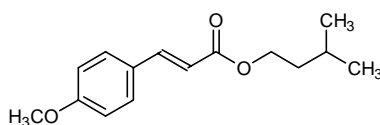
(*E*)-3-(4-méthoxyphényl)prop-2-énoate de 3-méthylbutyle  
*agent antisolaire*

amiloxato

*p*-metoxicinamato de isopentilo  
*filtro solar*

C<sub>15</sub>H<sub>20</sub>O<sub>3</sub>

71617-10-2



**atrasentanum**

atrasentan

(2*R*,3*R*,4*S*)-1-[(dibutylcarbamoyl)methyl]-2-(*p*-methoxyphenyl)-4-[3,4-(methylenedioxy)phenyl]-3-pyrrolidinecarboxylic acid  
*endothelin receptor antagonist*

atrasentan

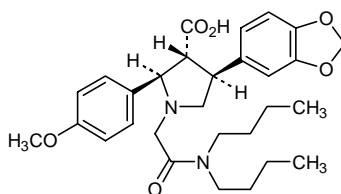
acide (2*R*,3*R*,4*S*)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoéthyl]-2-(4-méthoxyphényl)pyrrolidine-3-carboxylique  
*antagoniste du récepteur de l'endothéline*

atrasentán

ácido (2*R*,3*R*,4*S*)-1-[(dibutilcarbamoil)metil]-2-(*p*-metoxifenil)-4-[3,4-(metilenedioxi)fenil]-3-pirrolidinacarboxílico  
*antagonista del receptor de endotelina*

C<sub>29</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>

195733-43-8

**bevacizumabum**

bevacizumab

immunoglobulin G 1 (human-mouse monoclonal rhuMAb-VEGF  $\gamma$ -chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer  
*immunomodulator*

bévacizumab

immunoglobuline G1 anti-(facteur de croissance de l'endothélium vasculaire humain) (chaîne  $\gamma$ 1 de l'anticorps monoclonal de souris rhuMAb-VEGF humanisé), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris rhuMAb-VEGF humanisé  
*immunomodulateur*

bevacizumab

inmunoglobulina G 1 anti-(factor de crecimiento del endotelio vascular humano) (cadena  $\gamma$ 1 del anticuerpo monoclonal hombre ratón rhuMAb-VEGF), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal hombre-ratón rhuMAb-VEGF  
*immunomodulador*

C<sub>6638</sub>H<sub>10160</sub>N<sub>1720</sub>O<sub>2108</sub>S<sub>44</sub>

216974-75-3

**bivatuzumabum**

bivatuzumab

immunoglobulin G 1 (human-mouse monoclonal BIWA4  $\gamma$ 1-chain anti-human antigen CD44v8), disulfide with human-mouse monoclonal BIWA4  $\kappa$ -chain, dimer  
*immunomodulator*

bivatuzumab

immunoglobuline G1 anti-(antigène CD44v8 humain) (chaîne  $\gamma$ 1 de l'anticorps monoclonal de souris BIWA4 humanisé), dimère du disulfure avec la chaîne  $\kappa$  de l'anticorps monoclonal de souris BIWA4 humanisé  
*immunomodulateur*

bivatuzumab

inmunoglobulina G 1 anti-(antígeno humano CD44v8) cadena  $\gamma$ 1 del

anticuerpo monoclonal hombre-ratón BIWA4), dímero del disulfuro con la cadena  $\kappa$  del anticuerpo monoclonal hombre-ratón BIWA4  
*inmunomodulador*

214559-60-1

**capravirinum**

capravirine

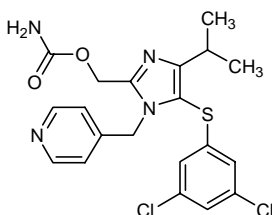
5-[(3,5-dichlorophenyl)thio]-4-isopropyl-1-(4-pyridylmethyl)imidazole-2-methanol carbamate (ester)  
*antiviral*

capravirine

carbamate de [5-[(3,5-dichlorophényl)sulfanyl]-4-(1-méthyléthyl)-1-(pyridin-4-ylméthyl)-1*H*-imidazol-2-yl]méthyle  
*antiviral*

capravirina

carbamato (éster)de 5-[(3,5-diclorofenil)tio]-4-isopropil-1-(4-piridilmetil)imidazol-2-metanol  
*antiviral*

C<sub>20</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>2</sub>S 178979-85-6**capromorelinum**

capromorelin

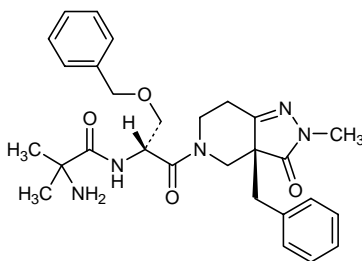
2-amino-*N*-[(1*R*)-1-[[3*aR*]-3*a*-benzyl-2,3,3*a*,4,6,7-hexahydro-2-methyl-3-oxo-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl]carbonyl]-2-(benzyloxy)ethyl]-2-methylpropanamide  
*growth hormone release stimulating peptide*

capromoréline

2-amino-*N*-[(1*R*)-2-[(3*aR*)-3*a*-benzyl-2-méthyl-3-oxo-2,3,3*a*,4,6,7-hexahydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl]-1-[(benzyloxy)méthyl]-2-oxoéthyl]-2-méthylpropanamide  
*peptide stimulant la libération de l'hormone de croissance*

capromorelina

2-amino-*N*-[(1*R*)-1-[[3*aR*]-3*a*-bencil-2,3,3*a*,4,6,7-hexahidro-2-metil-3-oxo-5*H*-pirazolo[4,3-*c*]piridin-5-il]carbonil]-2-(benciloxi)etil]-2-metilpropionamida  
*péptido estimulante de la liberación de la hormona del crecimiento*

C<sub>28</sub>H<sub>35</sub>N<sub>5</sub>O<sub>4</sub> 193273-66-4

**cridanimodum**

cridanimod

9-oxo-10-acridanacetic acid  
*immunomodulator*

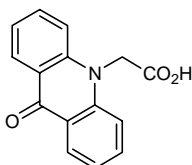
cridanimod

acide (9-oxoacridin-10(9*H*)-yl)acétique  
*immunomodulateur*

cridanimod

ácido 9-oxo-10-acridanacético  
*immunomodulador*C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub>

38609-97-1

**dabigatranum**

dabigatran

*N*-[[2-[(*p*-amidinoanilino)methyl]-1-methyl-5-benzimidazolyl]carbonyl]-*N*-2-pyridyl-β-alanine  
*thrombin inhibitor*

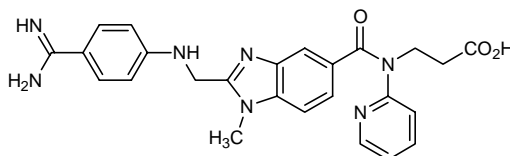
dabigatran

acide 3-[[[2-[[[4-(aminoiminométhyl)phényl]amino]méthyl]-1-méthyl-1*H*-benzimidazol-5-yl]carbonyl](pyridin-2-yl)amino]propanoïque  
*inhibiteur de la thrombine*

dabigatrán

*N*-[[2-[(*p*-amidinoanilino)metil]-1-metil-5-benzimidazolil]carbonil]-*N*-2-piridil-β-alanina  
*inhibidor de la trombina*C<sub>25</sub>H<sub>25</sub>N<sub>7</sub>O<sub>3</sub>

211914-51-1

**doripenemum**

doripenem

(+)-(4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-4-méthyl-7-oxo-3-[[3*S*,5*S*]-5-[(sulfamoylamino)méthyl]-3-pyrrolidinyl]thio]-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylic acid  
*antibacterial*

doripénem

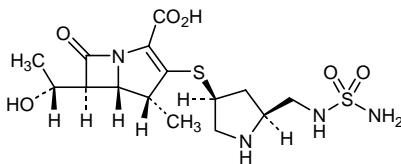
(+) -acide (4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyéthyl]-4-méthyl-7-oxo-3-[[3*S*,5*S*]-5-[(aminosulfonylamino)méthyl]pyrrolidin-3-yl]sulfanyl]-1-azabicyclo-[3.2.0]hept-2-ène-2-carboxylique  
*antibactérien*

doripenem

ácido (+)-(4*R*,5*S*,6*S*)-6-[(1*R*)-1-hidroxietil]-4-metil-7-oxo-3-[[3*S*,5*S*]-5-[(sulfamoilamino)metil]-3-pirrolidinil]tio]-1-azabicyclo[3.2.0]hept-2-eno-2-carboxílico  
*antibacteriano*

C<sub>15</sub>H<sub>24</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub>

148016-81-3

**ecraprostum**

ecraprost

butyl (4*R*,5*R*)-2,4-dihydroxy-5-[(1*E*,3*S*)-3-hydroxy-1-octenyl]-1-cyclopentene-1-heptanoate, 2-butyrate  
*prostaglandin*

écraprost

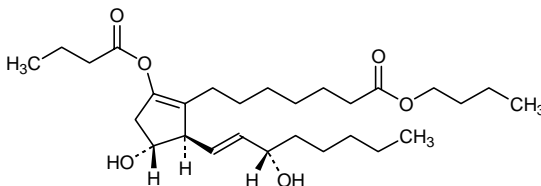
7-[(4*R*,5*R*)-2-(butanoyloxy)-4-hydroxy-5-[(1*E*,3*S*)-3-hydroxyoct-1-ényl]cyclopent-1-ényl]heptanoate de butyle  
*prostaglandine*

ecraprost

2-butirato de (4*R*,5*R*)-2,4-dihidroxi-5-[(1*E*,3*S*)-3-hidroxi-1-octenil]-1-ciclopenteno-1-heptanoato de butilo  
*prostaglandina*

C<sub>28</sub>H<sub>48</sub>O<sub>6</sub>

136892-64-3

**elarofibanum**

elarofiban

(*S*)-β-[(*R*)-1-[3-(4-piperidyl)propionyl]nipecotamido]-3-pyridinepropionic acid  
*fibrinogen receptor antagonist*

