

WHO Drug Information

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<http://www.who.int/druginformation>

Vaccines and Biomedicines

International reference materials for Creutzfeldt-Jakob disease

Transmissible spongiform encephalopathies (TSEs) include bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep, and Creutzfeldt-Jakob disease (CJD) in humans. TSEs are characterized by spongiform degeneration of the brain and the transformation of the normal form of a ubiquitous protein termed prion protein, PrP^c, into an abnormal isoform, PrP^{sc}. PrP^{sc} is the only marker of the disease.

Concern has been generated following the appearance of a variant Creutzfeldt-Jakob (vCJD) disease in the United Kingdom linked to bovine spongiform encephalopathy (BSE) and action has been taken to reduce channels of transmission. Cases of vCJD have now reached 130 internationally — raising the profile of this class of disease as a risk to human health.

Sporadic, familial and iatrogenic Creutzfeldt-Jakob disease

The accurate diagnosis of CJD is currently based on postmortem histopathological examination of the brain or immunohistopathology, which adds an extra level of certainty when appropriate antibodies and techniques are used. Pre-mortem diagnosis remains problematic and is limited to detection through clinical features or electroencephalographic (EEG) findings. No validated preclinical diagnostic tests are currently available for the detection of PrP^{sc}.

Bovine spongiform encephalopathy

Methods for the accurate diagnosis of pre- or post-mortem BSE which may be applied on a large scale to the examination of animals either at or prior to slaughter, would have major epidemiological implications in minimising the risk of infection to other animals or to humans through food or biological materials used in the production of medicinal products. ELISA and Western Blot testing of brain tissues can already be used to detect some pre-clinical cases postmortem. No ante-mortem diagnostic methods suitable for testing live asymptomatic animals during the incubation period of BSE are available.

Variant Creutzfeldt-Jakob Disease

The number of human subjects incubating vCJD remains unknown and concern about the potential infectivity of their blood is affecting public health policy on supply of blood products in several countries. As is the case for CJD, there has been no evidence of transmission of vCJD by blood or blood components or plasma-derived products. vCJD is however a new emerging disease and the risk is unknown.

Although novel antibodies and new applications of existing technologies have been developed as promising approaches for diagnostic procedures for vCJD, they are at a relatively early stage of development. Pre-mortem clinical diagnosis of vCJD by magnetic resonance imaging (MRI) seems to be reliable. However, diagnosis during the asymptomatic incubation period is not yet possible and a reliable diagnostic method based on easily accessible samples, such as serum, is indispensable. There is also a need for independent comparison of the various laboratory approaches to diagnosis.

WHO International Reference Materials

The availability of reliable diagnostic procedures would allow the detection of asymptomatic subjects during the long periods of incubation of CJD and vCJD. Panels of reference materials of various kinds need to be built up to compare the effectiveness of new in vitro and in vivo assay systems using animal models and relate detection of PrP^{sc} and infectivity. Comparability of levels of detection of TSE agents by different methods will only be possible through the availability of these preparations. Decisions concerning the safety of pharmaceuticals and blood products can then be taken based on scientific findings and would considerably strengthen precautionary measures implemented by medicines regulatory authorities.

The need to develop a panel of international reference materials for the diagnosis and study of transmissible spongiform encephalopathies (TSEs) for validation of CJD and vCJD diagnostic procedures and for the comparison of methods was first discussed during a WHO Consultation held in 1999. A WHO Working Group on International Reference Materials for Diagnosis and Study of TSEs was

established to identify needs and priorities for the production of international reference materials and development of a WHO repository. The development of human brain-derived materials as candidate biological reference materials to compare the sensitivity of assays for CJD and vCJD is now under way. Four human brain-derived homogenates have been prepared from:

- uninfected brain;
- sporadic CJD brain type 1 (sp1CJD);
- sporadic CJD brain type 2 (sp2CJD); and
- variant CJD brain (vCJD).

Thirteen international laboratories will characterize these materials and work on in vitro assays of PrP^{sc} content. The brain samples which have been provided for analysis cover all PrP^{sc} types described. These samples have also been distributed to twelve laboratories to perform Western immunoblot tests according to agreed protocols. Information from these activities will be fundamental in confirming their suitability for development as International Reference Materials. A WHO directed study of the Terminology of Human PrP^{sc} types and subtypes is also being carried out to resolve the current disparity in the literature on the existence of distinct human PrP^{sc} types associated with sporadic or acquired CJD.

Results from the in vitro studies were analysed at a meeting of the WHO Working Group on International Reference Materials for Diagnosis and Study of TSEs in April 2002. Results from laboratories using different modifications of Western immunoblot tests for detection and quantification of PrP^{sc} and other immunodetection techniques were also compared and discussed. Candidate reference materials will then be assayed for infectivity in a variety of conventional and transgenic mice.

Because neither infectivity nor the presence of PrP^{sc} has been detected in human blood, it is not clear whether blood or any component of blood can provide a useful biological reference material. Identification of candidate reference materials suitable for calibrating spike preparations used in process validation protocols for removal of PrP^{sc} and infectivity from blood is also under evaluation.

Ultimately, the materials described will be examined by a range of diagnostic procedures enabling a correlation to be made between in vitro and in vivo information. The development and provision of well characterized reference materials for comparison

will benefit public health internationally, and WHO will offer these materials as calibrants to laboratories seeking to optimize a variety of in vitro and in vivo diagnostic procedures for TSEs.

Development of brain derived materials from cattle with bovine spongiform encephalopathy (BSE) and from sheep with both BSE and scrapie infections will also be addressed in collaboration with the Organisation International des Epizooties (OIE).

References

1. Information on the WHO Working Group on International Reference Materials for Diagnosis and Study of TSEs: <http://www.who.int/biologicals>
2. World Health Organization. *Report of a WHO Consultation on Medicinal and other Products in Relation to Human and Animal Transmissible Spongiform Encephalopathies*. Geneva, Switzerland, 24–26 March 1997.
3. World Health Organization. *Report on a WHO Consultation on Diagnostic Procedures for Transmissible Spongiform Encephalopathies (TSEs): Need for Reference Reagents and Reference Panels*. Geneva, Switzerland, 22–23 March 1999.
4. World Health Organization. *Report on a Working Group on International Reference Materials for Diagnosis and Study of Transmissible Spongiform Encephalopathies (TSEs)*. Geneva, Switzerland, 21–22 September 1999.
5. World Health Organization. *Report on International Reference Materials for Diagnosis and Study of Transmissible Spongiform Encephalopathies (TSEs)*. Geneva, Switzerland, 25–26 May 2000.
6. World Health Organization. *Report on International Reference Materials for Diagnosis and Study of Transmissible Spongiform Encephalopathies (TSEs)*. Geneva, Switzerland, 1–2 March 2001.
7. WHO Working Group on International Reference Materials for Diagnosis and Study of TSEs. Reports published via Internet: www.who.int/technology/biological.html.

WHO position on rabies vaccine

Rabies is a viral zoonoses carried by carnivores and many bat species. Globally, in terms of human disease, dogs represent the most important reservoir of infection. More than 2.5 billion people live in regions where rabies is endemic and it is estimated that each year at least 50 000 people die from rabies and more than 10 million receive post-exposure vaccination against the disease. Where rabies is a public health issue, control of rabies in

dogs is an essential component. A combination of initiatives, including vaccination of dogs with minimum 80% coverage, is recommended.

More than 99% of all human deaths due to rabies occur in tropical developing countries in Africa, Asia and South America. Among human infections, rabies is believed to be the tenth most common cause of death. Once clinical symptoms have occurred, the disease is almost invariably fatal. However, reporting is often incomplete and the estimated 50 000 deaths per year may be an underestimate. India alone reports 30 000 deaths per year, i.e. an annual incidence of approximately 3 deaths per 100 000 population. Annual incidence of 0.01–0.2 deaths per 100 000 are reported from Latin America. In Africa, 0.001 to 13 deaths per 100 000 are reported. However, rabies is grossly under-reported in many countries.

Although all age groups are susceptible, rabies is more common in people aged under 15 years, with 30%–50% post-exposure treatments given to children aged 5–15 years, the majority being male. The most severe injuries such as multiple head and/or neck bites have the shorter incubation period and tend to occur in the youngest children. Since many of these exposures are never reported, it is likely that there is a high proportion of young children dying from undiagnosed rabies.

Rabies is currently an incurable disease. Antiviral agents, interferon and massive doses of rabies immune globulin have been used to treat human

cases, but seem only to prolong the clinical course without affecting fatality. However, post-exposure treatment initiated at an early stage using rabies vaccine in combination with rabies immunoglobulin may be 100% effective in preventing death. Given preemptively, modern rabies vaccines produce an antibody response in over 99% of vaccinees. In the United States, more than 50 000 doses have been given to persons at increased risk of rabies, and not a single case has been reported among these recipients.

Pre-exposure vaccination is recommended for all individuals at increased risk of contracting rabies, either by nature of their residence or occupation, or when travelling to rabies enzootic areas. In such areas children aged 5–15 years are at particular risk of exposure to rabies virus.

Vaccine types

The human diploid cell rabies vaccine was introduced in 1967 and is regarded as the gold standard for rabies vaccines. However, the more recently developed and less expensive purified chick embryo cell vaccine and purified Vero cell rabies vaccine have comparable characteristics. They are all lyophilized and must be reconstituted. The potency of all cell-derived vaccines is assessed using a National Institutes of Health test and the WHO requirement is potency of at least 2.5 IU per intramuscular dose.

Human diploid cell rabies vaccines are based on the Pitman-Moore L503 strain or, in one case, the Flury strain of rabies virus. Human diploid cell

WHO position on new vaccines

Vaccines for large-scale public health use should:

- meet quality requirements as defined by WHO;
- be safe and have a significant impact against the actual disease in all target populations;
- be easily adapted to schedules and timing of the national childhood immunization programmes if intended for infants or young children;
- not interfere significantly with the immune response of other vaccines given simultaneously;
- be formulated to meet common technical limitations i.e. in terms of refrigeration and storage capacity;
- be appropriately priced.

rabies vaccines have been given to more than 1.5 million people worldwide. Its protective efficacy in situations of heavy exposure has been shown in the Islamic Republic of Iran where none of 45 persons who received post-exposure treatment with this vaccine developed rabies following severe bites by rabid dogs or wolves.

The purified Vero cell rabies vaccine contains the Wistar strain of the virus, but with the Vero cell line as substrate. Clinical studies with the purified Vero cell vaccine show neutralizing antibody responses both after primary and secondary immunizations that are fully comparable to those seen after vaccination with the human diploid cell vaccines. In Thailand, post-exposure treatment using purified Vero cell vaccine and rabies immune globulin has been shown to be protective.

Purified chick embryo cell rabies vaccine is prepared from inactivated rabies virus of the Flury LEP-25 strain. No clinically important differences were observed when this vaccine was evaluated together with human diploid cell vaccines in studies on post-exposure protection of animals and humans and in pre-exposure immunogenicity studies. More than 30 million doses of the purified chick embryo cell vaccine have been administered worldwide.

Adverse reactions

Although associated with mild and transient reactions, all the cell-derived rabies vaccines are considered safe. With human diploid cell vaccines, which are most thoroughly investigated, pain, erythema and swelling or itching at the injection site occur among 30%–74% of the recipients. Systemic reactions involving headache, nausea, abdominal pain, muscle aches or dizziness are reported among 5%–40% of vaccinees, and allergic edema in 0.1%. One study reports fever among 3.6% of recipients of the human diploid cell vaccine. Systemic allergic reactions characterized by generalized urticaria accompanied in some cases by arthralgia, angioedema, fever, nausea and vomiting have been reported. They are uncommon in persons receiving primary vaccination, but have occurred in up to 6% of persons receiving a booster dose, with onset after 2–21 days.

These reactions have been shown to follow the development of 1gE antibodies to beta-propiolactone altered human serum albumin in the vaccine (beta-propiolactone is used as an inactivating agent). According to the manufacturers of purified Vero cell rabies vaccine and purified chick embryo cell vaccine, allergic reactions are very rare after both primary and booster doses with these vaccines.

Studies on the purified Vero cell rabies vaccine report local and general reactions in 10.6% and complaints of mild to moderate reactions in 7% of post-exposure treatment patients. Also, among intradermal or intramuscular recipients of this vaccine, low-grade fever was the only significant systemic event, occurring in 8% of all subjects and most frequently following intramuscular vaccination. In the same study, pruritus at the injection site was the only significant local reaction. Among 88 healthy adults receiving a total of 292 doses of purified chick embryo cell vaccine, 16.4% reported local side effects, whereas 15.1% reported general symptoms.

Other cell-derived vaccines

In the United States the Kissling rabies strain has been adapted to replicate in lung fibroblasts of fetal rhesus monkeys. The resulting vaccine, which is given according to the same pre- and post-exposure schedules as the human diploid cell vaccine, is considered equally effective and cause less allergic reactions. In Japan, a vaccine type similar to the purified chick embryo cell vaccine, but based on the Flury HEP strain, has reached limited distribution.

Pre-exposure schedule

Intramuscular doses of 1 ml or 0.5 ml, depending on the vaccine type, given on days 0, 7 and 28. Major vaccine manufacturers recommend 1 booster dose after 1 year, and to ensure protection in persons at continued risk, booster vaccinations every 5 years, or ideally, at intervals dictated by regular testing for antirabies antibodies (titres ~0.5 IU/ml required for protection). On the other hand, studies with the human diploid cell vaccine and the purified Vero cell rabies vaccine have shown that 10 years after a pre-exposure series followed by a single booster dose after 1 year, more than 96% of the vaccinees still have neutralizing antibodies against rabies virus.

Post-exposure schedule

Vaccination with or without rabies immune globulin depends on the type of contact with the rabid animal. Types of contact are defined as:

- category I — touching or feeding animals, licks on the skin;
- category II — nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on broken skin;
- category III — single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks.

For category I, no treatment is required, whereas for category II immediate vaccination and for category III immediate vaccination and administration of rabies immune globulin are recommended in addition to immediate washing and flushing of all bite wounds and scratches. Depending on vaccine type, the post-exposure schedule prescribes intramuscular doses of 1 ml or 0.5 ml given as 4–5 doses over 4 weeks. For rabies-exposed patients who have previously undergone complete pre-exposure vaccination or post-exposure treatment

with cell-derived rabies vaccines, two intramuscular doses of a cell-derived vaccine separated by 3 days are sufficient. Rabies immune globulin treatment is not necessary in such cases. The same rules apply to persons vaccinated against rabies who have demonstrated neutralizing antibody titres of at least 0.5 IU/ml.

Only the cell-derived vaccines that meet WHO requirements regarding safety, potency and efficacy for this application may be considered for intradermal use. Although rabies vaccines are usually administered under qualified medical supervision, field experience from routine infant immunization programmes with other intradermally injected vaccines highlights the potential difficulties in assuring proper delivery. This emphasizes the need for appropriate staff training to ensure correct storage, reconstitution and injection. Provided that a correct sterile technique is used, the remaining doses may be kept in the vial at 2–8 °C and used for another patient within 6 hours after reconstitution.

Reference: *Weekly Epidemiological Record*, **77**:109–112 (2002).

Safety Information

WHO international drug monitoring: cerivastatin and gemfibrozil

Cerivastatin was first approved for use in the United Kingdom in 1997 and was authorized in all European Union countries through the mutual recognition procedure. Subsequently, it was approved for use in at least 16 other countries throughout the world.

Between 1997 and 2000, a total of 549 cases of rhabdomyolysis in association with cerivastatin had been reported to the WHO Collaborating Centre for International Drug Monitoring and in 1999 a signal* was issued concerning an association between cerivastatin, myopathy and rhabdomyolysis. In November 1999 in the USA, and in March 2000 in Canada, the prescribing information was changed to include a contraindication for the combined use of cerivastatin and gemfibrozil. A similar action was taken in Australia in February 2001, and a warning was issued to alert prescribers to the possibility of rhabdomyolysis with all statins. However, it was not until June 2001 that Europe-wide regulatory action was taken to contraindicate the combined use of cerivastatin and on 8 August 2001 the manufacturer voluntarily withdrew cerivastatin (Lipobay®) from the market because of the increased risk of rhabdomyolysis associated with its use, particularly when used in combination with one of the fibrates, gemfibrozil (Lopid®).

The WHO Collaborating Centre for International Drug Monitoring carried out a preliminary assessment of cerivastatin using the WHO international data. This data is collected from 67 countries throughout the world and the database currently contains over 2.7 million adverse drug reactions.

The analysis was based on the concept that the positive and negative effects of drug action can be reduced to similar terms to allow comparison. No data on effectiveness were considered. All similar

* A signal is defined as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

drugs used for the reduction of cholesterol were included and the analysis considered their safety profile. However, the comparison included only the most frequently reported and the most serious adverse drug reactions (ADRs).

Material and methods

Reports of all the statin drugs in the Anatomical Therapeutic & Chemical classification (ATC) group C10AA (and gemfibrozil) (1) were selected from the WHO database. International Monitoring Service (IMS) Health sales figures for the same drugs worldwide and from similar countries were used. IMS does not have data from the Netherlands, Iran, Costa Rica and Croatia, but these countries contribute a relatively very small number of ADR reports. Data were provided by the manufacturer for the years 1989–2000. IMS data is difficult to obtain prior to that date and therefore misses the launch of the first statin on the market by two years. The IMS data was converted to million patient years and, since the mean dosages equate closely with dosage forms, were used as a rate denominator in all subsequent work.

Table 1— Sales denominators

<i>Drug name</i>	<i>Million Patient Years</i>
atorvastatin	22.49
cerivastatin	3.92
fluvastatin	8.44
lovastatin	20.51
pravastatin	46.55
simvastatin	44.97

Also, IMS data on co-prescription with statins and gemfibrozil and fibrates. Age and gender breakdowns of statin prescriptions in the USA were provided by the manufacturer.

All critical ADR terms associated with the statins, irrespective of frequency of reporting, were in-

spected by a clinician who selected the ADR terms with the most serious clinical import with regard to possible lethal outcome or permanent disability. They were then grouped, resulting in 13 ADR groups:

- Disseminated intravascular coagulation
- Neuroleptic malignant syndrome
- Cardiomyopathy
- Anaphylactic shock
- Death
- Serious hepatic damage
- Rhabdomyolysis
- Pulmonary fibrosis
- Stevens-Johnson syndrome
- Renal failure
- Myopathy
- Pancreatitis
- Serotonin syndrome

Analyses of data

Raw reports were analysed by drug and by extent of drug use (where described as 'suspected' or 'interacting') and serious ADR group. Because of the small numbers, anaphylactic shock, disseminated intravascular coagulation and neuroleptic malignant syndrome were not considered further. Within the context of spontaneous reporting and its uncertainties, the drugs have qualitatively similar profiles.

There are, however, some quantitative differences for consideration. When the rates are above one per million patient years, the rates which stand out are: cardiomyopathy, myopathy, renal failure, rhabdomyolysis and death with cerivastatin; and myopathy for lovastatin. This all suggests that a concentration on the issue of rhabdomyolysis, myopathy and renal failure is reasonable in comparing and differentiating the safety profiles of the drugs. Proceeding from the above, the data was further analysed to see if there were possible reasons for disproportionate reporting with cerivastatin, lovastatin and muscle and renal ADRs.

The total raw reporting numbers and rates were analysed by year. As noted above, the first two years for lovastatin and simvastatin are excluded. Reporting numbers for all drugs show an increase

from 1995, covering the period of cerivastatin launch. This might suggest some sensitization to reporting ADRs in general. The reporting rate for cerivastatin starts very high and diminishes rapidly: a pronounced Weber effect*. There is therefore probably both general over-reporting for cerivastatin combined with the Weber effect to consider when comparing with drugs longer on the market. In this respect it is noteworthy that the total reporting rates for lovastatin and simvastatin were similarly high at the beginning of their marketing.

Considering only the reporting rates of rhabdomyolysis, the rate for rhabdomyolysis and cerivastatin is clearly much higher than for the other drugs and goes contrary to the Weber effect for the total reporting rates. This suggests ongoing concern over this reaction, although this might be induced by the warnings given by the manufacturers. Furthermore, the term rhabdomyolysis was not available for use before 1992 in WHO-ART (2) and 1995 in the US FDA COSTART (3). Prior to these dates, it is likely that most reports were coded either as myopathy or as renal failure depending on the clinical presentation.

The myopathy group rates with cerivastatin do follow the Weber curve for the total reporting rate. The high rate of myopathy reports with lovastatin in the early years, particularly considering the large number of deaths reported with that drug and myopathy, may well be explained by miscoding and by including the more life-threatening rhabdomyolysis in with the more general myopathy group. If this is true, and bearing in mind all the pointers mentioned above, lovastatin may also have an associated rhabdomyolysis rate in a similar range to that of cerivastatin.

An analysis was also made of the more limited numbers of WHO reports with accurately recorded dates, to determine the time from start of drug use to onset of rhabdomyolysis. It seems clear that the time to onset is shorter and more confined with cerivastatin as compared with the others. This data, whilst having limitations, suggests that early monitoring for muscle injury might be a practical way to limit much of the damage with the statins, and particularly, cerivastatin.

An interaction with gemfibrozil and statins, particularly cerivastatin, has already been signalled and a new interaction seems possible with concomitant use of clopidogrel. Gemfibrozil is prescribed concomitantly with cerivastatin in 0.03%–1.5% of all

* This phenomenon was first described by Dr. Peter Weber denoting the combined effects of rapid uptake in the use of, and interest in, a new drug leading to a high rate of reporting which can make comparisons with older drugs with stable reporting misleading.

cerivastatin prescriptions in 16 major countries, except for Argentina, where the percentage was 3.94. The corresponding figures for all other fibrates are 0.37%–5.93%. The co-prescription figures for the other statins are in the same range. Nevertheless, 302/546 (55%) of all cerivastatin rhabdomyolysis cases recorded gemfibrozil as a concomitantly used drug. This disproportionate use suggests a strong interaction between the drugs, as has already been signalled. There is a much clearer disproportion with the cerivastatin/gemfibrozil combination compared to the other statin combinations with rhabdomyolysis, death, myopathy, myositis and acute renal failure/renal failure. The disproportion seen in relationship to hepatic failure is based on a single case of the combination. Lovastatin has a similar pattern, but less striking, except for renal failure, which is also strongly disproportionate. Atorvastatin shows a clear disproportionality as regards rhabdomyolysis, but not with the other terms/groups. The remaining statins fall in between.

Clopidogrel is also reported as a concomitant drug where cerivastatin was suspected of having caused rhabdomyolysis in 20 cases (out of 45 total reports of these two drugs in combination). Since the co-prescription of clopidogrel and cerivastatin is about 0.25%, there again seems to be a good case to consider a strong interaction between the drugs.

Whilst doses of drugs used are not reported to WHO frequently enough, 6/24 (25%) cases of rhabdomyolysis — where the dose was reliably known — were on doses 0.4 mg or higher of cerivastatin excluding cases of monotherapy, as opposed to 4/13 (31%) when used as monotherapy — no other statins, nor gemfibrozil were mentioned. This is a weak suggestion that higher doses are more likely to be related to rhabdomyolysis when cerivastatin is used alone and needs further consideration using primary data.

In summary, there is evidence that the other statins interact with gemfibrozil, but the disproportion between the reported combination rate compared to the proportion of prescriptions suggests a much lesser effect as compared to cerivastatin. This, and preliminary findings on clopidogrel, and limited dose information, suggests that cerivastatin might be particularly sensitive to drug interaction when rhabdomyolysis is the clinical endpoint.

Another factor relating to drug use is whether there is a disproportion in the basic demography of patients for whom the drugs are prescribed and for those who have rhabdomyolysis. A breakdown of the age and gender from the USA IMS data was carried out. From this, it appears that lovastatin has relatively more prescriptions in patients over 65. Fluvastatin is the only drug with a greater proportion of older males as compared with females. A breakdown of age and gender of the WHO ADR reports from the USA shows that cerivastatin has the highest ratio of older (>65 yr.) females to males (1:0.69) and the greatest disproportion between older males taking the drug (36% men) and those taking the drug and having rhabdomyolysis (70% men). Slightly more men than women take the statins as a whole but this is not true of fluvastatin nor, more strikingly, for lovastatin (males 41% : females 54% and 5% unknown).

It is possible therefore that rhabdomyolysis is more a problem of older patients, particularly seen in older males prescribed cerivastatin. If this is true, then there are relatively more patients in that group taking cerivastatin who are potentially at risk. Lovastatin is, relatively, the most highly used drug in older patients, particularly women, and relatively fewer patients over 65 years were reported with rhabdomyolysis. Thus, considering that older patients take the statins, cerivastatin seems particularly a problem for older men.

Conclusions

1. There is a similarity between the safety profiles of all the statins qualitatively for serious suspected adverse reactions and for the more frequently reported cases.
2. Based on an analysis of spontaneous reports there appears to be a strong link between cerivastatin and rhabdomyolysis and renal failure (possibly related) which is quantitatively greater than with the other statins.
3. Since cerivastatin is the most recently marketed this may increase the overall reporting rate compared with contemporary reporting with the other statins, but:
 - The Weber effect is not a full explanation for rhabdomyolysis reporting, and

- The availability of rhabdomyolysis as a used term dates from the mid 1990s and probably results in lower numbers of reports of rhabdomyolysis with other drugs, particularly lovastatin.
4. Reports of myopathy are high for lovastatin after the first years of launch. An association with deaths suggests misclassification of rhabdomyolysis.
 5. Disproportionality of the combination cerivastatin/gemfibrozil and cerivastatin/clopidogrel against their use strongly suggests interaction.
 - This almost entirely affects muscle ADRs.
 - This effect of the combination is not seen as strikingly with the other drugs, though it is obvious with lovastatin.
 6. Disproportionality of cerivastatin reports of rhabdomyolysis and its use in older men suggests they may be a risk group. Lovastatin is relatively highly used in older patients and may be less likely to cause rhabdomyolysis in this group, but:
 - The coding with lovastatin and rhabdomyolysis may be an issue here, giving a falsely low rate and,
 - Lovastatin has been on the market for a long time and there may be a depletion of susceptible effect.

There is a clear signal for a link between cerivastatin and rhabdomyolysis, and strongly, but not exclusively, linked to interaction (with gemfibrozil and clopidogrel). The statins have this reaction and interaction in common, and time on the market, warnings, and coding issues may have artificially elevated reporting of the problem with cerivastatin relative to the other statins.

Consideration should be given to the statins as a whole when switching from cerivastatin is likely to occur. Particular attention should be paid to lovastatin and its safety profile. Reasonable clinical monitoring of the first two months of treatment could very well reduce the serious impact of rhabdomyolysis, particularly with cerivastatin.

References

1. Anatomical, Therapeutic and Chemical classification C10AA: serum lipid reducing agent: HMGcoA reductase inhibitor. Guidelines for ATC classification and DDD assignment. 5th edition. WHO Collaborating Centre for Drug Statistics Methodology, Oslo.
2. WHO-ART Adverse Reaction Terminology. International Monitoring of Adverse Reactions to Drugs, December 2000. Uppsala Monitoring Centre, [http:// www.umc.se](http://www.umc.se)
3. US FDA COSTART. Coding Symbols for Thesaurus of Adverse Reaction Terms, 5th edition. [http:// www.fda.gov](http://www.fda.gov)

International Conference on Harmonization (ICH): pharmacovigilance activities

The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 to improve the harmonization of developing and registering new medicinal products in Europe, Japan and the United States, in order to make these products available to patients with a minimum of delay. ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines.

The focus of ICH has been on the technical requirements for medicinal products containing new drugs. The vast majority of those drugs and medicines are developed in Western Europe, Japan and the United States of America and therefore, when ICH was established, it was agreed that its scope would be confined to registration within those three regions. WHO is an observer at the ICH meetings, representing the interests of non-ICH countries.

To date, ICH has produced more than 45 guidelines; most of which focus on detailed technical requirements to evaluate quality, safety and efficacy of products before they are authorized for the market in the three regions.

NOTE: Using case report data in comparisons may be very misleading due to variables which are not easily apparent. This work should be regarded as a pointer to where more definitive studies can be directed.

Postmarketing as a new objective

In addition to the initial objectives, the fifth ICH meeting held in Tokyo in May 2001 identified post-marketing surveillance as one of the future objectives for the forum.

Three topics were identified as being possible for harmonization in ICH guidelines and were discussed in depth during an informal meeting of the ICH in Brussels in February 2002:

- Periodic Safety Update Report (PSUR);
- Case Management Practices; and
- Rollout of New Drug Products.

The WHO International Drug Monitoring Programme and its collaborating centre, the Uppsala Monitoring Centre, provide an independent and global perspective on drug safety. WHO made several interventions at the meeting on pharmacovigilance activities and how these can impact on the ICH.

1. Periodic Safety Update Report (PSUR)

The ICH guideline, Periodic Safety Update Reports for Marketed Drugs, (Topic E2C) was developed based on the final report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group and finalized in the year 1996 to harmonize the frequency of submission and content of safety updates, to avoid duplication of effort and to ensure that important safety data are submitted with consistency to regulatory authorities. Although this guideline describes the format and content of PSUR, there are regional differences in the implementation and utilization of PSUR which pose regulatory challenges. It is therefore urgent to harmonize the development of the PSUR guidance so that all regions may adopt similar reporting procedures in terms of frequency of reporting, quality of contents, etc. This would allow more harmonized regulatory control of drug products.

