WHO DRUG INFORMATION

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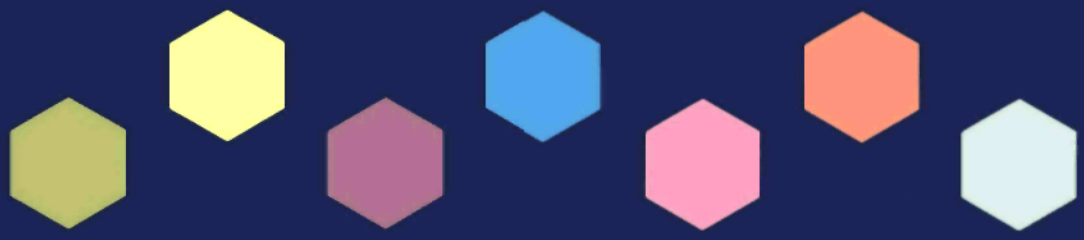
RECOMMENDED INN LIST 57

INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES



WORLD HEALTH ORGANIZATION · GENEVA

WHO Drug Information

Contents

Announcement

The 13th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the Swiss Medicines Agency SWISSMEDIC in collaboration with the World Health Organization.

The ICDRA will take place in Berne, Switzerland from 16 to 19 September 2008.

Updated information will be provided regularly at:
http://www.icdra.ch

or

http://www.who.int/medicines/icdra/en/index/html

Quality Assurance

International Conference on Harmonization (ICH)

The harmonization of regulatory requirements between Europe, Japan and the USA began to materialize as a result of discussions held in conjunction with the International Conference of Drug Regulatory Authorities (ICDRA) of the World Health Organization (WHO) in Paris, in 1989 (1). The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was soon born at a meeting in Brussels in April 1990. Representatives of the regulatory authorities and industry associations of Europe, Japan and the USA met to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH. The ICH Steering Committee — which was established at that meeting — has since met at least twice a year, with the location rotating between the three regions (1).

New developments in quality

The ICH Steering Committee (SC) and its Expert Working Groups (EWGs) met in Chicago, Illinois from 21 to 26 October 2006. WHO has observer status in ICH and participated in the discussions of the SC and various EWGs with the objective of providing input and disseminating information beyond the ICH regions.

ICH quality strategy discussion
The objective of the quality strategy meeting in Chicago was to identify those areas in pharmaceutical quality which need to be addressed at ICH level. General issues, which can have implications on the non-ICH Member States of WHO, are listed below:

- Agreement by regulators and industry on future quality vision as regards evolution of dossier assessment, (GMP) inspection and laboratory controls.
- ICH guidelines are globalizing regulatory expectations.
- Further discussion is needed in order to reach common understanding of concepts behind the definitions:

  Design space
  Quality by design (QbD)
  Regulatory flexibility

- Small and medium-size companies will not necessarily follow the QbD approach.
- Common training of assessors, inspectors and industry is needed to facilitate the implementation of the Q8, Q9 and Q10 guidelines.
- No new regulatory requirements beyond the current ones are intended by the tripartite adoption of Q8, Q9 and Q10 guidelines but their impact on dossier assessment, post-approval changes and inspections should be assessed.
- Further discussion will take place at the next EWG meeting in Brussels in May 2007 where the following issues will

have to be clarified: development/ manufacture guideline for APIs and implementation of Q8, Q9 and Q10 when it is finalized.

The existing portfolio of ICH guidelines was also reviewed. Progress of EWGs is summarized under the title of the corresponding guidelines.

Q4B – Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC)[1]

This document describes a procedure to facilitate acceptance by regulatory authorities of pharmacopoeial analytical procedures and/or acceptance criteria (APAC)[2] for use in the three ICH regions.

The Q4B process focuses on the following 11 General Test Chapters:

Dissolution	
Disintegration	
Uniformity of Content	→ Harmonized to Uniformity of
Uniformity of Mass	→ Dosage Units
Extractable Volume	
Particulate Matter	
Sterility	
Microbiological Quality	
Bacterial Endotoxins	
Residue on Ignition	
Colour and Clarity	

The harmonization of pharmacopoeial general chapters is important to WHO normative work in the area of pharmaceuticals because each of the general monographs affects a large number of finished pharmaceutical products (FPPs), which belong to the same dosage form. Particularly important are the monographs on the Dissolution and the Uniformity of Dosage Units. Both tests are extensively used not only for quality control (QC) purposes but also for manufacturing process validation. In addition, the Dissolution test is an essential tool for change detection and evaluation during the pharmaceutical development stage and the stability studies as well as for the assessment of post-approval variations to the marketing authorization (MA).

The output of this EWG depends on the input received from the Pharmacopoeial Discussion Group (PDG), which started before ICH and has proceeded in parallel. The work of ICH Q4B seems to be moving from pharmacopoeia to harmonized general ICH monographs.

Q8 – Pharmaceutical Development[3]

The ICH guidelines Q1 to Q6 are technical; the Q7 and Q9–Q10 guidelines are system-oriented, while the Q8 guideline is both technical and conceptual in character. The core guideline — recommended for adoption to the three regulatory parties to ICH — "describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format" and it also "provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management." "The guideline also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches." These three functions together could be

1. *http://www.ich.org/LOB/media/MEDIA3092. pdf*

2. *The term analytical procedures and/or acceptance criteria (APAC) refers to pharmacopoeial monographs, general test chapters, analytical methods, and/or associated acceptance criteria.*

3. *http://www.ich.org/LOB/media/MEDIA1707.pdf*

briefly described as the road from formulation development, through baseline in process control (IPC) and QC, to product and process know-how management.

The pharmaceutical development report has been a regulatory requirement in applications for MA in the European Union. However, the 2nd and the 3rd functions imply that if industry demonstrates product and process knowledge beyond QC specifications, stability studies and the three validation batches, then drug regulatory authorities do not require even notification after certain post-approval variations to the MA. As an illustration of the point, a definition is quoted from the Q8 core guideline:

"**Design Space**: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval."

The definition suggests that if critical product attributes or process variables are brought under control within the design space, then they become non-critical. Another interpretation opines that critical attributes or variables remain always critical only the product and process quality risk is reduced (possibly to a large extent) even if such parameters are monitored in line/on line to support real time batch release.

In the QbD methodology, the choice manufacturing process and details of each unit operation are evaluated to demonstrate a high level of process understanding and control.

The following points illustrate subjects of discussion at the EWG meeting on Q8(R1) Pharmaceutical Development in Chicago:

- There are overlapping areas between the baseline (conventional, traditional, and basic) and enhanced [expanded, intensive, quality-by-design (QbD)] experimentation methods of pharmaceutical development.
- Flexibility — regulatory including inspection, operational — (effect) is created by the design space and should be based on science (cause).
- Pharmaceutical development is discussed as a life cycle concept of the FPP (API is excluded as of today) against the everyday interpretation of pre-formulation, formulation and scale-up activities.

The Q8(R1) Pharmaceutical Development guideline is expected to be published after the next ICH Steering Committee meeting to be held in Brussels, Belgium, from 7 to 10 May 2007.

Q9 - Quality Risk Management[4]

"This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labelling materials in drug (medicinal) products, biological and biotechnological products)."

The ICH-Q9 guideline outlines a model for quality risk management, as follows:

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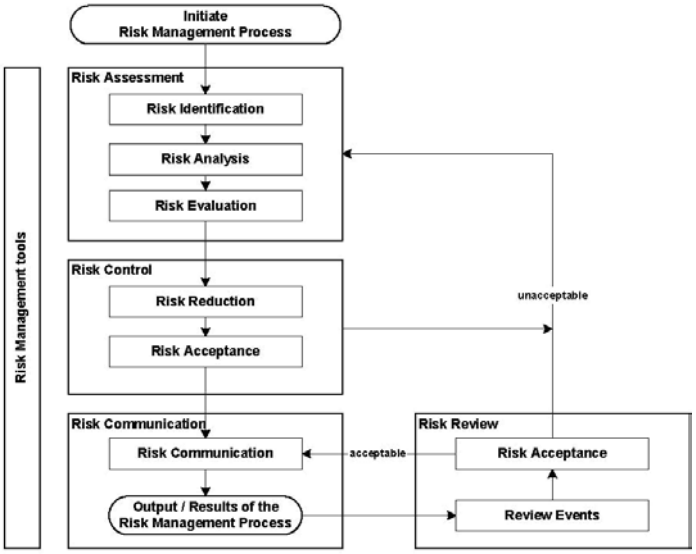
4. *http://www.ich.org/LOB/media/MEDIA1957.pdf*

Model for quality risk management



The Steering Committee encouraged implementation of the guideline, which is also quoted as a tool box because a Briefing Pack[5] is offered as a supplementary explanation of the ICH Q9 both for regulators and industry.

Q10 – Pharmaceutical Quality Systems (PQS)

The objective of this draft guideline is to establish a new tripartite guideline describing a model for an effective quality management system for the pharmaceutical industry, referred to as the pharmaceutical quality system, that:

- ensures the realization of a quality drug product.
- establishes and maintains a state of control.
- facilitates continual improvement over the product life cycle.

This guideline will complement existing good manufacturing practices (GMP) with effective pharmaceutical quality system elements, providing the opportunity for capable processes, resulting in drug substances and drug products that consistently meet their intended quality attributes. Q10 thereby serves as a bridge between different regional regulations, helping industry and regulators to achieve harmonization of pharmaceutical quality systems. This guideline is expected to focus on the pharmaceutical quality systems and complements and facilitates the implementation of ICH Q8 “Pharmaceutical Development” and ICH Q9 “Quality Risk Management”.

Pharmaceutical Quality System, Version 8.0, 26 October 2006 was completed in Chicago as a revised draft for the step 2 guideline which is expected to be finalized during the forthcoming meeting of the Steering Committee in Brussels, May 2007.