élarofiban

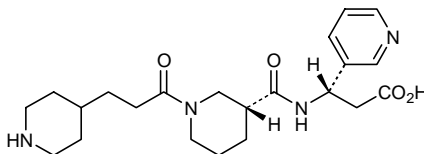
acide (3*S*)-3-[[[(3*R*)-1-[3-(pipéridin-4-yl)propanoyl]piperidin-3-yl]carbonyl]amino]-3-(pyridin-3-yl)propanoïque  
*antagoniste du récepteur du fibrinogène*

elarofibán

ácido (*S*)-β-[(*R*)-1-[3-(4-piperidil)propionil]nipecotamido]-3-piridinapropiónico  
*antagonista del receptor del fibrinógeno*

C<sub>22</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>

198958-88-2



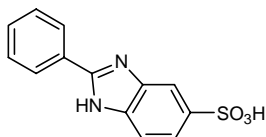
**ensulizolum**

ensulizole 2-phenyl-5-benzimidazolesulfonic acid  
*sunscreen*

ensulizole acide 2-phényl-1*H*-benzimidazole-5-sulfonique  
*agent antisolare*

ensulizol ácido 2-fenil-5-bencimidazolsulfónico  
*filtro solar*

C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>S 27503-81-7

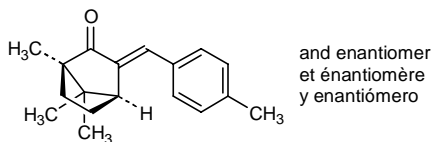
**enzacamenum**

enzacamene (±)-3-(*p*-methylbenzylidene)camphor  
*sunscreen*

enzacamène (*E*)-(1*RS*,4*SR*)-1,7,7-triméthyl-3-(4-méthylbenzylidène)bicyclo[2.2.1]=  
heptan-2-one  
*agent antisolare*

enzacameno 1,7,7-trimetil-3-(4-metilbencilideno)biciclo[2.2.1]heptan-2-ona  
*filtro solar*

C<sub>18</sub>H<sub>22</sub>O 36861-47-9

**eptaplatinum**

eptaplatin *cis*-[(4*R*,5*R*)-2-isopropyl-1,3-dioxolane-4,5-bis(methylamine)-  
*N,N'*][malonato(2-)-*O,O'*]platinum  
*antineoplastica*

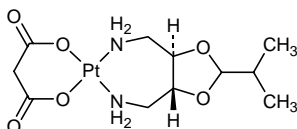
eptaplatine (*SP*-4-2)-[[*(4R,5R)*-2-(1-méthyléthyl)-1,3-dioxolane-4,5-  
diyl]bis(méthanamine)-*N,N'*][propanedioato(2-)-*O,O'*]platine  
*antineoplasique*

eptaplatino *cis*-[(4*R*,5*R*)-2-isopropil-1,3-dioxolano-4,5-bis(metilamina)-*N,N'*][malonato(2-)-  
*O,O'*]platino  
*antineoplásico*



C<sub>11</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>Pt

146665-77-2

**ezetimibum**

ezetimibe

(3*R*,4*S*)-1-(*p*-fluorophényl)-3-[(3*S*)-3-(*p*-fluorophényl)-3-hydroxypropyl]-4-(*p*-hydroxyphényl)-2-azétidinone  
*antihyperlipidaemic*

ézétimibe

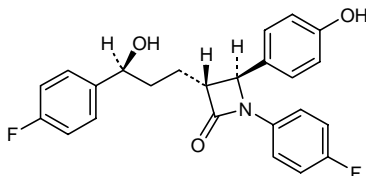
(3*R*,4*S*)-1-(4-fluorophényl)-3-[(3*S*)-3-(4-fluorophényl)-3-hydroxypropyl]-4-(4-hydroxyphényl)azétidin-2-one  
*antihyperlipidémique*

ezetimiba

(3*R*,4*S*)-1-(*p*-fluorofenil)-3-[(3*S*)-3-(*p*-fluorofenil)-3-hidroxiopropil]-4-(*p*-hidroxiifenil)-2-azetidina  
*antihiperlipémico*

C<sub>24</sub>H<sub>21</sub>F<sub>2</sub>NO<sub>3</sub>

163222-33-1

**fosamprenavirum**

fosamprenavir

(3*S*)-tetrahydro-3-furyl [(α*S*)-α-[(1*R*)-1-hydroxy-2-(*N*<sup>1</sup>-isobutylsulfanyl=amido)éthyl] phényl]carbamate, dihydrogen phosphate (ester)  
*antiviral*

fosamprénavir

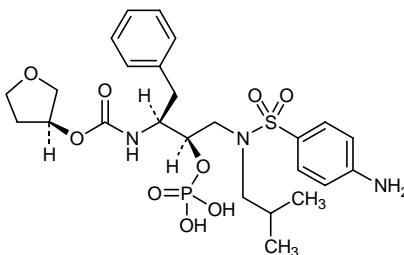
dihydrogénophosphate de (1*R*,2*S*)-1-[[[(4-aminophényl)sulfonyl](2-méthyl=propyl)amino]méthyl]-3-phényl-2-[[[(3*S*)-tétrahydrofuran-3-yl]oxy]=carbonyl]amino] propyle  
*antiviral*

fosamprenavir

dihidrógenofosfato (éster) de [(α*S*)-α-[(1*R*)-1-hidroxi-2-(*N*<sup>1</sup>-isobutilsulfanyl=amido)etil]fenetil]carbamato de(3*S*)-tetrahidro-3-furilo  
*antiviral*

C<sub>25</sub>H<sub>36</sub>N<sub>3</sub>O<sub>9</sub>PS

226700-79-4



**fosfluconazolum**

fosfluconazole

2,4-difluoro- $\alpha,\alpha$ -bis(1*H*-1,2,4-triazol-1-ylmethyl)benzyl alcohol, dihydrogen phosphate (ester)  
*antifungal*

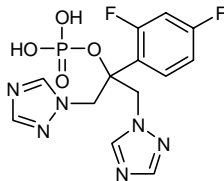
fosfluconazole

dihydrogénophosphate de 1-(2,4-difluorophényl)-2-(1*H*-1,2,4-triazol-1-yl)-1-(1*H*-1,2,4-triazol-1-ylméthyl)éthyle  
*antifongique*

fosfluconazol

dihidrógenofosfato (éster) de 2,4-difluoro- $\alpha,\alpha$ -bis(1*H*-1,2,4-triazol-1-ilmetil) bencilo  
*antifúngico*

C<sub>13</sub>H<sub>13</sub>F<sub>2</sub>N<sub>6</sub>O<sub>4</sub>P 194798-83-9

**fosvesetum**

fosveset

*N*-[2-[bis(carboxyméthyl)amino]éthyl]-*N*-[(*R*)-2-[bis(carboxyméthyl)amino]-3-hydroxypropyl]glycine, 4,4-diphénylcyclohexyl hydrogen phosphate (ester)  
*pharmaceutical aid*

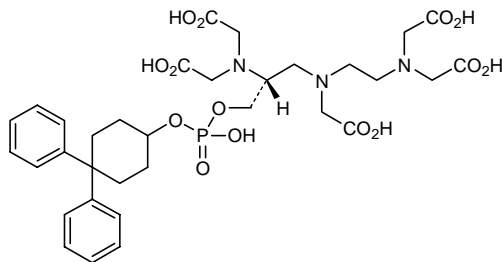
fosvését

acide 2,2'-[[1(*R*)-1-[[[2-[bis(carboxyméthyl)amino]éthyl](carboxyméthyl)=amino] méthyl]-2-[[[(4,4-diphénylcyclohexyl)oxy]hydroxyphosphoryl]=oxy]éthyl]imino] diacétique  
*auxiliaire pharmaceutique*

fosveset

4,4-difenilciclohexilhidrógenofosfato (éster) de *N*-[2-[bis(carboximetil)=amino]etil]-*N*-[(*R*)-2-[bis(carboximetil)amino]-3-hidroxiopropil]glicina  
*excipiente*

C<sub>33</sub>H<sub>44</sub>N<sub>3</sub>O<sub>14</sub>P 193901-91-6



**gadofosvesetum**

gadofosveset

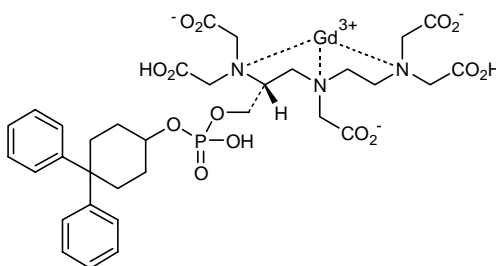
trihydrogen [*N*-[2-[bis(carboxymethyl)amino]ethyl]-*N*-[(*R*)-2-[bis(carboxymethyl)amino]-3-hydroxypropyl]glycine 4,4-diphenylcyclohexyl hydrogen phosphato(6-)]gadolate(3-)  
*diagnostic agent*

gadofosvészet

trihydrogéo[2,2'-[[1(*R*)-1-[[[2-[bis[(carboxy-κ-*O*)méthyl]amino-κ-*M*]éthyl]=[carboxy-κ-*O*]méthyl]amino-κ-*M*]méthyl]-2-[[[(4,4-diphénylcyclohexyl)=oxy]hydroxyphosphoryl]oxy]éthyl]imino-κ-*N*]diacétato(6-)-κ-*O*-κ-*O*]=gadolate(3-)  
*produit à usage diagnostique*

gadofosveset

[4,4-difenilciclohexilhidrógenofosfato de (6-)*N*-[2-[bis(carboximetil)amino]=etil]-*N*-[(*R*)-2-[bis(carboximetil)amino]-3-hidroxiopropil]glicina]gadolato(3-) de trihidrógeno  
*agente de diagnóstico*

C<sub>33</sub>H<sub>41</sub>GdN<sub>3</sub>O<sub>14</sub>P 193901-90-5**gemtuzumabum**

gemtuzumab

immunoglobulin G 4 (human-mouse monoclonal hP67.6 γ4-chain anti-human antigen CD 33), disulfide with human-mouse monoclonal hP67.6 κ-chain, dimer  
*immunomodulator*

gemtuzumab

immunoglobuline G 4 anti-(antigène CD 33 humain) (chaîne γ4 de l'anticorps monoclonal de souris hP67.6 humanisé), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris hP67.6 humanisé  
*immunomodulateur*

gemtuzumab

inmunoglobulina G 4 anti-(antígeno humano CD 33) (cadena γ4 del anticuerpo monoclonal hP67.6 hombre-ratón), dímero del disulfuro con la cadena κ del anticuerpo monoclonal hP67.6 hombre-ratón  
*inmunomodulador*