2. Case reporting

Extension of the ICH guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (Topic E2A) to postmarketing should include the proposals contained in the CIOMS V report that addresses the current challenges in pharmacovigilance with some pragmatic solutions. Emphasis should be laid on quality and not the quantity of reports generated and a harmonized core data sheet should be employed to distinguish between the expected and the unexpected adverse reactions with a product.

3. Safe rollout of new drug products

Safety concerns during the early phase of global marketing of new drug products should be addressed to improve product and public safety. Guidance on study design (criteria for postmarketing commitments) including postmarketing studies, based on pre-marketing data, should be explored. Safety studies on suspected safety issues at the time of authorization (for example, drug interaction information, paediatric information) should be dealt with in a careful rollout phase that would include risk communications/interactions with health professionals.

A report of this discussion was received by the Steering Committee of the ICH. It agreed to launch two new topics: the development of a further guidance on Periodic Safety Update Reports (PSURs), which will be an addendum to the existing E2C guideline, and a guidance on Good Case Management Practices which will be a follow-up of the E2A guideline. Both are expected to be reviewed in draft form at the next meeting in Washington DC in September 2002. Further discussions are also planned on a third item: Early Phase Postmarketing Vigilance.

The COX-2 inhibitors

COX-2 inhibitors were initially heralded as a breakthrough class of drugs. However, concerns have been expressed about cardiovascular toxicity (1). The issue has potential implications for physicians and patients far beyond this class of drugs. In Canada, celecoxib (Celebrex®) became available on prescription in early 1999.

The Therapeutics Letter of the University of British Columbia (<http://www.ti.ubc.ca>) contains an assessment and synthesis of publications concerning COX-2 inhibitors up to November 2001. The accuracy of the information contained in Therapeutics Letter No 43 was maintained by extensive literature searches and verification by both the authors and the editorial board. In addition it was submitted for review to 120 experts and primary care physicians in order to correct any identified shortcomings or inaccuracies and to ensure that the information is concise and relevant to clinicians. The assessment is summarized below.

What is the presumptive therapeutic advantage of COX-2 selective NSAIDs?

The COX-2 inhibitors have been successfully marketed based on the presumption that the main

mechanism by which nonselective NSAIDs cause gastrointestinal (GI) ulcers is inhibition of COX-1. Based on this hypothesis, drugs that selectively inhibit COX-2 enzymes will have similar anti-inflammatory activity with less GI toxicity. Short-term randomized clinical trials, in which all patients underwent endoscopy, showed fewer cumulative gastroduodenal erosions and ulcers with the COX-2 inhibitors (9–15%) than with nonselective NSAIDs (41–46%) (2).

Regulatory authorities judged this surrogate outcome insufficient to prove that COX-2 selective inhibitors were better than nonselective NSAIDs in terms of the life-threatening complications of NSAIDs: ulcers complicated by GI bleeds, perforations and obstructions. Thus the monographs of celecoxib, rofecoxib (Vioxx®) and meloxicam (Mobicox®) include the same warnings of the risk of GI toxicity as all other NSAIDs.

What was the objective of the CLASS and VIGOR comparative trials?

With the objective to demonstrate a reduced incidence of complicated ulcers with COX-2 inhibitors, the manufacturers of celecoxib and rofecoxib conducted two large randomized clinical trials, the CLASS and VIGOR trials. Major findings of these trials were published in 2000 (4, 5). In February 2001, The Therapeutics Letter No. 39 summarized the most important outcome data from the published reports. Shortly after circulation of Letter No. 39, the FDA published a complete review of the CLASS and VIGOR trials on their website (6), leading to a different interpretation of the overall safety of this class of drugs (9).

What do the FDA data tell us?

The FDA data reveal that the CLASS study as published (4), and summarized in Letter 39, reported only the first six months of data from two trials of longer duration. One of the trials was a 15-month trial comparing celecoxib with ibuprofen and the other was a 12-month trial comparing celecoxib with diclofenac. Both the six-month and full trial data are provided in the FDA review (6). The published VIGOR trial duration and GI outcome data are the same as that found on the FDA website, but the FDA report is more complete and provides overall serious adverse event data (8). As pointed out in Therapeutics Letter 42, total serious adverse events (SAEs) provide essential information about both harm and benefit. SAEs include death, hospitalization or extension of hospitalization and any life-threatening event or serious

disability. In the case of NSAIDs, complicated ulcers represent one of the SAEs.

Why do COX-2 inhibitors increase serious adverse events?

The reason for the increased incidence of serious adverse events with the COX-2 selective inhibitors cannot be completely answered from the available FDA data. SAEs are more completely reported in the FDA VIGOR report than the FDA CLASS report. Myocardial infarction (RR=4.9 [1.7-14.3], ARI=0.4%, NNH=250) and adjudicated thrombotic cardiovascular events (RR=2.38 [1.39-4.00], ARI=0.6%, NNH=167) are increased with rofecoxib as compared to naproxen (1, 8). The reason why COX-2 inhibitors might increase thrombosis is discussed (1). However, none of the reported individual or combined outcomes explain the overall 1.0–1.9% absolute risk increase of other serious adverse events associated with either celecoxib or rofecoxib.

Before making a claim of a safety benefit over a comparator, the total percent SAEs should be less than that observed with the comparator. For example, rofecoxib as compared to naproxen reduced complicated ulcers (ARR=0.5%) leading to a claim of a safety benefit, but the magnitude of this benefit is outweighed by the harm associated with rofecoxib in terms of other SAEs (ARI=1.9%).

What about less serious outcomes?

In the VIGOR trial, symptomatic ulcers were reduced with rofecoxib as compared to naproxen, and withdrawals due to adverse events were the same in both groups. The complete data for symptomatic ulcers in the CLASS trial are as follows: 0.65% of patients treated with celecoxib and 1.0% of patients on other NSAIDs had symptomatic ulcers (RR=0.63 [0.39-1.03]). Interpretation of this trend is complicated by the fact that fewer patients in the celecoxib group (3.4%) underwent endoscopies as compared to patients treated with the other NSAIDs (4.9%; RR=0.70 [0.57-0.87]).

The decrease in withdrawals due to adverse events with celecoxib at 6 months (4) was also seen in the full trial: 22.4% of celecoxib patients and 24.6% of patients on other NSAIDs withdrew due to adverse events (RR=0.91 [0.84-0.98], ARR=2.4%, NNT=42). This finding predominantly reflects a higher incidence of withdrawals due to GI symptoms and increase in hepatic enzymes in patients treated with diclofenac.

Conclusions

- Based on FDA data from the CLASS and VIGOR studies, COX-2 selective inhibitors are associated with an increased incidence of serious (life-threatening) adverse events as compared to nonselective NSAIDs.
- Published versions of the CLASS and VIGOR trials focused on GI events and failed to report other serious adverse events fully.
- In the interests of public safety, serious adverse event rates from all trials must be published.

References

1. Mukherjee, D., Nissen, S.E., Topol, E.J. Risk of cardiovascular events associated with selective COX-2 inhibitors. *Journal of the American Medical Association*, **286**: 954-959 (2001).
2. Goldstein, J.L., Correa, P., Zhao, W.W, et al. Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitor, compared to naproxen in patients with arthritis. *American Journal of Gastroenterology*, **96**: 1019-1027 (2001).
3. Laine, L., Harper, S., Simon, T., et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology*, **117**: 776-783 (1999).
4. Silverstein, F.E., Faich, G., Goldstein, J.L., et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *Journal of the American Medical Association*, **284**:1247-1255 (2000).
5. Bombardier, C, Laine L, Reicin A, et al, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New England Journal of Medicine*, **343**:1520-1528.
6. Witter, J. Medical Officer Review. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf
7. US Food and Drug Administration. Celebrex capsules (celecoxib) NDA 20-998/S-009—Medical Officer Review. 2000. Available at: <http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1.htm>
8. US Food and Drug Administration. NDA 21-042, s007, Vioxx Gastrointestinal Safety – Medical Officer Review. 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.doc.

9. FDA Panel finds no safety benefit for Celebrex. *Scrip World Pharmaceutical News*. February 9, 2001; 2616:19.

10. Wright, J.M., Perry, T.L., Bassett, K.L., Chambers, G.K. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib. *Journal of the American Medical Association*; **286**: 2398-2400 (2001).

Amiodarone and pulmonary toxicity

Amiodarone (Aratac®, Cardinorm®, Cordarone X®) is an anti-arrhythmic agent for the treatment of severe cardiac arrhythmia. The Australian Adverse Reactions Advisory Committee (ADRAC) regularly receives reports of suspected adverse reactions to amiodarone; in the year 2000 there were 61 reports, and in 2001 there were 74 reports, including 5 deaths.

Since 1981, there have been 31 reports to ADRAC of deaths in association with amiodarone use, 17 of which have involved pulmonary events (pulmonary fibrosis 8, pulmonary infiltration 5, pneumonitis 2, pulmonary effusion 1, respiratory failure 1). Although commonly insidious in onset, amiodarone-induced pulmonary toxicity may develop rapidly. For this reason, the lowest effective dose should be used, and patients should be instructed to report any dyspnoea or nonproductive cough (1). Amiodarone also has other toxicities including hepatotoxicity which can cause cirrhosis and hepatic failure, cardiovascular effects including bradycardia and tachycardia, skin reactions including photosensitivity and discoloration, neurotoxicity including ataxia and peripheral neuropathy, as well as both corneal deposits, hyper- and hypothyroidism.

Amiodarone has unique properties for the treatment of difficult cardiac arrhythmias and its use is increasing (2). It is particularly important for prescribers and patients to be aware of the risk of pulmonary toxicity and the presence of dyspnoea or cough should be investigated immediately.

References

1. Kanji Z, Sunderji R, Gin K. Amiodarone-induced pulmonary toxicity. *Pharmacotherapy*, **19**: 1463-1466 (1999).
2. Health Insurance Commission. Pharmaceutical Benefit Schedule Item Statistics [cited 2001 Jan 3]. http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml
3. *Australian Adverse Drug Reactions Bulletin*, **21**:(2) February 2002.

Alendronate: link with pancreatitis?

Six case reports of pancreatitis associated with alendronic acid have been received by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) between December 1995 and August 2001. However, it is difficult to establish a causal relationship because the case reports contain limited data.

One report describes a patient receiving alendronic acid monotherapy for 13 days when pancreatitis developed. The complication resolved after discontinuation. In the remaining case reports, the onset of symptoms of pancreatitis after initiation of alendronic acid therapy ranged from 48 days to several years (data not provided for 2 patients), and the patients were elderly and female where such data were provided. One death occurred and was reported to be possibly drug related. Continued reporting of other suspected cases of alendronic acid-associated pancreatitis is needed to assist in further assessment of this possible adverse drug reaction.

Reference: *Canadian Adverse Drug Reaction Newsletter* 12(1): 2–3, January 2002.

Endocrinotoxicity induced by *Coriandrum sativa*: a case report

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A 28 year old woman had taken an extract of *Coriandrum sativa* leaves and branches (200 ml of about 10% aqueous extract for 7 executive days) to augment lactation to breastfeed her 10-month-old infant. After 7 days she was admitted to the hospital with severe diarrhoea and stomach pain. The patient had no significant serum or urine test changes and recovered after common palliative therapy. Fifteen days later the patient came back complaining of skin darkness, depressed mood and loss of body fluids and amenorrhoea, which was diagnosed as an adrenal dysfunction. The patient said that she did not have any history of such a condition. The patient received intramuscular dexamethasone (4 mg/day) for 3 days then continued with pred-nisolone tablet (5 mg/day) for 10 consecutive days. She also received oral

contraceptive for relief of her menstruation cycle disturbances (spotting, oligomenorrhoea, dysmenorrhoea). After 10 days the patient was well and healthy.

Based on the literature, coriander seeds have been used as a herbal medicine (3 g/day) as antispasmodic and anticarminative (1, 2). Also its leaves and small branches are used as a vegetable and food supplement in Iran (3).

References

1. Blumenthal, M., Goldberg, A., Brinckmann. *Journal of Integrative Medicine*, 75–76 (2000).
2. Weis, R.F., Fintelmann, V. *Herbal Medicine*, 2nd ed., Thieme, 2000 pp. 77–78.
3. Zargari, A. *Herbal Drugs*, Teheran University Publication Inc., 13774, Vol. 2, 586–587.

Haemolysis after consumption of *Viola tricolor*

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A case of hemolysis caused by ingestion of watery extraction of *Viola tricolor* has been reported to the Drug and Poisoning Information Center (DPIC) of Tehran.

A 9-month-old infant with a history of glucose-6-phosphate-dehydrogenase (G6PD) deficiency received half a cup of boiled extract of *Viola tricolor* (commonly called heartsease or wild pansy) by his grandmother to relieve his restlessness. After one hour the parents recognized that the infant was ill and they transported him to the nearest hospital. Physicians diagnosed moderate haemolysis and started routine inter-ventions. After 24 hours, the infant was healthy and had recovered.

Historically, *Viola* is known to be useful in the treatment of skin problems such as eczema, itching, impetigo, rashes, rosacea, pustular eruptions and in the relief of urinary symptoms such as cloudy foul-smelling urine, frequent, profuse urination, bed wetting at night, and sharp pains in the urethra. It has also been reported to be helpful in treating children who are prone to disobedience (1). It relieves cough and induce diuresis (2).

It seems that existence of saponins and methyl ester of salicylic acid in the extract of *Viola* is the cause of hemolysis in G6PD deficiency patients (3). Also it contains volatile oil and anthocyanin, flavonoid, phenolic glycosides and carotenoid pigments (2).

This case suggests that the general public are not aware of some adverse effects of herbal drugs and indicates a need for improved information.

References

1. Lockie, A. *Encyclopedia of Homeopathy*. 172–310 (2000).
2. Evans, W.C. *Trease and Evans' Pharmacognosy*. 996: 43–44, 478, 503–504.
3. Volak J., Stodola J. *Plantas Medicinales*, 341–342 (1990).

Lipodystrophy syndrome under-reported

Antiretroviral therapy (ART)-related lipodystrophy syndrome is highly under-reported in Canada (1). The case definition of lipodystrophy syndrome is described as at least one metabolic abnormality and at least one clinical feature, in addition to no event or other serious condition, or the use of anabolic steroids, glucocorticoids or immune modulating agents within the three months before as-

essment. Using this definition, four case reports of ART-associated lipodystrophy syndrome were identified from the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) database.

These case reports came from a total of 119 reports of metabolic, nutritional or endocrine disorders associated with antiretroviral agents. In addition, there were three cases of potential lipodystrophy syndrome and 13 cases of fat disorder. Of the four cases of ART-associated lipodystrophy syndrome, three were associated with the protease inhibitors indinavir, saquinavir and ritonavir, and the remaining report was associated with stavudine.

Patients included three men and one woman, aged between 33–56 years. The clinical features of lipodystrophy syndrome included lipodystrophy (2 patients), fat disorder (2) enlarged abdomen (1). Metabolic abnormalities included hyperglycaemia (2), hypertriglyceridaemia (2) and diabetes mellitus (1). The article points out that the prevalence of lipodystrophy syndrome during highly-active antiretroviral therapy has been reported to be between 17 and 84%. As the incidence of lipodystrophy syndrome is therefore clearly under-reported, Health Canada has implemented a project to promote the reporting of adverse drug reactions in patients with HIV infection.

Reference: *Canadian Adverse Drug Reaction Newsletter* 12(1): 3–4, Jan 2002.

**Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.*

Current Topics

Progress in pharmacogenetics and pharmacogenomics*

Recent progress in unravelling the secrets of the human genome has led to increased knowledge of genetics in many fields of medicine and supports the promising development of two new branches of science – pharmacogenetics and pharmacogenomics. *Pharmacogenetics* refers to the study of DNA sequence variation as it relates to differential drug response of individuals, i.e. the use of genomics to determine an individual's response. *Pharmacogenomics* refers to the use of DNA-based genotyping in order to target pharmaceutical agents to specific patient populations in the design of drugs.

Pharmacogenetics — genetic factors affecting a patient's response to drugs — promises to change the way health care is practised. Increased understanding of genetic mechanisms responsible for drug response, non-response and toxicity offers new possibilities of meeting the needs of health care systems and the demands made upon them. For the individual patient, quality of life can be enhanced by improved selection of the most effective drug at the appropriate dose. Although pharmacogenetic diagnostics will increase the cost of health care initially, this is expected to be offset by the savings made in reducing the occurrence of unnecessary and inadequate drug use and adverse drug reactions — in particular those which are dose dependent. Getting the right drug at the right dose to the right patient first time and avoiding a "try and see" method will also reduce the number of visits to the physician.

Application of pharmacogenetics to drug development will also streamline the drug development process. It affects both pre-clinical drug development studies and, even more, clinical research. With more focused stratification of patient groups it is possible to make narrow, more specific indica-

tions. Such indications will apply to those diseases having certain established and clearly measurable features, such as multiple sclerosis. Given that such patient groups may not always represent commercially attractive markets for the pharmaceutical industry with current marketing paradigms, strategies will have to be remodelled. The ability to target patients more accurately, however, may represent considerable commercial value within a specific market sector, such as hypertensives.

Additionally, health care policies and structures must ensure that any short-term budget constraints are not allowed to take precedence over mid to long-term benefits. To realize the potential of pharmacogenetics, tailored communications and educational programmes will be necessary for key stakeholders — patients, patient groups, health care professionals, regulators, the health care industry and the biotechnology, pharmaceutical and diagnostic industry, health care funding and reimbursement organizations, governments and academia. Pharmacogenetics is likely to be introduced according to need, clinical validity and value, with resources first being directed at diseases for which it is vital to prescribe the right drug at the right dose from the outset.

The practice of drug therapy is confronted with two major problems: adverse drug reactions and non-response to treatment. Adverse drug reactions (ADRs) contribute substantially to morbidity and mortality according to a recent meta-analysis (1). To what extent pharmacogenetic factors are involved in ADRs remains open to discussion because this aspect has not been addressed in clinical studies. A substantial proportion of patients will show no or insufficient response to drugs. For instance, 15–25 % of patients are unresponsive to β -adrenoreceptor antagonists. The same holds true for statins: at least 30% of patients show no lowering of cholesterol levels.

In principle, there are three mechanisms responsible for genetic variability in drug response, non-response and toxicity.

- Genetic polymorphism of proteins involved in the biotransformation and transport of drugs following

*Summary of discussions at the CIOMS Working Group Meeting on Pharmacogenetics and Pharmacoeconomics, held from 11–15 September 2001 at the World Health Organization, Geneva, Switzerland.

administration of the same dose. Large inter-individual differences in drug concentrations are observed and, as a consequence, the intensity and duration of drug action and ADRs will vary substantially.

- Even if drug dose is individualized to achieve identical plasma concentrations, substantial variability in response will still be observed because concentrations at the site of action vary. It is increasingly recognized that transfer in and out of cells involves active transport. Moreover, variable expression of drug metabolizing enzymes at the site of action can modify drug response in albeit identical plasma concentrations.
- Finally, the same concentration of a drug at the site of action does not necessarily mean identical response, because drug target mutations can profoundly alter response.

Although examples show that pharmacogenetic testing can assist in selecting the appropriate dose for an individual patient, pharmacogenetics is still in its infancy and the majority of those genes which are of relevance to pharmacogenetics have not yet been identified. Clinical trials are lacking to demonstrate that pharmacogenetic testing can accomplish the selection of the appropriate drug and dose for the individual patient to achieve optimal therapeutic response, avoid therapeutic failure and minimize side effects and toxicity. With the rapid advances being made in molecular genetics, these questions will no doubt soon be answered. Pharmacogenetics will also have implications for the use of drugs among different ethnic groups. As a consequence of differences in allele frequencies for polymorphic enzymes or the occurrence of different mutations, drug response and dose can differ among different races. For obvious reasons, this has implications for drugs developed for international use.

Health economics and pharmacogenetics

Pharmacogenetics will have an impact on society as a whole. The better understanding of factors governing individual drug response will facilitate a more data-driven approach to drug prescribing and may contribute to the distribution of financial resources in the health care system in a more rational way. Drugs may be prescribed to those who are likely to derive the most benefit, while patients who are likely to derive little therapeutic benefit from a given drug or may experience a serious adverse drug reaction can receive different medication or non-therapeutic interventions, as appropriate.

In other words, the negative economic consequences of ADRs are likely to be reduced. Targeting health care to those who will benefit the most implies a more efficient use of health care expenditure with better health outcomes, on average, for those treated, and a freeing up of resources, including manpower. The potential exists for the identification of patients for whom current therapeutic options do not provide an adequate risk/benefit outcome, and therefore new therapies may be needed to target these patients to meet their clinical needs.

Pharmacogenetics and marketing

Experience with pharmacogenomics has already taken place. For example, administration of trastuzimab (Herceptin®), registered for the treatment of breast cancer, requires that subjects are tested to determine if their tumors express the *Her2* gene. Response to the antibody is related to expression levels of *Her2* (2). Only those women with breast cancer who have a very active *Her2* gene may be treated (about 30% of all breast-cancer cases), while women with low expression of *Her2* do not benefit and should therefore not be treated. Although the test does not determine the genotype, this product does provide an example of how understanding of a disease at the molecular level and being able to identify patients who would benefit from treatment, has enabled a focused drug development strategy and has been a critical component of successful regulatory approval.

Need to determine risk-benefit ratio

Clinical trial design, monitoring and pharmacovigilance methodology have all become more sophisticated over time. However, the ability to more precisely determine the risk-benefit ratio of a drug for an individual patient will be a major advance. During clinical trials, the risk-benefit ratio is assessed only for those subjects entering the trial and may not be a true reflection of the environment in which the product will ultimately be prescribed. There is a need to better define the drug response pattern and, with this knowledge, facilitate the use and safety monitoring of drugs to treat disease more effectively. Since it is acknowledged that drug interactions and especially adverse reactions can be a significant cause of hospitalization, the inclusion of drug response profiles in the prescribing process will help reduce such admissions.

The genetic constitution of a patient is an important factor explaining positive and negative reactions to treatment. In future clinical trials, randomization

according to genetic make-up will become as important as age, sex, or ethnic affiliation.

Health care and pharmacogenetics

The main focus of pharmacogenetics will be on the individual patient, who will benefit in the following ways:

- Diagnosis and therapy will be individualized for each patient.
- The clinician will have enhanced ability to predict the benefit or value of treatment against the risks of the drug for each individual patient.
- Enhanced ability to prescribe the most appropriate drug at optimal dose — in terms of risk/benefit — will lead to more effective treatment and potentially fewer ineffective medicines. There will be a reduced number of adverse events and overall increased quality of life.

The limits of pharmacogenetics

Gene-dose effect

In the case of polymorphisms of drug metabolizing enzymes there are no good data demonstrating that patients will achieve the required plasma concentration. The genotype is predictive only for patients who are homozygous for loss of function alleles. Better understanding of the genotype for dose selection is needed of promoter mutations, mutations of transcription factors, etc. No prospective clinical studies have yet been undertaken to show that pharmacogenetic testing can reduce toxicity and improve drug response.

Ignorance by physicians of the existence of these pharmacogenetic factors is a major problem. Although there are good data to show that toxicity can be avoided, genotyping is still the exception rather than the rule in clinical practice.

Genotyping methods are still laborious and expensive, but with rapid advances being made tests should soon be available at reasonable cost. Increased availability of such tests may allow clinical trials to be randomized on the basis of genotyping.

Conclusion

Advances in pharmacogenetics provide an opportunity to improve rational prescribing. However, this new specialty also brings challenges to health care systems. It will be the responsibility of the innovative pharmaceutical industry, in partnership with

health care providers, to develop new treatment methods and provide evidence of their benefits. Health care systems will need to integrate pharmacogenetics into health care and develop relationship with industry to ensure development of future treatments. Health care providers will need training to understand and apply the new treatments in the best way. The initial costs and challenges of implementing pharmacogenetics need to be viewed as an investment in health which will be off-set by improvements in patient health and quality of life, reductions in demands on the health care system and value for money.

Future action

The second CIOMS Working Group meeting on the impact of pharmacogenetics on drug development to optimize benefit/risk ratio in pharmacotherapy was held in February 2002 at the European Agency for the Evaluation of Medicinal Products (EMA) in London, and included participants from the World Health Organization, drug regulatory agencies, the pharmaceutical industry and universities. The following items were discussed:

- Terminology.
- Molecular knowledge of disease, drug action and evolution in clinical practice.
- Optimizing benefit/risk ratio (and risk management).
- New possibilities in therapeutics (e.g. individualized medicine) and tools for physicians.
- Cost/economics of innovative pharmacogenetics — who pays?
- Aspects of pre-clinical drug development.
- Understanding the genetic molecular basis for serious adverse reactions.
- Facilitating global drug development through identification of the genetic basis of drug action and optimizing the benefit of new drugs.
- Improvements of existing (generic) therapies ("well-established drugs")
- Barriers to progress
- Case studies to illustrate principles and basic problems.
- Creation of a database of clinical trials using pharmacogenetics.

- Financial impact of new technology.
- Cost of adverse drug reactions.
- Regulatory perspectives (EMEA, FDA, MCA)
- Ethical implications.
- Implementation of knowledge and education of stakeholders.
- Definition of data.
- Co-development of diagnostic tests.

References

1. Lazarou et al. *Journal of the American Medical Association*, **279**: 1200–1205 (1998).
2. Stebbing, J., Copson, E. and O'Reilly, S. Herceptin (trastuzumab) in advanced breast cancer. *Cancer Treatment Reviews*, **26**(4): 287–290 (2000).

Further reading:

1. Foot, E., Weihrauch, T.R., et al. The Society of Pharmaceutical Medicine Working Party Subgroup on Pharmacogenetics. Impact on Healthcare and Health economics. *International Journal of Pharmaceutical Medicine* (in press)
2. CIOMS/ WHO Planning Meeting: Global Network for Drug Regulatory Harmonisation. *International Journal of Pharmaceutical Medicine*, **14**: 295 (2000).
3. Human Genome Project. <http://www.ornl.gov/hgmis/>
4. Roses, A.D. Pharmacogenetics and the practice of medicine. *Nature*; **405**: 857–865 (2000).
5. Marchant, N. *Drivers of growth in medical expenditure*. Office of Health Economics, London, 1997.
6. Zuehlendorf, M.T. Relevance of pheno- and genotyping in clinical drug development. *International Journal of Clinical Pharmacology and Therapeutics*, **36**: 607–612 (1998).
7. Fears, R., Roberts, D., Poste, G. Rational or rationed medicine? The promise of genetics for improved practice? *British Medical Journal*, **320**: 933–935 (2000).
8. Wolf, C.R., Smith G., Smith, R.L. Pharmacogenetics. *British Medical Journal*, **320**: 987–990 (2000).
9. *Genomics, Healthcare and Public Policy*. Based on papers delivered at the OHE Conference on Genomics, Healthcare and Public Policy, London, 11 February 1999. Edited by Paul Williams and Sarah Crow, OHE, 1999

10. Venulet, J., ten Ham, M.: Methods for monitoring and documenting adverse drug reactions: *International Journal of Clinical Pharmacology and Therapeutics*, **34**:112–129 (1996).

11. The Pharmacogenetics Working Group. Terminology for sample collection in clinical genetic studies. *Pharmacogenetics Journal*, **1**: 101–105 (2001).

12. Danzon, P., Towse, A. *The economics of gene therapy and of pharmacogenetics*. Office of Health Economics. <http://www.ohe.org>

13. Mach, E.P., Venulet, J. *The economics of adverse drug reactions to drugs*. WHO Chronicle, **29**: 79–81 (1975).

14. Shah, R.R. Implications of pharmacogenetics for the regulatory assessment of new chemical entities. *Pharmaceutical News*, **7**: 32–38 (2000).

15. Committee for Proprietary Medicinal Products. *Position paper on terminology in pharmacogenetics*. London, December 2001. EMEA/CPMP/3070/01.

Internet sales and reimbursement by insurance companies

A Bavarian health insurance company has recently set up a contract with a Dutch internet pharmacy shop and has advised its 1.8 million members to order cheaper drugs via the internet. This would enable the company to reimburse prescriptions at lower cost than at a pharmacy and would also allow patients to buy non-prescription drugs more cheaply.

The insurance company faces strong opposition from local pharmacies as well as state institutions. The Bavarian Social Ministry has issued an order from the State Insurance Agency trying to stop the company accepting bills from the internet pharmacy.

However, a “round table” of the German Health Service, a body of health professionals and interest groups which advises the Minister, came down in favour of internet trade of pharmaceutical drugs — against strong protests of pharmacists who fear they will go out of business. Prescribed drugs may now be refunded as long as patient information is provided on the administration and side effects of the drug, which must be delivered speedily to customers homes. Drug safety and the nationwide closed network of basic pharmaceutical care could be at risk if local pharmacists have to compete with

internet shops. However, the Bavarian insurance group says that it has no doubts about the quality of the products available for German customers as well as the medical counselling provided by the internet pharmacy via a free hotline on the internet.