[5]. *http://www.ich.org/cache/compo/276-254-1.html*

Summary
This article has described progress achieved by ICH EWGs in Chicago, Illinois from 21 to 26 October 2006. ICH Q strategy discussion will be finalized in Brussels in May 2007 in order to work out a harmonized quality strategy and a work plan. The annexes of the Q4 guideline lead to internationally harmonized general pharmacopoeia monographs. Science- and risk-based concepts are described in the Q8, Q9 and Q10 guidelines. The implementation of these guidelines is intended to be voluntary; however, if implemented industry hopes to get regulatory flexibility in post-approval variations of the MA and during GMP inspections.

Reference

1. ICH website at http://www.ich.org

Safety and Efficacy Issues

Rotavirus vaccine and intussusception

United States of America — The Food and Drug Administration (FDA) has notified health care providers about 28 post-marketing reports of intussusception following administration of rotavirus live oral pentavalent vaccine (RotaTeq®), indicated for the prevention of rotavirus gastroenteritis. Intussusception is a serious and potentially life-threatening condition that occurs when the intestine gets blocked or twisted. One portion of the intestine telescopes into a nearby portion, causing intestinal obstruction (1).

Since its licensure on 3 February 2006 until 31 January 2007, 28 cases of intussusception have been reported in the US in infants who received RotaTeq®. Cases occurred after dose 1, dose 2 and dose 3. Approximately half of the cases occurred 1 to 21 days after vaccination, with a range of 0 to 73 days. Sixteen of the 28 infants with intussusception required hospitalization and surgery on their intestine. The remaining 12 infants had reduction of the intussusception by contrast or air enema. No deaths due to intussusception were reported.

The number of intussusception cases reported to date after RotaTeq® administration does not exceed the number expected based on background rates of 18–43 per 100 000 per year for an unvaccinated population of children 6 to 35 weeks. The FDA notification was issued to encourage reporting of any additional cases of intussusception that may have occurred or that occur in the future after administration of RotaTeq® to remind health care providers of Intussusception as a potential complication (2).

The WHO Global Advisory Committee on Vaccine Safety has previously concluded that clinical trial data and preliminary data from adverse event reports in the post-marketing phase, from the US and elsewhere, did not show an increased risk for intussusception following RotaTeq®; the committee further concluded that the recent information from the US does not change its previous conclusions that further monitoring is warranted (2).

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1. CBER, 13 February 2007 on MedWatch, http://www.fda.gov/medwatch and http://www.fda.gov/cber/safety/phnrota 021307.htm

2. World Health Organization Statement. http://www.who.int/vaccine_safety/topics/rotavirus/rotateq_statement/en/index.html

Zolpidem and bizarre sleep related effects

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 2002, the Australian Adverse Reactions Advisory Committee (ADRAC) reviewed the first year of use and it was noted about 75% of the reports received described one or more neurological or psychiatric reactions, especially visual hallucinations, confusion, depression and amnesia (1). This pattern, which is not shared by other hypnotics, has continued with hallucinations (104 reports) and amnesia (62) now the most frequently reported effects. Reactions associated with sleeping or falling asleep have been described in half of all reports submitted. Of particular interest have

been 16 reports of sleep walking, which describe inappropriate or strange automatic behaviour "while asleep", including binge eating and house painting.

There have been isolated reports in the literature describing sleep walking, including an article in the popular magazine *Time* which mentioned the impending publication of a case series describing a few dozen people who, after taking zolpidem, developed uncontrollable urges to eat while asleep and did not remember the feeding binges when they awoke (2). A case series describing 5 patients taking zolpidem who experienced uncontrolled eating while asleep has previously been published (3).

There are two reports to ADRAC that describe this situation. In one report, a patient put on 23 kg in weight over 7 months while taking zolpidem. It was only when she was discovered eating in front of an open refrigerator while asleep that the problem was resolved. In another report, a patient who had experienced significant weight gain was found by a relative taking food from the refrigerator and kitchen cupboards while asleep. Other reports to ADRAC describe a patient who woke with a paintbrush in her hand after painting the front door while asleep, a patient who walked around the house like a "mad man" while asleep, and two further reports which suggest the possibility of driving while asleep.

ADRAC recommends prescribers should be alert to the fact that zolpidem may be associated with distressing neurological or psychiatric reactions, including those associated with sleeping or falling asleep, and should warn their patients about the possibility of these untoward effects, particularly if they are going to take zolpidem for the first time.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 26, Number 1, February 2007.

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Rituximab: life–threatening brain infection

United States of America — The Food and Drug Administration (FDA) has received reports of death in two patients treated with rituximab (Rituxan®) for systemic lupus erythematosus (SLE). Both patients developed progressive multifocal leukoencephalopathy (PML). PML is usually fatal and there are no known effective treatments.

The signs of PML include confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems. Recognition of these warning signs of PML may be obscured by the fact that they are also associated with the underlying diseases for which rituximab may be prescribed.

Rituximab is a powerful medication used to suppress the immune system. It works by blocking the effect of specific immune cells in the blood for up to six to nine months. Rituximab is approved for use only in patients with non-Hodgkin lymphoma and for rheumatoid arthritis when other treatments have failed.

Reference: MedWatch, 18 December 2006. http://www.fda.gov/medwatch.

Methadone for pain: cardiac and respiratory changes

United States of America — The Food and Drug Administration (FDA) has received reports of death and life-threatening side effects in patients taking

methadone (Dolophine®). These have occurred in patients newly starting methadone for pain control and patients switched to methadone after being treated for pain with other strong narcotic pain relievers. Methadone can cause slow or shallow breathing and dangerous changes in heart beat that may not be felt by the patient.

Prescribing methadone is complex. Methadone should only be prescribed for patients with moderate to severe pain when their pain is not improved with other non-narcotic pain relievers. Pain relief from a dose of methadone lasts about 4 to 8 hours. However methadone stays in the body much longer—from 8 to 59 hours after it is taken. Methadone may build up in the body to a toxic level if it is taken too often, if the amount is too high, or if taken with certain other medicines or supplements.

Reference: MedWatch, 27 November 2006. http://www.fda.gov/medwatch.

Levofloxacin: dysglycemia and liver disorder

Canada — Levofloxacin, marketed in Canada since 1997, is a broad-spectrum fluoroquinolone antibiotic that is indicated for the treatment of certain respiratory tract, skin and urinary tract bacterial infections in adults (1). Dysglycemia (2–4) and liver disorders (5, 6) in association with levofloxacin have been reported in the literature.

From 1997–2006, Health Canada received 22 domestic reports of dysglycemia suspected of being associated with levofloxacin. Adverse reactions (ARs) included 1 report of diabetes mellitus, 2 reports of hyperglycemia alone, 16 of hypoglycemia alone and 3 of hyperglycemia and hypoglycemia combined.

It is postulated that one of the mechanisms behind the development of hypoglycemia with levofloxacin may involve the inhibition of pancreatic a-cell potassium channels. This inhibition results in the release of insulin, which in turn could result in hypoglycemia (7). Disturbances of blood glucose levels are labelled in the product monograph (1).

With regards to liver disorders, between 1997 and 2006, Health Canada received 44 domestic reports of liver and biliary disorders suspected of being associated with levofloxacin. Of these 44 cases, there were 5 cases of hepatic failure, 9 of hepatitis and 1 of hepatorenal syndrome. Five of these 15 cases of liver disorders were fatal. The remaining 29 reports included ARs of increased liver enzyme levels, cholestatic hepatitis and jaundice.

The mechanisms leading to the development of liver disorders with levofloxacin are not well defined. Although drug-induced liver diseases can mimic all forms of acute and chronic hepatobiliary diseases, a particular drug generally has a characteristic clinical and pathological signature and latency period when liver injury occurs. Most drug-induced liver disorders are similar to acute hepatitis, cholestasis, or mixed presentation (8).

Extracted from Canadian Adverse Reaction Newsletter, Volume 17(1), January 2007.

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2. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 2006;**354**(13):1352-61.

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Domperidone: heart rate and rhythm disorders

Domperidone is a peripheral dopamine antagonist structurally related to the butyrophenones with antiemetic and gastroprokinetic properties (1). In Canada, domperidone (Motilium®) was marketed in 1985 but has not been available since 2002. However, many generic brands are currently available.

Domperidone is indicated for the symptomatic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis. It may also be used to prevent gastrointestinal symptoms associated with the use of dopamine agonist antiparkinsonian agents (1). In addition, the off-label clinical use of antidopaminergic drugs to induce and maintain adequate lactation in breast-feeding women has been suggested (2, 3).

Health Canada has received 9 domestic reports of heart rate and rhythm disorders suspected of being associated with the use of domperidone. Domperidone has been reported in the medical literature to induce QTc prolongation and Torsade de Pointes (4, 5). Some non-drug-related factors that may be associated with QT prolongation include female sex, advanced age, bradycardia, cardiac disease and electrolyte disturbance (6).

The main metabolic pathway of domperidone is via cytochrome P450 3A4 (CYP3A4). Studies of interactions have shown marked CYP3A4 inhibition by ketoconazole, which results in an increased plasma concentration of domperidone and a slightly prolonged QT interval (7). Other examples of CYP3A4 inhibitors include macrolide antibiotics, HIV protease inhibitors, selective serotonin reuptake inhibitors (SSRIs) and grapefruit juice (1, 6, 8). The combined use of multiple drugs that prolong the QTc interval can also increase the risk for Torsade de Pointes (9).

Attention should be paid to any drug interactions and clinical risk factors that could result in an exaggerated prolongation of the QT interval. Health Canada continues to monitor ARs suspected of being associated with the use of domperidone and is working with the manufacturers of generic domperidone to update their product monographs.

Extracted from Canadian Adverse Reaction Newsletter, Volume 17(1), January 2007.