220578-59-6

**idraparinum natricum**

idraparinum sodium

methyl O-2,3,4-tri-O-methyl-6-O-sulfo- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- $\beta$ -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-methyl- $\alpha$ -L-idopyranuronosyl-(1 $\rightarrow$ 4)-2,3,6-tri-O-sulfo- $\alpha$ -D-glucopyranoside nonasodium

*antithrombotic*

idraparinum sodique

O-2,3,4-tri-O-méthyl-6-O-sulfo- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-méthyl- $\beta$ -D-glucopyranuronosyl-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-2,3-di-O-méthyl- $\alpha$ -L-idopyranuronosyl-(1 $\rightarrow$ 4)-2,3,6-tri-O-sulfo- $\alpha$ -D-glucopyranoside de méthyle nonasodique

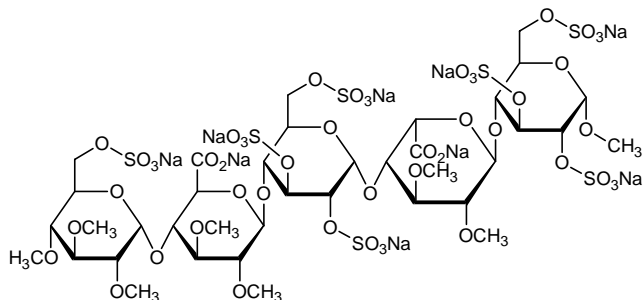
*antithrombotique*

idraparinum sódico

O-2,3,4-tri-O-metil-6-O-sulfo- $\alpha$ -D-glucopiranosil-(1 $\rightarrow$ 4)-O-2,3-di-O-metil- $\beta$ -D-glucopiranosil-(1 $\rightarrow$ 4)-O-2,3,6-tri-O-sulfo- $\alpha$ -D-glucopiranosil-(1 $\rightarrow$ 4)-O-2,3-di-O-metil- $\alpha$ -L-idopiranosil-(1 $\rightarrow$ 4)-2,3,6-tri-O-sulfo- $\alpha$ -D-glucopiranoside de metilo nonasódico

*antitrombótico*C<sub>38</sub>H<sub>55</sub>Na<sub>9</sub>O<sub>49</sub>S<sub>7</sub>

149920-56-9

**isatoribinum**

isatoribine

5-amino-3-( $\beta$ -D-ribofuranosyl)thiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione  
*immunomodulator*

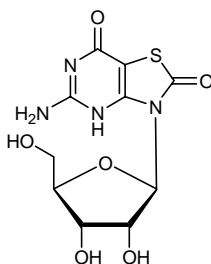
isatoribine

5-amino-3-( $\beta$ -D-ribofuranosyl)thiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione  
*immunomodulateur*

isatoribina

5-amino-3- $\beta$ -D-ribofuranosiltiazolo[4,5-*d*]pirimidina-2,7(3*H*,6*H*)-diona  
*inmunomodulador*

122970-40-5

**labradimilum**

labradimil

*N*<sup>2</sup>-[(*S*)-2-[L-arginyl-L-prolyl-*trans*-4-hydroxy-L-prolyl]glycyl-3-(2-thienyl)-L-alanyl-L-seryl-L-prolinamido]-3-(*p*-methoxyphenyl)propyl]-L-arginine  
*bradykinin receptor agonist*

labradimil

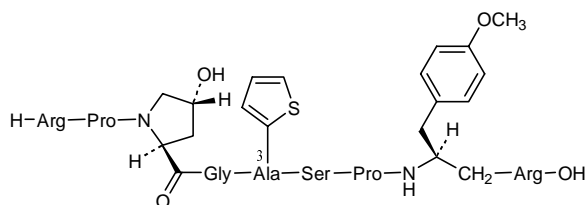
*N*<sup>2</sup>-[(2*S*)-2-[[L-arginyl-L-prolyl-[(4*R*)-4-hydroxy-L-prolyl]-glycyl-3-(thiophén-2-yl)]-L-alanyl]-L-seryl-L-prolyl]amino]-3-(4-méthoxyphényl)propyl]-L-arginine  
*agoniste de récepteurs de la bradykinine*

labradimil

*N*<sup>2</sup>-[(*S*)-2-[L-arginil-L-proliil-*trans*-4-hidroxi-L-proliilglicil-3-(2-tienil)-L-alanil-L-seril-L-prolinamido]-3-(*p*-metoxifenil)propil]-L-arginina  
*agonista de los receptores de bradiquinina*

C<sub>49</sub>H<sub>75</sub>N<sub>15</sub>O<sub>12</sub>S

159768-75-9

**ladirubicinum**

ladirubicin

(1*S*,3*S*)-3-acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-6,11-dioxo-1-naphthacenyl 3-(1-aziridinyl)-2,3,6-trideoxy-4-*O*-(methylsulfonyl)- $\alpha$ -L-lyxo-hexopyranoside  
*antineoplastic, antibiotic*

ladirubicine

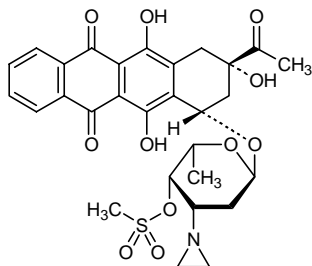
(7*S*,9*S*)-9-acétyl-7-[[3-(aziridin-1-yl)-4-*O*-(méthylsulfonyl)-2,3,6-tridésoxy- $\alpha$ -L-lyxo-hexopyranosyl]oxy]-6,9,11-trihydroxy-7,8,9,10-tétrahydratétracène-5,12-dione  
*antineoplasique, antibiotique*

ladirubicina

(1*S*,3*S*)-3-acetil-1,2,3,4,6,11-hexahidro-3,5,12-trihidroxi-6,11-dioxo-1-naftaceniil 3-(1-aziridinil)-2,3,6-tridesoxi-4-*O*-(metilsulfonil)- $\alpha$ -L-lixo-hexopiranosído  
*antineoplásico, antibiótico*

C<sub>29</sub>H<sub>31</sub>NO<sub>11</sub>S

171047-47-5

**lerdelimumabum**

lerdelimumab

immunoglobulin G4, anti-(human transforming growth factor b2) (human monoclonal CAT-152  $\gamma$  4-chain), disulfide with human monoclonal CAT-152  $\lambda$ -chain, dimer  
*immunomodulator*

lérdelimumab

immunoglobuline G4, anti-(facteur de croissance transformant humain b2) (chaîne  $\gamma$  4 de l'anticorps monoclonal humain CAT-152), dimère du disulfure avec la chaîne  $\lambda$  de l'anticorps monoclonal humain CAT-152  
*immunomodulateur*

lerdelimumab

inmunoglobulina G4, anti-(factor b2 de crecimiento transformador humano)(cadena  $\gamma$  4 del anticuerpo monoclonal humano CAT-152), dimero del disulfuro con la cadena  $\lambda$  del anticuerpo monoclonal humano CAT-152  
*inmunomodulador*

285985-06-0

**levmetamfetaminum**

levmetamfetamine

(-)-(R)-N, $\alpha$ -dimethylphenethylamine  
*sympathomimetic*

levmétamfétamine

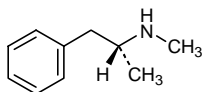
(-)-(2R)-N-méthyl-1-phénylpropan-2-amine  
*sympathomimétique*

levmetanfetamina

(-)-(R)-N, $\alpha$ -dimetilfenetilamina  
*simpaticomimético*

C<sub>10</sub>H<sub>15</sub>N

33817-09-3



**lixivaptanum**

lixivaptan

3'-chloro-5-fluoro-4'-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ylcarbonyl)-*o*-toluanilide  
*vasopressin V2 receptor antagonist*

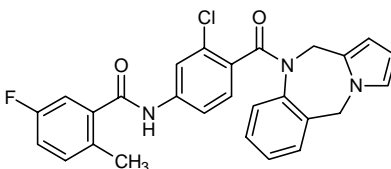
lixivaptan

*N*-[3-chloro-4-[(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazépin-10(11*H*)-yl)carbonyl]phényl]-5-fluoro-2-méthylbenzamide  
*antagoniste du récepteur V2 de la vasopressine*

lixivaptán

3'-cloro-5-fluoro-4'-(5*H*-pirrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ilcarbonyl)-*o*-toluanilida  
*antagonista del receptor V2 de la vasopresina*

C<sub>27</sub>H<sub>21</sub>ClFN<sub>3</sub>O<sub>2</sub>      168079-32-1

**melevodopum**

melevodopa

(-)-3,4-dihydroxy-L-phenylalanine, methyl ester  
*dopamine receptor agonist*

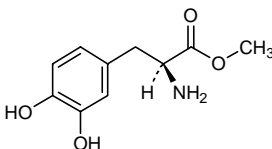
mélévodopa

(-)-(2*S*)-2-amino-3-(3,4-dihydroxyphényl)propanoate de méthyle  
*agoniste des récepteurs de la dopamine*

melevodopa

éster metílico de (-)-3,4-dihidroxi-L-fenilalanina  
*agonista de los receptores de la dopamina*

C<sub>10</sub>H<sub>13</sub>NO<sub>4</sub>      7101-51-1

**meradimatum**

meradimate

*p*-menth-3-yl anthranilate  
*sunscreen*

méradimate

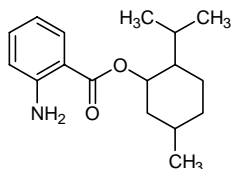
2-aminobenzoate de 5-méthyl-2-(1-méthyléthyl)cyclohexyle  
*agent antisolaire*

meradimato

antranilato de *p*-ment-3-ilo  
*filtro solar*

C<sub>17</sub>H<sub>25</sub>NO<sub>2</sub>

134-09-8

**norelgestrominum**

norelgestromin

13-ethyl-17-hydroxy-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one oxime  
*contraceptive*

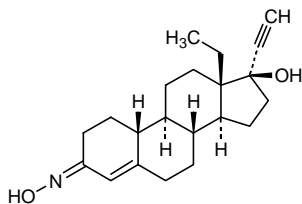
norélgestromine

13-éthyl-17-hydroxy-18,19-dinor-17 $\alpha$ -prégn-4-én-20-yn-3-one (*E*)-oxime  
*contraceptif*

norelgestromina

13-etil-17-hidroxi-18,19-dinor-17 $\alpha$ -pregn-4-en-20-in-3-ona oxima  
*contraceptivo*C<sub>21</sub>H<sub>29</sub>NO<sub>2</sub>