The insurance company says that customers appreciate the lower costs, which are about 20% below average for drugs on prescription. Doctors also profit from cheaper drugs because it reduces their drugs budget—doctors with their own practices, general practitioners, and specialists have a budget for treatment and are punished if they exceed it. Therefore they also want cheaper drugs, and are supportive of contracts with internet dealers. The insurance company estimates that German health insurance companies could save about US\$ 363 million by buying drugs over the internet.

However, the legal background is not yet clear. In the past two years, the German Pharmacists Association has tried to stop the internet pharmacy in question, which is said to have at least 20 000 customers in Germany, mainly for over-the-counter drugs. In November 2000, a court in Frankfurt ordered the Internet pharmacy to stop supplying German customers because trading drugs by post is not allowed in Germany. The internet pharmacy reacted by letting its customers pick up the drugs themselves or using special courier services. The matter has gone to the European Court for a ruling, and its decision is expected in 2003.

Meanwhile, the German federal health ministry is trying to take a position on this issue. On the one hand, given rising health costs, the admission of cheaper drug trading seems enticing. On the other, the German system of pharmaceutical care might be shattered by opening the doors to cost efficient competitors.

Reference: Internet sales threaten drug companies' supremacy. *British Medical Journal*; **324**: 998 (2002)

Nevirapine: comments on HIVNET 012 from the manufacturer

Questions have been raised regarding reporting and documentation in a study conducted in Uganda for prevention of the transmission of HIV from mother-to-child during birth, called HIVNET 012. The study, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), Bethesda,

Maryland, and conducted by Johns Hopkins University and Makerere University, Uganda, evaluated the use of nevirapine (VIRAMUNE®).

Study data from the trial were part of a pending supplemental NDA submitted to the Food and Drug Administration in support of this indication in the USA. The study results, published in the *Lancet*, concluded that nevirapine significantly lowered the risk of HIV transmission from mother to child during the first weeks of life. Extensive data from other trials support the safety of nevirapine in mothers and infants in this setting.

The National Institute of Allergy and Infectious Diseases (NIAID) is vigorously undertaking a comprehensive review of all the data collected in the course of the study. However, since the review could not be completed within the remaining timeline for FDA action for the supplement, the manufacturer, Boehringer Ingelheim Pharmaceuticals, has notified the FDA of its decision to withdraw the U.S. sNDA for prevention of mother-to-child transmission at this time.

The manufacturer continues to support the use of nevirapine and will continue to offer the drug to developing countries for the prevention of mother-to-child transmission of HIV as part of the VIRAMUNE Donation Programme.

Reference: Information provided by Boehringer Ingelheim Pharmaceuticals, Inc., 13 May 2002. <http://www.Boehringer-Ingelheim.com/corporate/asp/news>

Review of HIVNET 012

Since 1997, funding from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), supported a trial known as HIVNET 012, conducted by co-investigators at Makerere University in Kampala, Uganda, and the Johns Hopkins University in Baltimore, Maryland. The trial was designed to examine the effectiveness of nevirapine (NVP) in blocking transmission of HIV from a mother to her newborn baby by treating the mother and baby at the time of birth. NVP is approved by the US Food and Drug Administration (FDA) for the treatment of HIV infection in adults and children.

Enrollment in HIVNET 012 was completed in 1999. The results, published in *The Lancet* in 1999,

concluded that NVP significantly reduced the risk of HIV transmission from mother to child during the first week of life. Other studies conducted in the United States and internationally were consistent with the results from HIVNET 012. Based on the data from these studies, a US Public Health Service Task Force currently recommends NVP as an option for prevention of mother-to-child transmission (MTCT) for women and their newborns in the United States who have not received antiretroviral therapy during pregnancy.

An examination of the data to support an extension of the indication for the use of NVP to include prevention of MTCT was recently begun. Although no evidence has been found that the conclusions of HIVNET 012 are invalid or that any trial participants were placed at an increased risk of harm, certain aspects of the collection of the primary data may not conform to FDA regulatory requirements. A comprehensive effort to access the primary data has begun to determine the applicability of the data collection processes to these regulatory requirements.

The reduction in perinatal transmission by the use of NVP, an accessible, inexpensive regimen, represents a major public health advance in resource-poor settings and NIAID believes there is no reason for programmes implementing this life-saving regimen to change their practices.

Reference: NIH/NIAID statement dated 22 March 2002 <http://www.washingtonpost.com/wp-dyn/articles/A5310-2002Mar22.html> Mother-to-child transmission of HIV

Mother to child transmission of HIV: WHO statement

As stated, the manufacturer of nevirapine has requested the Food and Drug Administration to withdraw the NDA status for the mother-to-child transmission (MTCT) indication of nevirapine.

The World Health Organization and UNAIDS continue to support use of nevirapine for prevention of mother-to-child HIV transmission. They consider that a statement released on 22 March 2002 by the United States National Institutes of Health (NIH), concerning some reporting and documentation irregularities in clinical trial HIVNET 012, does not warrant any change in the recommendations issued by a WHO technical consultation on mother-to-child HIV transmission in October 2000.

This expert group, convened by WHO on behalf of UNICEF, UNFPA, and the UNAIDS Secretariat, concluded that the safety and effectiveness of antiretroviral regimens, including nevirapine, in preventing mother-to-child HIV transmission has been clearly documented and that the use of these regimens is thus warranted for preventing mother-to-child HIV transmission. The simplest regimen requires a single dose of nevirapine to the mother at delivery and a single dose to the newborn within 72 hours of birth.

The NIH statement (set out below) emphasized that, according to available information, there is no evidence that the scientific data from the HIVNET 012 study demonstrating the safety and effectiveness of nevirapine is invalid. Each year, more than 600 000 infants become infected with HIV, mainly through mother-to-child transmission. WHO and UNAIDS recommend that the prevention of mother-to-child transmission of HIV, including antiretroviral regimens such as nevirapine, should be included in the minimum standard package of care for HIV-positive women and their children.

Reference: *Press Release*, WHO, Geneva and UNAIDS, Geneva.

Regulatory and Safety Action

Enoxaparin sodium Injection: new safety warnings

United States of America — The manufacturer of enoxaparin sodium Injection (Lovenox®) has made the following additions to the warnings and precautions sections of the prescribing information.

In the warnings section, the following subsection has been added: *Prosthetic Heart Valves*. The use of enoxaparin sodium Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal or fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism.

In the precautions section, a new paragraph has been added to the Pregnancy subsection – Teratogenic Effects regarding *congenital anomalies*. There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population. The Non-teratogenic Effects subsection now states: There have been post-marketing reports of fetal death when pregnant women received enoxaparin sodium Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Haemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women

developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions.

Reference: Letter from Aventis Laboratories. Aventis Pharmaceuticals. <http://www.aventis.com> or <http://www.fda.gov/medwatch>

Ziprasidone hydrochloride: labelling clarifications

United States of America — The manufacturer of ziprasidone HCl capsules (Geodon®) has circulated a letter to inform healthcare professionals about clarifications to the labelling. Ziprasidone capsules were approved on 5 February 2001. Since approval, 563 000 prescriptions have been written and 156 000 individual patients have received ziprasidone. Postmarketing experience has been consistent with the clinical database, and not unexpected in this patient population.

In consultation with the Food and Drug Administration, clarifications have been made to the information included in the package insert. The Contraindications section included a list of seven drugs contraindicated with ziprasidone and stated that this list of drugs was "not a complete list". Not all physicians, pharmacists and pharmacy databases interpreted this language as intended. Some may have considered certain drugs excluded from the contraindication, while others believed that, irrespective of the level of documentation, any drug associated with QT-prolongation was contraindicated with ziprasidone.

Key sections have now been changed in the labelling. *Contraindications: QT Prolongation*. Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with:

dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levacetylmethadol, dolasetron mesilate, probucol, or tacrolimus.

Ziprasidone is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning.

Warnings: QT Prolongation and Risk of Sudden Death. Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. As previously mentioned, given that postmarketing experience with ziprasidone is consistent with the information generated during clinical trials, there are no other changes to the prescribing information.

Reference: Letter from Pfizer Inc. at <http://www.fda.gov/medwatch>

Kava kava products and potential liver injury

United States of America — The Food and Drug Administration has circulated a letter to health care professionals and has advised consumers concerning the potential risk of severe liver injury and rare hepatic failure associated with use of kava-containing dietary supplements. Persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, should consult a physician before using kava-containing supplements.

Kava (*Piper methysticum*) is a plant indigenous to the islands in the South Pacific where it is commonly used to prepare a traditional beverage. Supplements containing the herbal ingredient kava are promoted for relaxation (e.g., to relieve stress, anxiety, and tension), sleeplessness, menopausal symptoms and other uses. The FDA has not made

a determination about the ability of kava dietary supplements to provide such benefits.

Liver-related risks associated with the use of kava have prompted regulatory agencies in other countries, including those in Germany, Switzerland, France, Canada, and the United Kingdom, to take action ranging from warning consumers about the potential risks of kava use to removing kava-containing products from the marketplace. Although liver damage appears to be rare, the FDA believes consumers should be informed of this potential risk. Kava-containing products have been associated with liver-related injuries, including hepatitis, cirrhosis, and liver failure in over 25 reports of adverse events in other countries. Four patients required liver transplants. In the USA, the FDA has received a report of a previously healthy young female who required liver transplantation, as well as several reports of liver-related injuries.

Given these reports, persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, should consult a physician before using kava-containing supplements.

Consumers who use a kava-containing dietary supplement and who experience signs of illness associated with liver disease should also consult their physician. Symptoms of serious liver disease include jaundice (yellowing of the skin or whites of the eyes) and brown urine. Non-specific symptoms of liver disease can include nausea, vomiting, light-coloured stools, unusual tiredness, weakness, stomach or abdominal pain, and loss of appetite.

Reference: Letter to Health Care Professionals: FDA Issues Consumer Advisory that Kava products may be associated with severe liver injury 25 March 2002 <http://www.cfsan.fda.gov/~dms/supplmnt.html>

Kava kava: investigations into liver injury

New Zealand, Ireland, Canada — Further to precautionary warnings issued by the regulatory authorities in Germany, Switzerland, UK and USA the following actions have been recorded on the use of Kava.

16 January 2002: The New Zealand Ministry of Health has stated that it is looking into concerns expressed by overseas authorities about a reported

link between kava consumption and liver damage in some people. In New Zealand Kava is mostly consumed as a natural drink whereas in Europe it is consumed as a pre-packaged dietary supplement. Since factors other than kava consumption may have caused liver damage, it is difficult to draw a definite cause-effect relationship with the present evidence in New Zealand. However the Ministry has been working closely with the Australia New Zealand Food Authority (ANZFA) since it became aware of this issue in early January to gather relevant information and is awaiting further information from Europe before reaching a conclusion on whether any action is warranted.

16 January 2002: Health Canada has advised consumers not to use any products that contain kava although no cases of liver toxicity have been reported in Canada with Kava. Health Canada is conducting a comprehensive safety assessment of kava and will take further action, if required.

4 February 2002: The Irish Medicines Board in consultation with the industry initiated a voluntary withdrawal of all products containing kava from the Irish market with immediate effect although the Medical Director at IMB stated that the current data are confounding. The IMB based its withdrawal on similar actions by other EU Member States.

References

1. Media Release, 16 Jan 2002. <http://www.ndp.govt.nz/media>
2. Health Canada Warnings / Advisories, 16 Jan 2002. <http://www.hc-sc.gc.ca>
3. Current News and IMB Statements, 4 Feb 2002. <http://www.imb.ie/>

Rofecoxib interaction with warfarin

Australia — The Australian Drug Reactions Advisory Committee (ADRAC) has previously published a report on the interaction between celecoxib and warfarin (1). It now appears that rofecoxib (Vioxx®) and warfarin may also sometimes interact to a clinically significant extent.

ADRAC has received 416 reports of suspected adverse reactions to rofecoxib since its marketing in Australia in late 2000. Of these, 8 described an increase in the INR in patients taking warfarin. In 6 of those reports, INR values were given, ranging

from 3.8 to 11.8. In half of the reports, the timing of the reaction relative to the date of commencing rofecoxib was accurately described; this varied from 1 to 6 weeks. Five of the 8 reports did not describe haemorrhagic complications. However, bleeding was reported in 2 cases (epistaxis and rectal haemorrhage) and anaemia (haemoglobin 87 g/L) in one case. Five patients were hospitalized, and 2 received treatment with intravenous vitamin K. A further report described a patient taking both rofecoxib and warfarin, who died after a cerebral haemorrhage, although in this case the INR was stable (1.7–2.5) throughout.

A recently-published study showed that rofecoxib 25 mg daily for 21 days added to a stable warfarin regime increased INR by an average of 8% (2). Celecoxib and warfarin are both metabolised by the enzyme CYP2C9, which may provide an explanation for the interaction of those two drugs. A mechanism for the interaction of rofecoxib and warfarin is unknown.

ADRAC recommends that, in patients taking warfarin, increased monitoring of INR should be conducted when rofecoxib treatment is started, stopped or the dose changed.

References

1. ADRAC. Interaction of celecoxib and warfarin. *Australian Adverse Drug Reactions Bulletin*, **20**: 2 (2001).
2. Schwartz, J.I., Bugianesi, K.J., Ebel, D.L et al. The effect of rofecoxib on the pharmacodynamics and pharmacokinetics of warfarin. *Clinical Pharmacology and Therapeutics*, **68**: 626–636 (2000).
3. **Reference:** *Australian Adverse Drug Reactions Bulletin*, **21**:(2) February 2002.

Zolpidem and neurological reactions

Australia — Zolpidem (Stilnox®) was marketed in Australia in late 2000 for the short-term treatment of insomnia. It is structurally unrelated to the benzodiazepines, but has a similar pharmacological action. In 2001, the Australian Drug Reactions Advisory Committee (ADRAC) received 72 reports describing 170 reactions in association with zolpidem.

Of these 72 reports, 56 described one or more neurological or psychiatric reactions, especially visual hallucinations, confusion, depression and amnesia. Most reactions occurred with a daily dose

of 10 mg and 70% occurred after the first dose. Most of the 15 reports of hallucinations occurred within a few hours, often soon after the drug was taken. Half of the reports of amnesia described a total loss of memory for events immediately after the drug was taken, although two described poor memory on subsequent days. The onset of confusion and depression was sometimes apparent within hours of taking the drug but in most cases occurred the following day.

Prescribers should be alerted to the fact that zolpidem may be associated with distressing neurological or psychiatric reactions, including visual hallucinations, nausea, confusion, depression, amnesia, dizziness, headache, somnolence, depersonalisation, agitation, anxiety, somnambulism, or vomiting.

Reference: *Australian Adverse Drug Reactions Bulletin*, 21:(2) February 2002.

Paroxetine: severe withdrawal symptoms

United States of America — The Food and Drug Administration has published a product warning for paroxetine regarding severe withdrawal symptoms of the kind that could lead to dependence. Withdrawal symptoms such as bad dreams, paraesthesia and dizziness can occur in up to 7% of patients. The warning mentions anecdotal reports of agitation, sweating and nausea.

There is a danger of misdiagnosis and inappropriate investigation of the symptoms following paroxetine withdrawal. For example, severe dizziness can easily be diagnosed for labyrinthitis. Patients should be monitored when discontinuing treatment and doctors should taper the dose, while keeping a close watch for withdrawal symptoms.

Reference: <http://www.fda.gov/medwatch/safety/2001/dec01.htm>

Hua Fo: unknown substance

Canada — Health Canada is warning consumers not to use Hua Fo tablets after they were found to contain an unauthorized substance similar, but not identical to, sildenafil. Sildenafil is a prescription drug approved for male erectile dysfunction and sold under the brand name Viagra®. Inappropriate use of sildenafil could cause severe adverse reactions.

Health Canada issued a previous warning on 15 February 2002, concerning Hua Fo that contained sildenafil. At the time, Health Canada required the importer to remove the product from the shelves. Health Canada is again requiring the importer and distributor to remove Hua Fo from the market, and has issued a Customs Alert to stop importation of the product. Both the non-DIN and the DIN lots were sold in Canada by Shenlong Company Ltd.

Given the close chemical structural similarity between sildenafil and the substance identified in Hua Fo, known serious health risks associated with sildenafil could also occur after using this product. Since this substance was not approved in Hua Fo, the safety of the ingredient is unknown and there may be other unknown risks associated with its use.

Sildenafil should not be used by individuals who are taking any nitrate medication or products. Nitrate medications are commonly used for angina. Concurrent use could result in the development of potentially life-threatening low blood pressure. In extremely rare instances, use of sildenafil could result in penile tissue damage and permanent loss of potency.

Hua Fo (DIN 02243366) is manufactured in China by Guizhou Ribulo Medical Industry Inc. It is imported by Shenlong Company Ltd, and distributed by T.C. Unicorn. The label claim which was approved for this product is "This traditional herbal medicine can temporarily restore mental alertness when experiencing fatigue or drowsiness." The labelled contraindication is, "Do not consume if you are pregnant or nursing women; child under 12; Adult with high blood pressure".

Reference: Health Canada Online. <http://www.hc-sc.gc.ca/english/protection/warnings>

Sibutramine safety review

Canada/Italy/European Union — In light of recent international regulatory action and numerous reports of adverse reactions in Canada and elsewhere, Health Canada is conducting a safety review of the prescription drug Meridia® (sibutramine). Sibutramine was approved for sale in Canada on 28 December 2000 as a prescription drug for the treatment of obesity. Sibutramine is approved as an obesity treatment to be used in combination with diet and exercise. Patients who are currently taking sibutramine are advised to

consult with their physician if they have any questions or concerns regarding the treatment of their condition with this drug. Patients should be monitored by their physician while they are taking sibutramine.

Although no deaths have been reported, there have been 28 reported adverse reactions associated with the use of sibutramine in Canada from December 2000 to February 2002. These reports are consistent with the known adverse reactions of sibutramine, which include cardiovascular reactions such as increased blood pressure, chest pain, stroke, as well as disturbances of vision such as eye pain and eye haemorrhage. Health Canada is contacting and collaborating with foreign regulatory agencies in reviewing the safety of sibutramine. Health Canada will communicate the results to the public and take further action if required.

Internationally, Italian authorities temporarily suspended market authorization of all drugs containing sibutramine in that country on 6 March 2002, and have referred the matter to the European Medicines Evaluation Agency Secretariat for a comprehensive assessment of the risk/benefit profile of sibutramine. Sibutramine was approved for sale in Italy in April 2001, and since that time 50 adverse reactions have been reported to the Italian authorities. Seven of these reactions are considered to be serious, and 2 deaths have been reported. The most commonly reported reactions in Italy were tachycardia (increased heart rate) and hypertension (increased blood pressure). Arrhythmia (irregular heart rate) and cardiac arrest were reported to be associated with the 2 deaths.

Several European countries such as France, Germany, England, the Netherlands, Denmark, Portugal, Sweden, Finland and Spain have issued statements informing the public of the market suspension of sibutramine in Italy. France, Germany and England have announced that they are conducting reviews of sibutramine but have not withdrawn the drug from the market.

Reference: Health Canada Online. <http://www.hc-sc.gc.ca/english/protection/warnings>

Cyproterone with ethinylestradiol: risk of venous thromboembolism

New Zealand — Cyproterone-containing estrogen pills are used to treat androgen-dependent dis-

eases and polycystic ovary syndrome. They also provide oral contraception. In a letter to doctors, midwives and pharmacists, the Medicines Adverse Reactions Committee (MARC) has advised that the risk of venous thromboembolism with oral contraceptives containing cyproterone acetate and ethinylestradiol is at least as great as that with third-generation oral contraceptives. The Centre for Adverse Reactions Monitoring has received 18 reports of venous thromboembolism, including 15 of pulmonary embolism, in women taking cyproterone-ethinylestradiol pills.

All patients currently on these medicines should be reviewed at their next visit (or repeat prescription) for the appropriateness of this therapy. Both new and current patients should be fully advised of the risks of venous thromboembolism and be informed of the symptoms and situations of increased risk. The advice from MARC is based on studies. The patient leaflet has been updated to include the above information.

References

1. Prescriber Update Article – Letter to Doctors / Midwives/Pharmacists about VTE with cyproterone-containing OCs, Mar 2002. Available from <http://www.medsafe.gov.nz>
2. Medsafe Patient Information Leaflet on Oral contraceptives and blood clots, Mar 2002. Available from: <http://www.medsafe.gov.nz>

Alfa interferons: labelling change

United States of America — The manufacturer of interferon alfa 2b (Intron A®) has issued a letter to health professionals informing them of safety related labelling changes to the product information for alfa interferons. The change includes the addition of a boxed warning stating that neuropsychiatric, autoimmune, ischemic and infectious disorders may be aggravated in patients taking interferon alfa 2b. The revised warning also includes specific requirements for monitoring these patients for life-threatening adverse events. Patients with persistently severe or worsening signs or symptoms of the above mentioned conditions should be withdrawn from therapy. In many, but not all, cases these disorders are expected to resolve after stopping therapy.

Reference: 'Dear Health Professional' letter from Schering Corporation, 14 Mar 2002. <http://www.fda.gov/medwatch/SAFETY/2002>

Nefazodone: rare cases of liver failure

United States of America — Due to reports of rare cases of liver failure leading to transplant and/or death, a black box warning has been added to the product information for nefazodone (Serzone®). The warning is based on postmarketing experience of > 7.2 million US patients, and includes the following information.

- The reported rate of liver failure associated with nefazodone is approximately 1 case per 250,000-300,000 patient-years.*
- Nefazodone is not recommended for use in patients with acute liver disease or elevated baseline aminotransferase levels, which can complicate patient monitoring.
- Patients should be advised to be vigilant for symptoms or signs of liver dysfunction, and to seek advice from their physician should any become apparent.
- Nefazodone should be withdrawn in patients who exhibit signs or symptoms of liver failure, or if evidence of hepatocellular injury develops. Furthermore, such patients should be assumed to be at increased risk of developing liver injury if nefazodone is restarted, and therefore this should not be considered.

Additional information is included in the appropriate sections of the labelling for nefazodone.

Reference: Dear Healthcare Practitioner' letter from Bristol-Myers Squibb, 9 Jan 2002. <http://www.fda.gov>.

Acarbose, zafirlukast and vincristine: revised precautions

Japan — The Ministry of Health, Welfare and Labour has ruled that the package inserts for acarbose, zafirlukast and vincristine sulfate should be appropriately revised to reflect the serious adverse drug reactions (ADRs) being reported with these drugs. The precautions section in the package insert for acarbose (Glucobay®) will now include the statement that acarbose can cause serious hepatic function disorders such as fulminant hepatitis. Hepatic function tests are advised once a month during the first six months after starting

treatment with the drug and at longer but regular intervals thereafter. Hepatic function disorders and jaundice are to be added as serious ADRs in the package insert for zafirlukast (Accolate®) while 'bone marrow depression' and 'interstitial pneumonia' will be in the precautions section for vincristine sulfate (Oncovin®).

Reference: *Pharma Japan*, 1785: 11, 4 March 2002.

Clozapine and myocarditis

Post marketing surveillance data from Australia, Canada, United Kingdom, and United States of America that employ haematological monitoring of clozapine-treated patients has revealed 15 reports of myocarditis with 5 fatalities in 8000 Australian patients (March 1999); 7 reports of myocarditis with 1 fatality in 15600 Canadian patients (August 2001); 30 reports of myocarditis with 8 fatalities in 24108 UK patients; 30 reports of myocarditis with 1 fatality in 205493 US patients.

These reports suggest a strong association for clozapine with cardiovascular events. The manufacturer of clozapine (Clozaril®), has alerted health professionals to this information in January, 2002. More recently the Boxed Warning has been revised to indicate:

- Consideration of myocarditis in treated patients presenting with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs of symptoms of heart failure, ST-T wave abnormalities or arrhythmias. Tachycardia has been noted as a presenting sign in patients with myocarditis. Therefore, patients experiencing tachycardia during the first month of therapy should be closely monitored for other signs of myocarditis.
- Prompt discontinuation of clozapine therapy upon suspicion of myocarditis. Re-challenge should not be initiated in patients with clozapine-induced myocarditis.

References:

1. 'Dear Healthcare Professional' letter from Novartis, 14 January 2002. <http://www.hc-sc.gc.ca>
2. 'Dear Healthcare Provider' letter from Novartis, February 2002. <http://www.hc-sc.gc.ca>

Methotrexate: interactions

India — A variety of adverse reactions and drug interactions recently reported in association with methotrexate have prompted the revision of prescribing and treatment indications. Skin and soft tissue necrosis has been reported when methotrexate and radiotherapy have been administered concomitantly. Also, methotrexate may augment the hepatotoxic effects of other drugs, and patients should be closely monitored for liver disorders. Intervention should involve discontinuation or dosage reduction of methotrexate, together with specific treatment for the adverse reaction.

Reference: *Newsletter of the Indian National Pharmacovigilance Centre*, 3(1): 3 Nov 2001.

Stavudine: neuromuscular weakness

Canada/United States of America — A 'Dear Healthcare Professional' letter has been issued by the manufacturer of stavudine (Zerit®) advising that reports have been received of rare occurrences of rapidly ascending neuromuscular weakness, mimicking the clinical presentation of Guillain-Barré syndrome (including respiratory failure), in patients with HIV infection receiving stavudine in combination with other antiretrovirals. There have been 22 such reports worldwide since 1994, seven of which were fatal. Patient exposure to stavudine during this time is estimated at 832 383 patient-years.

Stavudine should be discontinued in patients who develop motor weakness. Healthcare providers should be vigilant in identifying early signs of hyperlactacidaemia due to the life-threatening potential of its most extreme manifestation, lactic acidosis syndrome. Early symptoms associated with elevated serum lactate may include generalised fatigue and/or various gastrointestinal, respiratory or neuromuscular symptoms. Patients presenting with such symptoms should have their antiretroviral therapy interrupted and a full medical investigation performed. Patients with hyperlactacidaemia may experience persistence or worsening of symptoms despite discontinuation of antiretroviral therapy.

Reference: 'Dear Healthcare Professional' letter from Bristol-Myers Squibb Company, 6 March 2002. <http://www.hc-sc.gc.ca> and <http://www.fda.gov>.

Recommended influenza virus vaccine composition

World Health Organization — It is recommended that the influenza virus vaccines for the 2002–2003 northern hemisphere winter season contain:

- an A/New Caledonia 20/99 (H1N1)-like virus
- an A/moscow/10/99 (H3N2)-like virus (such as A/Panama/2007/99.
- a B/Hong Kong/330/2001-like virus

Reagents for use in the laboratory standardization of inactivated vaccine may be obtained from:

Immunology (Vaccines),
Therapeutic Goods Administration Laboratories,
P.O. Box 100, Woden, ACT, Australia
(fax: 61262 32 8564) or

Division of Virology,
National Institute for Biological Standards and
Control, South Mimms, Potters Bar, Hertfordshire,
EN6 3QG, United Kingdom
(fax: 44 1707 64 6730)

Division of Viral Products,
Center for Biologics Evaluation and Research,
Food and Drug Administration,
Rockville, MD 20892, United States of America
(fax: 1 301 402 5128).

Requests for reference strains for antigenic analysis should be addressed to:

WHO Collaborating Centre for Reference and
Research on Influenza,
45 Poplar Road, Parkville, Victoria, Australia
(fax: 61 393 89 1881)

WHO Collaborating Centre for Reference and
Research on Influenza,
National Institute of Infectious Diseases,
Toyama 1-23-1, Shinjuku-ku, Tokyo 162, Japan
(fax: 81 353 85 1155)

WHO Collaborating Centre for Reference and
Research on Influenza,
National Institute for Medical Research
The Ridgeway, Mill Hill, London NW71AA,
United Kingdom
(Fax: 44 208 906 4477).

WHO Collaborating Centre for Surveillance,
Epidemiology and Control of Influenza,
Centers for Disease Control and Prevention,
1600 Clifton Road, Atlanta, Georgia 30333,
United States of America
(fax: 1 404 639 2334)

Reference: *Weekly Epidemiological Record*, 77: 65–66 (2002)

Sodium phosphate oral solution: electrolyte balance disturbance

Canada — Sodium phosphate oral solution has been marketed in Canada since 1987 as a laxative for the relief of occasional constipation. The product is also used as part of a bowel-cleansing regimen in preparing patients for surgery or for colonoscopy. Between 1987 and 2001 the Canadian Adverse Drug Reaction Monitoring Program has received 10 domestic reports of serious electrolyte disturbances (hypocalcaemia, hyperphosphataemia, hypernatraemia, hypokalaemia and acidosis), dehydration, renal failure and tetany in patients ingesting

more than 45 mL solution, in patients at medical risk and/or in patients using multiple purgatives for bowel preparation. In view of these reports, all manufacturers have issued a letter to health professionals with information related to the safe use of sodium phosphate oral solution.

References

1. 'Dear HealthCare Professional' letter by Johnson & Johnson, Merck Consumer Pharmaceuticals, Canada, 15 Mar 2002. <http://www.hc-sc.gc.ca>
2. 'Dear HealthCare Professional' letter by Pharmascience Inc. Canada, 18 Mar 2002. <http://www.hc-sc.gc.ca>

Correction:

In *WHO Drug Information*, volume 15, No. 2, 2001, an error was made on page 77 in the summarized information: Terbinafine and hepatic failure. The brand name product in question is Lamisil® (and **not** Lamictal® as stated).

**Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.*

Quality Assurance Issues

Pilot Procurement Project for Quality and Sourcing (Pre-qualification) of HIV/AIDS drugs

In October 2000, WHO, UNICEF, UNFPA, and UNAIDS, supported by the World Bank, invited manufacturers of drugs for treatment of HIV infection (antiretrovirals) and HIV-related illnesses (anti-infectives, anticancer drugs, and pain killers) to become suppliers to United Nations drug procurement agencies. Drugs required for the treatment of HIV infection were selected for evaluation because they remain largely inaccessible in the countries that are most affected by HIV/AIDS. For the antiretroviral group of drugs, there is currently limited regulatory experience and well-established quality standards, such as pharmacopoeial monographs, are not generally available.

The overall aim of the Pilot Procurement Project, a collaborative initiative between WHO, UNICEF, UNFPA, and UNAIDS, supported by the World Bank, is to provide quality assessment of a selected number of pharmaceutical products considered for purchase by UN agencies involved in the procurement of drugs and diagnostics. WHO manages the project and provides technical support and assistance. UNICEF provides administrative support and infrastructure. An additional objective is to develop a harmonized quality assessment system for use by the collaborating UN agencies

This initiative was based on experience with the *WHO Procedures for Assessing the Acceptability, in Principle, of Vaccines for Purchase by United Nations Agencies* (WHO/VSQ/97.06). Pre-qualification of drugs is carried out in accordance with the WHO document *Guiding Principles for the Evaluation of Manufacturers for the Procurement and Sourcing of Pharmaceutical Products* which is based on *General Procedures for the Pre-Qualification of Manufacturers for the Procurement and Sourcing of Pharmaceutical Products* adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its meeting in October 2001.

The pre-qualification principles were discussed during meetings of the Interagency Pharmaceutical Coordination Group, comprising UNICEF, UNAIDS, UNFPA, WHO and the World Bank, in Washington and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) in Prague, Czech Republic in 2001. The draft *General Procedure for the Pre-Qualification of Manufacturers for the Procurement and Sourcing of Pharmaceutical Products* was circulated on 25 July 2001 for comment to regulatory information officers appointed by WHO Member States, selected WHO collaborating centres, national pharmacopoeial commissions, and organizations such as the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and International Pharmaceutical Federation (FIP). Comments were incorporated into a revised draft, reviewed and adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (available on <http://www.who.int/medicines>).

Current status of the project

Steps in the assessment process and timelines

The process began with a public invitation to suppliers of pharmaceutical products for "Expressions of Interest" which was posted in October 2001 on the websites of collaborating UN agencies and published through the media. A second invitation was

posted in August 2001, and a third in May 2002. Responses from interested suppliers were expected within 60 days. A further 60-day period was allowed to submit the required product information dossiers. Guidelines covering the process are available on <http://www.who.int/medicines>. All product information dossiers were evaluated within 10 days of the submission deadline. In cases where the product information submitted was incomplete,

the companies concerned were granted a further 60 days within which to compile additional information.

The assessment procedure consists of an evaluation of product quality based on data provided by the suppliers and followed by inspections of manufacturing sites for compliance with WHO Good Manufacturing Practices (GMP). Guidelines on the contents of product data dossiers for quality assurance and on inspection of manufacturing sites are available from WHO. Quality control analysis of selected samples of drugs is planned.

Suppliers interest to participate

In all, almost 40 suppliers responded to the first two invitations for expression of interest. Only suppliers who submitted dossiers as requested were evaluated. Up to 20 March 2002, 33 product dossiers from 21 suppliers of different product strengths and formulations have been evaluated or are in the process of being evaluated. As stated, products include antiretroviral drugs and drugs used in the treatment of HIV-related opportunistic infections and cancers.

Delays encountered during the pilot project

It took longer than expected for many of the suppliers to submit product data which met the specifications requested. Data on product quality and bioequivalence were, in certain cases, inadequate and some manufacturing sites have requested postponement of scheduled site inspections. Products and suppliers meeting the WHO recommended standards as at 20 March 2002, are listed on pages 33–34. Suppliers and products not meeting the required standards have been requested to review their product dossiers and to address outstanding quality issues.

Participating in the project is voluntary

Expression of Interest is a voluntary process. The range of products submitted for evaluation is therefore at the discretion of the participating suppliers.

However, this is an ongoing project and several additional products, both innovator and generic, are still under evaluation. Moreover, new applications are accepted as the project progresses. Instructions for companies who wish to apply are posted on the WHO project website (www.who.int/medicines) and on the websites of collaborating UN agencies.

Other benefits of the project

As a result of this project, a *Model Quality Assurance System for Procurement Organizations* is being developed. Those manufacturers whose products have been assessed and manufacturing sites inspected, have received the corresponding reports. Manufacturers who do not yet meet international requirements obviously benefit from these detailed written reports, which indicate existing deficiencies and provide pointers on how to upgrade dossiers and improve GMP compliance. As the project has progressed, an improvement has been observed in the quality of product dossiers submitted by suppliers and a willingness to upgrade manufacturing sites has become apparent. This will doubtless have repercussions on improving the quality of HIV/AIDS medicines.

Unique experience concerning the quality of generic antiretroviral drugs obtained through this project is also communicated to the national drug regulatory authorities through workshops organized in the WHO Regions. The first was organized in Washington, United States of America, in the Americas Region in April 2002, and the next will take place in Pretoria, South Africa, in the African Region in June 2002.

Updating the list of suppliers

The list of suppliers (pages 33–34) will be updated at roughly two monthly intervals as new information on products that meet the specified standards becomes available. Lists will be posted on the WHO project website (www.who.int/medicines) and on the websites of collaborating United Nations agencies.

List of pre-qualified products — 20 March 2002

INN	strength	dosage form	supplier site	manu- facturing site	packaging material and pack
abacavir	300 mg	tablet	GlaxoSmithKline	UK	blister 60
abacavir	20 mg/ml	oral solution	GlaxoSmithKline	UK	HDPE 240 ml (bottle)
aciclovir	5%	cream	Cipla Ltd	India	Al tube G
amprenavir	15 mg/ml	oral solution	GlaxoSmithKline	UK	HDPE 240 ml (bottle)
amprenavir 150mg	50mg	capsule	GlaxoSmithKline	France	HDPE 480 (50 mg) (bottle) 240 (150 mg)
ciprofloxacin	750 mg	tablet	Laboratorios Cinfa	Spain	blister 10
ciprofloxacin	500 mg	tablet	Laboratorios Cinfa	Spain	blister 10/20
ciprofloxacin	250 mg	tablet	Laboratorios Cinfa	Spain	blister 10/20
ciprofloxacin	100 mg	tablet	Cipla Ltd	India	blister 10
ciprofloxacin	250 mg	tablet	Cipla Ltd	India	blister 10
ciprofloxacin	500 mg	tablet	Cipla Ltd	India	blister 10
ciprofloxacin	750 mg	tablet	Cipla Ltd	India	blister 10
didanosine	25 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle) 60
didanosine	50 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle) 60
didanosine	100 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle) 60
didanosine	150 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle) 60
didanosine	200 mg	chewable/ dispersable tablet	Bristol Myers Squibb	France	HDPE (bottle) 60
lamivudine	50 mg/5	solution	Cipla Ltd	India	PET (bottle)100ml
lamivudine	150 mg	tablet	GlaxoSmithKline	UK	HDPE (bottle) 60
lamivudine	10 mg/ml	oral solution	GlaxoSmithKline	UK	HDPE (bottle) 240 ml
lamivudine	150 mg	tablet	GlaxoSmithKline	UK	blister
+zidovudine	+300 mg				HDPE (bottle) 60
lamivudine	150 mg	tablet	GlaxoSmithKline	UK	blister 40, 60
+zidovudine	+300 mg				HDPE (bottle) 60
+abacavir	+300 mg				
nevirapine	200 mg	tablet	Cipla Ltd	India	blister 10
ritonavir	100 mg	capsule	Abbott Laboratories	USA, France	HDPE (bottle) 84
ritonavir	80 mg/ml	oral solution	Abbott Laboratories	UK	PET (bottle)90 ml
ritonavir	33.3 mg	capsule	Abbott Laboratories	USA	HDPE (bottle) 90
+lopinavir	+ 133.3				
ritonavir	20mg +	oral	Abbott Laboratories	UK	PET (bottle) 60 ml
+lopinavir	80mg/ml	solution			
saquinavir	200 mg	soft capsule	Roche	Germany	6 or 180
stavudine	15 mg	capsule	Bristol Myers Squibb	France	blister 56 HDPE (bottle) 60
stavudine	20 mg	capsule	Bristol Myers Squibb	France	blister 56 HDPE (bottle) 60

List of pre-qualified products — 20 March 2002 (continued)

INN	strength	dosage form	supplier site	manu- facturing site	packaging material and pack site
stavudine	30 mg	capsule	Bristol Myers Squibb	France	blister 56 HDPE (bottle) 60
stavudine	40 mg	capsule	Bristol Myers Squibb	France	blister 56 HDPE (bottle) 60
sulfadiazine	500 mg	tablet	Doms Recordati	France	blister 10
vinblastine sulfate	10mg/ 10ml	injection	Cipla Ltd	India	vial 10 ml
vincristine sulfate	1mg/ml	Injection	Cipla Ltd	India	vial 1ml
zalcitabine	0.375 mg	tablet	Roche	USA Switzerland	blister (Al) 6 glass bottle 100
zalcitabine	0.75 mg	tablet	Roche	USA	blister (Al) 5 glass bottle 100
zidovudine	100 mg	capsule	Combino Pharm SL	Spain	Al-Al STRIP 100
zidovudine	50 mg/5	solution	Cipla Ltd	India	PET (bottle)100 ml
zidovudine	10 mg/ml	Infusion	GlaxoSmithKline	USA	amber glass vial 20 ml
zidovudine	50 mg/ 5 ml	oral solution	GlaxoSmithKline	UK	amber glass bottle 200 ml

Al: Aluminium

HDPE: High Density Poly Ethylene

PET: Polyethylene Terphthalate

Recent Publications and Sources of Information

WHO Guidelines on stability testing

Work on stability of pharmaceutical products was initiated by WHO in 1988 and the WHO Guidelines on stability testing were adopted in 1996 by the WHO Expert Committee on Specifications for Pharmaceutical Preparations following extensive consultation. In 2000, discussions were initiated between the ICH Expert Working Group Q1 (stability) and WHO to harmonize the number of stability tests and conditions undertaken worldwide. Non-governmental organizations, international professional associations and specialists, and members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations were among those consulted.

As a result, a proposal was received from the ICH Expert Working Group to modify the WHO guidelines concerning long-term conditions for climatic zone IV (hot and humid climate) from 30 °C and 70% relative humidity (RH) to 30 °C and 60% respectively. Responses to this proposal were divided. A number of experts agreed that the proposal constituted a sound scientific approach. It was recognized that packaging was very important and common testing conditions should be agreed upon for WHO and ICH guidelines.

Other views criticized the approach as being too scientific and impractical while pointing out that actual meteorological and physical storage conditions in these countries would not allow simulation of long-term storage conditions as defined by the new proposal. Arguments were also made against the application of some parameters used in the calculations.

In a further round of discussions, it was proposed to change the real-time storage conditions for zone IV from 30 °C and 70% RH to 30 °C and 65% RH. This suggestion was again circulated for comments and the results discussed in July 2001.

In October 2001 the WHO Expert Committee modified storage conditions and these have now been published in the *WHO guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms*, to read 30 °C ($\pm 2^\circ$ C) and 65% ($\pm 5\%$)

RH for real-time stability studies defined for climatic zone IV. It was also agreed that where special transportation and storage conditions did not comply with these criteria, additional study data supporting these conditions may be needed.

WHO Guidelines on stability testing are available at <http://www.who.int/medicines>

WHO Model Formulary now available

In 1995, the WHO Expert Committee on the Use of Essential Drugs recommended development of a WHO Model Formulary to complement the WHO Model List of Essential Drugs. It was considered that this would be a useful resource for countries wishing to develop their own national formulary.

In November 1999, the Expert Committee on the Use of Essential Drugs recommended that WHO accept an offer by the Royal Pharmaceutical Society of Great Britain (which together with the British Medical Association, publishes the British National Formulary) to take responsibility for final data validation, editing and layout.

A full record has been made of the validation process and technical and editorial changes, with relevant references. This was the first edition of a new reference text and the work took almost two years to complete. During this process, the text was updated as necessary to take into account new information as it became available. Monographs were included for the essential drugs that had been added to the Model List in November 1999 and April 2002.

Although the initial plan was to maintain the section headings and numbering system of the Model List, this proved difficult in practice. The sections of the Model List are not always useful as therapeutic categories, and do not easily lend themselves to introductory evaluative statements. Small changes were therefore introduced. The Model Formulary has also been relatively generous in repeating the formulary text of essential drugs under other relevant therapeutic categories.

The lack of full concurrence with the numbering system of the Model List should not be a major problem for users who will be able to access information readily either through the content list or through the main index which includes both drug names and disease terms. Dissemination of the Model List and the Model Formulary will also take place via electronic access such as a CD-ROM or the WHO Medicines website, and will include electronic links between the Model Formulary and the Model List.

The electronic version of the Model Formulary is also intended as a starting point for developing national or institutional formularies which can adapt the text of the Model Formulary to their own needs by changing the text or aligning the formulary to their own list of essential drugs.

The Model Formulary is in press, and will be available from Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland. The electronic versions are expected to become available in the course of 2002 and will be posted on <http://www.who.int/medicine>

Direct to consumer advertising

The Council of the Royal Pharmaceutical Society of Great Britain has today decided its position on the issue of direct-to-consumer advertising (DCTA) of prescription medicines. The Council recognises that further developments in DCTA are likely, and it will revisit the issue as necessary. The Council's position is:

"The demand for information about prescribed medicines from patients and the public is likely to increase, but DCTA is unlikely to be the best way of providing it because the aim of advertising is to persuade, not to give balanced information about benefits and risks. DCTA, moreover, carries a significant risk of exposing more patients to the adverse effects of new drugs. If DCTA is successful, it may well adversely affect doctor-patient relationships, distort public health priorities and disrupt the cost controls operated by the NHS. The Society therefore supports increased provision of balanced information to the public, while taking into account the above points." (5 December 2001).

For further information on the Society's work on DCTA, contact Eileen Neilson, Head of Policy Support, Tel: 020 7572 2217, Fax: 020 7572 2501 Reports and policy evidence are available at: <http://www.rpsgb.org.uk/news/policy.htm#dtca>

The information gap: new resource for developing countries

www.scidev.net was launched last week to bridge the divide between knowledge-rich developed countries and the knowledge-poor developing world. Sponsored by the journals Nature and Science, the site was created on the premise that "those who stand to benefit most from modern science and technology tend to be those who have least access to information."

Over the past few years there has been increasing recognition of impact of the knowledge gap on developing countries. To this end free access to medical research published by the British Medical Journal (BMJ) has been possible via bmj.com since 1995. All 23 specialist journals published by the BMJ Publishing Group are currently available free of charge to 44 low income nations and there are plans to extend this access to 34 lower middle income countries. Earlier this year six of the world's leading medical publishers signed a "statement of intent" to provide free access to scientific information for more than 100 of the poorest countries in the world.

Against this background, [scidev.net](http://www.scidev.net) is now the first website dedicated to the needs of the developing world. It reports and discusses aspects of science and technology that are relevant to sustainable development and specific to the needs of developing countries. Each week up to four full length research articles from each of the journals Science and Nature are posted on the site. There is also a news section on development related scientific and policy issues, and in depth dossiers are being created on topics such as gene cloning, climate change, and malaria.

The site is funded by UK, Swedish, and Canadian development agencies and also advertises job opportunities and international meetings. Links are available to funding agencies, and other development agencies. Overall the site gives the feel of being a forum where connections are made, ideas exchanged, and information shared. Together with the changes in publishing, it shows how the electronic revolution could help to abolish the information gap.

Contact avass@bmj.com. British Medical Journal, 323: 1434 (2001). <http://bmj.com/cgi/content/full/323/7326/1434/a>

International Nonproprietary Names for Pharmaceutical Substances (INN)

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

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

Dénominations communes internationales des Substances pharmaceutiques (DCI)

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

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

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

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

Proposed International Nonproprietary Names: List 86

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 86 Proposed INN not later than 31 October 2002**.

Dénominations communes internationales proposées: Liste 86

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 86 de DCI Proposées le 31 octobre 2002 au plus tard**.

Denominaciones Comunes Internacionales Propuestas: Lista 86

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 86 de DCI Propuestas el 31 de octubre de 2002 a más tardar**.

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

acolbifenum

acolbifene

(+)-(2S)-3-(4-hydroxyphenyl)-4-methyl-2-[4-[2-(piperidin-1-yl)ethoxy]phenyl]-2H-1-benzopyran-7-ol
antiestrogen

acolbifène

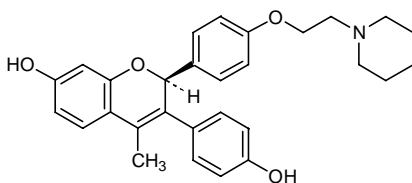
(+)-(2S)-3-(4-hydroxyphényl)-4-méthyl-2-[4-[2-(pipéridin-1-yl)éthoxy]phényl]-2H-1-benzopyran-7-ol
antiœstrogène

acolbifeno

(+)-(2S)-3-(4-hidroxifenil)-4-metil-2-[4-[2-(piperidin-1-il)etoxi]fenil]-2H-1-benzopiran-7-ol
antiestrógeno

$C_{29}H_{31}NO_4$

182167-02-8



asoprisnilum

asoprisnil

11 β -[4-[(*E*)-(hydroxyimino)methyl]phenyl]-17 β -methoxy-
17-(methoxymethyl)estra-4,9-dien-3-one
progesterone receptor modulator

asoprisnil

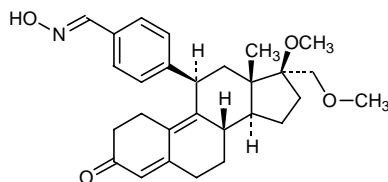
11 β -[4-[(*E*)-(hydroxyimino)méthyl]phényl]-17 β -méthoxy-
17-(méthoxyméthyl)estra-4,9-dién-3-one
modulateur des récepteurs de la progestérone

asoprisnilo

11 β -[4-[(*E*)-(hidroxiimino)metil]fenil]-17 β -metoxi-17-(metoximetil)estra-
4,9-dien-3-ona
modulador del receptor de progesterona

C₂₈H₃₅NO₄

163883-84-9

**bazedoxifenum**

bazedoxifene

1-[4-[2-(hexahydro-1*H*-azepin-1-yl)ethoxy]benzyl]-2-(4-hydroxyphenyl)-
3-méthyl-1*H*-indol-5-ol
antiestrogen

bazédoxifène

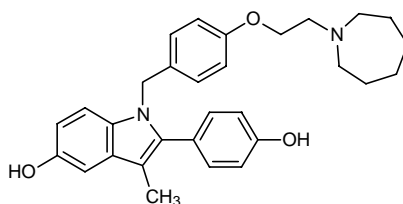
1-[4-[2-(hexahydro-1*H*-azépin-1-yl)éthoxy]benzyl]-2-(4-hydroxyphényl)-
3-méthyl-1*H*-indol-5-ol
antiœstrogène

bazedoxifeno

1-[4-[2-(hexahidro-1*H*-azepin-1-il)etoxi]bencil]-2-(4-hidroxifenil)-3-metil-
1*H*-indol-5-ol
antiestrógeno

C₃₀H₃₄N₂O₃

198481-32-2



bifarceptum

bifarcept

interferon α/β receptor (human isoform p40 precursor)
immunomodulator

bifarcept

précurseur de la partie soluble de la chaîne 2 du récepteur humain de type I
de l'interféron α et β
immunomodulateur

bifarcept

precursor de la fracción soluble de la cadena 2 del receptor humano de tipo
I del interferón α y β
immunomodulador $C_{1100}H_{1673}N_{271}O_{337}S_{10}$

163796-60-9

MLLSQNAFIV	RSLNLVLMVY	ISLVFGISYD	SPDYTDESCT
FKISLRNFRS	ILSWELKNHS	IVPTHYTLLY	TIMSKPEDLK
VVKNCANTTR	SFCDLTDEWR	STHEAYVTVL	EGFSGNTTLF
SCSHNFWLAI	DMSFEPPEFE	IVGFTNHINV	MVKFPSIVEE
ELQFDLSLVI	EEQSEGIVKK	HKPEIKGNMS	GNFTYIIDKL
IPNTNYCVSV	YLEHSDEQAV	IKSPLKCTLL	PPGQESEFS

coluracetamum

coluracetam

N-(2,3-dimethyl-5,6,7,8-tetrahydrofuro[2,3-*b*]quinolin-4-yl)-
2-(2-oxopyrrolidin-1-yl)acetamide
nootropic agent

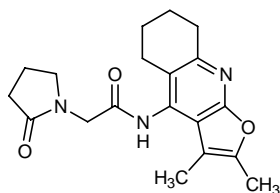
coluracétam

N-(2,3-diméthyl-5,6,7,8-tétrahydrofuro[2,3-*b*]quinoléin-4-yl)-
2-(2-oxopyrrolidin-1-yl)acétamide
nootrope

coluracetam

N-(2,3-dimetil-5,6,7,8-tetrahydrofuro[2,3-*b*]quinolin-4-il)-2-(2-oxopirrolidin-
1-il)acetamida
nootrópico $C_{19}H_{23}N_3O_3$

135463-81-9



dapivirinum

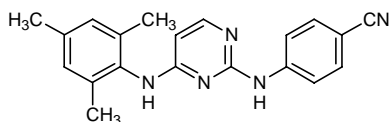
dapivirine 4-[[4-[(2,4,6-triméthylphényl)amino]pyrimidin-2-yl]amino]benzonitrile
antiviral

dapivirine 4-[[4-[(2,4,6-triméthylphényl)amino]pyrimidin-2-yl]amino]benzonitrile
antiviral

dapivirina 4-[[4-[(2,4,6-triméthylfenil)amino]pirimidin-2-il]amino]benzonitrilo
antiviral

 $C_{20}H_{19}N_5$

244767-67-7

**deferasiroxum**

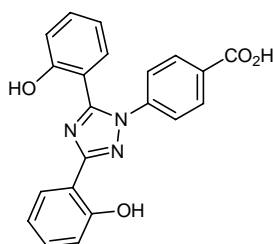
deferasirox 4-[3,5-bis(2-hydroxyphényl)-1*H*-1,2,4-triazol-1-yl]benzoic acid
chelating agent

déférasirox acide 4-[3,5-bis(2-hydroxyphényl)-1*H*-1,2,4-triazol-1-yl]benzoïque
agent de chélation

deferasirox ácido 4-[3,5-bis(2-hidroxifenil)-1*H*-1,2,4-triazol-1-il]benzoico
quelante

 $C_{21}H_{15}N_3O_4$

201530-41-8

**degarelixum**

degarelix *N*-acetyl-3-(naphtalen-2-yl)-*D*-alanyl-4-chloro-*D*-phenylalanyl-3-(pyridin-3-yl)-*D*-alanyl-*L*-seryl-4-[[[(4*S*)-2,6-dioxohexahydropyrimidin-4-yl]carbonyl]amino]-*L*-phenylalanyl-4-(carbamoylamino)-*D*-phenylalanyl-*L*-leucyl-*N*⁶-(1-méthylethyl)-*L*-lysyl-*L*-prolyl-*D*-alaninamide
gonadotropin-releasing hormone antagonist

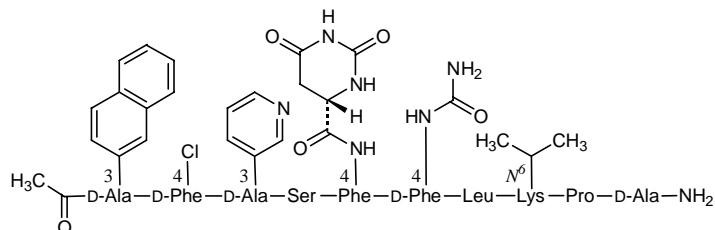
dégarélix acétyl-[3-(naphtalén-2-yl)-*D*-alanyl]-(4-chloro-*D*-phénylalanyl)-[3-(pyridin-3-yl)-*D*-alanyl]-*L*-séryl-[4-[[[(4*S*)-2,6-dioxohexahydropyrimidin-4-yl]carbonyl]amino]-*L*-phénylalanyl]-[4-(carbamoylamino)-*D*-phénylalanyl]-*L*-leucyl-[*N*⁶-(1-méthyléthyl)-*L*-lysyl]-*L*-prolyl-*D*-alaninamide
antagoniste de l'hormone de libération de la gonadotropine

degarelix

[*N*-acetil-3-(naftalen-2-il)-*D*-alanil]-(4-cloro-*D*-fenilalanil)-[3-(piridin-3-il)-*D*-alanil]-*L*-seril-[4-[[[(4*S*)-2,6-dioxohexahidropirimidin-4-il]carbonil]amino]-*L*-fenilalanil]-[4-(carbamoilamino)-*D*-fenilalanil]-*L*-leucil-[*N*⁶-(1-metiletil)-*L*-lisil]-*L*-proil-*D*-alaninamida
antagonista de la hormona de liberación de la gonadotropina

C₈₂H₁₀₃ClN₁₈O₁₆

214766-78-6



dersalazinum

dersalazine

2-hydroxy-5-[[4-[(1*Z*)-3-[4-[(2-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)methyl]piperidin-1-yl]-3-oxo-1-phenylprop-1-enyl]phenyl]diazenyl]benzoic acid
anti-inflamatory

dersalazine

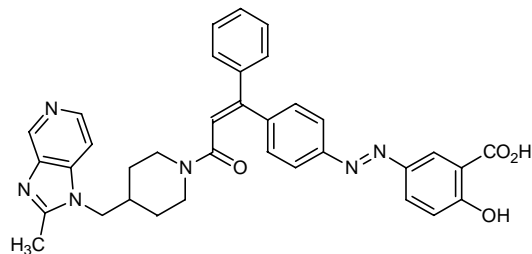
acide 2-hydroxy-5-[[4-[(1*Z*)-3-[4-[(2-méthyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)méthyl]pipéridin-1-yl]-3-oxo-1-phénylprop-1-ényl]phényl]diazényl]benzoïque
anti-inflammatoire

dersalazina

ácido 2-hidroxi-5-[[4-[(1*Z*)-3-[4-[(2-metil-1*H*-imidazo[4,5-*c*]piridin-1-il]metil]piperidin-1-il]-3-oxo-1-fenilprop-1-enil]fenil]diazenil]benzoico
antiinflamatorio

C₃₅H₃₂N₆O₄

188913-58-8



detiviciclovirum

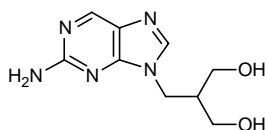
detiviciclovir 2-[(2-amino-9H-purin-9-yl)methyl]propane-1,3-diol
antiviral

détiviciclovir 2-[(2-amino-9H-purin-9-yl)méthyl]propane-1,3-diol
antiviral

detiviciclovir 2-[(2-amino-9H-purin-9-il)metil]propano-1,3-diol
antiviral



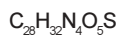
220984-26-9

**edonentanum**

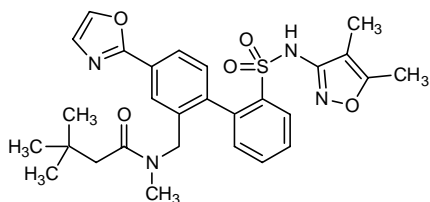
edonentan *N*-[[2'-[(4,5-dimethylisoxazol-3-yl)sulfamoyl]-4-(oxazol-2-yl)biphenyl-2-yl]methyl]-*N*,3,3-trimethylbutanamide
endothelin receptor antagonist

édonentan *N*-[[2'-[(4,5-diméthylisoxazol-3-yl)sulfamoyl]-4-(oxazol-2-yl)biphényl-2-yl]méthyl]-*N*,3,3-triméthylbutanamide
antagoniste du récepteur de l'endothéline

edonentán *N*-[[2'-[(4,5-dimetilisoxazol-3-il)sulfamoil]-4-(oxazol-2-il)bifenil-2-il]metil]-*N*,3,3-trimetilbutanamida
antagonista del receptor de endotelina



210891-04-6



efaproxiralum

efaproxiral

2-[4-[2-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methylpropanoic acid

allosteric modifier of hemoglobin

éfaproxiral

acide 2-[4-[2-[(3,5-diméthylphényl)amino]-2-oxoéthyl]phénoxy]-2-méthylpropanoïque