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Complications with use of bone cement

Canada — Reports have been received relating to serious complications, including death, associated with the use of bone cement in vertebroplasty and kyphoplasty procedures.

Vertebroplasty and kyphoplasty are relatively new procedures that are being increasingly used in the treatment of patients with vertebral compression fractures. Advocates of both procedures claim to offer advantages over the conservative therapy in immediate pain relief and mechanical stabilization of the vertebral body. Vertebroplasty is performed by percutaneously injecting bone cement into the vertebral bodies under fluoroscopic and/or computed tomography guidance. Kyphoplasty includes an attempt to expand the vertebra with an inflatable balloon prior to the injection of bone cement. Currently, only certain polymethylmethacrylate (PMMA) bone cements are licensed by Health Canada for use in these procedures.

Serious complications associated with the use of the bone cements in these procedures have been reported. They include:

- Death due to sudden blood pressure drop that may be related to the release of the PMMA monomer into the vascular system;
- Bone cement extravasation into the spinal canal leading to neurologic deficit, with compression of the spinal cord and/or nerve roots;
- New fractures, usually of adjacent non-augmented vertebrae;
- Pulmonary embolism of the PMMA.

These adverse events can result in neurologic complications ranging from minor motor and sensory loss to paraplegia. Further intervention (surgical correction, rehabilitation therapy) is required in many cases. Deaths due to sudden blood pressure drop, PMMA embolism and other factors related to pre-existing cardiovascular disease, have been reported internationally. More of these serious complications at this time appear to be related to the balloon kyphoplasty, possibly related to greater disruption of the vertebral body in attempting to regain vertebral body height.

In order to minimize the risk, Health Canada recommends the following:

- A period of conservative therapy should be considered in all patients having acute osteoporotic vertebral body fractures.
- Only qualified physicians who are thoroughly trained in performing vertebroplasty and kyphoplasty should perform these procedures.
- Use only bone cements indicated for vertebroplasty and kyphoplasty procedures, and carefully review and follow the Instructions for Use.
- Monitor the procedures with high quality imaging systems to allow recognition of PMMA leakage.
- Closely monitor patients' blood pressure during and immediately after the procedures; multiple-level treatment may increase the risk of sudden drop in blood pressure related to the release of

PMMA monomer into the circulation. No more than 3 vertebral level treatment should be done in a single visit.

Careful diagnosis and special precautions should be taken when the procedures are performed in treating patients with spinal tumours that have eroded the posterior vertebral body wall.

Traumatic burst fractures with disruption of the posterior vertebral body should be a relative contraindication to vertebroplasty or kyphoplasty.

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Infant deaths sssociated with cough and cold medications

United States of America — Cough and cold medications that contain nasal decongestants, antihistamines, cough suppressants, and expectorants commonly are used alone or in combination in attempts to temporarily relieve symptoms of upper respiratory tract infection in children aged <2 years. However, during 2004—2005, an estimated 1519 children aged <2 years were treated in US emergency departments for adverse events, including overdoses, associated with cough and cold medications.

In response to reports of infant deaths after such events, CDC and the National Association of Medical Examiners (NAME) investigated deaths in U.S. infants aged <12 months associated with cough and cold medications. Deaths were identified in three infants aged <6 months in 2005, for which cough and cold medications were determined by medical examiners or coroners to be the underlying cause.

The three infants ranged in age from 1 to 6 months; two were male. All three infants had what appeared to be high levels of pseudoephedrine (a nasal decongestant) in postmortem blood samples. One infant (patient 2) had received both a prescription and an over-the-counter cough and cold combination medication at the same time; both medications contained pseudoephedrine. The other two infants also had received pseudoephedrine-containing medications (one prescription and one over the counter). Two of the infants (patients 1 and 2) had been administered prescription medications containing carbinoxamine (an antihistamine), although neither had detectable postmortem blood levels of carbinoxamine. Two of the infants (patients 2 and 3) had

detectable blood levels of dextromethorphan (a cough suppressant) and acetaminophen (an antipyretic and analgesic).

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Ranibizumab and stroke

United States of America — The manufacturer of ranibizumab injection (Lucentis®) has advised healthcare professionals of new safety information.

In an ongoing study (SAILOR) of ranibizumab delivered intravitreally to patients with neovascular (wet) age-related macular degeneration (AMD), a planned interim safety analysis of Cohort 1 showed a higher incidence of strokes in the 0.5 mg dose group compared with the 0.3 mg dose group. Patients with a history of prior stroke appeared to be at higher risk for a subsequent stroke.

Reference: Communication dated 24 January 2007 from Genentech, Inc. on http://www.accessdata.fda.gov/scripts/medwatch/

Increased risk of fractures: antiepileptic medicines

Australia — Reduced bone mineral density and subsequent increased risk of fractures is documented in patients taking enzyme-inducing antiepileptic medicines such as phenytoin, phenobarbitone, and primidone long-term (1). The risk is higher in women and increases with duration of exposure. Patients with epilepsy may have many reasons for increased fracture risk, e.g. seizures, lack of exposure to sunlight and reduced mobility. Abnormalities of bone metabolism are seen with increased frequency in people taking antiepileptic medications. Biochemical abnormalities include: hypocalcemia, hypophosphatemia, reduced serum levels of biologically active vitamin D metabolites, and hyperparathyroidism. Bone turnover is also accelerated (1).

Medicines which induce cytochrome-P450 enzymes are thought to increase the metabolism of vitamin D_3, thus lead-

ing to vitamin D deficiency or insufficiency and a reduction in bone mineral density. A recent case control study noted a statistically significant reduction in bone mineral density in women aged over 40 years taking enzyme-inducing antiepileptic medicines for at least 2 years, but it was a small study and could not distinguish between the effects of individual antiepileptic medicines (2).

ADRAC has received relatively few reports of reduced bone mineral density in association with antiepileptic medicines. This may reflect a low level of awareness of this important adverse effect and the delayed nature of the events, often occurring years after commencement of medication.

Patients taking antiepileptic medicines long-term should be advised to have safe but adequate sun exposure, perform weight-bearing exercise and avoid other risk factors for reduced bone mineral density such as alcohol and smoking. In some cases periodic monitoring of bone mineral density may be appropriate and use of supplemental calcium and vitamin D should be considered.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 26, Number 1, February 2007.

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Vasovist® and nephrogenic systemic fibrosis

European Union — The Pharmacovigilance Working Party (PhVWP) has discussed the issue of nephrogenic systemic fibrosis (NSF) associated with gadolinium-containing contrast agents for magnetic resonance imaging (MRI).

Nephrogenic systemic fibrosis is a rare, debilitating and sometimes fatal condition, that only occurs in patients with severe renal impairment.

The CHMP is not aware of reports of NSF with Vasovist® which is centrally authorized and currently marketed in 13 European Union countries, but has requested a warning to be added to the labelling on the occurrence of NSF in patients with severe renal impairment. Products reviewed were gadodiamide (Omniscan): gadobenic acid (Multihance®), gadobutrol (Gadovist®), gadofosveset (Vasovist®), gadopentetic acid (Magnevist®), gadoteric acid (Artirem®, Dotirem®), gadteridol (Prohance®) and gadoxetic acid (Primovist®).

This subject will be discussed further at the February 2007 CHMP meeting.

Reference: EMEA Public Statement, EMEA/49741/2007. 7 February 2007. http://www.emea.europa.eu

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.

Access to Medicines

The challenges of ensuring pain medication

On page 18 of this issue of *WHO Drug Information*, Dr Jack Jagwe describes how action by Hospice Africa Uganda (HAU) has made a dramatic difference to the lives of people in his country suffering from pain.

WHO estimates that annually over 60 million people are adversely affected by lack of access to effective pain medicines controlled within the United Nations Single Convention on Narcotic Drugs (1961) and the United Nations Convention on Psychotropic Substances (1971). These two treaties provide the legal basis for the international prevention of drug abuse, together with the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988) (1). For almost 50 years, the focus has been on prevention of abuse, but this has led to overly strict rules or inappropriate implementation of the international drug control treaties in many countries. As a result, the medical use of controlled substances has been hampered and in some cases prohibited. Severe undertreatment is reported in more than 150 countries, both developing and industrialized, involving about 80% of the world's population. A balance therefore needs to be sought between medical need and regulatory requirements.

By not being able to use these substances on a regular basis, physicians became less and less experienced in prescribing pain medication. Pain patients can live for very long periods when using the correct dosage of opioids and there is no proof of undue shortening of life. Conversely, freeing patients of pain prolongs the quality, usefulness and extent of their lives. As proposed in the *WHO Guideline on Cancer Pain Relief,* (2) pain medication can be effectively evaluated and dosed as part of a Pain Ladder as follows.

Step 1: (mild pain) non-opioid analgesics (e.g. paracetamol, NSAIDS), to which if necessary an adjuvant can be added. When a non-opioid no longer adequately controls the pain, an opioid analgesic should be added.

Step 2: (mild to moderate pain) weak acting opioid analgesics (e.g. codeine), to which non-opioid analgesics and adjuvants can be added if the pain is still persisting or increasing.

Step 3: (moderate to severe pain) strong acting opioids, to which non-opioid analgesics and adjuvants can be added if necessary.

If the pain is increasing, the dosage of the opioid should be increased in steps until the patient is free of pain. The effective analgesic dose of morphine will vary considerably and ranges from as little as 5 mg to more than 1000 mg every four hours. The effective dose varies because of individual variations in systemic bioavailability, so that the correct dose is the dose that works.

The *WHO Model List of Essential Medicines* includes opioids and analgesics (3) and supports their use within the framework of human rights and health, that is "*the Right of everyone to enjoy the highest attainable standards of physical*

and mental health" (4). In 2005, WHO was urged to develop the Access to Controlled Medications Programme in consultation with the International Narcotics Control Board (INCB). The Programme sets out to improve legitimate medical access to all medications controlled under the drug conventions. Lack of access to controlled medicines does not only affect low-income countries, but many middle- and high-income countries as well. Countries willing to improve access can follow the advice provided in the WHO publication *Achieving Balance in National Opioids Control Policies, Guidelines for Assessment* available on the internet in 22 languages (5).