53016-31-2

**ocinoxatum**

ocinoxate

2-ethylhexyl *p*-methoxycinnamate  
*sunscreen*

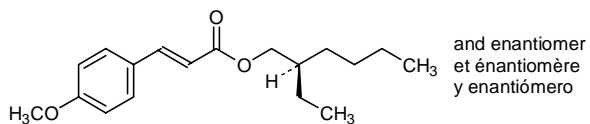
ocinoxate

(*E*)-3-(4-méthoxyphényl)prop-2-énoate de (2*RS*)-2-éthylhexyle  
*agent antisolare*

ocinoxato

*p*-metoxicinamato de 2-etilhexilo  
*filtro solar*C<sub>18</sub>H<sub>26</sub>O<sub>3</sub>

5466-77-3





**octisalatum**

octisalate

2-ethylhexyl salicylate  
*sunscreen*

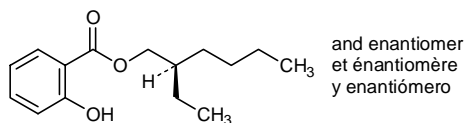
octisalate

2-hydroxybenzoate de (2RS)-2-éthylhexyle  
*agent antisoilaire*

octisalato

salicilato de 2-etilhexilo  
*filtro solar*C<sub>15</sub>H<sub>22</sub>O<sub>3</sub>

118-60-5

**opaviralinum**

opaviraline

isopropyl (S)-2-ethyl-7-fluoro-3,4-dihydro-3-oxo-1(2H)-  
quinoxalinecarboxylate  
*antiviral*

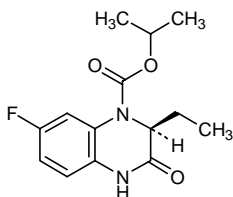
opaviraline

(2S)-2-éthyl-7-fluoro-3-oxo-3,4-dihydroquinoxaline-1(2H)-carboxylate de  
1-méthyléthyle  
*antiviral*

opaviralina

(S)-2-etil-7-fluoro-3,4-dihidro-3-oxo-1(2H)-quinoxalinacarboxilato de  
isopropilo  
*antiviral*C<sub>14</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>3</sub>

178040-94-3



**opebacanum**

opebacan 132-L-alanine-1-193-bactericidal/permeability-increasing protein (human)  
*antimicrobial*

opébacan [132-L-alanine]-1-193-protéine humaine augmentant la perméabilité et à  
action bactéricide  
*antimicrobien*

opebacán 132-L-alanina-1-193-proteína(humana) bactericida/incrementadora de la  
permeabilidad  
*antimicrobial*

206254-79-7

VNPGVVVRIS	QKGLDYASQQ	GTAALQKELK	RIKIPDYSDS
FKIKHLGKGH	YSFYSM DIRE	FQLPSSQISM	VPNVGLKFISI
SNANIKISGK	WKAQKRFLKM	SGNFDSLIEG	MSISADLKLG
SNPTSGKPTI	TASSCSSHIN	SVHVHISKSK	VGWLIQLFHK
KIESALRNKM	NSQVCEKVTN	SVSSELQPYF	QTL

**oritavancinum**

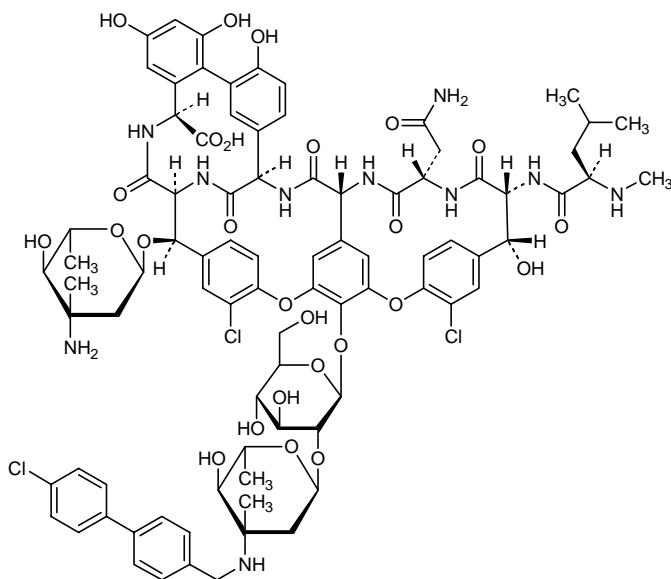
oritavancin (4''R)-22-O-(3-amino-2,3,6-trideoxy-3-C-methyl- $\alpha$ -L-arabino-  
hexopyranosyl)-N<sup>β</sup>-[p-(p-chlorophenyl)benzyl]vancomycin  
*antibacterial*

oritavancine acide (3S,6R,7R,22R,23S,26S,36R,38aR)-22-(3-amino-3-C-méthyl-2,3,6-  
tridésoxy- $\alpha$ -L-arabino-hexopyranosyloxy)-3-(2-amino-2-oxoéthyl)-10,19-  
dichloro-44-[[2-O-[3-[[4'-chlorobiphényl-4-yl)méthyl]amino]-3-C-méthyl-  
2,3,6-tridésoxy- $\alpha$ -L-arabino-hexopyranosyl]- $\beta$ -D-glucopyranosyl]oxy]-  
7,28,30,32-tétrahydroxy-6-[[2R)-4-méthyl-2-(méthylamino) pentanoyl]=  
amino]-2,5,24,38,39-pentaoso-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-  
tétradécahydro-8,11:18,21-diéthéno-22H-13,16:31,35-diméthéno-1H,13H-  
[1,6,9]oxadiazacyclohexadécino [4,5-m][10,2,16]=  
benzoxadiazacyclotétracosène-26-carboxylique  
*antibactérien*

oritavancina (4''R)-22-O-(3-amino-2,3,6-tridesoxi-3-C-metil- $\alpha$ -L-arabino-hexopiranosil)-  
N<sup>β</sup>-[p-(p-clorofenil)bencil]vancomicina  
*antibacteriano*

C<sub>86</sub>H<sub>97</sub>Cl<sub>3</sub>N<sub>10</sub>O<sub>26</sub>

171099-57-3



ozogamicin

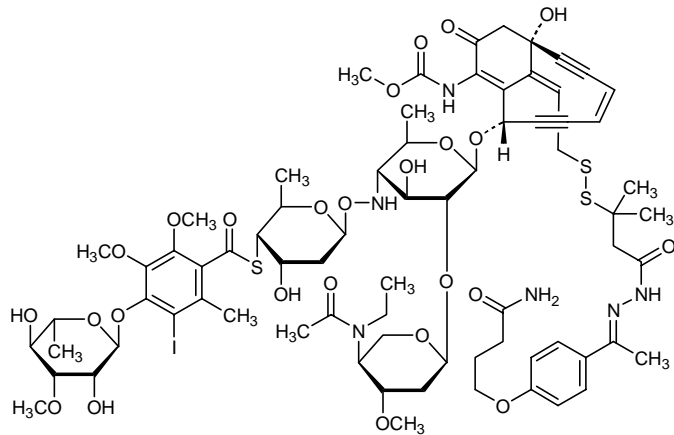
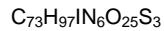
methyl (1*R*,4*Z*,8*S*,13*E*)-13-[2-[[2-[[[*p*-(3-carbamoylpropoxy)- $\alpha$ -methylbenzylidene]hydrazino]carbonyl]-1,1-dimethylethyl]dithio]ethylidene]-8-[[4,6-dideoxy-4-[[[2,6-dideoxy-4-*S*-[4-[[6-deoxy-3-*O*-methyl- $\alpha$ -*L*-mannopyranosyl]oxy]-3-iodo-5,6-dimethoxy-*o*-toluoyl]-4-thio- $\beta$ -*D*-ribohexopyranosyl]oxy]amino]-2-*O*-[2,4-dideoxy-4-(*N*-ethylacetamido)-3-*O*-methyl- $\alpha$ -*L*-threo-pentopyranosyl]- $\beta$ -*D*-glucopyranosyl]oxy]-1-hydroxy-11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diène-10-carbamate  
*immunomodulator*

ozogamicine

[(1*R*,4*Z*,8*S*,13*E*)-8-[[2-*O*-[4-(acétyléthylamino)-3-*O*-méthyl-2,4-didésoxy- $\alpha$ -*L*-thréo-pentopyranosyl]-4-[[[4-*S*-[3-iodo-5,6-diméthoxy-2-méthyl-4-[[3-*O*-méthyl-6-désoxy- $\alpha$ -*L*-mannopyranosyl]oxy]benzoyl]-2,6-didésoxy-4-thio- $\beta$ -*D*-ribohexopyranosyl]oxy]amino]-4,6-didésoxy- $\beta$ -*D*-glucopyranosyl]oxy]-13-[2-[[3-[[1-4-(4-amino-4-oxobutoxy)phényl]éthylidène]hydrazino]-1,1-diméthyl-3-oxopropyl]disulfanyl]éthylidène]-1-hydroxy-11-oxobicyclo[7.3.1]tridéca-4,9-diène-2,6-diyn-10-yl]carbamate de méthyle  
*immunomodulateur*

ozogamicina

(1*R*,4*Z*,8*S*,13*E*)-13-[2-[[2-[[[*p*-(3-carbamoylpropoxy)- $\alpha$ -metilbencilideno]hidrazino]carbonil]-1,1-dimetiletil]ditio]etilideno]-8-[[4,6-didesoxi-4-[[[2,6-didesoxi-4-*S*-[4-[[6-desoxi-3-*O*-metil- $\alpha$ -*L*-manopiranosil]oxi]-3-iodo-5,6-dimetoxi-*o*-toluocil]-4-tio- $\beta$ -*D*-ribohexopiranosil]oxi]amino]-2-*O*-[2,4-didesoxi-4-(*N*-etilacetamido)-3-*O*-metil- $\alpha$ -*L*-treo-pentopiranosil]- $\beta$ -*D*-glucopiranosil]oxi]-1-hidroxi-11-oxobicyclo[7.3.1]tridéca-4,9-dieno-2,6-diina-10-carbamato de metilo  
*immunomodulador*