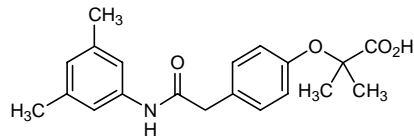
modificateur de l'affinité de l'oxygène pour l'hémoglobine

efaproxiral

ácido 2-[4-[2-[(3,5-dimetilfenil)amino]-2-oxoetil]fenoxi]-2-metilpropanoico

modificador alostérico de la hemoglobina $C_{20}H_{23}NO_4$

131179-95-8

**flindokalnerum**

flindokalner

(3S)-3-(5-chloro-2-methoxyphenyl)-3-fluoro-6-(trifluoromethyl)-1,3-dihydro-2H-indol-2-one

opener of calcium-activated (maxi-K) K⁺ channels

flindokalner

(3S)-3-(5-chloro-2-méthoxyphényl)-3-fluoro-6-(trifluorométhyl)-1,3-dihydro-2H-indol-2-one

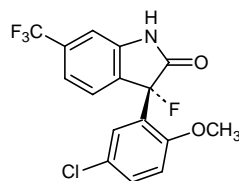
activateur des canaux potassiques (maxi-K) dépendant du calcium

flindokalner

(3S)-3-(5-cloro-2-metoxifenil)-3-fluoro-6-(trifluorometil)-1,3-dihidro-2H-indol-2-ona

estimulante de la apertura de los canales del K⁺ activados por calcio (maxi K) $C_{16}H_{10}ClF_4NO_2$

187523-35-9



gimatecanum

gimatecan

(4*S*)-11-[(*E*)-[(1,1-dimethylethoxy)imino]methyl]-4-ethyl-4-hydroxy-1,12-dihydro-14*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione
antineoplastic

gimatécan

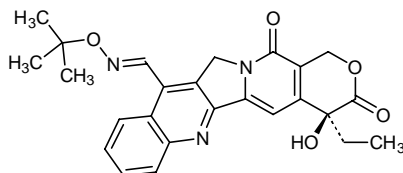
(4*S*)-11-[(*E*)-[(1,1-diméthyléthoxy)imino]méthyl]-4-éthyl-4-hydroxy-1,12-dihydro-14*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoléine-3,14(4*H*)-dione
antineoplasique

gimatecán

(4*S*)-11-[(*E*)-[(1,1-dimetiletoxi)imino]metil]-4-etil-4-hidroxi-1,12-dihidro-14*H*-pirano[3',4':6,7]indolizino[1,2-*b*]quinolina-3,14(4*H*)-diona
antineoplásico

 $C_{25}H_{25}N_3O_5$

292618-32-7

**icaridinum**

icaridin

1-methylpropyl 2-(2-hydroxyethyl)piperidine-1-carboxylate
insect repellent

icaridine

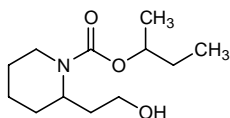
2-(2-hydroxyéthyl)pipéridine-1-carboxylate de 1-méthylpropyle
insectifuge

icaridina

2-(2-hidroxietyl)piperidina-1-carboxilato de *sec*-butilo
repelente de insectos

 $C_{12}H_{23}NO_3$

119515-38-7



iguratimodum

iguratimod

N-[7-[(methylsulfonyl)amino]-4-oxo-6-phenoxy-4*H*-1-benzopyran-3-yl]formamide
immunomodulator

iguratimod

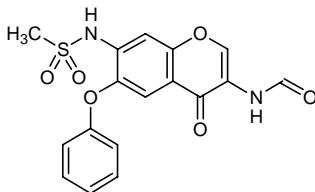
N-[7-[(méthylsulfonyl)amino]-4-oxo-6-phénoxy-4*H*-1-benzopyran-3-yl]formamide
immunomodulateur

iguratimod

N-[7-[(metilsulfonil)amino]-4-oxo-6-fenoxi-4*H*-1-benzopiran-3-il]formamida
immunomodulador

C₁₇H₁₄N₂O₆S

123663-49-0

**ilaprazolum**

ilaprazole

2-[(*RS*)-[4-methoxy-3-methylpyridin-2-yl)methyl]sulfinyl]-5-(1*H*-pyrrol-1-yl)-1*H*-benzimidazole
antiulcer agent

ilaprazole

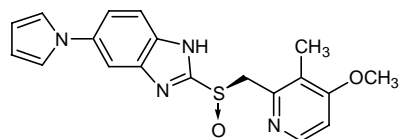
2-[(*RS*)-[4-méthoxy-3-méthylpyridin-2-yl)méthyl]sulfinyl]-5-(1*H*-pyrrol-1-yl)-1*H*-benzimidazole
antiulcéreux

ilaprazol

2-[(*RS*)-[4-metoxi-3-metilpiridin-2-il)metil]sulfinil]-5-(1*H*-pirrol-1-il)-1*H*-bencimidazol
antiulceroso

C₁₉H₁₈N₄O₂S

172152-36-2



and enantiomer
et énantiomère
y enantiómero

indiplonum

indiplon

N-methyl-*N*-[3-[3-(thiophen-2-ylcarbonyl)pyrazolo[1,5-*a*]pyrimidin-7-yl]phenyl]acetamide
sedative, hypnotic

indiplone

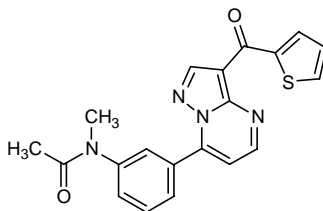
N-méthyl-*N*-[3-[3-(thiophén-2-ylcarbonyl)pyrazolo[1,5-*a*]pyrimidin-7-yl]phényl]acétamide
sédatif, hypnotique

indiplón

N-metil-*N*-[3-[3-(tiofen-2-ilcarbonil)pirazolo[1,5-*a*]pirimidin-7-il]fenil]acetamida
sedante, hipnótico

C₂₀H₁₆N₄O₂S

325715-02-4

**indisulamum**

indisulam

N-(3-chloro-1*H*-indol-7-yl)benzene-1,4-disulfonamide
antineoplastic

indisulam

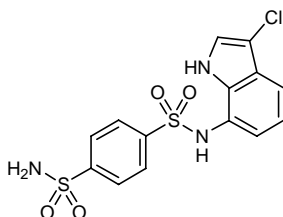
N-(3-chloro-1*H*-indol-7-yl)benzène-1,4-disulfonamide
antineoplasique

indisulam

N-(3-cloro-1*H*-indol-7-il)benceno-1,4-disulfonamida
antineoplásico

C₁₄H₁₂ClN₃O₄S₂

165668-41-7



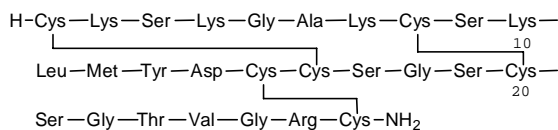
leconotidum

leconotide omega-conopeptide MVIIA
analgesic

léconotide conopeptide MVIIA oméga
analgésique

leconotida conopéptido MVIIA omega
analgésico

$C_{107}H_{179}N_{35}O_{36}S_7$ 247207-64-3

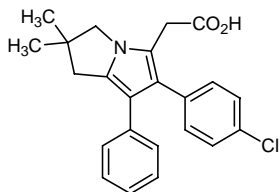
**licofelonum**

licofelone [6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl]acetic acid
anti-inflammatory

licofélone acide [6-(4-chlorophényl)-2,2-diméthyl-7-phényl-2,3-dihydro-1H-pyrrolizin-5-yl]acétique
anti-inflammatoire

licofelona ácido [6-(*p*-clorofenil)-7-fenil-2,2-dimetil-2,3-dihidro-1H-pirrolizin-5-il]acético
antiinflamatorio

$C_{23}H_{22}ClNO_2$ 156897-06-2



lonafarnibum

lonafarnib

(+)-4-[2-[4-[(11*R*)-3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxamide
antineoplástico

lonafarnib

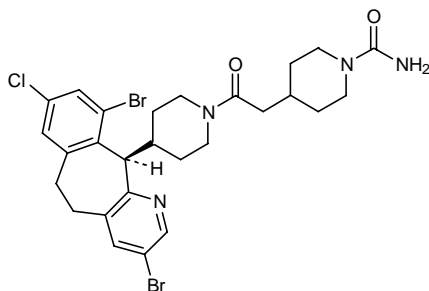
(+)-4-[2-[4-[(11*R*)-3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]pipéridin-1-yl]-2-oxoéthyl]pipéridine-1-carboxamide
antinéoplasique

lonafarnib

(+)-4-[2-[4-[(11*R*)-3,10-dibromo-8-cloro-6,11-dihidro-5*H*-benzo[5,6]ciclohepta[1,2-*b*]piridin-11-il]piperidin-1-il]-2-oxoetil]piperidina-1-carboxamida
antineoplásico

C₂₇H₃₁Br₂ClN₄O₂

193275-84-2

**lubazodonum**

lubazodone

(2*S*)-2-[[[(7-fluoro-2,3-dihydro-1*H*-inden-4-yl)oxy]methyl]morpholine
antidepressant

lubazodone

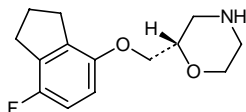
(2*S*)-2-[[[(7-fluoro-2,3-dihydro-1*H*-indén-4-yl)oxy]méthyl]morpholine
antidépresseur

lubazodona

(2*S*)-2-[[[(7-fluoro-2,3-dihidro-1*H*-inden-4-il)oxi]metil]morfolina
antidepresivo

C₁₄H₁₈FNO₂

161178-07-0



luliconazolum

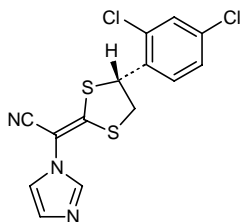
luliconazole (-)-(E)-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene](1H-imidazol-1-yl)acetonitrile
antifungal

luliconazole (-)-(E)-[(4R)-4-(2,4-dichlorophényl)-1,3-dithiolan-2-ylidène](1H-imidazol-1-yl)acétonitrile
antifongique

luliconazol (-)-(E)-[(4R)-4-(2,4-diclorofenil)-1,3-ditiolan-2-ilideno](1H-imidazol-1-il)acetonitrilo
antifúngico

 $C_{14}H_9Cl_2N_3S_2$

187164-19-8

**meldonium**

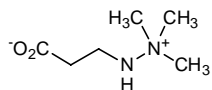
meldonium 3-(2,2,2-trimethyldiazaniumyl)propanoate
cardioprotectant

meldonium 3-(2,2,2-triméthylidiazaniumyl)propanoate
cardioprotecteur

meldonio 3-(2,2,2-trimetildiazanioil)propanoato
cardioprotector

 $C_6H_{14}N_2O_2$

76144-81-5



metelimumabum

metelimumab immunoglobulin G4, anti-(human transforming growth factor β 1) (human monoclonal CAT-192 γ 4-chain), disulfide with human monoclonal CAT-192 κ -chain, dimer
immunomodulator

mételimumab immunoglobuline G4, anti-(facteur de croissance transformant humain β 1) (chaîne γ 4 de l'anticorps monoclonal humain CAT-192), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal humain CAT-192
immunomodulateur

metelimumab inmunoglobulina G4, anti-(factor de crecimiento transformador humano β 1) (cadena γ 4 del anticuerpo monoclonal humano CAT-192), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humano CAT-192
inmunomodulador

272780-74-2

mitemcinalum

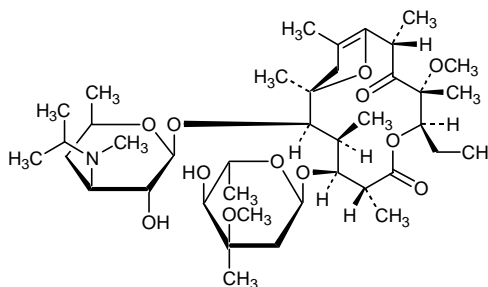
mitemcinal 8,9-didehydro-*N*-demethyl-9-deoxo-6,11-dideoxy-6,9-epoxy-12-*O*-methyl-*N*-(1-methylethyl)-11-oxoerythromycin
motilin agonist

mitemcinal (2*S*,4*R*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-9-[(2,6-didésoxy-3-*C*-méthyl-3-*O*-méthyl- α -*L*-ribo-hexopyranosyl)oxy]-5-éthyl-4-méthoxy-2,4,8,10,12,14-hexaméthyl-11-[[[3,4,6-tridésoxy-3-[méthyl(1-méthyléthyl)amino]- β -*D*-xylo-hexopyranosyl]oxy]-6,15-dioxabicyclo[10.2.1]pentadéc-1(14)-ène-3,7-dione agoniste de la motiline

mitemcinal (2*S*,4*R*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*)-9-[(2,6-didesoxi-3-*C*-metil-3-*O*-metil- α -*L*-ribo-hexopiranosil)oxi]-5-etil-4-metoxi-2,4,8,10,12,14-hexametil-11-[[[3,4,6-tridesoxi-3-[metil(1-metiletil)amino]- β -*D*-xilo-hexopiranosil]oxi]-6,15-dioxabicyclo[10.2.1]pentadec-1(14)-eno-3,7-diona agonista de la motilina

C₄₀H₆₉NO₁₂

154738-42-8



naxifyllinum

naxifylline

8-[(1*S*,2*R*,4*S*,5*S*,6*S*)-3-oxatricyclo[3.2.1.0^{2,4}]oct-6-yl]-1,3-dipropyl-
3,7-dihydro-1*H*-purine-2,6-dione
adenosine receptor antagonist

naxifylline

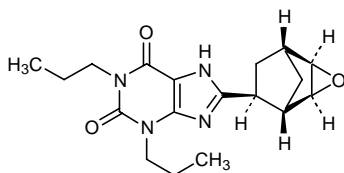
8-[(1*S*,2*R*,4*S*,5*S*,6*S*)-3-oxatricyclo[3.2.1.0^{2,4}]oct-6-yl]-1,3-dipropyl-
3,7-dihydro-1*H*-purine-2,6-dione
antagoniste des récepteurs de l'adénosine

naxifilina

8-[(1*S*,2*R*,4*S*,5*S*,6*S*)-3-oxatriciclo[3.2.1.0^{2,4}]oct-6-il]-1,3-dipropil-
3,7-dihidro-1*H*-purina-2,6-diona
antagonista del receptor de adenosina

C₁₆H₂₄N₄O₃

166374-49-8

**oglufanidum**

oglufanide

L- α -glutamyl-L-tryptophan
immunomodulator

oglufanide

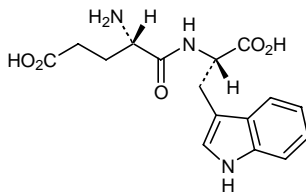
L- α -glutamyl-L-tryptophane
immunomodulateur

oglufanida

L- α -glutamil-L-triptófano
inmunomodulador

C₁₆H₁₉N₃O₅

38101-59-6



olcegepantum

olcegepant

N-[(1*R*)-2-[[[(1*S*)-5-amino-1-[[4-(pyridin-4-yl)piperazin-1-yl]carbonyl]pentyl]amino]-1-(3,5-dibromo-4-hydroxybenzyl)-2-oxoethyl]-4-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)piperidine-1-carboxamide
antimigraine agent, calcitonin gene related peptide receptor antagonist

olcégépant

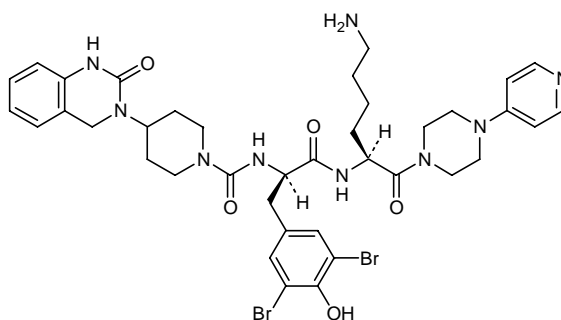
N-[(1*R*)-2-[[[(1*S*)-5-amino-1-[[4-(pyridin-4-yl)pipérazin-1-yl]carbonyl]pentyl]amino]-1-(3,5-dibromo-4-hydroxybenzyl)-2-oxoéthyl]-4-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)pipéridine-1-carboxamide
antimigraineux, antagoniste du récepteur du CGRP (peptide lié à la calcitonine dans son précurseur)

olcegepant

N-[(1*R*)-2-[[[(1*S*)-5-amino-1-[[4-(piridin-4-il)piperazin-1-il]carbonil]pentil]amino]-1-(3,5-dibromo-4-hidroxi-bencil)-2-oxoetil]-4-(2-oxo-1,4-dihidroquinazolin-3(2*H*)-il)piperidina-1-carboxamida
antimigrañoso, antagonista del receptor del péptido relacionado con el gen de la calcitonina (CGRP)

C₃₈H₄₇Br₂N₉O₅

204697-65-4

**oregovomabum**

oregovomab

immunoglobulin G1, anti-(human CA125 (carbohydrate antigen)) (mouse monoclonal B43.13 γ 1-chain), disulfide with mouse monoclonal B43.13 κ -chain, dimer
immunomodulator

orégovomab

immunoglobuline G1, anti-(antigène osidique humain CA125) (chaîne γ 1 de l'anticorps monoclonal de souris B43.13), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris B43.13
immunomodulateur

oregovomab

immunoglobulina G1, anti-(antígeno osídico humano CA125) (cadena γ 1 del anticuerpo monoclonal de ratón B43.13), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón B43.13
immunomodulador

213327-37-8

otamixabanum

otamixaban

methyl (2*R*,3*R*)-2-(3-carbamimidoylbenzyl)-3-[[4-(1-oxidopyridin-4-yl)benzoyl]amino]butanoate
blood-coagulation factor Xa inhibitor

otamixaban

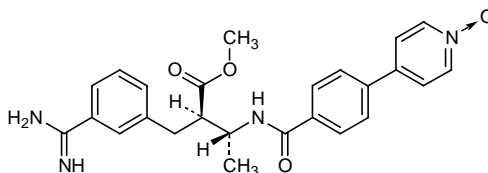
(2*R*,3*R*)-2-(3-carbamimidoylbenzyl)-3-[[4-(1-oxypyridin-4-yl)benzoyl]amino]butanoate de méthyle
inhibiteur du facteur Xa de coagulation sanguine

otamixabán

(2*R*,3*R*)-2-(3-carbamimidoilbencil)-3-[[4-(1-oxidopiridin-4-il)benzoil]amino]butanoato de metilo
inhibidor del factor Xa de la coagulación sanguínea

C₂₅H₂₆N₄O₄

193153-04-7

**paliferminum**

palifermin

[23-methionine]-23-163-fibroblast growth factor 7 (human clone 32/49 reduced)
fibrinoblast growth factor

palifermine

[23-méthionine]-23-163-facteur 7 de croissance du fibroblaste, protéine réduite produite par le clone humain 32/49
facteur de croissance des fibroblastes

palifermina

[23-metionina]-23-163-factor 7 de crecimiento de fibroblastos, proteína reducida producida por el clon humano 32/49
factor de crecimiento de fibroblastos

C₇₂₉H₁₁₅₆N₂₀₄O₂₀₇S₁₀

178254-26-7

MSYDMEGGD	IRVRRLFCRT	QWYLRIKRG	KVKGTOEMKN
NYNIMEIRTV	AVGIVAIGV	ESEFYLAMNK	EGKLYAKKEC
NEDCNFKELI	LENHYNTYAS	AKWTHNGGEM	FVALNQKGIP
VRGKKTKEQ	KTAHFLPMAI	T	

peramivirum

peramivir (1S,2S,3R,4R)-3-[(1S)-1-(acetylamino)-2-ethylbutyl]-4-(carbamimidoylamino)-2-hydroxycyclopentanecarboxylic acid
antiviral

péramivir

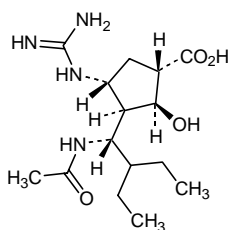
acide (1S,2S,3R,4R)-3-[(1S)-1-(acétylamino)-2-éthylbutyl]-4-(carbamimidoylamino)-2-hydroxycyclopentanecarboxylique
antiviral

peramivir

ácido (1S,2S,3R,4R)-3-[(1S)-1-(acetilamino)-2-etilbutil]-4-(carbamimidoilamino)-2-hidroxiciclopentanocarboxílico
antiviral

$C_{15}H_{26}N_4O_4$

229614-55-5

**talibegronum**

talibegron [4-[2-[[2R]-2-hydroxy-2-phenylethyl]amino]ethoxy]phenyl]acetic acid
 β_3 -adrenoreceptor agonist (*veterinary drug*)

talibégron

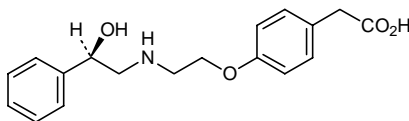
acide [4-[2-[[2R]-2-hydroxy-2-phényléthyl]amino]éthoxy]phényl]acétique
agoniste β_3 -adrénergique (*médicament vétérinaire*)

talibegrón

ácido [4-[2-[[2R]-2-hidroxi-2-feniletíl]amino]etoxi]fenil]acético
agonista de los receptores β_3 -adrenérgicos (*medicamento veterinario*)

$C_{18}H_{21}NO_4$

146376-58-1

**tariquidarum**

tariquidar N-[2-[[4-[2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl]phenyl]carbamoyl]-4,5-dimethoxyphenyl]quinoline-3-carboxamide
multidrug resistant inhibitor, antineoplastic

tariquidar

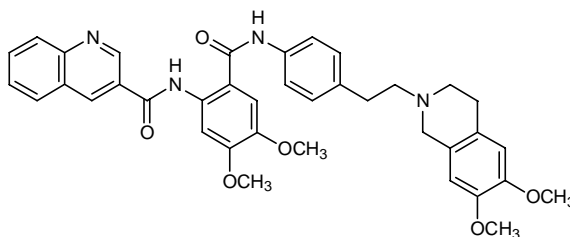
N-[2-[[4-[2-(6,7-diméthoxy-3,4-dihydroisoquinoléin-2(1H)-yl)éthyl]phényl]carbamoyle]-4,5-diméthoxyphényl]quinoléine-3-carboxamide
inhibiteur de la multirésistance aux médicaments, antinéoplasique

tariquidar

N-[2-[[4-[2-(6,7-dimetoxi-3,4-dihidroisoquinolin-2(1*H*)-il)etil]fenil]carbamoil]-4,5-dimetoxifenil]quinolina-3-carboxamida
inhibidor de la resistencia a múltiples fármacos, antineoplásico

C₃₈H₃₈N₄O₆

206873-63-4

**tebaniclinum**

tebanicline

5-[(2*R*)-azetidín-2-ylmetoxi]-2-cloropiridina
analgesic, nicotinic acetylcholine receptor agonist

tébanicline

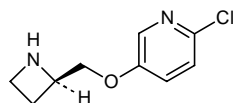
5-[(2*R*)-azetidín-2-ylméthoxy]-2-cloropiridina
analgésique, agoniste des récepteurs nicotiniques à l'acétylcholine

tebaniclina

5-[(2*R*)-azetidín-2-ilmetoxi]-2-cloropiridina
analgésico, agonista de los receptores nicotínicos de la acetilcolina

C₉H₁₁ClN₂O

198283-73-7

**tecastemizolum**

tecastemizole

1-(4-fluorobenzil)-*N*-(piperidín-4-yl)-1*H*-benzimidazol-2-amina
antihistaminic

técastémizole

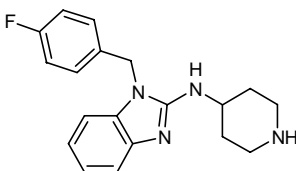
1-(4-fluorobenzil)-*N*-(pipéridín-4-yl)-1*H*-benzimidazol-2-amina
antihistaminique

tecastemizol

1-(4-fluorobencil)-*N*-(piperidín-4-il)-1*H*-bencimidazol-2-amina
antihistamínico

C₁₉H₂₁FN₄

75970-99-9



technetium (99mTc) fanolesomabum

technetium (99mTc) fanolesomab	immunoglobulin M, anti-(human CD15 antigen) (mouse monoclonal RB5 μ -chain), disulfide with mouse monoclonal RB5 light chain, pentamer, [99mTc]technetium salt <i>immunomodulator, radiodiagnostic agent</i>
technétium (99mTc) fanolésomab	immunoglobuline M, anti-(antigène CD15 humain) (chaîne μ de l'anticorps monoclonal de souris RB5), pentamère du disulfure de la chaîne légère de l'anticorps monoclonal de souris RB5, sel de [99mTc]technétium <i>immunomodulateur, produit à usage radiodiagnostique</i>
tecnecio (99mTc) fanolesomab	inmunoglobulina M, anti-(antígeno CD15 humano) (cadena μ del anticuerpo monoclonal de ratón RB5), pentámero del disulfuro de la cadena ligera del anticuerpo monoclonal de ratón RB5, sal de [99mTc]tecnecio <i>immunomodulador, agente de radiodiagnóstico</i>

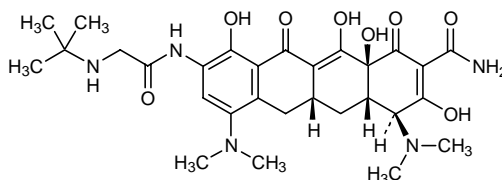
225239-31-6

tigecyclinum

tigecycline	(4S,4aS,5aR,12aS)-4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino]acetyl]amino]-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide <i>antibiotic</i>
tigécycline	(4S,4aS,5aR,12aS)-4,7-bis(diméthylamino)-9-[[[(1,1-diméthyléthyl)amino]acétyl]amino]-3,10,12,12a-tétrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotétracène-2-carboxamide <i>antibiotique</i>
tigeciclina	(4S,4aS,5aR,12aS)-4,7-bis(dimetilamino)-9-[[[(1,1-dimetiletil)amino]acetil]amino]-3,10,12,12a-tetrahidroxi-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahidrotetraceno-2-carboxamida <i>antibiótico</i>

 $C_{29}H_{39}N_5O_8$

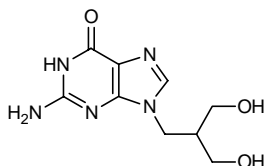
220620-09-7

**tiviciclovirum**

tiviciclovir	2-amino-9-[3-hydroxy-2-(hydroxymethyl)propyl]-1,9-dihydro-6H-purin-6-one <i>antiviral</i>
tiviciclovir	2-amino-9-[3-hydroxy-2-(hydroxyméthyl)propyl]-1,9-dihydro-6H-purin-6-one <i>antiviral</i>
tiviciclovir	2-amino-9-[3-hidroxi-2-(hidroximetil)propil]-1,9-dihidro-6H-purin-6-ona <i>antiviral</i>

$C_9H_{13}N_5O_3$

103024-93-7

**tosagestinum**

tosagestin

17-hydroxy-11-methylene-19-nor-17 α -pregna-4,15-dien-20-yn-3-one
contraceptive

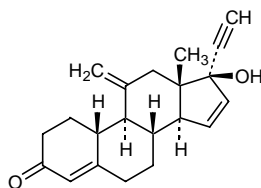
tosagestin

17-hydroxy-11-méthylène-19-nor-17 α -prègna-4,15-dièn-20-yn-3-one
progestagène contraceptif

tosagestina

17-hidroxi-11-metilen-19-nor-17 α -pregna-4,15-dien-20-in-3-ona
anticonceptivo $C_{21}H_{24}O_2$

110072-15-6

**trabectedinum**

trabectedin

(1'*R*,6*R*,6*aR*,7*R*,13*S*,14*S*,16*R*)-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-19-oxo-3',4',6,7,12,13,14,16-octahydrospiro[6,16-(epithiopropanooxymethano)-7,13-imino-6*aH*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1'(2'*H*)-isoquinolin]-5-yl acetate
antineoplastique

trabectédine

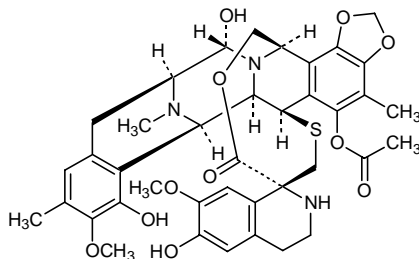
acétate de (1'*R*,6*R*,6*aR*,7*R*,13*S*,14*S*,16*R*)-6',8,14-trihydroxy-7',9-diméthoxy-4,10,23-triméthyl-19-oxo-3',4',6,7,12,13,14,16-octahydrospiro[6,16-(épithiopropanooxyméthano)-7,13-imino-6*aH*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1'(2'*H*)-isoquinoléin]-5-yle
antineoplasique

trabectedina

acetato de (1'*R*,6*R*,6*aR*,7*R*,13*S*,14*S*,16*R*)-6',8,14-trihidroxi-7',9-dimetoxi-4,10,23-trimetil-19-oxo-3',4',6,7,12,13,14,16-octahidrospiro[6,16-(epitiopropanooximetano)-7,13-imino-6*aH*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocina-20,1'(2'*H*)-isoquinolin]-5-ilo
antineoplásico