As proposed by the World Health Assembly, it is the responsibility of governments to make every effort to bring pain medications within the reach of those who need them. Every year 6 million people die from cancer without sufficient analgesia and often without any treatment for their pain. About half of all end stage AIDS patients suffer from severe pain. Then, there are many people with acute severe pain from injuries (e.g. car accidents, victims of war), myocardial infarction and chronic pain patients. Regulations for obtaining pain medicines have become more and more stringent amid concerns for prevention of drug abuse which override the legitimate medical needs of patients. However, evidence shows that the majority of narcotic and psychotropic substances reach drug abusers through illicit trade rather than pharmacy channels.

Additionally, misconceptions have spread based on the unjustified fear that opioid medication may cause dependence or death in patients. The mere presence of physical dependence on opioids prescribed for pain control does not, of itself, constitute drug dependence syndrome or "addiction". In fact, becoming dependent when using a controlled medicine, after prescription for a legitimate medical purpose, is rare. If it does occur, it can be treated in the same way as any other side-effect.

Ephedrine and ergometrine are essential medicines used in obstetrics and delivery that can be life saving. Although they are not abused as drugs, they can be used to synthesize other drug substances — and for that reason they are controlled under the 1988 Convention. Unfortunately, it is reported that these medicines are often not available when most needed, thus contributing to the 250 000 maternal deaths annually.

Dr Jagwe modestly describes what his organization has achieved. However, the importance of his work cannot be underestimated, either for Ugandans directly, or for the many other countries that may use the work carried out in Uganda as a model. The joint efforts of Hospice Uganda Africa and the Ugandan Ministry of Health to provide regulations and organize pain care and medication in such a way that it reaches many has taken a number of years of enduring effort. The innovation of nurse training to carry out the task of prescribing and administration was an important achievement in finding a solution to overcome the shortage of physicians. A similar innovation has been implemented in the state of Kerala, India, where the shortage of pharmacy assistants was overcome by laymen volunteering to dispense the morphine tablets to the patient at home.

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Import and safe distribution of oral morphine for pain relief in Uganda

Early beginnings of palliative care

With support from friends in the United Kingdom, Dr Anne Merriman introduced palliative care to Uganda in 1993 based on methods of dealing with severe pain originally devised at St. Christopher's Hospice, London. Her vision was to relieve the suffering of people with serious illnesses such as cancer. Relying on WHO Foundation measures to initiate a palliative care programme and with political support from the Government, Dr Merriman was able to advocate availability of oral morphine.

As a consequence, oral morphine was registered by the National Drug Authority (NDA) for the first time in 1993 and powdered morphine sulphate was imported by the Government. The Programme embarked on education, training and offering a service to the people of Uganda. Initially, it addressed cases of severe pain arising from cancer. Later, it was called upon to help patients with AIDS and cancer arising from HIV infection through adaptation of measures used for cancer pain management. Hospice Africa Uganda (HAU), in Kampala, is now an outstanding health centre offering clinical management for severe pain and training of health professionals in this new specialty of palliative medicine.

Progress and organization

Palliative care is an interdisciplinary specialty addressing a patient with a life-limiting illness, such as cancer or HIV/AIDS. Such health conditions have thrown Uganda into a public health turmoil. HAU follows a holistic approach to the problem of severe pain, and interventions include supportive and home care. HAU collaborates with doctors, nurses, pharmacists, policy makers and health institutions to reach out to as many suffering Ugandans as possible to improve the quality of their life. They also network with many nongovernmental organizations operating in Uganda since HIV/AIDS was first publicly declared a health problem by the Government in 1986, and collabate with treatment organizations, income generating organizations, organizations dealing with legal issues and orphanages.

A clinical service is offered and covers a radius of 20 km from the centre of Kampala, reaching into the poor suburbs. HAU collaborates with the main National Referral and Teaching Mulago Hospital and several other hospitals in the city. Although it runs an outpatient service for those who can come to Makindye, many patients receive regular visits at their homes.

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Model for making simple affordable morphine solution: Peter in the pharmacy

Since HAU started, it has trained health professionals in the art and science of palliative care. It has given lectures at medical schools situated in Makerere University, Kampala and Mbarara University of Science and Technology. In order to meet the needs of teaching and research, HAU has opened a branch Mbarara Mobile Hospice near the University of Science and Technology in the west and the Little Hospice Hoima in a rural underserved district of Uganda to evaluate in what ways palliative care services can be effectively extended to rural areas.

Changing attitudes and behaviour

With the increasing number of trained health professionals, palliative care is extending to more districts of Uganda. Major progress has been made not only in initiating palliative care but breaking the myths, fears and misconceptions about the use of morphine for severe pain. The WHO 3-step ladder of analgesia has been fully utilized to underscore management of severe pain by health professionals. HAU has incorporated the statements made by WHO over the years into its cancer pain relief services. For example, WHO stated in 1986 that morphine is the drug of choice for severe pain and that freedom from cancer pain is a right of every cancer patient, with access to pain therapy a measure of respect for this right. WHO has advised that for the majority of patients with cancer, a realistic treatment regimen must include pain relief and palliative care.

HAU has also noted and used pronouncements from the international Narcotics Control Board which has stated that in many countries consumption of opioid analgesics remain extremely low in comparison to medical needs, and that governments have yet to address this important deficit. Presently, oral morphine is widely accepted in Uganda as the drug of choice for severe pain. HAU teaches that the feared myth of addiction is very rare when morphine is used for the indication of severe pain. But HAU also cautions that addiction may occur when morphine is used for non-medical purposes.

Extending involvement and cooperation

HAU has been invited to help other countries wishing to introduce palliative care in their countries. Advocacy has been carried out in a number of sub-Saharan countries and palliative care is taking root in Ghana, Malawi, Nigeria, Republic of Tanzania, Sierra Leone and Zambia.

HAU has participated in a regional workshop for the Eastern Africa Region to advocate for use of opioid analgesics. A member of HAU was invited to present a paper jointly with WHO and the Pain and Policy Studies Group (PPSG) at the 12th ICDRA held in Seoul, Korea in 2006 and at the UICC Cancer Congress in Washington DC, USA, to discuss how, in working with Government and nursing personnel at HAU it has proved possible to take pain relief to the periphery in Uganda.

The prospects for extending palliative care programmes currently look good. HAU personnel have developed international collaboration on morphine use with such organizations as the Pain and Policy Study Group in Madison, Wisconsin, USA. Recently, a member of HAU participated in an International Expert Collaboration workshop to help representatives from Colombia, Nigeria, Panama, Serbia, Sierra Leone, Uganda, and Vietnam to develop action plans for the introduction of palliative care and to make opioids available for use. HAU has also linked up with other organizations wishing to help sub-Saharan Africa to develop palliative care programmes. These include National Hospice and Palliative Care Organization of USA (NHPCO), Foundation for Hospices in Subsaharan Africa (FHSSA), Medicines Policy and Standards Department at WHO, Open Society Institute (OSI), and USAID.

Defining achievements

Through advocacy to political leaders, Ministry of Health officials, policy makers, health professionals and the public, the HAU programme has facilitated access to oral morphine for cancer and AIDS patients, procured by the Government of Uganda and provided without cost to the patient. The programme has been able to influence the Government to accept and incorporate palliative care into the Health Sector Support Programme as an essential service offered in all governmental health institutions.

Despite limited resources and many obstacles, HAU has managed to train nurses and clinical officers to the level of specialized palliative care professionals certified by the Ministry of Health who are authorized to prescribe morphine and other palliative care drugs. This is a major achievement in sub-Saharan Africa! Planning and initiation of the above three activities should be considered the minimum recommended requirement for other countries in Africa to alleviate the suffering of people afflicted with cancer, HIV/AIDS and other life-limiting diseases.

The epidemic of pain now affecting Africa and extending to other countries of the world due to cancer and HIV/AIDS can be addressed by simple management of palliative care and application of the WHO 3-step ladder of Analgesia. Together with the introduction of palliative care, advocacy, education and sensitization can demystify the fear of addiction attributed to morphine. In this way, the quality of life of patients with devastating illnesses can be improved.

"Change is a law of life: And those who look only to the past or present are certain to miss the future".
President J. F. Kennedy.

Topics of Current Interest

Developments in biological quality, safety and efficacy

Biological medical products such as vaccines, blood products, biotherapeutics and associated diagnostics save lives, reduce suffering and improve health, but only if products and technologies are of good quality, safe, effective, available, affordable and properly used. In many countries, not all of these conditions are met. This may be due to:

- Lack of awareness of the potential benefits in medical outcomes and economic savings.
- Lack of political will and public investment.
- Commercial and political pressure, including donor pressure.
- Fragmented financing and supply strategies.

WHO is working to promote production and use of biological medicines of assured quality in national health systems. The aim of the WHO Expert Committee on Biological Standardization (ECBS) is to establish global norms and standards that help define products of assured quality.

Highlights of the 2006 ECBS meeting

- A new written standard was established for human papillomavirus vaccines.

This new vaccine has potential to prevent morbidity and mortality due to certain types of cervical cancer. The new WHO standard paves the way for prequalification of the vaccine.

- A new written standard for meningococcal type A conjugate vaccine was adopted.

Although group A isolates were at one time a common cause of meningococcal disease worldwide, they are now principally responsible for recurrent epidemics in the “meningitis belt” countries of sub-Saharan Africa. If a major epidemic occurs, the availability of WHO guidance will assist Member States in the evaluation and licensure of candidate vaccines that are currently under development.

- A new written standard that defines regulatory expectations for the evaluation of the stability of vaccines was established.