### paliperidonum

paliperidone

(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one  
*antidepressant*

palipéridone

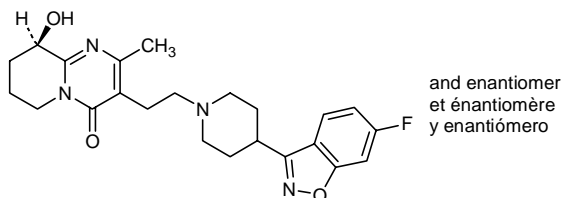
(9*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)pipéridin-1-yl]éthyl]-2-méthyl-4-oxo-6,7,8,9-tétrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yle  
*antidépresseur*

paliperidona

(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-il)piperidino]etil]-6,7,8,9-tetrahydro-9-hidroxi-2-metil-4*H*-pirido[1,2-*a*]pirimidin-4-ona  
*antidepressivo*

C<sub>23</sub>H<sub>26</sub>FN<sub>4</sub>O<sub>3</sub>

144598-75-4

**ravuconazolum**

ravuconazole

*p*-[2-[( $\alpha R, \beta R$ )-2,4-difluoro- $\beta$ -hydroxy- $\alpha$ -methyl- $\beta$ -(1*H*-1,2,4-triazol-1-yl)methyl]phenethyl]-4-thiazolyl]benzonitrile  
*antifungal*

ravuconazole

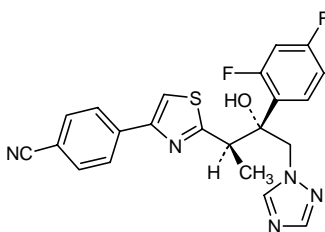
4-[2-[(1*R,2R*)-2-(2,4-difluorophényl)-2-hydroxy-1-méthyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]thiazol-4-yl]benzonitrile  
*antifongique*

ravuconazol

*p*-[2-[( $\alpha R, \beta R$ )-2,4-difluoro- $\beta$ -hidroxi- $\alpha$ -metil- $\beta$ -(1*H*-1,2,4-triazol-1-ilmetil)fenetil]-4-tiazolil]benzonitrilo  
*antifúngico*

C<sub>22</sub>H<sub>17</sub>F<sub>2</sub>N<sub>5</sub>OS

182760-06-1

**rimonabantum**

rimonabant

5-(*p*-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidinopyrazole-3-carboxamide  
*CB1 cannabinoid receptor antagonist*

rimonabant

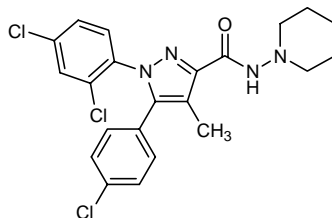
5-(4-chlorophényl)-1-(2,4-dichlorophényl)-4-méthyl-*N*-(pipéridin-1-yl)-1*H*-pyrazole-3-carboxamide  
*antagoniste des récepteurs CB1 aux cannabinoïdes*

rimonabant

5-(*p*-clorofenil)-1-(2,4-diclorofenil)-4-metil-*N*-piperidinopirazol-3-carboxamida  
*antagonista del receptor CB1 del cannabinoid*

C<sub>22</sub>H<sub>21</sub>Cl<sub>3</sub>N<sub>4</sub>O

168273-06-1

**rostoporfinum**

rostoporfin

(OC-6-13)-dichloro[ethyl (18*RS*, 19*SR*)-3,4,20,21-tetrahydro-4,9,14,19-tetraethyl-18,19-dihydro-3,8,13,18-tetramethyl-20-phorbinecarboxylato (2-)-*N*<sup>23</sup>,*N*<sup>24</sup>,*N*<sup>25</sup>,*N*<sup>26</sup>]tin  
*photosensitizer*

rostoporfine

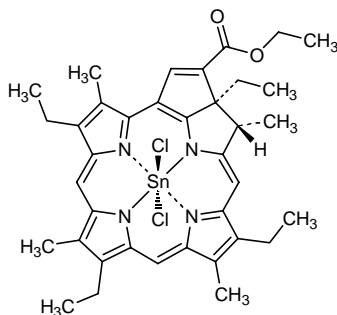
(OC-6-13)-dichloro[(2*RS*,3*SR*)-2,7,12,17-tétraéthyl-3,8,13,18-tétraméthyl-2,3-dihydrocyclopenta[*a*,*h*]porphyrine-2<sup>1</sup>-carboxylato(3-)-*N*<sup>21</sup>,*N*<sup>22</sup>,*N*<sup>23</sup>,*N*<sup>24</sup>]stannate(2-) d'éthyle  
*photosensibilisant*

rostoporfina

(OC-6-13)-dicloro[(18*RS*, 19*SR*)-3,4,20,21-tetradeshidro-4,9,14,19-tetraetil-18,19-dihidro-3,8,13,18-tetrametil-20-forbinacarboxilato de etilo (2-)-*N*<sup>23</sup>,*N*<sup>24</sup>,*N*<sup>25</sup>,*N*<sup>26</sup>]estaño  
*agente fotosensibilizante*

C<sub>37</sub>H<sub>42</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>2</sub>Sn

114494-17-6



and enantiomer  
et énantiomère  
y enantiómero

**rosuvastatinum**

rosuvastatin

(3*R*,5*S*,6*E*)-7-[4-(*p*-fluorophenyl)-6-isopropyl-2-(*N*-methylmethane sulfonamido)-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid  
*antihyperlipidaemic*

rosuvastatine

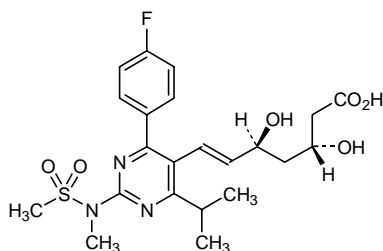
acide (3*R*,5*S*,6*E*)-7-[4-(4-fluorophényl)-6-(1-méthyléthyl)-2-[méthyl(méthylsulfonyl)amino]pyrimidin-5-yl]-3,5-dihydroxyhept-6-énoïque  
*antihyperlipidémiant*

rosuvastatina

ácido (3*R*,5*S*,6*E*)-7-[4-(*p*-fluorofenil)-6-isopropil-2-(*N*-metilmetano sulfonamido)-5-pirimidinil]-3,5-dihidroxi-6-heptenoico  
*antihiperlipémico*

C<sub>22</sub>H<sub>21</sub>Cl<sub>3</sub>N<sub>4</sub>O

168273-06-1

**rotigotinum**

rotigotine

(-)-(S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol  
*antiparkinsonian, dopamine D2 receptor agonist*

rotigotine

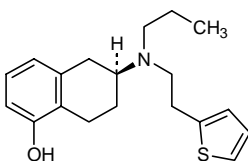
(-)-(6S)-6-[propyl[2-(thiophén-2-yl)éthyl]amino]-5,6,7,8-tétrahydronaphtalén-1-ol  
*antiparkinsonien, agoniste des récepteurs dopaminergiques D2*

rotigotina

(-)-(S)-5,6,7,8-tetrahidro-6-[propil[2-(2-tienil)etil]amino]-1-naftol  
*antiparkinsoniano, agonista del receptor D2 de la dopamina*

C<sub>19</sub>H<sub>25</sub>NOS

99755-59-6

**ruplizumabum**

ruplizumab

immunoglobulin G 1 (human-mouse monoclonal 5c8  $\gamma$ 1-chain anti-human CD 40 ligand), disulfide with human-mouse monoclonal 5c8  $\kappa$ -chain, dimer  
*immunomodulator*

ruplizumab

immunoglobuline G1 anti-(ligand CD 40 humain) (chaîne  $\gamma$ 1 de l'anticorps monoclonal de souris 5c8 humanisé), dimère du disulfure avec la chaîne  $\kappa$  de l'anticorps monoclonal de souris 5c8 humanisé  
*immunomodulateur*

ruplizumab

inmunoglobulina G 1 anti-(ligando CD 40 humano) (cadena  $\gamma$ 1 del anticuerpo monoclonal hombre-ratón 5c8), dímero del disulfuro con la cadena  $\kappa$  del anticuerpo monoclonal hombre-ratón 5c8  
*immunomodulador*

220651-94-5

**sitaxentanum**

sitaxentan

*N*-(4-chloro-3-methyl-5-isoxazolyl)-2-[[4,5-(methylenedioxy)-*o*-tolyl]acetyl]-3-thiophenesulfonamide  
*endothelin receptor antagonist*

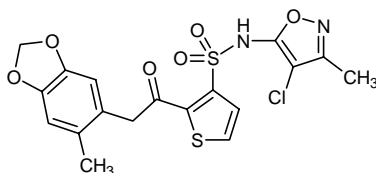
sitaxentan

*N*-(4-chloro-3-méthylisoxazol-5-yl)-2-[(6-méthyl-1,3-benzodioxol-5-yl)acétyl]thiophène-3-sulfonamide  
*antagoniste du récepteur de l'endothéline*

sitaxentán

*N*-(4-cloro-3-metil-5-isoxazolil)-2-[[4,5-(metilenedioxi)-*o*-tolil]acetil]-3-tiofenosulfonamida  
*antagonista del receptor de la endotelina*

C<sub>18</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>6</sub>S<sub>2</sub> 184036-34-8

**talaporfinum**

talaporfin

*N*-[[[(2*S*,3*S*)-18-carboxy-2-(2-carboxyethyl)-13-ethyl-2,3-dihydro-3,7,12,17-tetramethyl-8-vinylporphyrin-20-yl]acetyl]-*L*-aspartic acid  
*photosensitizer*

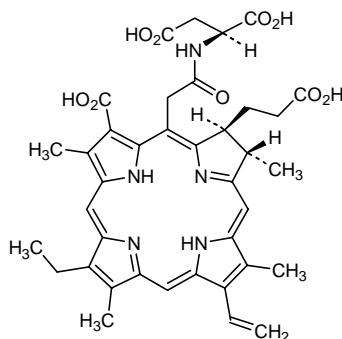
talaporfine

(2*S*)-2-[[[(7*S*,8*S*)-3-carboxy-7-(2-carboxyéthyl)-13-éthényl-18-éthyl-2,8,12,17-tétraméthyl-7,8-dihydroporphyrin-5-yl]acétyl]amino]butanedioïque  
*photosensibilisateur*

talaporfina

*N*-[[[(2*S*,3*S*)-18-carboxi-2-(2-carboxietil)-13-etil-2,3-dihidro-3,7,12,17-tetrametil-8-vinilporfirin-20-il]acetil]-ácido-*L*-aspártico  
*agente fotosensibilizante*