114899-77-3

**zosuquidarum**

zosuquidar

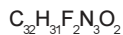
(2*R*)-1-[4-[(1*aR*,6*r*,10*bS*)-1,1-difluoro-1,1*a*,6,10*b*-tetrahydrodibenzo[*a,e*]cyclopropano[*c*]cyclohepten-6-yl]piperazin-1-yl]-3-(quinolin-5-yloxy)propan-2-ol
multidrug resistant inhibitor, antineoplastic

zosuquidar

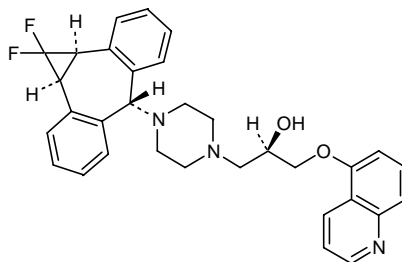
(2*R*)-1-[4-[(1*aR*,6*r*,10*bS*)-1,1-difluoro-1,1*a*,6,10*b*-tétrahydrodibenzo[*a,e*]cyclopropano[*c*]cycloheptén-6-yl]pipérazin-1-yl]-3-(quinoléin-5-yloxy)propan-2-ol
inhibiteur de la multirésistance aux médicaments, antinéoplasique

zosuquidar

(2*R*)-1-[4-[(1*aR*,6*r*,10*bS*)-1,1-difluoro-1,1*a*,6,10*b*-tetrahydrodibenzo[*a,e*]cyclopropano[*c*]cyclohepten-6-yl]piperazin-1-yl]-3-(quinolin-5-iloxy)propan-2-ol
inhibidor de la resistencia a múltiples fármacos, antineoplásico



167354-41-8



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

**Proposed International Nonproprietary Names (Prop. INN): List 49
(WHO Chronicle, Vol. 37, No. 2, 1983)**

p. 19	<i>delete</i>	<i>insert</i>
	tomoxetine	atomoxetine
	tomoxetine	atomoxetine

**Dénominations communes internationales proposées (DCI Prop.): Liste 49
(Chronique OMS, Vol. 37, No. 2, 1983)**

p. 19	<i>supprimer</i>	<i>insérer</i>
	tomoxétinum	atomoxétinum
	tomoxétine	atomoxétine

**Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 49
(Crónica de la OMS, Vol. 37, No. 2, 1983)**

p. 19	<i>suprimase</i>	<i>insértese</i>
	tomoxetinum	atomoxetinum
	tomoxetina	atomoxetina

**Proposed International Nonproprietary Names (Prop. INN): List 78
Dénominations communes internationales proposées (DCI Prop.): Liste 78
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 78
(WHO Drug Information, Vol. 11, No. 4, 1997)**

p. 269	carafibanum	<i>sustituyase la descripción por la siguiente:</i>
	carafibán	(S)-β-[2-[(S)-4-(p-amidinofenil)-4-metil-2,5-dioxo-1-imidazolidinil]acetamido]hidrocinamato de etilo
p. 272	<i>suprimase</i>	<i>insértese</i>
	efavirenzo	efavirenz
	efavirenzo	efavirenz
p. 279	<i>suprimase</i>	<i>insértese</i>
	moxifloxacina	moxifloxacino
	moxifloxacina	moxifloxacino

- p. 292 **technetii (99mTc) apcitidum**
 tecnecio (99mTc) apcitida *sustituyase la descripción por la siguiente:*
 hidrógeno [*N*-(mercaptoacetil)-*D*-tirosil-*S*-(3-aminopropil)-*L*-cisteinilglicil-*L*- α -aspartil-*L*-cisteinilglicilglicil-*S*-(acetamidometil)-*L*-cisteinilglicil-*S*-(acetamidometil)-*L*-cisteinilglicilglicil-*L*-cisteinamida (1 \rightarrow 5)-sulfuro cíclico (5-)-*N*¹¹,*N*¹²,*N*¹³,*S*¹³]oxo[^{99m}Tc]tecnetato(V) de sodio
- p. 294 **tobicillinum**
 tobicillina *sustituyase la descripción por la siguiente:*
 (2*S*,5*R*,6*R*)-3,3-dimetil-7-oxo-6-(2-fenilacetamido)-4-tia-1-azabicyclo-[3.2.0]heptano-2-carboxilato de α -hidroxi-*m*-tolilo, isobutirato (éster)

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. 102 **anatumomabum mafenatoxum**
 anatumomab mafenatox *sustituyase la descripción por la siguiente:*
 inmunoglobulina G1 (cadena γ 1 del fragmento Fab del anticuerpo monoclonal humanizado de ratón, clon pMB125, dirigido contra la glicoproteína 72 humana asociada a tumores)-[227-alanina]enterotoxina A (*Staphylococcus aureus*) complejada con la cadena κ del anticuerpo monoclonal de ratón clon pMB125
- p. 110 *suprimase*
 olamufloxacina *insértese*
 olamufloxacino
- p. 112 *suprimase*
 estansoporquina *insértese*
 estansoporquina
- p. 112 **stansoporfinum**
 estansoporquina *sustituyase la descripción por la siguiente:*
 (OC-6-13)-dicloro[7,12-dietil-3,8,13,17-tetrametilporfirina-2,18-dipropionato(4-)-*N*²¹,*N*²²,*N*²³,*N*²⁴]estannato(2-) de dihidrógeno
- p. 115 *suprimase*
 clorprotixeno *insértese*
 clorprotixeno

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. 261 *suprimase*
 enrasentano *insértese*
 enrasentán

p. 269 **minopafantum**
minopafant

sustituyase la descripción por la siguiente:
(+) cloruro de 1-etil-2-[[N-[(2R)-2-metoxi-3-[[[4-[(octadecilcarbamoil)=oxi]piperidino]carbonil]oxi]propoxi]carbonil]-o-anisamido]metil]piridinio

p. 277 **tabimorelinum**
tabimorelina

sustituyase la descripción por la siguiente:
(R)- α -[(E)-5-amino-N,5-dimetil-2-hexenamido]-N-metil-N-[(R)- α -(metilcarbamoil)fenetil]-2-naftalenopropionamida

Proposed International Nonproprietary Names (Prop. INN): List 81
Dénominations communes internationales proposées (DCI Prop.): Liste 81
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 81
(WHO Drug Information, Vol. 13, No. 2, 1999)

p. 111 **cadrofloxacinum**
cadrofloxacine

remplacer la description par la suivante:
(-)-acide 1-cyclopropyl-8-(difluorométoxy)-6-fluoro-7-[(3S)-3-méthylpipérazin-1-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique

p. 115 **finrozolum**
finrozole

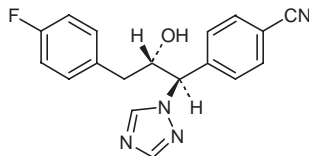
replace the description and the graphic formula by the following:
p-[(1RS,2SR)-3-(p-fluorophenyl)-2-hydroxy-1-(1H-1,2,4-triazol-1-yl)propyl]benzonitrile

finrozole

remplacer la description et la formule développée par la suivante:
4-[(1RS,2SR)-3-(4-fluorophényl)-2-hydroxy-1-(1H-1,2,4-triazol-1-yl)propyl]benzonitrile

finrozol

sustituyase la descripción y la fórmula empírica por la siguiente:
p-[(1RS,2SR)-3-(p-fluorofenil)-2-hidroxi-1-(1H-1,2,4-triazol-1-il)propil]benzonitrilo



and enantiomer
et énantiomère
y enantiómero

finrozole
finrozole
finrozol

replace the CAS registry number by the following:
remplacer le numéro dans le registre du CAS par:
sustituyase le número dans le registre du CAS por:

160146-17-8

p. 117 **ibritumomabum tiuxetanum**

ibritumomab tiuxetán

sustituyase la descripción por la siguiente:

inmunoglobulina G1, anti-(antígeno CD20 humano) (cadena γ 1 del anticuerpo monoclonal de ratón IDEC-Y2B8), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón IDEC-Y2B8, conjugada con *N*-[2-[bis(carboximetil)amino]-3-(4-isotiocianatofenil)propil]-*N*-[2-[bis(carboximetil)amino]propil]glicina

p. 125 **sibrotuzumabum**

sibrotuzumab

sustituyase la descripción por la siguiente:

inmunoglobulina G1, anti-(FAP (proteína de activación de los fibroblastos humana) (cadena γ 1 del anticuerpo monoclonal humanizado de ratón BIBH1), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón BIBH1

p. 131 **sulesomabum**

sulesomab

sustituyase la descripción por la siguiente:

inmunoglobulina G1, anti-(antígeno celular NCA-90 de granulocito humano) fragmento Fab' (cadena γ 1 del anticuerpo monoclonal de ratón IMMU-MN3), disulfuro con la cadena ligera del anticuerpo monoclonal de ratón IMMU-MN3

p. 131 **technetium (99mTc) pintumomabum**

tecnecio (99mTc) pintumomab

sustituyase la descripción por la siguiente:

sal de [99mTc]tecnecio de la inmunoglobulina G1 anti-(antígeno asociado a los adenocarcinomas humanos) (cadena γ 1 del anticuerpo monoclonal de ratón 170), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón 170

p. 133 **lintuzumabum**

lintuzumab

sustituyase la descripción por la siguiente:

inmunoglobulina G1, anti-(antígeno CD33 humano) (cadena γ 1 del anticuerpo monoclonal humanizado de ratón HuM195), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón HuM195

p. 134 **igovomabum**

igovomab

sustituyase la descripción por la siguiente:

inmunoglobulina G1, anti-[(antígeno osídico) CA 125 humano] (fragmento F(ab')₂ (cadena γ 1 del anticuerpo monoclonal de ratón OC125F(AB')₂), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal de ratón OC125F(AB')₂)

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. 284 **prinomastatum**

prinomastat

replace the description by the following:

(*S*)-2,2-dimethyl-4-[[*p*-(4-pyridyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxylic acid

- p. 285 **pumafentrinum**
pumafentrina
sustituyase la descripción por la siguiente:
(-)-*p*-[(4aR*,10bS*)-9-etoxi-1,2,3,4,4a,10b-hexahidro-8-metoxi-2-metilbenzo[*c*][1,6]naftiridin-6-il]-*N,N*-diisopropilbenzamida
- p. 285 *delete/supprimer/suprimase*
radolmidinum
radolmidine
radolmidine
radolmidina
insert/insérer/insértese
fadolmidinum
fadolmidine
fadolmidine
fadolmidina
- p. 288 **tanomastatum**
tanomastat
sustituyase la descripción por la siguiente:
ácido (2*S*)-4-(4'-clorobifenil-4-il)-4-oxo-2-[(fenilsulfanil)metil]butanoico
- p. 293 *suprimase*
olmesartán medoxmilo
insértese
olmesartán medoxomilo

Proposed International Nonproprietary Names (Prop. INN): List 83
Dénominations communes internationales proposées (DCI Prop.): Liste 83
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 83
(WHO Drug Information, Vol. 14, No. 2, 2000)

- p. 110 **bevacizumabum**
bevacizumab
sustituyase la descripción por la siguiente:
immunoglobulina G1 anti-(factor de crecimiento del endotelio vascular humano) (cadena γ 1 del anticuerpo monoclonal humanizado de ratón rhuMab-VEGF), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de ratón rhuMab-VEGF
- p. 110 **bivatuzumabum**
bivatuzumab
replace the description by the following:
immunoglobulin G1 (human-mouse monoclonal BIWA4 γ 1-chain anti-human antigen CD44v6), disulfide with human-mouse monoclonal BIWA4 κ -chain, dimer
remplacer la description par la suivante:
immunoglobuline G1 anti (antigène CD44v6 humain) (chaîne γ 1 de l'anticorps monoclonal de souris BIWA4 humanisé), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris BIWA4 humanisé
sustituyase la descripción por la siguiente:
immunoglobulina G1 anti-(antígeno humano CD44v6) (cadena γ 1 del anticuerpo monoclonal humanizado de ratón BIWA4), dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón BIWA4

- p. 117 **gadofosvesetum**
gadofosveset *sustituyase la descripción por la siguiente:*
trihidrogeno[2,2'-[[[(1R)-1-[[[2-bis[(carboxi-κ-O)metil]amino-κ-N]etil][carboxi-κ-O)metil]amino-κ-N]etil]2-[[[(4,4,-difenilciclohexil)oxi]hidroxifosforil]=oxi]etil]imino-κ-N]diacetato(6-)-κ-O-κ-O']gadolinato(3-)
- p. 120 *supprimer*
lérdelimumab *insérer*
lérdelimumab
- p. 120 **lerdelimumabum**
lerdelimumab *replace the description by the following:*
immunoglobulin G4, anti-(human transforming growth factor β2) (human monoclonal CAT-152 γ4-chain), disulfide with human monoclonal CAT-152 λ-chain, dimer
- lérdelimumab *remplacer la description par la suivante:*
immunoglobuline G4, anti-(facteur de croissance transformant humain β2) (chaîne γ4 de l'anticorps monoclonal humain CAT-152), dimère du disulfure avec la chaîne λ de l'anticorps monoclonal humain CAT-152
- lerdelimumab *sustituyase la descripción por la siguiente:*
immunoglobulina G4, anti-(factor β2 de crecimiento transformador humano) (cadena γ4 del anticuerpo monoclonal humano CAT-152), dímero del disulfuro con la cadena λ del anticuerpo monoclonal humano CAT-152
- p. 125 **ozogamicinum**
ozogamicina *sustituyase la descripción por la siguiente:*
(1R,4Z,8S,13E)-13-[2-[2-[[[p-(3-carbamoilpropoxi)-α-metilbencilideno]=hidrazino]carbonil]-1,1-dimetiletil]ditio]etilideno]-8-[[[4,6-didesoxi-4-[[[2,6-didesoxi-4-S-[4-[(6-desoxi-3-O-metil-α-L-manopiranosil)oxi]-3-iodo-5,6-dimetoxi-o-toluoil]-4-tio-β-D-ribo-hexopiranosil]oxi]amino]-2-O-[2,4-didesoxi-4-(N-etilacetamido)-3-O-metil-α-L-treo-pentopiranosil]-β-D-glucopiranosil] oxil]-1-hidroxi-11-oxobiciclo[7.3.1]trideca-4,9-dieno-2,6-diino-10-carbamato de metilo
- p. 132 **pitavastatinum**
pitavastatina *sustituyase la descripción por la siguiente:*
ácido (3R,5S,6E)-7-[2-ciclopropil-4-(p-fluorofenil)-3-quinolil]-3,5-dihidroxi-6-heptenoico

Proposed International Nonproprietary Names (Prop. INN): List 84**Dénominations communes internationales proposées (DCI Prop.): Liste 84****Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 84***(WHO Drug Information, Vol. 14, No. 4, 2000)*

- p. 250 **aviscuminum**
aviscumina *sustituyase la descripción por la siguiente:*
toxina ML-I (lectina I de muérdago) (*Viscum album*) obtenida por ingeniería genética, constituida por dos cadenas peptídicas A (250 aminoácidos) y B (264 aminoácidos) unidas entre sí por un puente disulfuro

- p. 259 **imatinibum**
imatinib
sustituyase la descripción por la siguiente:
 α -(4-metil-1-piperazinil)-3'-[[4-(3-piridil)-2-pirimidinil]amino]-*p*-toluidida
- p. 260 **lemalesomabum**
lemalesomab
sustituyase la descripción por la siguiente:
immunoglobulina G1, anti (antígeno celular del granulocito humano NCA 90) (cadena γ 1 del anticuerpo monoclonal de ratón IMMU MN3), dímero del disulfuro con la cadena κ del anticuerpo monoclonal de ratón IMMU MN3
- p. 265 **pitakinraum**
pitakinra
sustituyase la descripción por la siguiente:
L-metionil-[121-ácido aspártico,124-ácido aspártico]interleukina-4
- p. 266 *suprimase*
pradofloxacina
insértese
pradofloxacino
- p. 272 **tipifarnibum**
tipifarnib
sustituyase la descripción por la siguiente:
(+)-6-[(*R*)-amino(4-clorofenil)(1-metil-1*H*-imidazol-5-il)metil]-4-(3-clorofenil)-1-metilquinolin-2(1*H*)-ona
- p. 272 **traxoprodilum**
traxoprodil
replace the description by the following:
1-[(1*S*,2*S*)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]-4-phenylpiperidin-4-ol
- traxoprodil
remplacer la description par la suivante:
1-[(1*S*,2*S*)-2-hydroxy-2-(4-hydroxyphényl)-1-méthyléthyl]-4-phénylpipéridin-4-ol
- traxoprodil
sustituyase la descripción por la siguiente:
1-[(1*S*,2*S*)-2-hidroxi-2-(4-hidroxifenil)-1-metiletil]-4-fenilpiperidin-4-ol
- p. 275 **zelandopamum**
zelandopam
sustituyase la descripción por la siguiente:
(-)-(S)-4-(3,4-dihroxifenil)-1,2,3,4-tetrahydro-7,8-isoquinolinadiol

Proposed International Nonproprietary Names (Prop. INN): List 85**Dénominations communes internationales proposées (DCI Prop.): Liste 85****Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 85****(WHO Drug Information, Vol. 15, No. 2, 2001)**

- p. 96 **acidum gadocoleticum**
gadocoletic acid
acide gadocolétique
ácido gadocolético
add the following CAS registry number:
insérer le numéro dans le registre du CAS suivant:
insértese el número de registro del CAS siguiente:

280776-87-6

- p. 97 **afeletecanum**
afeletecan
replace the description by the following:
camptothecin, ester with *N*-[[*p*-[(3-*O*-methyl-β-*L*-fucopyranosyl)oxy]phenyl]thiocarbamoyl]-*L*-histidyl-*L*-valine
- afélétécan
remplacer la description par la suivante:
(2*S*)-2-[[[(2*S*)-3-(1*H*-imidazol-4-yl)-2-[[[4-[(3-*O*-méthyl-6-désoxy-β-*L*-galactopyranosyl)oxy]phényl]amino]thiocarbonyl]amino]propanoyl]=amino]-3-méthylbutanoate de (4*S*)-4-éthyl-3,14-dioxo-3,4,12,14-tétrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoléin-4-yle
- afeletecán
sustituyase la descripción por la siguiente:
éster de la camptotecina con *N*-[[*p*-[(3-*O*-metil-β-*L*-fucopiranosil)oxi]fenil]=tiocarbamoil]-*L*-histidil-*L*-valina
- p. 100 **amelubantum**
amelubant
amélubant
amelubant
add the following CAS registry number:
insérer le numéro dans le registre du CAS suivant:
insértese el número de registro del CAS siguiente:

346735-24-8
- p. 102 **dalbavancinum**
dalbavancin
replace the description by the following:
5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-[2-deoxy-2-[(10-methylundecanoyl)amino]-β-*D*-glucopyranuronosyl]-38-[[3-(diméthylamino)propyl]carbamoil]-42-*O*-α-*D*-mannopyranosyl-15-*N*-methyl(ristomycin A aglicone)
- dalbavancine
remplacer la description par la suivante:
acide 2-désoxy-1-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50*aR*)-5,31-dichloro-38-[[3-(diméthylamino)propyl]carbamoil]-6,11,34,40,44-pentahydroxy-42-(α-*D*-mannopyranosyloxy)-15-(méthylamino)-2,16,36,50,51,59-hexaoxo-2,3,16,17,18,19,35,36,37,38,48,49,50,50*a*-tétradécahydro-20,23:30,33-diéthéno-3,18:35,48-bis(iminométhano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tétraméthéno-34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotétracosén-56-yl]-2-[(10-méthylundécanyloyl)amino]-β-*D*-glucopyranuronique
- p. 103 *delete/supprimer/suprimase* *insert/insérer/insértese*
drotrecoginum alfa **drotrecoginum alfa (activatum)**
drotrecogin alfa drotrecogin alfa (activated)
drotrécogine alfa drotrécogine alfa (activé)
drotrecogina alfa drotrecogina alfa (activada)
- p. 108 *supprimer* *insérer*
febuxostat febuxostat
- p. 108 **finafloxacinum**
finafloxacin
replace the description by the following:
(-)-8-cyano-1-cyclopropyl-6-fluoro-7-[(4*aS*,7*aS*)-hexahydropyrrolo[3,4-*b*]-1,4-oxazin-6(2*H*)-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

-
- p. 108 *suprimase*
finafloxacina *insértese*
finafloxacino
- p. 109 **gadolmitolum**
gadolmitol
gadolmitol
gadolmitol
add the following CAS registry number:
insérer le numéro dans le registre du CAS suivant:
insértese el número de registro del CAS siguiente:

227622-74-4
- p. 110 **garnocestimum**
garnocestim *sustituyase la descripción por la siguiente:*
CXC quimiokina GRO β -(5-73)-péptido (GRO β : proteína inflamatoria humana secretada por los macrófagos)
- p. 113 **lapisteridum**
lapistéride *remplacer la description par la suivante:*
N-[1-(4-méthoxyphényl)-1-méthyléthyl]-3-oxo-4-aza-5 α -androst-1-ène-17 β -carboxamide

lapisterida *sustituyase la descripción por la siguiente:*
N-[1-(4-metoxifenil)-1-metiletil]-3-oxo-4-aza-5 α -androst-1-eno-17 β -carboxamida
- p.114 **laronidasum**
laronidase *replace the description by the following:*
8-L-histidine- α -L-iduronidase (human)

laronidase *remplacer la description par la suivante:*
[8-L-histidine]- α -L-iduronidase humaine

laronidasa *sustituyase la descripción por la siguiente:*
8-L-histidina- α -L-iduronidasa (humana)
- p. 115 **lirimilastum**
lirimilast *sustituyase la descripción por la siguiente:*
metanosulfonato de 2-(2,4-diclorobenzoil)-3-ureidobenzofuran-6-ilo

lirimilast *add the following CAS registry number:*
lirimilast *insérer le numéro dans le registre du CAS suivant:*
lirimilast *insértese el número de registro del CAS siguiente:*

329306-27-6
-

- p. 115 **livaraparinum calcium**
livaraparine calcique
- remplacer la description par la suivante:*
sel calcique d'une héparine de basse masse moléculaire obtenue par dépolymérisation, au moyen d'acide nitreux, d'héparine de muqueuse intestinale de porc ; la majorité des composants de la livaraparine calcique possèdent une structure acide 2-O-sulfo- α -L-idopyranosuronique à l'extrémité non réductrice de leur chaîne et une structure 6-O-sulfatée à l'extrémité réductrice de leur chaîne ; la masse moléculaire relative moyenne est de 3000 à 5000, 75% étant inférieur à 8000 ; le degré de sulfatation par unité disaccharide est voisin de 2
- livaraparina cálcica
- sustituyase la descripción por la siguiente:*
sal cálcica de una heparina de baja masa molecular obtenida de heparina de mucosa intestinal de cerdo por despolimerización con ácido nitroso; la mayoría de los componentes de la livaraparina cálcica tienen ácido 2-O-sulfo- α -L-idopiranosurónico en el extremo no reductor de la cadena y una estructura 6-O-sulfatada en el extremo reductor de la cadena; la masa molecular relativa media es de 3000 a 5000, siendo el 75% inferior a 8000; el grado de sulfatación por unidad de disacárido es aproximadamente 2
- p. 117 **mureletecanum**
mureletecan
murelétécán
mureletecán
- add the following CAS registry number:*
insérer le numéro dans le registre du CAS suivant:
insértese el número de registro del CAS siguiente:
- 246527-99-1
- p. 118 **nasaruplasum beta**
nasaruplasa beta
- sustituyase la descripción por la siguiente:*
prourokinasa (activador de enzima) humana glicosilada cuyo gen se clona en el vector pUK4/pUK18 y se expresa en la línea celular murina SP2/0
- p. 120 **pegfilgrastimum**
pegfilgrastim
- sustituyase la descripción por la siguiente:*
N-(3-hidroxiopropil)metionilfactor de estimulación de colonias humano, 1-éter con el α -metil- ω -hidroxipoli(oxietileno)
- pegfilgrastim
pegfilgrastim
pegfilgrastim
- replace the molecular formula by the following:*
remplacer la formule brute par:
sustitúyase la fórmula molecular por:
- $$C_{849}H_{1347}N_{223}O_{244}S_9(C_2H_4O)_n$$
- p. 121 **pexelizumabum**
pexelizumab
- sustituyase la descripción por la siguiente:*
inmunoglobulina, anti-(cadena- α del complemento C5 humano) (mono cadena del anticuerpo monoclonal humanizado de ratón 5G1.1-SC)

-
- p. 132 **zoticasonum**
zoticasone
- replace the description by the following:*
S-[(3R)-2-oxotetrahydrofuran-3-yl] 6 α ,9-difluoro-12 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate
- zoticasone
- remplacer la description par la suivante:*
6 α ,9-difluoro-12 β ,17-dihydroxy-16 α -méthyl-3-oxoandrosta-1,4-diène-17 β -carbothioate de S-[(3R)-2-oxotétrahydrofuran-3-yle]
- zoticasona
- sustitúyase la descripción por la siguiente:*
6 α ,9-difluoro-12 β ,17-dihidroxi-16 α -metil-3-oxoandrosta-1,4-dieno-17 β -carbotioato de S-[(3R)-2-oxotetrahidrofuran-3-ilo]
- p. 134 **evernimicinum**
evernomicina
- sustitúyase la descripción por la siguiente:*
O-3-C-metil-4-O-metil-3-nitro-2,3,6-tridesoxi- α -L-arabino-hexopiranosil-(1 \rightarrow 3)-O-4-O-(3,5-dicloro-4-hidroxi-2-metoxi-6-metilbenzoil)-2,6-didesoxi- β -D-arabino-hexopiranosil-(1 \rightarrow 4)-O-(1R)-2,6-didesoxi- β -D-arabino-hexopiranosilideno-(1 \rightarrow 3-4)-O-3-C-metil-6-desoxi- β -D-manopiranosil-(1 \rightarrow 3)-O-4-O-metil-6-desoxi- β -D-galactopiranosil-(1 \rightarrow 4)-2,6-di-O-metil- β -D-manopiranosido de O-(1R)-4-O-(2,4-dihidroxi-6-metilbenzoil)-2,3-O-metileno-D-xilopiranosilideno-(1 \rightarrow 3-4)- α -L-lixopiranosilo
- p. 134 **onerceptum**
onercept
- sustitúyase la descripción por la siguiente:*
péptido (20-180) TNF-BP (parte del dominio extracelular del receptor 1 humano del factor de necrosis tumoral glicosilado)
- p. 134 **posaconazolum**
posaconazol
- sustitúyase la descripción por la siguiente:*
4-[p-[4-[p-[(3R,5R)-5-(2,4-difluorofenil)tetrahidro-5-(1H-1,2,4-triazol-1-ilmetil)-3-furil]metoxi]fenil]-1-piperazinil]fenil]-1-[(1S,2S)-1-etil-2-hidroxipropil]- Δ^2 -1,2,4-triazolin-5-ona

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*¹ 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*.¹

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*.¹

A. Such objection shall:

(i) identify the person objecting;

* 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).

¹ 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*.

(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.

* 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.¹ 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-	antifibrillat 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 ₂ -receptor antagonists
-trexatum	-trexate	folic acid antagonists
-verinum	-verine	spasmolytics with a papaverine-like action
vin-	vin-)	vinca alkaloids
-vin-	-vin-)	

¹ 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*¹ 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*¹ (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).

¹ 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*¹ (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:

* 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.¹ 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 β -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
-conazolom	-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 hypoglycémiants
io-	io-	produits de contraste iodés
-ium	-ium	ammoniums quaternaires
-metacinum	-métacine	substances anti-inflammatoires du groupe de l'indométacine

¹ 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>
-nidazolom	-nidazole	substancias antiprotozoarias del grupo del metronidazol
ololum	-olol	antagonistas de los receptores β -adrenérgicos
-oxacinum	-oxacine	substancias antibacterianas del grupo de l'acido nalidixique
-pridum	-pride	substancias del grupo del sulpiride
-profenum	-profène	substancias anti-inflamatorias del grupo de l'ibuprofène
-pril(at)um	-pril(ate)	inhibidores de la 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 los receptores H_2 de l'histamina
-trexatum	-trexate	antagonistas de l'acido folico ²
-verinum	-vérine	espasmolíticos 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*¹ 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).

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

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.

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 vengán 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 fabrique 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.¹ Cuando la partícula no lleva ningún guión, cabe utilizarla en cualquier parte de la denominación.

* 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.

¹ 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
-adolum	-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 β-lactamasas
bol	bol	esteroides anabólicos
-buzonium	-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
-conazolium	-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>
-nidazolium	-nidazol	antiprotozoarios del grupo del metronidazol
-ololum	-olol	bloqueadores β-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 ₂ 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- }	

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 47

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–85) and Recommended (1–45) International Nonproprietary Names can be found in *Cumulative List No. 10, 2002* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES (DCI Rec): Liste 47

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9)] les dénominations ci-dessous sont choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–85) et recommandées (1–45) dans la *Liste récapitulative No. 10, 2002* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 47

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–85) y Recomendadas (1–45) se encuentran reunidas en *Cumulative List No. 10, 2002* (disponible sólo en CD-ROM).