This standard opens a new regulatory pathway for vaccine stability studies. To promote and gain experience in the evaluation of vaccine stability, a series of in-country workshops will be conducted.

A new project to develop strategies to monitor the implementation of WHO norms and standards in Member States was endorsed by the ECBS. Networking with national regulatory authorities and WHO Regional Offices will be established to survey the implementation of WHO written and measurement standards in countries. Results from the survey will assist the committee in developing or revising WHO standards.

Strategic initiatives for quality, safety and efficacy of blood products and quality of related in vitro diagnostic devices during the next five to seven years were endorsed.

Biological substances: International standards and reference reagents

At its meeting in October 2006, the WHO Expert Committee on Biological Standardization made the following additions to the previous list. *(These substances are held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts., EN6 3QG, England.)*

Preparation	Activity	Status
	Antigens and related substances	
Pertussis vaccine (whole cell)	40 IU per ampoule	Fourth International Standard
Poliovirus, Sabin, type 3	No assigned value	WHO(SO+2)/III Neurovirulence Reference Preparation
Smallpox vaccine	7.3 log10 chorioallantoic membrane pock forming units/ml after reconstitution in 0.25ml sterile water	Second International Standard
	Antisera	
Anti-measles (plasma)	3 IU per ampoule of neutralizing antibody	Third International Standard
Anti-poliovirus serum types, 1,2 & 3	11, 32 and 3 IU per vial of neutralizing antibody to poliovirus types 1, 2 and 3 respectively	Third International Standard
	Blood products and related substances	
Alpha-1-antitrypsin, plasma	243 nmoles (12.4 mg) active alpha-1-antitrypsin per ampoule	First International Standard
Blood coagulation Factor XIII, plasma, human	0.93 IU/ampoule of FXIII antigen	First International Standard
Protein C, plasma, human	0.85 IU/ampoule of protein C functional activity; and 0.84 IU/ampoule of protein C antigen	Second International Standard
Protein S, plasma, human	0.83 IU/ampoule total protein S antigen; 0.81 IU/ampoule free protein protein S antigen; and 0.77 IU/ampoule protein S functional activity	Second International Standard

Preparation	Activity	Status
Cytokines, growth factors and endocrinological substances		
Thyroid-stimulating hormone, human, recombinant, for bioassay	9.5 IU/ampoule	First International Standard
Interleukin 17	10,000 U/ampoule	Reference reagent
Interleukin 18	10,000 U/ampoule	Reference reagent
Diagnostic reagents		
Hepatitis B DNA, for nucleic acid amplification test assays	$5x10^5$ IU/vial	Second International Standard
Plasmodium falciparum, in whole blood, for nucleic acid amplification test assays	$5x10^8$ IU/vial	First International Standard
Anti-human immunodeficiency virus tests	No assigned unitage	First International Reference Panel
Anti-human platelet antigen 3a, for minimum potency estimations	No assigned activity; however a 1 in 8 dilution should define the minimum potency specification for anti-HPA-3a detection	First International Standard

A WHO project on “Animal-derived sera” was endorsed. Animal-derived sera are crucial in the treatment or prevention of a number of human and veterinary diseases. These include snake bites and other venomous bites and stings, rabies, botulism, tetanus, gas gangrene, diphtheria, digoxin and other poisoning. The diagnosis, treatment and prevention of bioterrorism agents may also require specific animal-derived sera.

A total of 16 new or replacement global reference preparations for the control of vaccines, biotherapeutics, blood products and associated in vitro diagnostic medical devices was established (see table). Among them, reference materials for the control of whole cell pertussis, smallpox and polio vaccines and for the validation of hepatitis B, *Plasmodium falciparum* and anti-HIV diagnostic tests. These are the primary calibrants against which regional or national measurement standards are benchmarked.

A list of International Standards and Reference Reagents for biological substances was published in the WHO *Technical Report Series*, No. 897, 2000 (Annex 4) and an updated version is available on the Internet at http://www.who.int/biologicals.

Reference: Biologicals: http://www.who.int/biologicals/en/

Transparency in Medicines Management

The value of the global pharmaceutical market is estimated to be over US$ 500 billion, making the pharmaceutical sector highly vulnerable to corruption and unethical practices. Transparency International estimates that, on average, 10 to 25% of public procurement spending in the health sector is lost to corruption. It also reports that in some countries up to two thirds of medicines supplies at hospitals are lost through corruption and fraud. Resources that could otherwise be used to buy medicines or recruit much needed health professionals are wasted as a result of corruption, which reduces the availability of essential medicines and can cause prolonged illness and even deaths.

WHO Programme on Good Governance for Medicines

In response to the current situation, and guided by its Medicines Strategy (1), WHO has initiated the Good Governance for Medicines Programme. Established in late 2004, the Programme's overall goal is to curb corruption in medicines procurement and regulation through application of transparent procedures and the promotion of ethical practices by health professionals and others involved in the handling of pharmaceutical products.

WHO recognizes that corruption is an immense, complex problem, and one that is difficult to tackle. The World Bank identifies it as the single greatest obstacle to economic and social development. The WHO Programme is promoting action by making public health colleagues in ministries of health and national medicines regulatory authorities more aware of the negative consequences of corrupt practices.

Good governance is particularly relevant to the pharmaceutical sector because of the impact on the health, future and wellbeing of populations. Corrupt practices can impact the pharmaceutical sector in at least three ways:

Health impact
Wastage of public resources reduces government capacity to provide access to good-quality essential medicines, while the risk of unsafe medical products on the market increases due to counterfeiting and/or to bribery of officials.

Economic impact
Pharmaceutical expenditure in low-income countries may represent up to 50% of total health care costs, which means that corrupt pharmaceutical practices are extremely detrimental to national health budgets and to households paying out-of-pocket expenses for medicines, which will then be overpriced or ineffective.

Government image and trust impact
Inefficiency and lack of transparency reduce the credibility of public institutions, and erode public and donor confidence in government capacity to deliver policy.

In addition, the donor community is providing sizeable grants or contributions of in-kind medicines for global public health problems such as high child mortality, the spread of infectious diseases and neglected diseases (e.g. the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Bill & Melinda Gates Foundation, PEPFAR). However, corruption within the public sector risks undermining these efforts by misappropriating some of this vital aid. Ultimately, successful allocation and use of such funds will depend on good governance at national level.

Need for coordinated application of two basic approaches for impact

Tackling corruption in the pharmaceutical sector requires a long-term strategy. Experience to date shows that strategies addressing corruption require the coordinated application of two basic approaches:

1. A discipline-based approach, consisting generally of a legislative reform whereby laws against corruption are established, procedures promoting transparency and accountability are put in place, with appropriate punitive consequences for violations. This top-down approach attempts to deter corruption practices through the fear of punishment.

2. A value-based approach, that attempts to increase institutional integrity through promotion moral values and ethical principles. This bottom-up approach seeks to motivate public servants to act ethically.

Neither approach alone is sufficient to have significant impact.

Progress in implementing the Good Governance for Medicines Programme
The Good Governance for Medicines Programme is designed and implemented as a bottom-up approach. Tools and policies are pilot tested and refined in light of country experience. The Programme operates currently in eight Asia-Pacific countries and one Latin American. It is implemented through a three-step approach.

Phase I: National assessment of transparency and potential vulnerability to corruption
In order to address the problem of corruption in the pharmaceutical sector, it is necessary to assess the level of transparency and potential vulnerability to corruption of key functions in medicines regulation and procurement. The national assessment is carried out after government clearance, by independent national investigators and using the standardized WHO assessment instrument (2). The national investigators collect information through a combination of desk research and semi-structured interviews, and the assessment focuses on five key functions of the pharmaceutical sector, namely *registration* of medicines, control of medicine *promotion, inspection* of establishments, *selection* of essential medicines, and *procurement* of medicines.

Phase II: Development of national ethical infrastructure
Assessing the level of transparency and the potential vulnerability to corruption is not an end in itself. It is rather the beginning of a process aimed at bringing long-lasting changes to promote good governance practices among health professionals in the public pharmaceutical sector. Once a national assessment has been carried out and problems identified, WHO suggests developing, through a consultation process, a national ethical infrastructure responding to the needs of individual countries. The WHO Ethical Infrastructure for Good Governance in the Public Pharmaceutical Sector (3) can serve as reference in developing the national ethical infrastructure.

Phase III: Socializing the national ethical infrastructure
It is very important to avoid a national ethical infrastructure remaining just another policy document developed by a few key actors at central level and not widely applied. Socialization is the process by which an ethical framework and code of conduct can be learnt, internalized, applied and promoted by a group of key actors within the pharmaceutical sector of ministries of health, until the process becomes fully integrated into the institutional culture (4).

Stakeholder group meeting
About 40 participants representing countries involved in the Good Governance for Medicines Programme, the World Bank, Transparency International, donors (DFID, Australian government), and the Global Fund attended a 2-day meeting, 30–31 October 2006.

Promoting transparency and tackling corruption in medicines regulation and procurement is without doubt a priority and an essential component of development efforts aimed at increasing access to essential medicines. The discussions helped to increase awareness of the impact of corruption in the pharmaceutical sector and to generate a clearer vision of what actions are needed on the part of different stakeholders to promote good governance. The recommendations of this meeting included (1) endorsement of the current strategic lines of action for WHO's work on Good Governance for Medicines as described above, and (2) the establishment of an international group of experts to guide WHO's work on this important subject.

Looking ahead
The focus is now on consolidating ongoing efforts in the countries which are already part of the programme, and on adding new ones, specially in regions such as Africa, the Eastern Mediterranean, Latin America and Europe. Selection of countries and activities will be based upon requests from governments, in collaboration with WHO Regional Offices.