C<sub>38</sub>H<sub>41</sub>N<sub>5</sub>O<sub>9</sub> 220201-39-8





**ticalopridum**

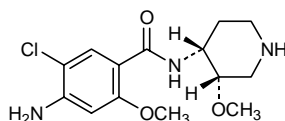
ticalopride

4-amino-5-chloro-*N*-[(3*S*,4*R*)-3-methoxy-4-piperidyl]-*o*-anisamide  
*D2/5HT2A antagonist*

ticalopride

4-amino-5-chloro-2-méthoxy-*N*-[(3*S*,4*R*)-3-méthoxypipéridin-4-yl]benzamide  
*antagoniste des récepteurs D2 et 5HT2A*

ticaloprida

4-amino-5-cloro-*N*-[(3*S*,4*R*)-3-metoxi-4-piperidil]-*o*-anisamida  
*antagonista del receptor D2 et 5HT2A*C<sub>14</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>3</sub> 202590-69-0**tolvaptanum**

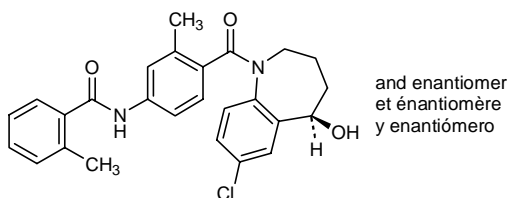
tolvaptan

(±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide  
*vasopressin V2 receptor antagonist*

tolvaptan

*N*-[4'-[(5*RS*)-7-chloro-5-hydroxy-2,3,4,5-tétrahydro-1*H*-1-benzazépin-1-yl] carbonyl]-3-méthylphényl]-2-méthylbenzamide  
*antagoniste du récepteur V2 de la vasopressine*

tolvaptán

(±)-4'-[(7-cloro-2,3,4,5-tetrahidro-5-hidroxi-1*H*-1-benzazepin-1-il)carbonyl]-*o*-tolu-*m*-toluidida  
*antagonista del receptor V2 de la vasopresina*C<sub>26</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub> 150683-30-0

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

**Proposed International Nonproprietary Names (Prop. INN): List 31****Dénominations communes internationales proposées (DCI Prop.): Liste 31****Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 31***(WHO Chronicle/Chronique OMS/Cronica de la OMS, Vol. 28, No. 3, 1974)*

p. 133	<i>delete</i>		<i>insert</i>
	<b>amfebutamonum</b>		<b>bupropionum</b>
	amfebutamone		bupropion
p. 145	<b><i>supprimer</i></b>		<b><i>insérer</i></b>
	amfébutamone		bupropione
p. 145	<b><i>suprimase</i></b>		<b><i>insértese</i></b>
	anfebutamona		bupropiona

**Proposed International Nonproprietary Names (Prop. INN): List 79****Dénominations communes internationales proposées (DCI Prop.): Liste 79****Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 79***(WHO Drug Information, Vol. 12, No. 2, 1998)*

p. 107	<i>delete/supprimer/suprimase</i>		<i>insert/insérer/insértese</i>
	<b>fondaparinum natricum</b>		<b>fondaparinuxum natricum</b>
	fondaparín sodium		fondaparínux sodium
	fondaparine sodique		fondaparínux sodique
	fondaparína sódica		fondaparínux sódico

**Proposed International Nonproprietary Names (Prop. INN): List 80****Dénominations communes internationales proposées (DCI Prop.): Liste 80****Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 80***(WHO Drug Information, Vol. 12, No. 4, 1998)*

p. 266	<i>delete/supprimer/suprimase</i>		<i>insert/insérer/insértese</i>
	<b>itavastatinum</b>		<b>pitavastatinum</b>
	itavastatin		pitavastatin
	itavastatine		pitavastatine
	itavastatina		pitavastatina

**Proposed International Nonproprietary Names (Prop. INN): List 82****Dénominations communes internationales proposées (DCI Prop.): Liste 82****Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 82***(WHO Drug Information, Vol. 13, No. 4, 1999)*p. 281 **motexafinum**

motexafin

*replace the description by the following:*

9,10-diethyl-20,21-bis[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-4,15-dimethyl-8,11-imino-3,6:16,13-dinitrilo-1,18-benzodiazacycloeicosine-5,14-dipropanol

motexafina

*sustitúyase la descripción por la siguiente:*

9,10-dietil-20,21-bis[2-[2-(2-metoxietoxi)etoxi]etoxi]-4,15-dimetil-8,11-imino-3,6:16,13-dinitrilo-1,18-benzodiazacycloeicosina-5,14-dipropanol

motexafin

*replace the molecular formula by the following:*

motéxafine

*remplacer la formule brute par:*

motexafina

*sustitúyase la fórmula molecular por:* $C_{48}H_{67}N_5O_{10}$ *add the following CAS registry number:**insérer le numéro dans le registre du CAS suivant:**insértese el número de registro del CAS siguiente:*

189752-49-6

p. 289 **tebipenemum**

tebipenem

*replace the description by the following:*

(+) -hydroxymethyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[[1-(2-thiazolin-2-yl)-3-azetidiny]thio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate, 2-pivalate

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## Annex 1

### PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES\*

The following procedure shall be followed by the World Health Organization in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with the World Health Assembly resolution WHA3.11:

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefor.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the "General principles for guidance in devising International Nonproprietary Names", appended to this procedure. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

A. Such notice shall be given by publication in the *Chronicle of the World Health Organization*<sup>1</sup> and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

(i) Notice may also be sent to specific persons known to be concerned with a name under consideration.

B. Such notice shall:

(i) set forth the name under consideration;

(ii) identify the person who submitted a proposal for naming the substance, if so requested by such person;

(iii) identify the substance for which a name is being considered;

(iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;

(v) state the authority under which the World Health Organization is acting and refer to these rules of procedure.

C. In forwarding the notice, the Director-General of the World Health Organization shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization*.<sup>1</sup>

5. A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization*.<sup>1</sup>

A. Such objection shall:

(i) identify the person objecting;

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\* Text adopted by the Executive Board of WHO in resolution EB15.R7 (*Off. Rec. Wld Health Org.*, 1955, 60, 3) and amended by the Board in resolution EB43.R9 (*Off. Rec. Wld Hlth Org.*, 1969, 173, 10).

<sup>1</sup> The title of this publication was changed to *WHO Chronicle* in January 1959. From 1987 onwards lists of INNs are published in *WHO Drug Information*.

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(ii) state his interest in the name;

(iii) set forth the reasons for his objection to the name proposed.

6. Where there is a formal objection under article 5, the World Health Organization may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by the World Health Organization of a substitute name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:

A. request that it be recognized as the nonproprietary name for the substance; and

B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or trade-name.

## Annex 2

### GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES\*

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

*These primary principles are to be implemented by using the following secondary principles:*

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. "oxacillin" and "oxacillin sodium", "ibufenac" and "ibufenac sodium".

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

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\* In its twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic "stem" indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed.

7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.<sup>1</sup> Where a stem is shown without any hyphens it may be used anywhere in the name.

<i>Latin</i>	<i>English</i>	
-acum	-ac	anti-inflammatory agents of the ibufenac group
-actidum	-actide	synthetic polypeptides with a corticotropin-like action
-adolum	-adol )	analgetics
-adol-	-adol- )	
-astum	-ast	antiasthmatic, antiallergic substances not acting primarily as antihistaminics
-astinum	-astine	antihistaminics
-azepamum	-azepam	diazepam derivatives
-bactamum	-bactam	β-lactamase inhibitors
bol	bol	steroids, anabolic
-buzonum	-buzone	anti-inflammatory analgesics, phenylbutazone derivatives
-cain-	-cain-	antifibrillant substances with local anaesthetic activity
-cainum	-caine	local anaesthetics
cef-	cef-	antibiotics, cephalosporanic acid derivatives
-cillinum	-cillin	antibiotics, derivatives of 6-aminopenicillanic acid
-conazolium	-conazole	systemic antifungal agents, miconazole derivatives
cort	cort	corticosteroids, except prednisolone derivatives
-dipinum	-dipine	calcium channel blockers, nifedipine derivatives
-fibratum	-fibrate	clofibrate derivatives
gest	gest	steroids, progestogens
gli-	gli-	sulfonamide hypoglycaemics
io-	io-	iodine-containing contrast media
-ium	-ium	quaternary ammonium compounds
-metacinum	-metacin	anti-inflammatory substances, indometacin derivatives
-mycinum	-mycin	antibiotics, produced by <i>Streptomyces</i> strains
-nidazolium	-nidazole	antiprotozoal substances, metronidazole derivatives
-ololum	-olol	β-adrenoreceptor antagonists
-oxacinum	-oxacin	antibacterial agents, nalidixic acid derivatives
-pridum	-pride	sulpiride derivatives
-pril(at)um	pril(at)	angiotensin-converting enzyme inhibitors
-profenum	-profen	anti-inflammatory substances, ibuprofen derivatives
prost	prost	prostaglandins
-relinum	-relin	hypophyseal hormone release-stimulating peptides
-terolum	-terol	bronchodilators, phenethylamine derivatives
-tidinum	-tidine	histamine H <sub>2</sub> -receptor antagonists
-trexatum	-trexate	folic acid antagonists
-verinum	-verine	spasmolytics with a papaverine-like action
vin-	vin- )	vinca alkaloids
-vin-	-vin- )	

<sup>1</sup> A more extensive listing of stems is contained in the working document WHO/EDM/QSM 99.6 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.

## Annexe 1

### PROCEDURE A SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDEES POUR LES SUBSTANCES PHARMACEUTIQUES\*

L'Organisation mondiale de la Santé observe la procédure exposée ci-dessous pour l'attribution de dénominations communes internationales recommandées pour les substances pharmaceutiques, conformément à la résolution WHA3.11 de l'Assemblée mondiale de la Santé:

1. Les propositions de dénominations communes internationales recommandées sont soumises à l'Organisation mondiale de la Santé sur la formule prévue à cet effet.