Latin, English, French, Spanish:

Recommended INN Chemical name or description; Molecular formula; Graphic formula

DCI Recommandée Nom chimique ou description; Formule brute; Formule développée

DCI Recomendada Nombre químico o descripción; Fórmula empírica; Fórmula desarrollada

acidum gadocoleticum

gadocoletic acid

trihydrogen [3β-[[[(4S)-4-[bis[2-[bis[(carboxy-κO)methyl]amino-κM]ethyl]amino-κN]-4-(carboxy-κO)butanoyl]amino]-12α-hydroxy-5β-cholan-24-oato(6-)]]=gadolate(3-)

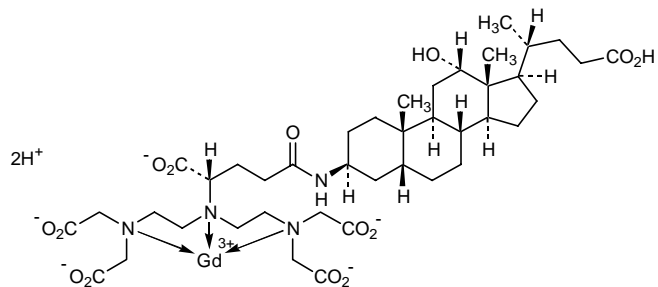
acide gadocolétique

trihydrogène[3β-[[[(4S)-4-[bis[2-[bis[(carboxy-κO)méthyl]amino-κM]éthyl]amino-κN]-4-(carboxy-κO)butanoyl]amino]-12α-hydroxy-5β-cholan-24-oato(6-)]]=gadolate(3-)

ácido gadocolético

trihidrógeno[3β-[[[(4S)-4-[bis[2-[bis[(carboxi-κO)metil]amino-κM]etil]amino-κN]-4-(carboxi-κO)butanoi]amino]-12α-hidroxi-5β-colan-24-ato(6-)]]=gadolinato(3-)

C₄₁H₆₃GdN₄O₁₄



afeletecanum

afeletecan

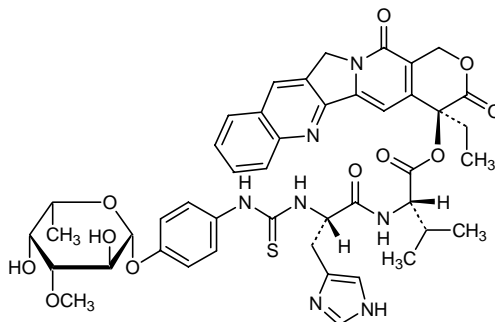
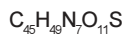
camptothecin, ester with *N*-[[*p*-[(3-*O*-methyl-β-*L*-fucopyranosyl)oxy]phenyl]=thiocarbamoyl]-*L*-histidyl-*L*-valine

afélétecán

(2*S*)-2-[[[(2*S*)-3-(1*H*-imidazol-4-yl)-2-[[[[4-[(3-*O*-méthyl-6-désoxy-β-*L*-galactopyranosyl)oxy]phényl]amino]thiocarbonyl]amino]propanoyl]amino]-3-méthylbutanoate de (4*S*)-4-éthyl-3,14-dioxo-3,4,12,14-tétrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoléin-4-yle

afeletecán

éster de la camptotecina con *N*-[[*p*-[(3-*O*-metil-β-*L*-fucopiranosil)oxi]fenil]=tiocarbamoil]-*L*-histidil-*L*-valina

**alfimeprasum**

alfimeprase

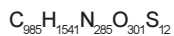
[3-L-serine]fibrolase-(3-203)-peptide (fibrolase : fibrinolytic enzyme isolated from *Agkistrodon conrix conrix* venom)

alfiméprase

[3-L-sérine]fibrolase-(3-203)-peptide (fibrolase : enzyme fibrinolytique extraite de venin d'*Agkistrodon conrix conrix*)

alfimeprasa

[3-L-serina]fibrolasa-(3-203)-péptido (fibrolasa : enzime fibrinolítica extraida de veneno de *Agkistrodon conrix conrix*)

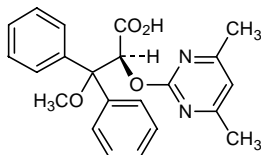
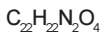


SFPQRYVQ	LVIVADHRMN	TKYNGDSDKI	RQVWHQIVNT
INEIYRPLNI	QFTLVGLEIW	SNQDLITVTS	VSHDTLASFG
NWRETDLLRR	QRHDNAQLLT	AIDFDGDTVG	LAYVGGMCQL
KHSTGVIQDH	SAINLLVALT	MAHELGHNLG	MNHDGNQCHC
GANSCVMAAM	LSDQPSKLFS	DCSKKDYQTF	LTVNNPQCIL

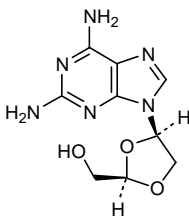
NKP

ambrisentanum

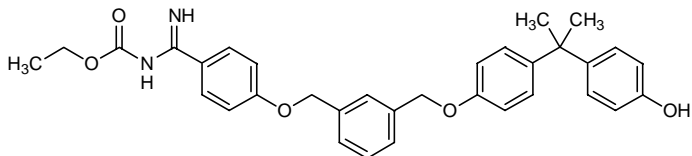
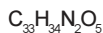
ambrisentan	(+)-(2 <i>S</i>)-2-[(4,6-diméthylpyrimidin-2-yl)oxy]-3-méthoxy-3,3-diphénylpropanoic acid
ambrisentan	(+)-acide (2 <i>S</i>)-2-[(4,6-diméthylpyrimidin-2-yl)oxy]-3-méthoxy-3,3-diphénylpropanoïque
ambrisentan	(+)-ácido (2 <i>S</i>)-2-[(4,6-dimetilpirimidin-2-il)oxi]-3-metoxi-3,3-difenilpropanoico

**amdoxovirum**

amdoxovir	[(2 <i>R</i> ,4 <i>R</i>)-4-(2,6-diamino-9 <i>H</i> -purin-9-yl)-1,3-dioxolan-2-yl]methanol
amdoxovir	[(2 <i>R</i> ,4 <i>R</i>)-4-(2,6-diamino-9 <i>H</i> -purin-9-yl)-1,3-dioxolan-2-yl]méthanol
amdoxovir	[(2 <i>R</i> ,4 <i>R</i>)-4-(2,6-diamino-9 <i>H</i> -purin-9-il)-1,3-dioxolan-2-il]metanol

**amelubantum**

amelubant	ethyl [[4-[[3-[[4-[1-(4-hydroxyphenyl)-1-méthylethyl]phénoxy]méthyl]benzyl]=oxy]phényl](imino)méthyl]carbamate
amélubant	[[4-[[3-[[4-[1-(4-hydroxyphényl)-1-méthyléthyl]phénoxy]méthyl]benzyl]oxy]=phényl](imino)méthyl]carbamate d'éthyle
amelubant	[[4-[[3-[[4-[1-(4-hidroxfenil)-1-metiletil]fenoxi]metil]bencil]oxi]fenil](imino)metil]=carbamato de etilo

**amotosalenum**

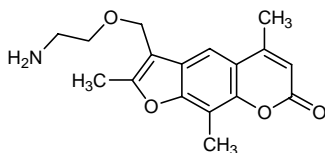
amotosalen

3-[(2-aminoethoxy)methyl]-2,5,9-trimethyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one

amotosalène

3-[(2-aminoéthoxy)méthyl]-2,5,9-triméthyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one

amotosaleno

3-[(2-aminoetoxi)metil]-2,5,9-trimetil-7*H*-furo[3,2-*g*][1]benzopiran-7-ona**bimatoprostum**

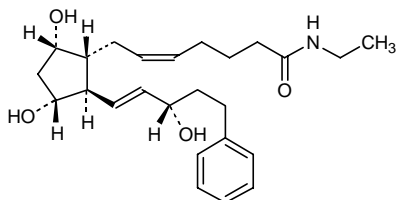
bimatoprost

(Z)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-*N*-ethyl-5-heptenamide

bimatoprost

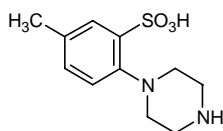
(Z)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-5-phénylpent-1-ényl]cyclopentyl]-*N*-éthylhept-5-énamide

bimatoprost

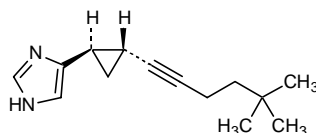
(Z)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihidroxi-2-[(1*E*,3*S*)-3-hidroxi-5-fenilpent-1-enil]ciclopentil]-*N*-etilhept-5-enamida

caldaretum

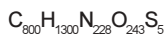
caldaret	5-methyl-2-(piperazin-1-yl)benzenesulfonic acid
caldaret	acide 5-méthyl-2-(pipérazin-1-yl)benzènesulfonique
caldaret	ácido 5-metil-2-(piperazin-1-il)benzenosulfónico

**cipralisantum**

cipralisant	4-[(1 <i>R</i> ,2 <i>R</i>)-2-(5,5-dimethylhex-1-ynyl)cyclopropyl]-1 <i>H</i> -imidazole
cipralisant	4-[(1 <i>R</i> ,2 <i>R</i>)-2-(5,5-diméthylhex-1-ynyl)cyclopropyl]-1 <i>H</i> -imidazole
cipralisant	4-[(1 <i>R</i> ,2 <i>R</i>)-2-(5,5-dimetilhex-1-inil)ciclopropil]-1 <i>H</i> -imidazol

**darbepoetinum alfa**

darbepoetin alfa	[30-L-asparagine,32-L-threonine,87-L-valine,88-L-asparagine,90-L-threonine]erythropoietin (human)
darbépoétine alfa	[30-L-asparagine,32-L-thréonine,87-L-valine,88-L-asparagine,90-L-thréonine]érythropoïétine humaine
darbepoetina alfa	[30-L-asparagina,32-L-treonina,87-L-valina,88-L-asparagina,90-L-treonina]eritropoietina humana



APPRLICDSR	VLERYLLEAK	EAENITTCGN	ETCSLNENIT
VPDTKVNIFYA	WKRMEVGQQA	VEVWQGLALL	SEAVLRGQAL
LVNSSQVNET	LQLHVDKAVS	GLRSLTTLR	ALGAQKEAIS
PPDAASAAPL	RTITADTFRK	LFRVYSNFLR	GKCLKLYTGEA
CRTGD			

drotrecoginum alfa (activatum)

drotrecogin alfa (activated)

blood coagulation factor XIV (human)

drotrecogine alfa (activé)

facteur XIV humain de coagulation sanguine

drotrecogina alfa (activada)

factor XIV de coagulación sanguínea (humano)

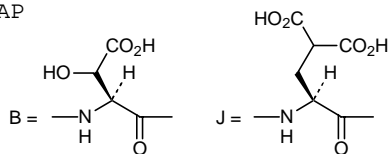


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ANSFLJLRLH  SSLJRJCIJJ  ICDFJYAKJI  FQNVDLTLAF
WSKHVDGDQC  LVLPLEHPCA  SLCCGHGTCT  BGIGSFSCDC
RSGWEGRFCQ  REVSFLNCSL  DNGGCTHYCL  EEVWRRCCSC
APGYKLGDDL  LQCHPAVKFP  CGRPWKRMEK  KRSHL
                                     DTE
DQEDQVDPRL  IDGKMTRRGD  SPWQVLLDS  KKKLACGAVL
IHPSWVLTAA  HCMDESKLL  VRLGEYDLRR  WEKWELDLDI
KEVFVHPNYS  KSTTDNDIAL  LHQAQATLS  QTIVPICLPD
SGLAERELNQ  AGQETLVTGW  GYHSSREKEA  KRNRTFVLNF
IKIPVVPHNE  CSEVMSNMVS  ENMLCAGILG  DRQDAÇEGDS
GGPMVASFHG  TWFLVGLVSW  GEGCGLLHNY  GVYTKVSRYL
DWIHGHIRDK  EAPQKSWAP

```

* glycosylation sites
 * sites de glycosylation
 * posiciones de glicosilación

**ecalcedinum**

ecalcedine

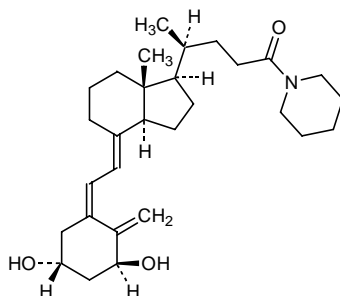
1-[(5Z,7E,20S)-1 α ,3 β -dihydroxy-9,10-secochola-5,7,10(19)-trien-24-oyl]piperidine

écalcidène

1-[(5Z,7E,20S)-1 α ,3 β -dihydroxy-9,10-sécochola-5,7,10(19)-trién-24-oyl]pipéridine

ecalcedino

1-[(5Z,7E,20S)-1 α ,3 β -dihidroxi-9,10-secocola-5,7,10(19)-trien-24-oil]piperidina



efalizumabum
efalizumab

immunoglobulin G1, anti-(human antigen CD11a) (human-mouse monoclonal hu1124 γ 1-chain), disulfide with human-mouse monoclonal hu1124 light chain, dimer

éfalizumab

immunoglobuline G1, anti-(antigène CD11a humain) (chaîne γ 1 de l'anticorps monoclonal de souris humanisé hu1124), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris humanisé hu1124

efalizumab

immunoglobulina G1, anti-(antígeno CD11a humano) (cadena γ 1 del anticuerpo monoclonal humanizado de ratón hu1124), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de ratón hu1124

enfuvirtidum
enfuvirtide

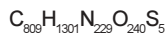
acetyl-L-tyrosyl-L-threonyl-L-seryl-L-leucyl-L-isoleucyl-L-histidyl-L-seryl-L-leucyl-L-isoleucyl-L- α -glutamyl-L- α -glutamyl-L-seryl-L-glutaminyll-asparaginyll-glutaminyll-glutaminyll- α -glutamyl-L-lysyl-L-asparaginyll- α -glutamyl-L-glutaminyll- α -glutamyl-L-leucyl-L-leucyl-L- α -glutamyl-L-leucyl-L- α -aspartyl-L-lysyl-L-tryptophyl-L-alanyl-L-seryl-L-leucyl-L-tryptophyl-L-asparaginyll-tryptophyl-L-phenylalaninamide

enfuvirtide

acétyl-L-tyrosyl-L-thréonyl-L-séryl-L-leucyl-L-isoleucyl-L-histidyl-L-séryl-L-leucyl-L-isoleucyl-L- α -glutamyl-L- α -glutamyl-L-séryl-L-glutaminyll-asparaginyll-glutaminyll-glutaminyll- α -glutamyl-L-lysyl-L-asparaginyll- α -glutamyl-L-glutaminyll- α -glutamyl-L-leucyl-L-leucyl-L- α -glutamyl-L-leucyl-L- α -aspartyl-L-lysyl-L-tryptophyl-L-alanyl-L-séryl-L-leucyl-L-tryptophyl-L-asparaginyll-tryptophyl-L-phénylalaninamide

enfuvirtida

acetil-L-tirosil-L-treonil-L-seril-L-leucil-L-isoleucil-L-histidil-L-seril-L-leucil-L-isoleucil-L- α -glutamyl-L- α -glutamyl-L-seril-L-glutaminyll-asparaginyll-glutaminyll-glutaminyll- α -glutamyl-L-lisil-L-asparaginyll- α -glutamyl-L-glutaminyll- α -glutamyl-L-leucil-L-leucil-L- α -glutamyl-L-leucil-L- α -aspartil-L-lisil-L-triptofil-L-alanyl-L-seril-L-leucil-L-triptofil-L-asparaginyll-triptofil-L-fenilalaninamida



APPRLICDSR	VLERYLLEAK	EAENITTGCA	EHCSLNENIT
VPDTKVNIFYA	WKRMEVGQQA	VEVWQGLALL	SEAVLRGQAL
LVN [*] SSQPWEP	LQLHVDKAVS	GLRSLTLLR	ALGAQKEAIS
PPDAASA [*] APL	RTITADTFRK	LFRVYSNFLR	GKCLKLYTGEA
CRTGD			

* : glycosylation sites / sites de glycosylation / posiciones de glicosilación

erlotinibum

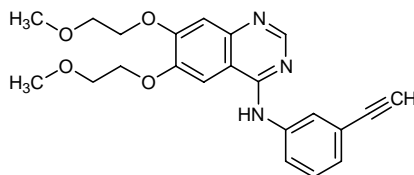
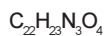
erlotinib

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine

erlotinib

N-(3-éthynylphényl)-6,7-bis(2-méthoxyéthoxy)quinazolin-4-amine

erlotinib

N-(3-etinilfenil)-6,7-bis(2-metoxietoxi)quinazolin-4-amina**febuxostatatum**

febuxostat

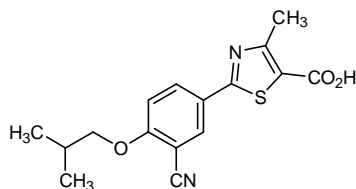
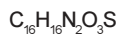
2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid

fébuxostat

acide 2-[3-cyano-4-(2-méthylpropoxy)phényl]-4-méthylthiazole-5-carboxylique

febuxostat

ácido 2-[3-ciano-4-(2-metilpropoxi)fenil]-4-metiliazol-5-carboxílico

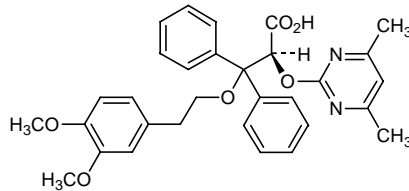
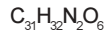


felopreptanum

felopreptan (2*S*)-3-[2-(3,4-dimethoxyphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropanoic acid

félopreptan acide (2*S*)-3-[2-(3,4-diméthoxyphényl)éthoxy]-2-[(4,6-diméthylpyrimidin-2-yl)oxy]-3,3-diphénylpropanoïque

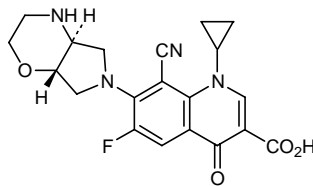
felopreptán ácido (2*S*)-3-[2-(3,4-dimetoxifenil)etoxi]-2-[(4,6-dimetilpirimidin-2-il)oxi]-3,3-difenilpropanoico

**finafloxacinum**

finafloxacin (-)-8-cyano-1-cyclopropyl-6-fluoro-7-[(4*aS*,7*aS*)-hexahydropyrrolo[3,4-*b*]-1,4-oxazin-6(2*H*)-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

finafloxacine (-)-acide 8-cyano-1-cyclopropyl-6-fluoro-7-[(4*aS*,7*aS*)-hexahydropyrrolo[3,4-*b*]-1,4-oxazin-6(2*H*)-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique

finafloxacino (-)-ácido 8-ciano-1-ciclopropil-6-fluoro-7-[(4*aS*,7*aS*)-hexahidropirrolo[3,4-*b*]-1,4-oxazin-6(2*H*)-il]-4-oxo-1,4-dihidroquinolina-3-carboxílico

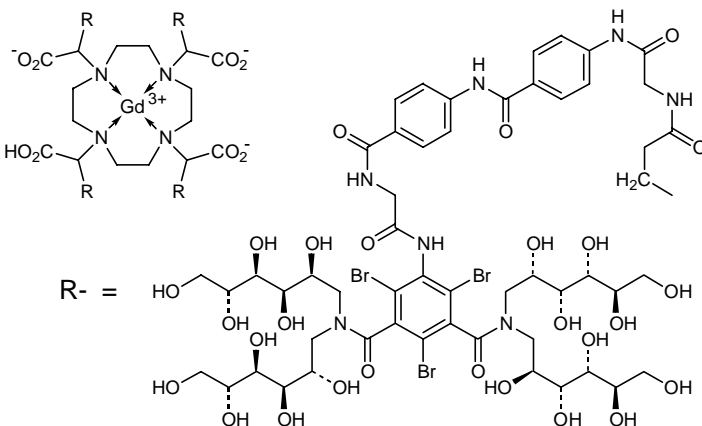
**gadolmelitolum**

gadolmelitol hydrogen [2,2',2'',2'''-[1,4,7,10-tetraazacyclododecane-1,4,7,10-triyl]tetrakis-[5-[[2-[[4-[[4-[[2-[[3,5-bis[bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl-2,4,6-tribromo]carbamoil]phényl]amino]-2-oxoethyl]carbamoil]phényl]=carbamoil]phényl]amino]-2-oxoethyl]amino]-5-oxopentanoato](4-)]]=gadolate(1-)

gadolmétilo hidrogéno-[2,2',2'',2'''-[1,4,7,10-tétrazacyclododécane-1,4,7,10-triyl]tétrakis [5-[[2-[[4-[[4-[[2-[[3,5-bis[bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl-2,4,6-tribromo]carbamoil]phényl]amino]-2-oxoéthyl]carbamoil]phényl]=carbamoil]phényl]amino]-2-oxoéthyl]amino]-5-oxopentanoato](4-)]]=gadolate(1-)

gadomelitol

hidrógeno-[2,2',2'',2''']-[1,4,7,10-tetraazaciclododecano-1,4,7,10-triil]tetrakis=[5-[[2-[[4-[[4-[[2-[[3,5-bis[bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahidroxihexil-2,4,6-tribromo]carbamoil]fenil]amino]-2-oxoetil]carbamoil]fenil]carbamoil]fenil]=amino]-2-oxoetil]amino]-5-oxopentanoato](4-)]gadolinato(1-)

**garnocestimum**

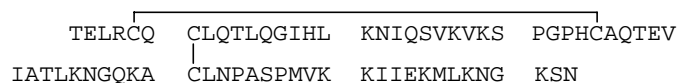
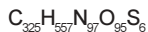
garnocestim

5-73-macrophage inflammatory protein 2 α (human gene gro2)

garnocestim

CXC chimiokine GRO β -(5-73)-peptide (GRO β : protéine inflammatoire humaine sécrétée par les macrophages)

garnocestim

CXC quimiokina GRO β -(5-73)-péptido (GRO β : proteína inflamatoria humana secretada por los macrófagos)**gefitinibum**

gefitinib

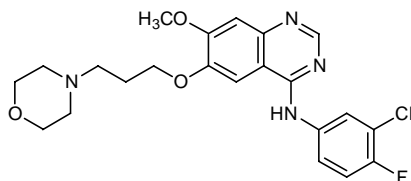
N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine

géfitinib

N-(3-chloro-4-fluorophényl)-7-méthoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine

gefitinib

N-(3-cloro-4-fluorofenil)-7-metoxi-6-[3-(morfolin-4-il)propoxi]quinazolin-4-amina

**ingliforibum**

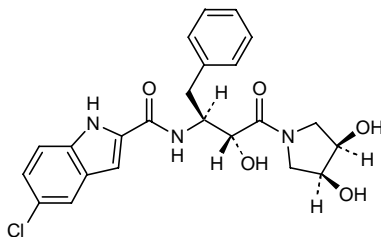
ingliforib

5-chloro-*N*-[(1*S*,2*R*)-1-benzyl-3-(*cis*-3,4-dihydroxypyrrolidin-1-yl)-2-hydroxy-3-oxopropyl]-1*H*-indole-2-carboxamide

ingliforib

5-chloro-*N*-[(1*S*,2*R*)-1-benzyl-3-(*cis*-3,4-dihydroxypyrrolidin-1-yl)-2-hydroxy-3-oxopropyl]-1*H*-indole-2-carboxamide

ingliforib

5-cloro-*N*-[(1*S*,2*R*)-1-bencil-3-(*cis*-3,4-dihidroxipirrolidin-1-il)-2-hidroxi-3-oxopropil]-1*H*-indol-2-carboxamida**ipravacainum**

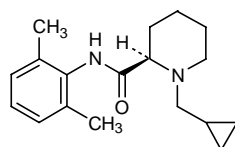
ipravacaine

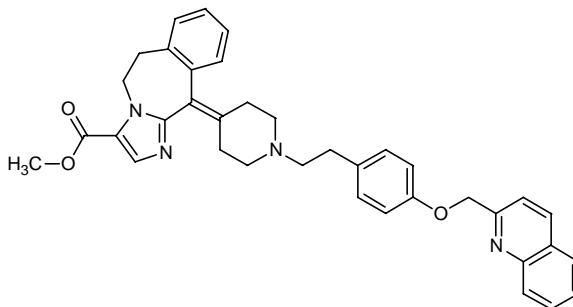
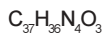
(2*RS*)-1-(cyclopropylmethyl)-2',6'-diméthyl-2-piperidinecarboxanilide

ipravacaïne

(2*RS*)-1-(cyclopropylméthyl)-*N*-(2,6-diméthylphényl)pipéridine-2-carboxamide

ipravacaína

(2*RS*)-1-(ciclopropilmetil)-*N*-(2,6-dimetilfenil)piperidina-2-carboxamidaand enantiomer
et énantiomère
y enantiómero

**lapisteridum**

lapisteride

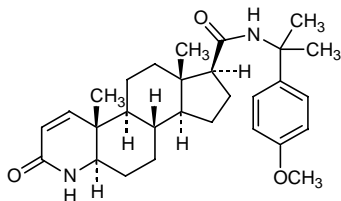
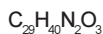
N-[1-(4-methoxyphenyl)-1-methylethyl]-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

lapistéride

N-[1-(4-méthoxyphényl)-1-méthyléthyl]-3-oxo-4-aza-5 α -androst-1-ène-17 β -carboxamide

lapisterida

N-[1-(4-metoxifenil)-1-metiletil]-3-oxo-4-aza-5 α -androst-1-eno-17 β -carboxamida

**laquinimodum**

laquinimod

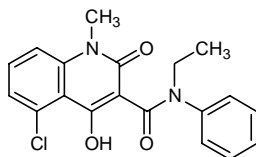
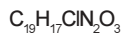
5-chloro-*N*-ethyl-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-1,2-dihydroquinoline-3-carboxamide

laquinimod

5-chloro-*N*-éthyl-4-hydroxy-1-méthyl-2-oxo-*N*-phényl-1,2-dihydroquinoléine-3-carboxamide

laquinimod

5-cloro-*N*-etil-4-hidroxi-1-metil-2-oxo-*N*-fenil-1,2-dihidroquinolina-3-carboxamida

**laronidasum**

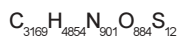
laronidase

8-L-histidine- α -L-iduronidase (human)

laronidase

[8-L-histidine]- α -L-iduronidase humaine

laronidasa

8-L-histidina- α -L-iduronidasa (humana)

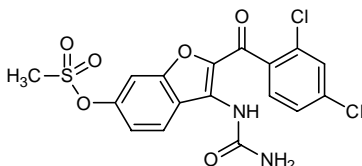
AEAPHLVHVD	AARALWPLRR	FWRSTGFCPP	LPHSQADQYV
LSWDQQLNLA	YVGAVPHRGI	KQVRTHWLE	LVTTRGSTGR
GLSYNFTHLD	GYLDLLRENQ	LLPGFELMGS	ASGHFTDFED
KQQVFEWKDL	VSSLARRYIG	RYGLAHVSKW	NFETWNEPDH
HDFDNVSMTM	QGFLNYYDAC	SEGLRAASPA	LRLGGPGDSF
HTPPRSPLSW	GLLRHCHDGT	NFFTGEAGVR	LDYISLHRKG
ARSSISILEQ	EKVVAQQIRQ	LFPKFADTPI	YNDEADPLVG
WSLPQPWRAD	VTYAAMVVKV	IAQHQNLLLA	NTTSAFPYAL
LSNDNAFLSY	HPHPFAQRTL	TARFQVNNTR	PPHVQLLRKP
VLTAMGLLAL	LDEEQLWAEV	SQAGTVLDSN	HTVGVLASAH
RPQGPADAWR	AAVLIYASDD	TRAHPNRSVA	VTLRLRGVPP
GPGLVYVTRY	LDNGLCSPDG	EWRLGRPVF	PTAEQFRRMR
AAEDPVAAAP	RPLPAGGRLT	LRPALRLPSL	LLVHVCARPE
KPPGQVTRLR	ALPLTQGQLV	LVWSDEHVGS	KCLWTYEQF
SQDGKAYTPV	SRKPSTFNLF	VFSPDTGAVS	GSYRVRALDY
WARPGPFSDP	VPLYEVPVPR	GPPSPGNP	

* : glycosylation sites / sites de glycosylation / posiciones de glicosilación

↳ : disulfide / disulfure / disulfuro

lirimilastum

lirimilast	2-(2,4-dichlorobenzoyl)-3-ureidobenzofuran-6-yl methanesulfonate
lirimilast	méthanesulfonate de 2-(2,4-dichlorobenzoyl)-3-uréidobenzofuran-6-yle
lirimilast	metanosulfonato de 2-(2,4-diclorobenzoil)-3-ureidobenzofuran-6-ilo

**livaraparinum calcium**

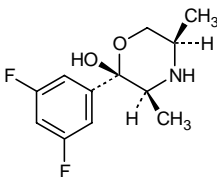
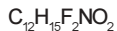
livaraparin calcium	calcium salt of a low molecular mass heparin that is obtained by nitrous acid depolymerization of heparin from porcine intestinal mucosa; the majority of the components have a 2-O-sulfo- α -L-idopyranosuronic acid structure at the non-reducing end and a 6-O-sulfo-structure at the reducing end of their chain; the mass-average molecular mass ranges between 3000 and 5000 with 75% is less than 8000; the degree of sulfatation is approximately 2 per disaccharidic unit
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livaraparine calcique	sel calcique d'une héparine de basse masse moléculaire obtenue par dépolymérisation, au moyen d'acide nitreux, d'héparine de muqueuse intestinale de porc ; la majorité des composants de la livaraparine calcique possèdent une structure acide 2-O-sulfo- α -L-idopyranosuronique à l'extrémité non réductrice de leur chaîne et une structure 6-O-sulfatée à l'extrémité réductrice de leur chaîne ; la masse moléculaire relative moyenne est de 3000 à 5000, 75% étant inférieur à 8000 ; le degré de sulfatation par unité disaccharide est voisin de 2
-----------------------	--

livaraparina cálcica	sal cálcica de una heparina de baja masa molecular obtenida de heparina de mucosa intestinal de cerdo por despolimerización con ácido nitroso; la mayoría de los componentes de la livaraparina cálcica tienen ácido 2-O-sulfo- α -L-idopiranosurónico en el extremo no reductor de la cadena y una estructura 6-O-sulfatada en el extremo reductor de la cadena; la masa molecular relativa media es de 3000 a 5000, siendo el 75% inferior a 8000; el grado de sulfatación por unidad de disacárido es aproximadamente 2
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manifaxinum

manifaxine	(2S,3S,5R)-2-(3,5-difluorophenyl)-3,5-dimethylmorpholin-2-ol
manifaxine	(2S,3S,5R)-2-(3,5-difluorophényl)-3,5-diméthylmorpholin-2-ol
manifaxina	(2S,3S,5R)-2-(3,5-difluorofenil)-3,5-dimetilmorfolin-2-ol

**miglustatum**

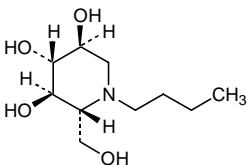
miglustat

(2*R*,3*R*,4*R*,5*S*)-1-butyl-2-(hydroxymethyl)piperidine-3,4,5-triol

miglustat

(2*R*,3*R*,4*R*,5*S*)-1-butyl-2-(hydroxyméthyl)pipéridine-3,4,5-triol

miglustat

(2*R*,3*R*,4*R*,5*S*)-1-butil-2-(hidroximetil)piperidina-3,4,5-triol**miriplatinum**

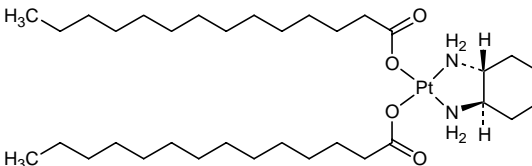
miriplatin

(SP-4-2)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]=bis(tetradecanoato-*O*)platinum

miriplatine

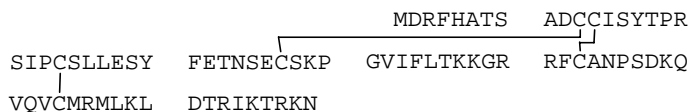
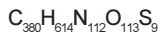
(SP-4-2)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]=bis(tétradécanoato-*O*)platine

miriplatino

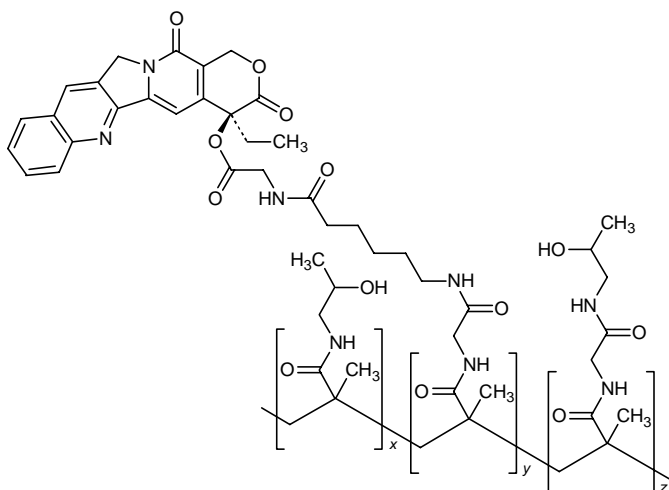
(SP-4-2)-[(1*R*,2*R*)-ciclohexano-1,2-diamina-*N,N'*]=bis(tetradecanoato-*O*)platino

mirostopenium

mirostopen	[23-methionine]human myeloid progenitor inhibitory factor 1-(23-99)-peptide
mirostopen	[23-méthionine]facteur 1 d'inhibition du précurseur myéloïde humain-(23-99)-peptide
mirostopeno	[23-metionina]-(23-99)-péptido del factor 1 de inhibición del progenitor mieloido humano

**mureletecanum**

mureletecan	poly[[<i>N</i> -(2-hydroxypropyl)methacrylamide]-co-[camptothecin ester with <i>N</i> -[6-(2-methacrylamidoacetamido)hexanoyl]glycine]-co-[<i>N</i> -[(2-hydroxypropyl)carbamoyl]methyl]methacrylamide]]
murélétécán	copolymère de <i>N</i> -[(2 <i>RS</i>)-2-hydroxypropyl]-2-méthylpropénamide, de <i>N</i> -[2-[[6-[[[2-[[[(4 <i>S</i>)-4-éthyl-3,14-dioxo-3,4,12,14-tétrahydro-1 <i>H</i> -pyrano[3',4':6,7]indolizino[1,2- <i>b</i>]quinoléin-4-yl]oxy]-2-oxoéthyl]amino]-6-oxohexyl]amino]-2-oxoéthyl]-2-méthylpropénamide et de <i>N</i> -[2-[[[(2 <i>RS</i>)-2-hydroxypropyl]amino]-2-oxoéthyl]-2-méthylpropénamide
mureletecán	poli[[<i>N</i> -(2-hidroxiopropil)metacrilamida]-co-[éster de camptotecina con <i>N</i> -[6-(2-metacrilamidoacetamido)hexanoil]glicina]-co-[<i>N</i> -[(2-hidroxiopropil)carbamoil]metil]metacrilamida]]



nasaruplasum beta

nasaruplase beta

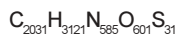
prourokinase (enzyme-activating) human (clone pUK4/pUK18 protein moiety), glycosylated (murine cell line SP2/0)

nasaruplase bêta

prourokinase (activateur d'enzyme) humaine glycosylée dont le gène est cloné dans le vecteur pUK4/pUK18 et exprimée dans la lignée cellulaire murine SP2/0

nasaruplase beta

prourokinasa (activador de enzima) humana glicosilada cuyo gen se clona en el vector pUK4/pUK18 y se expresa en la línea celular murina SP2/0



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      *
      |
SNELHQVPSN  CDCLNGGTCV  SNKYFSNIHW  CNCPKKFGGQ
      |-----|
HCEIDKSKTC  YEGNGHFYRG  KASTDTMGRP  CLPWNSATVL
      |-----|
QQTYHAHRSD  ALQLGLGKHN  YCRNPDNRRR  PWCYVQVGLK
      |-----|
PLVQECMVHD  CADGKKPSSP  PEELKFQCGQ  KTLRPRFKII
      |-----|
GGEFTTIENQ  PWFAAIYRRH  RGGSVTYVCG  GSLISPCWVI
      |-----|
SATHCFIDYP  KKEDYIVYLG  RSRLNSNTQG  EMKFEVENLI
      |-----|
LHKDYSADTL  AHHNDIALLK  IRSKEGRCAQ  PSRTIQTICL
      |-----|
PSMYNDPQFG  TSCEITGFGK  ENSTDYLYPE  QLKMTVVKLI
      |-----|
SHRECQQPHY  YGSEVTTKML  CAADPQWKTD  SCQGDSSGPL
      |-----|
VCSLQGRMTL  TGIVSWGRGC  ALKDKPGVYT  RVSHFLPWIR
SHTKEENGLA  L
  