At the global level, lessons learnt in countries will continue to be used in revising and adjusting the WHO tools and policy documents for this Programme. Efforts will also focus on maintaining the momentum created among partners during the October Stakeholder Meeting, as well as raising additional resources for the expansion and further development of the Good Governance for Medicines Programme.

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Rational Use of Medicine

Use of concordance to improve patient adherence

Poor adherence to long-term therapies severely compromises the effectiveness of treatment, making this a critical issue in public health both from the perspective of improved quality of life and health economics. Increasing the effectiveness of adherence can have an important impact on health outcomes, and interventions could provide significant positive return on investment through primary prevention of risk factors and secondary prevention of adverse health (1).

However, studies have shown that patient adherence to long-term medication may be as low as 50% and interventions aimed at improving adherence have not as yet been particularly successful. A three year national information project was carried out in a primary health care setting in Sweden.* The aim was to create understanding among patients and health care providers of the need for adherence through use of concordance. Concordance is a fundamentally different approach to compliance or adherence: it focuses on the consultation process rather than on specific patient behaviour, and it has an underlying ethos of a shared approach to decision-making (2) and agreement between a patient and healthcare professional about whether, when and how medicines are to be taken (3).

By the end of the project, target groups had been acquainted with the project message and, in particular, doctors accepted that the rate of adherence in long-term treatment was low. Although prescribers overall consider adherence as a responsibility of the patient, they also recognize that their actions can strongly influence better patient behaviour.

Influencing health professionals for better health outcomes

Effectiveness of drug therapy depends to a great extent on patient adherence to prescribed medication. However, there is abundant evidence [1] that patient adherence may sometimes average no more than 50% in long-term treatment. Non-compliance is a multifactorial problem and sub-compliance with the full prescribed dose is a major concern [4]. Enhancing adherence leads to improved therapy and better public health outcomes [5]. According to US estimates, [6,7] the cost of drug related morbidity and mortality is often attributable to low adherence and, in these circumstances, up to two-thirds of therapy failures are considered as preventable [8].

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A Cochrane review [5] indicates that activities to improve short-term adherence can be relatively successful, whereas methods to improve long-term adherence are not so effective. Since evidence for a solution is scant, it has been proposed that activities to improve adherence need to continue for as long as medication is necessary [5].

However, several reports [2,3, 9–12] now indicate that creation of concordance between patients and care givers is a promising alternative to such interventions. Concordance is presented as a new relationship between patients and doctors, nurses and pharmacists, i.e., a therapeutic alliance that recognizes the health beliefs of both patients and professionals, while at the same time aimed at avoiding misunderstandings and misconceptions.

Interventions for improved adherence have been generally patient rather than professionally directed [5]. No reports have been identified in the literature concerning interventions directed to health professionals based on the concept of concordance, although one unpublished project has been conducted in the United Kingdom (3).

The project

The project on Influencing health professionals for better concordance and adherence was conducted to:

1. Raise awareness among doctors, nurses and pharmacists of the reasons driving low adherence in patients on long-term medication, and

2. Show how concordance can lead to improved adherence.

An outline of the project was formulated by a core group of three doctors, three nurses and three pharmacists and published in 2001 [13]. To facilitate the creation of concordance the following three objectives were identified.

- See the patient as a partner — each patient should share responsibility and actively participate in the treatment regimen.

- When prescribing or monitoring drug treatment – identify the patient's experience and attitude to the disease and its treatment, and ascertain that the patient understands how and why prescribed medicines should be used.

- Consider each health profession (doctors, nurses and pharmacists) as a partnership – develop a mutual understanding of each other's functions, and collaborate and use each other's competence to improve active patient participation in the treatment.

It is claimed that improved adherence can be achieved when these three objectives are applied at each patient encounter [2,3,9–12].

The study target group comprised almost 30 000 individuals. Approximately 8000 doctors in general practice and internal medicine represented a group of high prescribers issuing 60–70% of all prescriptions to ambulatory patients in Sweden. Additionally, almost 20 000 district nurses and nurses working with outpatients and in nursing homes and 100 pharmacists specializing in providing information completed the group.

Communication is all important

A doctor, a nurse and a pharmacist (the ABLA Group) were hired full time for the three year project 2003–2005. The project also had a steering committee with members from the national health and pharmacy administrations and from professional associations for doctors, nurses and pharmacists. The objective was to disseminate, clarify and discuss the "ABLA message", i.e., that adherence in long-term medication is low but improved adherence can be achieved through concordance.

The ABLA Group used all available channels of communication to gain attention, including news media and health professional outlets. ABLA Group members were interviewed several times on TV and radio, and in newspapers and magazines. A website was set up to provide information (http://www.abla.se). Two films were also produced, a short video (4 minutes) for patients and a longer educational video (20 minutes) for health care personnel. The short video was shown extensively in customer areas of Swedish pharmacies.

Printed materials were also developed, including a pamphlet presenting scientific evidence to support action, and a textbook on concordance and adherence intended for use in teaching and continuing education [14]. Numerous lectures, seminars and discussions with individuals took place and local, national and international conferences for health professionals were organized. Meetings were held with the faculties of medicine, nursing and pharmacy to introduce concordance and adherence as part of the student curriculum.

In Sweden, regional government county councils are responsible for managing health care. Support for the project was obtained from drug and therapeutics committees [15] in each of the 21 county councils, and local projects were set up early to identify adherence problems.

First year progress

After one year in operation, project information dissemination was measured based on:

- number of participants in lectures and seminars organized by the ABLA Group;
- number of recipients of printed material; and
- estimated number of listeners to TV and radio interviews.

This gave an estimation of the extent to which target audiences had heard of or otherwise been acquainted with the ABLA message

Within the study, patient refill adherence was evaluated based on an analysis of repeat prescriptions [16]. Such data had been unavailable before the project, so the study was important in determining if the project had affected patient refill adherence. Randomly selected pharmacies collected data on prescriptions between March 2003 and October 2005. Satisfactory refill adherence was defined as dispensed refills covering 80–120% of the prescribed treatment time. A divergence from prescribed treatment time below 20% would indicate undersupply and treatment gaps and above 20%, oversupply or drug stockpiling [16]. (See Table 1 on page 30).

Before the end of the project, a questionnaire containing five statements regarding drug use and adherence was distributed to 1000 general practitioners (GPs) at 183 health centres within Stockholm county, which has a population of about 1.9 million or 21% of the population of Sweden. (See Table 2 on page 30).

At the end of the first project year, the message had reached at least 5600 doctors (70% of the target group), 12 400 nurses (62%) and more than 1000 pharmacists (100%). It was concluded that the ABLA message had successfully reached almost all of the target groups.

It was observed that some GPs had difficulty accepting that up to 50% of their patients did not adhere to long-term medication regimens. Individual doctors often claimed that the low level of adherence did not apply to their patients. However, the level of disbelief was not formally measured. On the other hand, nurses and pharmacists did not appear to doubt the low adherence levels.

Table 1. Refill adherence during the project

	March 2003		October 2005	
	Men %	Women %	Men %	Women %
Undersupply	26	25	25	28
Satisfactory refill adherence	56	56	56	55
Oversupply	18	19	20	17

The ABLA Group held meetings with drug therapeutics committees in Sweden. These were encouraged to start local projects to assess and solve local adherence problems although, by the end of the ABLA Project, only a few of the committees had set this in motion.

Refill adherence of all types of drugs used in long-term treatments was measured early and late in the project (Table 1). In March 2003, 19 randomly selected pharmacies located in different parts of Sweden collected 6634 copies of refill prescriptions and in November 2005, 15 of the same pharmacies collected 5281 copies. Refill adherence was determined as described in Table 1 [16]. Levels of satisfactory refill adherence, undersupply and oversupply were very similar between data sets. This was also the case for adherence levels of individual drug groups.

A 42% response rate was recorded from the questionnaire distributed to 1000 GPs in Stockholm County (Table 2). In conclusion, GPs recognized that their behaviour determines patient adherence, but they also consider that adherence is the responsibility of the patients.

Discussion

Literature studies undertaken prior to the ABLA Project identified non-adherence to long-term medication as one of the most

Table 2. Survey on GP opinions: adherence and drug use

Statement in the survey	% of GPs who agree completely or partly
1. When I have prescribed a medicine it is the patient's responsibility to use it in a correct way.	85
2. It is my behavior in relation to the patient that determines if the patient will use the medicine as prescribed.	91
3. Drugs are my most important tool in the treatment of patients.	36
4. It is easy to find out if my patients have been adherent.	15
5. I have the tools I need to follow up patient use of drugs.	19

important drug therapy problems [13], and evidence for action has been reviewed in a recent WHO report [1]. Additionally, it is advocated [2,3,9–13] that shared decision-making in the consultation process, i.e. concordance, improves adherence.

Because the ABLA Project was not primarily designed or financed as a research project, some of the pursued objectives were difficult to measure. Also, during preparatory work, doctors, nurses and pharmacists often asked for advice on how to create concordance, indicating that the concept was not always easy to grasp [9].

To make the concept more tangible, the three stated objectives incorporate ideas of concordance as follows.

- *See the patient as a partner — each patient should share responsibility and actively participate in the treatment regimen.*

  Since it is the patient who ultimately decides whether or not to take the prescribed medication, the health provider has to take the patients' opinion into consideration if the drugs are to be properly used. If this objective is achieved at every patient encounter, a positive commitment and shared responsibility for the treatment is created. The patient becomes an active participant with shared responsibility for the treatment regimen proposed during the consultation.

- *When prescribing or monitoring drug treatment – identify the patient's experience and attitude to the disease and its treatment, and ascertain that the patient understands how and why prescribed medicines should be used.*

  If there is no two-way communication during consultation and/or if the patients do not know why the medicines have been prescribed, there is no concordance and adherence will probably be low. However, if this objective is achieved at every patient encounter, experience and knowledge of the care provider is added to the experience and knowledge of the patient and concordance is possible.