2. Ces propositions sont soumises par le Directeur général de l'Organisation mondiale de la Santé aux experts désignés à cette fin parmi les personnalités inscrites au Tableau d'experts de la Pharmacopée internationale et des Préparations pharmaceutiques; elles sont examinées par les experts conformément aux "Directives générales pour la formation des dénominations communes internationales", reproduites ci-après. La dénomination acceptée est la dénomination employée par la personne qui découvre ou qui, la première, fabrique et lance sur le marché une substance pharmaceutique, à moins que des raisons majeures n'obligent à s'écarter de cette règle.

3. Après l'examen prévu à l'article 2, le Directeur général de l'Organisation mondiale de la Santé notifie qu'un projet de dénomination commune internationale est à l'étude.

A. Cette notification est faite par une insertion dans la *Chronique de l'Organisation mondiale de la Santé*<sup>1</sup> et par l'envoi d'une lettre aux Etats Membres et aux commissions nationales de pharmacopée ou autres organismes désignés par les Etats Membres.

(i) Notification peut également être faite à toute personne portant à la dénomination mise à l'étude un intérêt notoire.

B. Cette notification contient les indications suivantes:

(i) dénomination mise à l'étude;

(ii) nom de l'auteur de la proposition tendant à attribuer une dénomination à la substance, si cette personne le demande;

(iii) définition de la substance dont la dénomination est mise à l'étude;

(iv) délai pendant lequel seront reçues les observations et les objections à l'égard de cette dénomination; nom et adresse de la personne habilitée à recevoir ces observations et objections;

(v) mention des pouvoirs en vertu desquels agit l'Organisation mondiale de la Santé et référence au présent règlement.

C. En envoyant cette notification, le Directeur général de l'Organisation mondiale de la Santé demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l'étude par l'Organisation mondiale de la Santé.

4. Des observations sur la dénomination proposée peuvent être adressées à l'Organisation mondiale de la Santé par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans la *Chronique de l'Organisation mondiale de la Santé*<sup>1</sup> (voir l'article 3).

\* Le texte reproduit ici a été adopté par le Conseil exécutif dans la résolution EB15.R7 (*Actes off. Org. mond. Santé*, 1955, **60**, 3) qui l'a ultérieurement amendé par la résolution EB43.R9 (*Actes off. Org. mond. Santé*, 1969, **173**, 10).

<sup>1</sup> Depuis janvier 1959, cette publication porte le titre de *Chronique OMS*. A partir de 1987, les listes des DCIs sont publiées dans les *Informations pharmaceutiques OMS*.

5. Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans la *Chronique de l'Organisation mondiale de la Santé*<sup>1</sup> (voir l'article 3).

A. Cette objection doit s'accompagner des indications suivantes:

- i) nom de l'auteur de l'objection;
- ii) intérêt qu'il porte à la dénomination en cause;
- iii) raisons motivant l'objection contre la dénomination proposée.

6. Lorsqu'une objection formelle est formulée en vertu de l'article 5, l'Organisation mondiale de la Santé peut soit soumettre la dénomination proposée à un nouvel examen, soit intervenir pour tenter d'obtenir le retrait de l'objection. Sans préjudice de l'examen par elle d'une ou de plusieurs appellations de remplacement, l'Organisation mondiale de la Santé n'adopte pas d'appellation comme dénomination commune internationale recommandée tant qu'une objection formelle présentée conformément à l'article 5 n'est pas levée.

7. Lorsqu'il n'est formulé aucune objection en vertu de l'article 5 ou que toutes les objections présentées ont été levées, le Directeur général de l'Organisation mondiale de la Santé fait une notification conformément aux dispositions de la sous-section A de l'article 3, en indiquant que la dénomination a été choisie par l'Organisation mondiale de la Santé en tant que dénomination commune internationale recommandée.

8. En communiquant aux Etats Membres, conformément à l'article 7, une dénomination commune internationale recommandée, le Directeur général de l'Organisation mondiale de la Santé:

A. demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée, et

B. demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur cette dénomination, notamment en interdisant le dépôt de cette dénomination comme marque ou appellation commerciale.

## Annexe 2

### DIRECTIVES GENERALES POUR LA FORMATION DE DENOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES\*

1. Les dénominations communes internationales (DCI) devront se distinguer les unes des autres par leur consonance et leur orthographe. Elles ne devront pas être d'une longueur excessive, ni prêter à confusion avec des appellations déjà couramment employées.

2. La DCI de chaque substance devra, si possible, indiquer sa parenté pharmacologique. Les dénominations susceptibles d'évoquer pour les malades des considérations anatomiques, physiologiques, pathologiques ou thérapeutiques devront être évitées dans la mesure du possible.

*Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants:*

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\* Dans son vingtième rapport (Série de Rapports techniques de l'OMS, No. 581, 1975), le Comité OMS d'experts des Dénominations communes pour les Substances pharmaceutiques a examiné les directives générales pour la formation des dénominations communes internationales et la procédure à suivre en vue de leur choix, compte tenu de l'évolution du secteur pharmaceutique au cours des dernières années. La modification la plus importante a été l'extension aux substances de synthèse de la pratique normalement suivie pour désigner les substances tirées ou dérivées de produits naturels. Cette pratique consiste à employer des syllabes communes ou groupes de syllabes communes (segments clés) qui sont caractéristiques et indiquent une propriété commune aux membres du groupe des substances pour lequel ces segments clés ont été retenus. Les raisons et les conséquences de cette modification ont fait l'objet de discussions approfondies.



3. Lorsqu'on formera la DCI de la première substance d'un nouveau groupe pharmacologique, on tiendra compte de la possibilité de former ultérieurement d'autres DCI appropriées pour les substances apparentées du même groupe.

4. Pour former des DCI des acides, on utilisera de préférence un seul mot. Leurs sels devront être désignés par un terme qui ne modifie pas le nom de l'acide d'origine: par exemple "oxacilline" et "oxacilline sodique", "ibufénac" et "ibufénac sodique".

5. Les DCI pour les substances utilisées sous forme de sels devront en général s'appliquer à la base active (ou à l'acide actif). Les dénominations pour différents sels ou esters d'une même substance active ne différeront que par le nom de l'acide inactif (ou de la base inactive).

En ce qui concerne les substances à base d'ammonium quaternaire, la dénomination s'appliquera de façon appropriée au cation et à l'anion en tant qu'éléments distincts d'une substance quaternaire. On évitera de choisir une désignation évoquant un sel aminé.

6. On évitera d'ajouter une lettre ou un chiffre isolé; en outre, on renoncera de préférence au trait d'union.

7. Pour simplifier la traduction et la prononciation des DCI, la lettre "f" sera utilisée à la place de "ph", "t" à la place de "th", "e" à la place de "ae" ou "oe" et "i" à la place de "y"; l'usage des lettres "h" et "k" sera aussi évité.

8. On retiendra de préférence, pour autant qu'elles respectent les principes énoncés ici, les dénominations proposées par les personnes qui ont découvert ou qui, les premières, ont fabriqué et lancé sur le marché les préparations pharmaceutiques considérées, ou les dénominations déjà officiellement adoptées par un pays.

9. La parenté entre substances d'un même groupe (voir Directive générale 2) sera si possible indiquée dans les DCI par l'emploi de segments clés communs. La liste ci-après contient des exemples de segments clés pour des groupes de substances, surtout pour des groupes récents. Il y a beaucoup d'autres segments clés en utilisation active.<sup>1</sup> Les segments clés indiqués sans trait d'union pourront être insérés n'importe où dans une dénomination.

<i>Latin</i>	<i>Français</i>	
-acum	-ac	substances anti-inflammatoires du groupe de l'ibufénac
-actidum	-actide	polypeptides synthétiques agissant comme la corticotropine
-adolum	-adol )	analgésiques
-adol-	-adol- )	
-astum	-ast	antiasthmatiques, antiallergiques n'agissant pas principalement en tant qu'antihistaminiques
-astinum	-astine	antihistaminiques
-azepamum	-azépam	substances du groupe du diazépam
-bactamum	-bactame	inhibiteurs de $\beta$ -lactamases
bol	bol	stéroïdes anabolisants
-buzonum	-buzone	analgésiques anti-inflammatoires du groupe de la phénylbutazone
-cain-	-caïn-	substances antifibrillantes à action anesthésique locale
-cainum	-caïne	anesthésiques locaux
cef-	céf-	antibiotiques, dérivés de l'acide céphalosporanique
-cillinum	-cilline	antibiotiques, dérivés de l'acide 6-aminopénicillanique
-conazolium	-conazole	agents antifongiques systémiques du groupe du miconazole
cort	cort	corticostéroïdes, autres que les dérivés de la prednisolone
-dipinum	-dipine	inhibiteurs du calcium du groupe de la nifédipine
-fibratum	-fibrate	substances du groupe du clofibrate
gest	gest	stéroïdes progestogènes
gli-	gli-	sulfamides hypoglycémiantes
io-	io-	produits de contraste iodés
-ium	-ium	ammoniums quaternaires
-metacinum	-métacine	substances anti-inflammatoires du groupe de l'indométacine

<sup>1</sup> Une liste plus complète de segments clés est contenue dans le document de travail WHO/EDM/QSM 99.6 qui est régulièrement mis à jour et qui peut être demandé auprès du Programme des DCI, OMS, Genève.

<i>Latin</i>	<i>Français</i>	
-mycinum	-mycine	antibióticos producidos por cepas de <i>Streptomyces</i>
-nidazololum	-nidazole	substancias antiprotozoarias del grupo del metronidazol
ololum	-olol	antagonistas de receptores $\beta$ -adrenérgicos
-oxacinum	-oxacine	substancias antibacterianas del grupo de l'acido nalidixico
-pridum	-pride	substancias del grupo del sulpirido
-profenum	-profène	substancias anti-inflamatorias del grupo de l'ibuprofène
-pril(at)um	-pril(ate)	inhibidores de l'enzima de conversión de l'angiotensina
prost	prost	prostaglandinas
-relinum	-réline	peptidos estimulando la liberación de hormonas hipofisarias
-terolum	-térol	broncodilatadores, derivados de la fenétilamina
-tidinum	-tidine	antagonistas de receptores $H_2$ de l'histamina
-trexatum	-trexate	antagonistas de l'acido folico
-verinum	-vérine	spasmolíticos actuando como la papaverina
vin-	vin- )	alcaloides del tipo vinca
-vin-	-vin- )	

## Anexo 1

### PROCEDIMIENTO DE SELECCION DE DENOMINACIONES COMUNES INTERNACIONALES RECOMENDADAS PARA LAS SUSTANCIAS FARMACEUTICAS\*

La Organización Mundial de la Salud seguirá el procedimiento que se expone a continuación para la selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11 de la Asamblea Mundial de la Salud:

1. Las propuestas de denominaciones comunes internacionales recomendadas se presentarán a la Organización Mundial de la Salud en los formularios que se proporcionen a estos efectos.