```

* : glycosylation sites / sites de glycosylation / posiciones de glicosilación

netoglitazonum

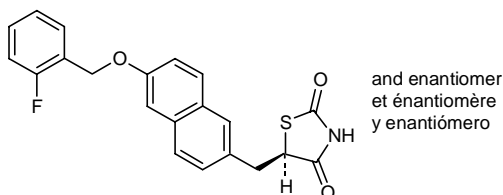
netoglitazone

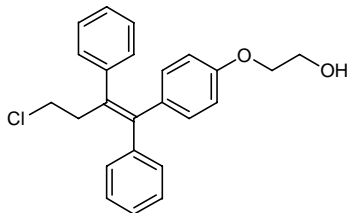
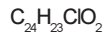
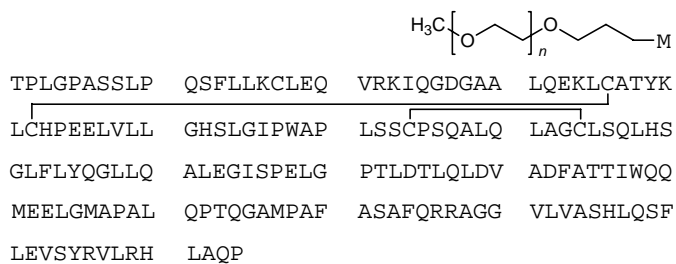
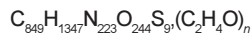
(5*RS*)-5-[[6-[(2-fluorophenyl)methoxy]naphthalen-2-yl]methyl]thiazolidine-2,4-dione

nétoɡlitazone

(5*RS*)-5-[[6-[(2-fluorophényl)méthoxy]naphtalén-2-yl]méthyl]thiazolidine-2,4-dione

netoglitazona

(5*RS*)-5-[[6-[(2-fluorofenil)metoxi]naftalen-2-il]metil]tiiazolidina-2,4-diona

ospemifenumospemifene 2-[*p*-[(*Z*)-4-chloro-1,2-diphenyl-1-butenyl]phenoxy]ethanolospémifène (*Z*)-2-[4-(4-chloro-1,2-diphénylbut-1-ényl)phénoxy]éthanolospemifeno 2-[*p*-[(*Z*)-4-cloro-1,2-difenil-1-butenil]fenoxi]etanol**pegfilgrastimum**pegfilgrastim *N*-(3-hydroxypropyl)methionylcolony-stimulating factor (human), 1-ether with α -methyl- ω -hydroxypoly(oxyethylene)pegfilgrastim *N*-(3-hydroxypropyl)méthionylfacteur de stimulation de colonie humain, 1-éther avec le α -méthyl- ω -hydroxypoly(oxyéthylène)pegfilgrastim *N*-(3-hidroxiopropil)metionilfactor de estimulación de colonias humano, 1-éter con el α -metil- ω -hidroxipoli(oxietileno)**pexelizumabum**pexelizumab immunoglobulin, anti-(human complement C5 α -chain) (human-mouse monoclonal 5G1.1-SC single chain)pexélizumab immunoglobuline, anti-(chaîne- α du complément C5 humain) (mono chaîne de l'anticorps monoclonal de souris humanisé 5G1.1-SC)pexelizumab inmunoglobulina, anti-(cadena- α del complemento C5 humano) (mono cadena del anticuerpo monoclonal humanizado de ratón 5G1.1-SC)

pralnacasanum

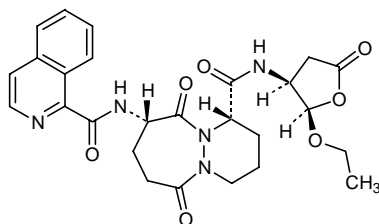
pralnacasan

(1*S*,9*S*)-*N*-[(2*R*,3*S*)-2-ethoxy-5-oxotetrahydrofuran-3-yl]-9-[(isoquinolin-1-ylcarbonyl)amino]-6,10-dioxooctahydro-6-*H*-pyridazino[1,2-*a*][1,2]=diazepine-1-carboxamide

pralnacasan

(1*S*,9*S*)-*N*-[(2*R*,3*S*)-2-éthoxy-5-oxotétrahydrofuran-3-yl]-9-[(isoquinoléin-1-ylcarbonyl)amino]-6,10-dioxooctahydro-6-*H*-pyridazino[1,2-*a*][1,2]diazépine-1-carboxamide

pralnacasán

(1*S*,9*S*)-*N*-[(2*R*,3*S*)-2-etoxi-5-oxotetrahidrofuran-3-il]-9-[(isoquinolin-1-ilcarbonyl)amino]-6,10-dioxooctahidro-6-*H*-piridazino[1,2-*a*][1,2]diazepina-1-carboxamida $C_{25}H_{29}N_5O_7$ **pratsartanum**

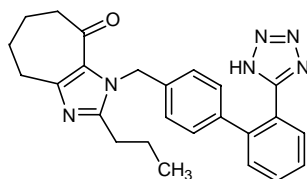
pratsartan

2-propyl-3-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-5,6,7,8-tetrahydrocycloheptimidazol-4(3*H*)-one

pratsartan

2-propyl-3-[[2'-(1*H*-tétrazol-5-yl)biphényl-4-yl]méthyl]-5,6,7,8-tétrahydrocycloheptimidazol-4(3*H*)-one

pratsartán

2-propil-3-[[2'-(1*H*-tetrazol-5-il)bifenil-4-il]metil]-5,6,7,8-tetrahidrocicloheptaimidazol-4(3*H*)-ona $C_{25}H_{28}N_6O$ **ragaglitazarum**

ragaglitazar

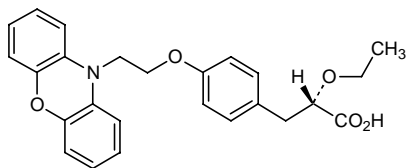
(-)-(2*S*)-2-ethoxy-3-[4-[2-(10*H*-phenoxazin-10-yl)ethoxy]phenyl]propanoic acid

ragaglitazar

(-)-acide (2*S*)-2-éthoxy-3-[4-[2-(10*H*-phénoxazin-10-yl)éthoxy]phényl]=propanoïque

ragaglitazar

(-)-ácido (2*S*)-2-etoxi-3-[4-[2-(10*H*-fenoxazin-10-il)etoxi]fenil]propanoico

**reslizumabum**

reslizumab

immunoglobulin G4, anti-(human interleukin 5) (human-rat monoclonal SCH 55700 γ 4-chain), disulfide with human-rat monoclonal SCH 55700 light chain, dimer

reslizumab

immunoglobuline G4, anti-(interleukine 5 humaine), (chaîne γ 4 de l'anticorps monoclonal de rat humanisé SCH 55700), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de rat humanisé SCH 55700

reslizumab

immunoglobulina G4, anti-(interleukina 5 humana), (cadena γ 4 del anticuerpo monoclonal humanizado de rata SCH 55700), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de rata SCH 55700

ruboxistaurinum

ruboxistaurin

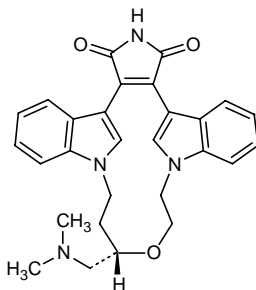
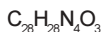
(9S)-9-[(dimethylamino)methyl]-6,7,10,11-tetrahydro-9H,19H-5,21:12,17-dimethenodibenzo[e,k]pyrrolo[3,4-h][1,4,13]oxadiazacyclohexadecene-18,20-dione

ruboxistaurine

(9S)-9-[(diméthylamino)méthyl]-6,7,10,11-tétrahydro-9H,19H-5,21:12,17-diméthénodibenzo[e,k]pyrrolo[3,4-h][1,4,13]oxadiazacyclohexadécène-18,20-dione

ruboxistaurina

(9S)-9-[(dimetilamino)metil]-6,7,10,11-tetrahidro-9H,19H-5,21:12,17-dimetenodibenzo[e,k]pirrolo[3,4-h][1,4,13]oxadiazaciclohexadeceno-18,20-diona



semaxanibum

semaxanib

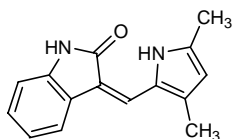
3-[(Z)-(3,5-dimethylpyrrol-2-yl)methylene]-2-indolinone

sémaxanib

(Z)-3-[(3,5-diméthyl-1*H*-pyrrol-2-yl)méthylène]-1,3-dihydro-2*H*-indol-2-one

semaxanib

3-[(Z)-(3,5-dimetilpirrol-2-il)metileno]-2-indolinona

 $C_{15}H_{14}N_2O$ **senazodanum**

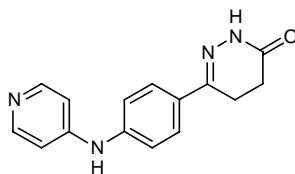
senazodan

6-[4-(pyridin-4-ylamino)phenyl]-4,5-dihydropyridazin-3(2*H*)-one

sénazodan

6-[4-(pyridin-4-ylamino)phényl]-4,5-dihydropyridazin-3(2*H*)-one

senazodán

6-[4-(piridin-4-ilamino)fenil]-4,5-dihidropiridazin-3(2*H*)-ona $C_{15}H_{14}N_4O$ **silodosinum**

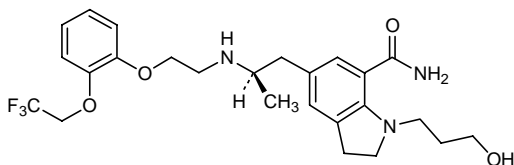
silodosin

(-)-1-(3-hydroxypropyl)-5-[(2*R*)-2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-2,3-dihydro-1*H*-indole-7-carboxamide

silodosine

(-)-1-(3-hydroxypropyl)-5-[(2*R*)-2-[[2-[2-(2,2,2-trifluoroéthoxy)phénoxy]éthyl]amino]propyl]-2,3-dihydro-1*H*-indole-7-carboxamide

silodosina

(-)-1-(3-hidroxiopropil)-5-[(2*R*)-2-[[2-[2-(2,2,2-trifluoroetoxi)fenoxi]etil]amino]propil]-2,3-dihidro-1*H*-indol-7-carboxamida $C_{25}H_{32}F_3N_3O_4$ 

solifenacinum

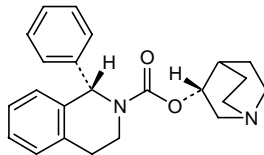
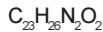
solifenacin (3*R*)-1-azabicyclo[2.2.2]oct-3-yl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate

solifénacine

(1*S*)-1-phényl-3,4-dihydroisoquinoléine-2(1*H*)-carboxylate de (3*R*)-1-azabicyclo[2.2.2]oct-3-yle

solifenacina

(1*S*)-1-fenil-3,4-dihidroisoquinolina-2(1*H*)-carboxilato de (3*R*)-1-azabicyclo[2.2.2]oct-3-ilo

**tadalafilum**

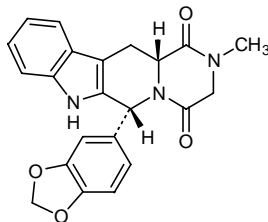
tadalafil (6*R*,12*aR*)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12*a*-hexahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione

tadalafil

(6*R*,12*aR*)-6-(1,3-benzodioxol-5-yl)-2-méthyl-2,3,6,7,12,12*a*-hexahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione

tadalafilo

(6*R*,12*aR*)-6-(1,3-benzodioxol-5-il)-2-metil-2,3,6,7,12,12*a*-hexahidropirazino[1',2':1,6]pirido[3,4-*b*]indol-1,4-diona

**tafluposidum**

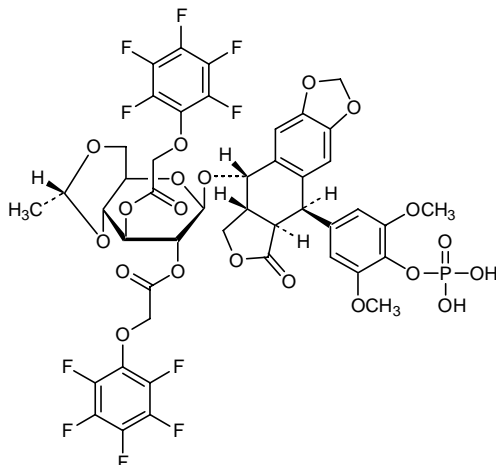
tafluposide 4-[(5*R*,5*aR*,8*aR*,9*S*)-9-[[4,6-*O*-[(1*R*)-ethylidene]-2,3-bis-*O*-[(pentafluorophenoxy)acetyl]-β-*D*-glucopyranosyl]oxy]-6-oxo-5,5*a*,6,8,8*a*,9-hexahydrofuro[3',4':6,7]naphtho[2,3-*d*]-1,3-dioxol-5-yl]-2,6-dimethoxyphenyle dihydrogen phosphate

tafluposide

dihidrogénophosphate de 4-[(5*R*,5*aR*,8*aR*,9*S*)-9-[[4,6-*O*-[(1*R*)-éthylidène]-2,3-bis-*O*-[(pentafluorophénoxy)acétyle]-β-*D*-glucopyranosyl]oxy]-6-oxo-5,5*a*,6,8,8*a*,9-hexahydrofuro[3',4':6,7]naphtho[2,3-*d*]-1,3-dioxol-5-yl]-2,6-diméthoxyphényle

taflupósido

dihidrógenofosfato de 4-[(5*R*,5*aR*,8*aR*,9*S*)-9-[[4,6-*O*-[(1*R*)-etilideno]-2,3-bis-*O*-[(pentafluorofenoxi)acetil]-β-*D*-glucopiranosil]oxi]-6-oxo-5,5*a*,6,8,8*a*,9-hexahidrofuro[3',4':6,7]nafto[2,3-*d*]-1,3-dioxol-5-il]-2,6-dimetoxifenilo

**telberminum**

telbermin

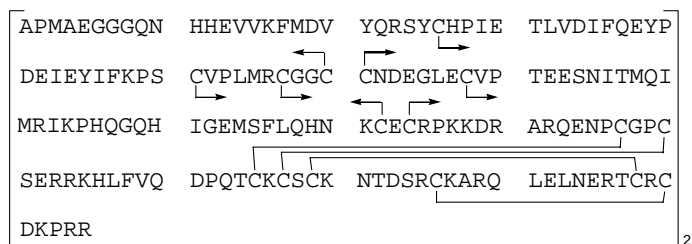
vascular endothelial growth factor (human), dimer

telbermine

facteur de croissance de l'endothélium vasculaire humain (dimère)

telbermina

factor de crecimiento del endotelio vascular (humano), dímero



↪ : disulfide / disulfure / disulfuro

tenivastatinum

tenivastatin

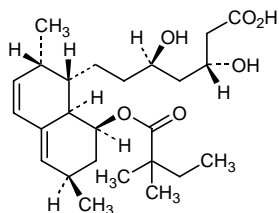
(3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8*aR*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphtalen-1-yl]-3,5-dihydroxyheptanoic acid

ténivastatine

acide (3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8*aR*)-8-[(2,2-diméthylbutanoyl)oxy]-2,6-diméthyl-1,2,6,7,8,8a-hexahydronaphtalén-1-yl]-3,5-dihydroxyheptanoïque

tenivastatina

ácido (3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8*aR*)-8-[(2,2-dimetilbutanoil)oxi]-2,6-dimetil-1,2,6,7,8,8a-hexahidronaftalen-1-il]-3,5-dihidroxiheptanoico

**tesaglitazarum**

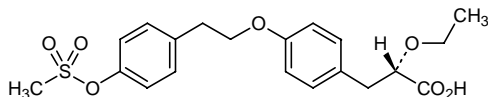
tesaglitazar

(2*S*)-2-ethoxy-3-[4-[2-[4-[(methylsulfonyl)oxy]phenyl]ethoxy]phenyl]=propanoic acid

tésaglitazar

acide (2*S*)-2-éthoxy-3-[4-[2-[4-[(méthylsulfonyl)oxy]phényl]éthoxy]phényl]=propanoïque

tesaglitazar

ácido (2*S*)-2-etoxi-3-[4-[2-[4-[(metilsulfonil)oxi]fenil]etoxi]fenil]propanoico**tofimilastum**

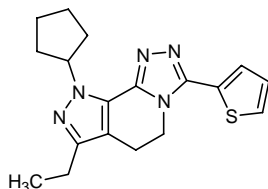
tofimilast

9-cyclopentyl-7-ethyl-3-(thiophen-2-yl)-6,9-dihydro-5*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridine

tofimilast

9-cyclopentyl-7-éthyl-3-(thiophén-2-yl)-6,9-dihydro-5*H*-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridine

tofimilast

9-ciclopentil-7-etil-3-(tiofen-2-il)-6,9-dihidro-5*H*-pirazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]piridina

xidecaflurum

xidecaflur

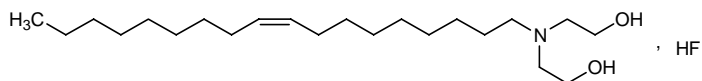
2,2-[(9Z)-9-octadecenylimino]diethanol hydrofluoride

xidécaflur

fluorhydrate de 2,2'-[(9Z)-octadec-9-énylimino]diéthanol

xidecaflur

hidrofluoruro de 2,2 -[(9Z)-9-octadecenilimino]diethanol

 $C_{22}H_{46}FNO_2$ **zanapezilum**

zanapezil

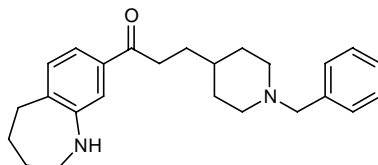
3-(1-benzylpiperidin-4-yl)-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)propan-1-one

zanapézil

3-(1-benzylpipéridin-4-yl)-1-(2,3,4,5-tétrahydro-1H-1-benzazépin-8-yl)propan-1-one

zanapezilo

3-(1-bencilpiperidin-4-il)-1-(2,3,4,5-tetrahidro-1H-1-benzazepin-8-il)propan-1-ona

 $C_{25}H_{32}N_2O$ **zonampanelum**

zonampanel

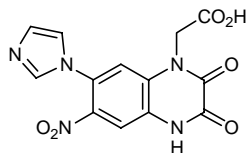
[7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxalin-1(2H)-yl]acetic acid

zonampanel

acide [7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxalin-1(2H)-yl]acétique

zonampanel

ácido [7-(1H-imidazol-1-il)-6-nitro-2,3-dioxo-3,4-dihidroquinoxalin-1(2H)-il]acético

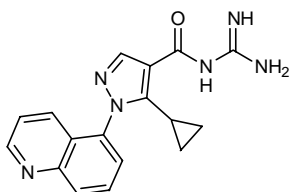
 $C_{13}H_9N_5O_6$ 

zoniporidum

zoniporide *N*-carbamimidoyl-5-cyclopropyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide

zoniporide *N*-carbamimidoyl-5-cyclopropyl-1-(quinoléin-5-yl)-1*H*-pyrazole-4-carboxamide

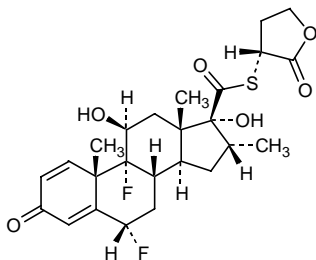
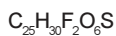
zoniporida *N*-carbamimidoiil-5-ciclopropil-1-(quinolin-5-il)-1*H*-pyrazol-4-carboxamida

**zoticasonum**

zoticasone *S*-[(3*R*)-2-oxotetrahydrofuran-3-yl] 6 α ,9-difluoro-12 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate

zoticasone 6 α ,9-difluoro-12 β ,17-dihydroxy-16 α -méthyl-3-oxoandrosta-1,4-diène-17 β -carbothioate de *S*-[(3*R*)-2-oxotétrahydrofuran-3-yle]

zoticasona 6 α ,9-difluoro-12 β ,17-dihidroxi-16 α -metil-3-oxoandrosta-1,4-dieno-17 β -carbotoiato de *S*-[(3*R*)-2-oxotetrahidrofuran-3-ilo]



Recommended International Nonproprietary Names (Rec. INN): List 45**Dénominations communes internationales recommandées (DCI Rec.): Liste 45****Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 45***(WHO Drug Information, Vol. 15, No. 1, 2001)*p. 55 **evernimicinum**

evernimicina

sustitúyase la descripción por la siguiente:

O-3-C-metil-4-O-metil-3-nitro-2,3,6-tridesoxi- α -L-arabino-hexopiranosil-(1 \rightarrow 3)-O-4-O-(3,5-dicloro-4-hidroxi-2-metoxi-6-metilbenzoil)-2,6-didesoxi- β -D-arabino-hexopiranosil-(1 \rightarrow 4)-O-(1R)-2,6-didesoxi-D-arabino-hexopiranosilideno-(1 \rightarrow 3-4)-O-3-C-metil-6-desoxi- β -D-manopiranosil-(1 \rightarrow 3)-O-4-O-metil-6-desoxi- β -D-galactopiranosil-(1 \rightarrow 4)-2,6-di-O-metil- β -D-manopiranosido de O-(1R)-4-O-(2,4-dihidroxi-6-metilbenzoil)-2,3-O-metileno-D-xilopiranosilideno-(1 \rightarrow 3-4)- α -L-lixopiranosilo

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

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

Les textes de la *Procédure à suivre en vue du choix de dénominations communes internationales recommandées pour les substances pharmaceutiques* et des *Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques* seront publiés seulement dans les numéros impaires des listes des DCI proposées.

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