- *Consider each health profession (doctors, nurses and pharmacists) as a partnership – develop a mutual understanding of each other's functions, and collaborate and use each other's competence to improve active patient participation in the treatment.*

  No professional group has all the answers and solutions to problems that patients experience. It is often the patient who is the messenger between members of the health professions with all the misunderstandings that this may imply. A high degree of collaboration between professions is therefore in everyone's interest.

Estimations based on refill adherence from prescription records are claimed to be the most reliable measure of adherence in large patient groups [17,18]. Since no similar project had previously been reported in the literature, a comparison of the results could not be undertaken. Levels of refill adherence were steady throughout the study duration, which may indicate that a 3-year timeframe is too short to accomplish a change in behaviour in health professionals. However, measurement was important to illustrate the need for continued efforts among health care workers.

Conclusions

Introduction of the concept of concordance into Swedish primary health care was slower than expected. At the end of the 3-year project, doctors recognized that adherence is low but still consider adherence as a responsibility of the

patient. None the less, they accepted that their behaviour was a major influence in shaping patient adherence.

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ATC/DDD Classification

ATC/DDD Classification (temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology 30–31 October 2006. Comments or objections to the decisions should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. The new ATC codes and DDDs will be considered final and be included in the January 2008 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted through e-mail at: whocc@fhi.no.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
Agents for age related macular degeneration		S01L[1]
Calcineurin inhibitors		L04AD
Dipeptidyl peptidase 4 (DPP-4) inhibitors		A10BH
Interleukin receptor inhibitors		L04AC
Muscle relaxants		C05AE
Other antiobesity drugs		A08AX
Other estrogens		G03CX
Tumor necrosis factor alpha (TNF-α) inhibitors		L04AB

[1] For the complete classification of S01L, see Summary of the main ATC alterations

[2] For the complete classification of J05AR, see Summary of the main ATC alterations

New ATC 5th level codes:

Adapalene, combinations	D10AD53
Amifampridine	N07XX05
Certolizumab pegol	L04AB05
Dabigatran etexilate	B01AE07
Eculizumab	L04AA25
Fesoterodine	G04BD11
Fluticasone furoate	R01AD12
Glimepiride and pioglitazone	A10BD06
Hemoglobin glutamer (bovine)	B05AA10
Haemophilus influenzae B, combinations with meningococcus C, conjugated	J07AG53
Ixabepilone	L01DC04
Lapatinib	L01XE07

ATC level	INN/Common name	ATC code
New ATC 5th level codes **(continued)**		
	Mecasermin rinfabate	H01AC05
	Metformin and pioglitazone	A10BD05
	Metformin and sitagliptin	A10BD07
	Mifamurtide	L03AX15
	Misoprostol	G02AD06
	Nepafenac	S01BC10
	Nilotinib	L01XE08
	Oblimersen	L01XX36
	Pegzerepoetin alfa	B03XA03
	Ramelteon	N05CM19
	Retapamulin	D06AX13
	Rimonabant	A08AX01
	Rotavirus, pentavalent, live, reassorted	J07BH02
	Sitagliptin	A10BH01
	Sitaxentan	C02KX03
	Telavancin	J01XA03
	Vapreotide	H01CB04
	Vildagliptin	A10BH02
	Xenon	N01AX15

INN/Common name	Previous ATC	New ATC
ATC code changes: *(changes will not be implemented before January 2008)*		
Adalimumab	L04AA17	L04AB04
Afelimomab	L04AA16	L04AB03
Anakinra	L04AA14	L04AC03
Basiliximab	L04AA09	L04AC02
Ciclosporin	L04AA01	L04AD01
Daclizumab	L04AA08	L04AC01
Etanercept	L04AA11	L04AB01
Glyceryl trinitrate	D03AX07	C05AE01
Infliximab	L04AA12	L04AB02
Isosorbide dinitrate	D03AX08	C05AE02
Tacrolimus	L04AA05	L04AD02
Tetrabenazine	N05AK01	N07XX06
Tibolone	G03DC05	G03CX01

Previous	New	ATC code
ATC name changes		
Antihemorrhoidals for topical use	Agents for treatment of hemorrhoids and anal fissures for topical use	C05A
Cytokines and immunomodulators	Immunostimulants	L03A
Delapril and calcium channel blockers	Delapril and manidipine	C09BB12
Enalapril and calcium channel blockers	Enalapril and lercanidipine	C09BB02

Previous	New	ATC code
ATC name changes (continued)		
Immunosuppressive agents	Immunosuppressants	L04
Immunosuppressive agents	Immunosuppressants	L04A
Omega-3-triglycerides	Omega-3-triglycerides incl. other esters and acids	C10AX06
Other antihemorrhoidals for topical use	Other agents for treatment of hemorrhoids and anal fissures for topical use	C05AX
Other cytokines and immunomodulators	Other immunostimulants	L03AX
Other immunosuppressive agents	Other immunosuppressants	L04AX
Ramipril and calcium channel blockers	Ramipril and felodipine	C09BB05
Selective immunosuppressive agents	Selective immuno-suppressants	L04AA

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
Abatacept	27	mg	P	L04AA24
Alglucosidase alfa	0.1	g	P	A16AB07
Carglumic acid	0.2	g	O	A16AA05
Insulin (human)	15	mg	Inhal	A10AF01
Lenalidomide	10	mg	O	L04AX04
Parathyroid hormone	0.1	mg	P	H05AA03
Ranolazine	1.5	g	O	C01EB18
Rimonabant	20	mg	O	A08AX01
Rotigotine	6	mg	TD (patch)	N04BC09
Tigecycline	0.1	g	P	J01AA12
Varenicline	2	mg	O	N07BA03

ATC/DDD Classification

ATC/DDD Classification (final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in March 2006. They came into force on 1 October 2006 and will be included in the January 2007 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
Ocular vascular disorder agents		S01L
Angiotensin II antagonists and calcium channel blockers		C09DB
Antivirals for treatment of HIV infections, combinations		J05AR
Insulins and analogues, for inhalation		A10AF
Antineovascularisation agents		S01LA
Papillomavirus vaccines		J07BM
New ATC 5th level codes:		
	Abatacept	L04AA24
	Aliskiren	C09XA02
	Ambrisentan	C02KX02
	Dasatinib	L01XE06
	Deferasirox	V03AC03
	Desvenlafaxine	N06AX23
	Emtricitabine, tenofovir disoproxil and efavirenz	J05AR06
	Fluocinolone acetonide	S01BA15
	Gadofosveset	V08CA11
	Garenoxacin	J01MA19
	Insulin (human)	A10AF01
	Medical air	V03AN05
	Nelarabine	L01BB07
	Nitrous oxide, combinations	N01AX63
	Panitumumab	L01XC08
	Papillomavirus (human types 6, 11, 16, 18)	J07BM01
	Papillomavirus (human types 16, 18)	J07BM02
	Ranibizumab	S01LA04
	Sapropterin	A16AX07
	Telbivudine	J05AF11

ATC level	INN/Common name	ATC code
***New ATC 5th level codes* (continued):**		
	Valsartan and amlodipine	C09DB01
	Varenicline	N07BA03
	Zidovudine, lamivudine and nevirapine	J05AR05
	Zoster, live attenuated	J07BK02

INN/Common name	Previous ATC	New ATC
ATC code changes:		
Anecortave	S01XA16	S01LA02
Lamivudine and abacavir	J05AF30[1)]	J05AR02
Pegaptanib	S01XA17	S01LA03
Tenofovir disoproxil and emtricitabine	J05AF30[1)]	J05AR03
Verteporfin	L01XD02	S01LA01
Zidovudine and lamivudine	J05AF30[1)]	J05AR01
Zidovudine, lamivudine and abacavir	J05AF30[1)]	J05AR04

[1)] J05AF30: ATC level name: Combinations

Previous	New	ATC code
ATC name changes		
Insulins and analogues, fast-acting	Insulins and analogues for injection, fast-acting	A10AB
Insulins and analogues, intermediate-acting	Insulins and analogues for injection, intermediate-acting	A10AC
Insulins and analogues, intermediate-acting combined with fast-acting	Insulins and analogues for injection, intermediate-acting combined with fast-acting	A10AD
Insulins and analogues, long-acting	Insulins and analogues for injection, long-acting	A10AE

New DDDs:

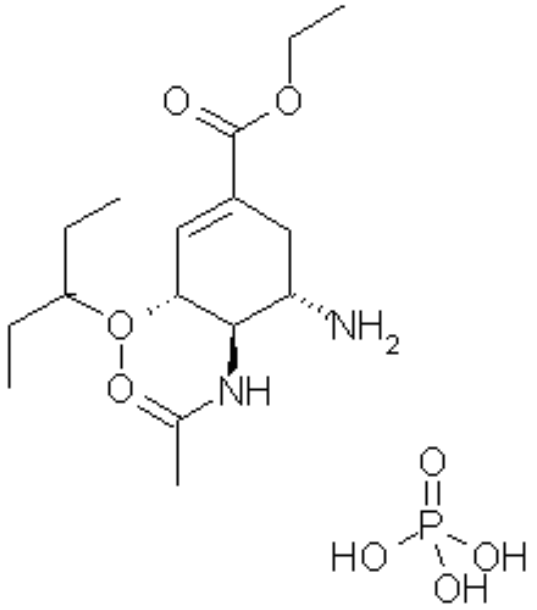
INN/common name	DDD	Unit	Adm.R	ATC code
Cefditoren	0.4	g	O	J01DD16
Entecavir	0.5	mg	O	J05AF10
Erdosteine	0.6	g	O	R05CB15
Estradiol	7.5	mcg	V[1)]	G03CA03
Hydroxybutyric acid	7.5	g	O	N07XX04
Ibuprofen	30	mg	P	C01EB16
Ivabradine	10	mg	O	C01EB17
Natalizumab	10	mg	P	L04AA23
Posaconazole	0.8	g	O	J02AC04
Tipranavir	1	g	O	J05AE09

[1)] vaginal ring, refers to amount delivered per 24 hours

International Pharmacopoeia

Draft proposal for *The International Pharmacopoeia* (December 2006)

Oseltamivir phosphate



$C_{16}H_{28}N_2O_4$, H_3PO_4

Relative molecular mass. 410.4

Chemical name. (3R,4R,5S)-4-Acetylamino-5-amino-3-(1-ethylpropoxy)-1 -cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1)

Description. A white to off-white powder.