2. Estas propuestas serán sometidas por el Director General de la Organización Mundial de la Salud a los Miembros del Cuadro de Expertos de la Farmacopea Internacional y las Preparaciones Farmacéuticas encargados de su estudio, para que las examinen de conformidad con los "Principios Generales de Orientación para formar Denominaciones Comunes Internacionales para Sustancias Farmacéuticas", anexos a este Procedimiento. A menos que haya poderosas razones en contra, la denominación aceptada será la empleada por la persona que haya descubierto, fabricado o puesto a la venta por primera vez una sustancia farmacéutica.

3. Una vez terminado el estudio a que se refiere el artículo 2, el Director General de la Organización Mundial de la Salud notificará que está en estudio un proyecto de denominación internacional.

A. Esta notificación se hará mediante una publicación en la *Crónica de la Organización Mundial de la Salud*<sup>1</sup> y el envío de una carta a los Estados Miembros y a las comisiones nacionales de las farmacopeas u otros organismos designados por los Estados Miembros.

(i) La notificación puede enviarse también a las personas que tengan un interés especial en una denominación objeto de estudio.

\* El texto corregido que aquí se reproduce fue adoptado por el Consejo Ejecutivo en la resolución EB15.R7 (*Act. of. Org. mund. Salud*, 1955, 60, 3) y enmendado por el Consejo en la resolución EB43.R9 (*Act. of. Org. mund. Salud*, 1969, 173, 10).

<sup>1</sup> Denominada *Crónica de la OMS* desde enero de 1959. A partir de 1987, las listas de DCI se publican en *Información Farmacéutica OMS*.

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B. En estas notificaciones se incluyen los siguientes datos:

- (i) denominación sometida a estudio;
- (ii) nombre de la persona que ha presentado la propuesta de denominación de la sustancia si lo pide esta persona;
- (iii) definición de la sustancia cuya denominación está en estudio;
- (iv) plazo fijado para recibir observaciones y objeciones, así como nombre y dirección de la persona a quien deban dirigirse, y
- (v) mención de los poderes conferidos para el caso a la Organización Mundial de la Salud y referencia al presente procedimiento.

C. Al enviar esta notificación, el Director General de la Organización Mundial de la Salud solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación propuesta, durante el periodo en que la Organización Mundial de la Salud tenga en estudio esta denominación.

4. Toda persona puede formular a la Organización Mundial de la Salud observaciones sobre la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la *Crónica de la Organización Mundial de la Salud*, conforme a lo dispuesto en el artículo 3.

5. Toda persona interesada puede presentar una objeción formal contra la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la *Crónica de la Organización Mundial de la Salud*, conforme a lo dispuesto en el artículo 3.

A. Esta objeción deberá acompañarse de los siguientes datos:

- i) nombre de la persona que formula la objeción;
- ii) causas que motivan su interés por la denominación, y
- iii) causas que motivan su objeción a la denominación propuesta.

6. Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la Organización Mundial de la Salud puede someter a nuevo estudio la denominación propuesta, o bien utilizar sus buenos oficios para lograr que se retire la objeción. Sin perjuicio de que la Organización Mundial de la Salud estudie una o varias denominaciones en sustitución de la primitiva, ninguna denominación podrá ser seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada en tanto que exista una objeción formal, presentada como previene el artículo 5, que no haya sido retirada.

7. Cuando no se haya formulado ninguna objeción en la forma prevista en el artículo 5, o cuando todas las objeciones presentadas hayan sido retiradas, el Director de la Organización Mundial de la Salud notificará, conforme a lo dispuesto en el párrafo A del artículo 3, que la denominación ha sido seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada.

8. Al comunicar a los Estados Miembros una denominación común internacional conforme a lo previsto en el artículo 7, el Director General de la Organización Mundial de la Salud:

A. solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate, y

B. solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación, incluso la prohibición de registrarla como marca de fábrica o como nombre comercial.

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## Anexo 2

### PRINCIPIOS GENERALES DE ORIENTACION PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACEUTICAS\*

1. Las Denominaciones Comunes Internacionales (DCI) deberán diferenciarse tanto fonética como ortográficamente. No deberán ser incómodamente largas, ni dar lugar a confusión con denominaciones de uso común.

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse los nombres que puedan inducir fácilmente en el paciente sugerencias anatómicas, fisiológicas, patológicas o terapéuticas.

*Estos principios primarios deberán ser tenidos en cuenta al aplicar los siguientes principios secundarios:*

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de formar DCI convenientes para las sustancias emparentadas que vengan a incrementar el nuevo grupo.

4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre de ácido; p. ej., "oxacilina" y "oxacilina sódica", "ibufenaco" e "ibufenaco sódico".

5. Las DCI para las sustancias que se usan en forma de sal, deberán en general aplicarse a la base activa o, respectivamente, al ácido activo. Las denominaciones para diferentes sales o ésteres de la misma sustancia activa solamente deberán diferir en el nombre de ácido o de la base inactivos.

En los compuestos de amonio cuaternario, el catión y el anión deberán denominarse adecuadamente por separado, como componentes independientes de una sustancia cuaternaria y no como sales de una amina.

6. Deberá evitarse el empleo de una letra o un número aislados; también es indeseable el empleo de guiones.

7. Para facilitar la traducción y la pronunciación se emplearán de preferencia las letras "f" en lugar de "ph", "t" en lugar de "th", "e" en lugar de "ae" u "oe" e "i" en lugar de "y"; se deberá evitar el empleo de las letras "h" y "k".

8. Siempre que las denominaciones que se sugieran estén de acuerdo con estos principios, recibirán una consideración preferente las denominaciones propuestas por la persona que haya descubierto la sustancia, o la que primeramente fabrica o ponga a la venta la sustancia farmacéutica, así como las denominaciones oficialmente adoptadas en cualquier país.

9. En las DCI, la relación de grupo o parentesco (véanse los Principios Generales de Orientación, apartado 2) se indicará en lo posible utilizando una partícula común. En la lista siguiente se dan algunos ejemplos de estas partículas en relación con diversos grupos de sustancias, en particular los de nuevo cuño. Hay otras muchas partículas comunes en uso.<sup>1</sup> Cuando la partícula no lleva ningún guión, cabe utilizarla en cualquier parte de la denominación.

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\* En su 20º informe (OMS, Serie de Informes Técnicos, No. 581, 1975) el Comité de Expertos de la OMS en Denominaciones Comunes para Sustancias Farmacéuticas examina los principios generales de orientación para formar denominaciones comunes internacionales (DCI) y el procedimiento de selección de las mismas, teniendo en cuenta las novedades registradas en los últimos años en materia de preparaciones farmacéuticas. Entre las modificaciones, la más importante ha sido la extensión a las sustancias químicas sintéticas de la práctica reservada anteriormente para designar sustancias originarias o derivadas de productos naturales. Esta práctica consiste en emplear una partícula característica que indique una propiedad común a los miembros de un determinado grupo de sustancias. En el informe se examinan a fondo las razones de esta modificación y sus consecuencias.

<sup>1</sup> El documento de trabajo WHO/EDM/QSM 99.6, que se pone al día regularmente, contiene una lista más extensa de partículas comunes. Las personas que deseen recibirlo deberán solicitar su envío al Programa DCI, OMS, Ginebra (Suiza).

<i>Latin</i>	<i>Español</i>	
-acum	-aco	antiinflamatorios del grupo del ibufenaco
-actidum	-actida	polipéptidos sintéticos de acción semejante a la corticotropina
-adolom	-adol }	analgésicos
-adol-	-adol- }	
-astum	-ast	antiasmáticos y antialérgicos que no actúan principalmente como antihistamínicos
-astinum	-astina	antihistamínicos
-azepamum	-azepam	sustancias del grupo del diazepam
-bactamum	-bactam	inhibidores de $\beta$ -lactamasas
bol	bol	esteroides anabólicos
-buzonum	-buzona	analgésicos antiinflamatorios del grupo de la fenilbutazona
-cain-	-cain-	antifibrilantes con actividad anestésica local
-cainum	-caina	anestésicos locales
cef-	cef-	antibióticos derivados del ácido cefalosporánico
-cillinum	-cilina	antibióticos derivados del ácido 6-aminopenicilánico
-conazolom	-conazol	antifúngicos sistémicos del grupo del miconazol
cort	cort	corticosteroides, excepto los del grupo de la prednisolona
-dipinum	-dipino	antagonistas del calcio del grupo del nifedipino
-fibratum	-fibrato	sustancias del grupo del clofibrato
gest	gest	esteroides progestágenos
gli-	gli-	sulfonamidas hipoglucemiantes
io-	io-	medios de contraste que contienen yodo
-ium	-io	compuestos de amonio cuaternario
-metacinum	-metacina	antiinflamatorios del grupo de la indometacina
-mycinum	-micina	antibióticos, producidos por cepas de <i>Streptomyces</i>
-nidazolom	-nidazol	antiprotozoarios del grupo del metronidazol
-ololum	-olol	bloqueadores $\beta$ -adrenérgicos
-oxacinum	-oxacino	antibacterianos del grupo del ácido nalidíxico
-pridum	-prida	sustancias del grupo de la sulpirida
-pril(at)um	-pril(at)	inhibidores de la enzima transformadora de la angiotensina
-profenum	-profeno	antiinflamatorios del grupo del ibuprofeno
prost	prost	prostaglandinas
-relinum	-relina	péptidos estimulantes de la liberación de hormonas hipofisarias
-terolum	-terol	broncodilatadores derivados de la fenetilamina
-tidinum	-tidina	antagonistas del receptor H <sub>2</sub> de la histamina
-trexatum	-trexato	antagonistas del ácido fólico
-verinum	-verina	espasmolíticos de acción semejante a la de la papaverina
vin-	vin- }	alcaloides de la vinca
-vin-	-vin- }	