Solubility. Freely soluble in water.

Category. Antiviral.

Storage. Oseltamivir phosphate should be kept in a well-closed container.

Requirements

Definition. Oseltamivir phosphate contains not less than 98.0% and not more than 101.5% of $C_{16}H_{28}N_2O_4$, H_3PO_4, calculated with reference to the anhydrous substance.

Manufacture. The production method is validated to ensure that the substance is the (3R, 4R, 5S) enantiomer and that less than 100 ppm of the impurity ethyl (2R, 3R, 4R, 5S)-2-azido-4-acetylamino-5-amino-3-(1-ethyl-propoxy)-cyclohexane-1-carboxylate is present, when determined by a suitable method such as liquid chromatography combined with mass spectrometry (LC-MS). Where necessary, the production method is also validated to demonstrate that tributyl phophine oxide is not detectable in the final product, when examined by a suitable method such as gas chromatography (GC).

Identity test

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from oseltamivir phosphate RS or with the *reference spectrum* of oseltamivir phosphate.

B. Determine the specific optical rotation (as described under method 1.4) using a 10 mg/ml solution and calculate with reference to the anh
ydrous substance; $[\alpha]_D^{25^\circ C}$ = - 30.7 to – 32.6˚.

[Note from the Secretariat: It is intended to include additional, alternative identification tests, if possible. However, it is noted that oseltamivir does not exhibit a suitable UV spectrum. The possibility of a thin-layer chromatographic test is under investigation.]

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 1 and determine the heavy metal content according to Method A; not more than 10 μg/g.

Sulfated ash (as described under method 2.3). Not more than 2.0 mg/g.

Water. Determine as described under 2.8 Determination of water by Karl Fischer Method, Method A. Use 1.0 g of the test substance. The water content is not more than
5 mg/g.

Related substances. Carry out the assay as described under 1.14.4 High performance liquid chromatography, using the same conditions as under Assay, using solutions (1) (3) and (4).

Inject separately 15 μl each of solution (1), (3) and (4) and of the dissolution solvent in the chromatographic system. Examine the blank chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

Use the chromatogram obtained with solution (4) to identify the peaks due to impurities A, B, C, D, E and F. The impurity peaks are eluted at the following relative retention times with reference to oseltamivir phosphate (retention time about 19 minutes): impurity A about 0.16, impurity B about 0.17, impurity C about 0.51, impurity D about 0.55, impurity E about 0.59, impurity F about 1.5. The test is not valid unless the resolution between the peaks due to impurities A and B and that between the peaks due to impurities C, D and E is at least 1.0.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.4, is not greater than 3 times the area of the peak in the chromatogram obtained with solution (3) (0.3%), the area of any peak corresponding to impurity C , when multiplied by a correction factor of 2.7, is not greater than the area of the peak in the chromatogram obtained with solution (3) (0.1%), the area of any other peak, apart from the principal peak, is not greater than the area of the peak in the chromatogram obtained with solution (3) (0.1%). The sum of the areas of all the peaks, apart from the principal peak, is not greater than 7 times the area of the peak obtained with solution (3) (0.7%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (3) (0.05%).

Assay

[Note from the Secretariat: A potentiometric titration will be included as an alternative assay to HPLC if a suitable method is available.]

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with octylsilyl silica gel for chromatography (5 μm).

The mobile phase consists of a mixture of 620 ml of 0.05 M potassium dihydrogen phosphate (adjusted to pH 6 with potassium hydroxide (~110g/l TS), 245 ml methanol R and 135 ml acetonitrile R.

Operate with a flow rate of 1.2 ml per minute and the column oven temperature at 50°C. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 207 nm.

Prepare the following solutions in the dissolution solvent by mixing 620 ml of water R, 245 ml of methanol R and 135 ml of acetonitrile R.

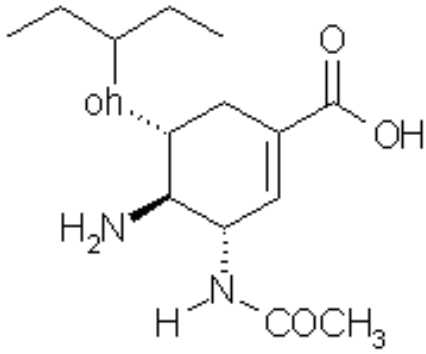
For solution (1) dissolve 50 mg of the test substance in the dissolution solvent and dilute to 50.0 ml with the same solvent. For solution (2) dissolve 50 mg of oseltamivir phosphate RS in the dissolution solvent and dilute to 50 ml with the same solvent. For solution (3) dilute 1.0 ml of solution (1) to 100 ml with dissolution solvent and then dilute 1.0 ml of this solution to 10 ml with the same solvent. For solution (4) dissolve 5 mg of oseltamivir phosphate for system suitability RS (containing oseltamivir phosphate and impurities A to F) in the dissolution solvent and dilute to 5 ml with the same solvent.

[Note from the Secretariat: the means of identifying the impurity peaks is subject to confirmation.]

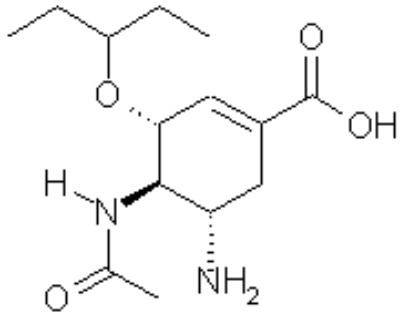
Inject separately 15 µl each of solution (1), (2) and (4) and of the dissolution solvent in the chromatographic system. Examine the blank chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solutions (1) and (2). The assay is not valid unless, in the chromatogram obtained with solution (4), the resolution between the peaks due to impurities A and B and that between the peaks due to impurities C, D and E is at least 1.0.

Measure the areas of the peak responses in the chromatograms obtained with solutions (1) and (2). Calculate the percentage of oseltamivir phosphate, $C_{16}H_{28}N_2O_4$, H_3PO_4.

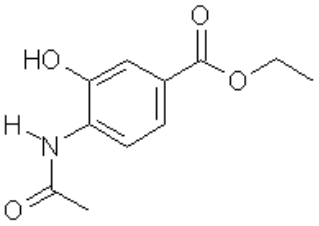
Impurities



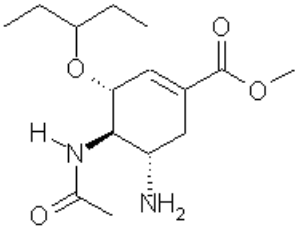
A. Ro 0640951 (N5-acetyl carboxylic acid)



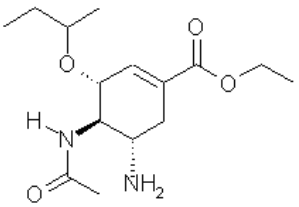
B. Ro 0640802 (Carboxylic acid)



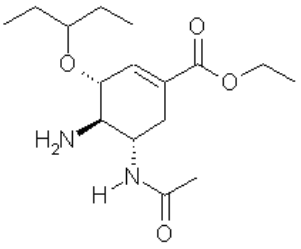
C. Ro 0646661



D. Ro 0641634 (Methyl ester)



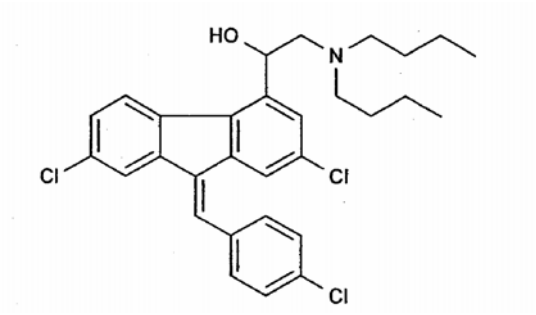
E. Ro 0647943 (Isobutylether derivative)



F. Ro 0640952 (N-5 acetyl derivative)

Draft proposal for *The International Pharmacopoeia* (October 2006)

Lumefantrinum
Lumefantrine



$C_{30}H_{32}Cl_3NO$

Relative molecular mass. 528.9

Chemical name. 2-Dibutylamino-1-[2, 7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl]-ethanol (racemate); CAS Reg. No. 82186-77-4

[Note from Secretariat: Name and structure to be checked.]

Other name. Benflumetol.

Description. A yellow crystalline powder.

Solubility. Practically insoluble in water; freely soluble in dimethylformamide R and ethyl acetate R; soluble in dichloromethane R; slightly soluble in ethanol R and methanol R.

Category. Antimalarial.

Storage. Lumefantrine should be kept in a well-closed container.

Additional information. Lumefantrine melts at 128 –132 °C.

Requirements

Definition. Lumefantrine contains not less than 98.5% and not more than 101.0% of $C_{30}H_{32}Cl_3NO$, calculated with reference to the dried substance.

Identity test

Either tests A and B or tests C may be applied.

A. Carry out test A.1. or, where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 40 volumes of light petroleum R1, 10 volumes of ethyl acetate R and 5 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 μl of each of 2 solutions in ethyl acetate R, containing (A) 5 mg of the test substance per ml and (B) 5 mg of lumefantrine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B.

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 40 volumes of light petroleum R1, 10 volumes of ethyl acetate R and 5 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 μl of each of 2 solutions in ethyl acetate R, containing (A) 5 mg of the test substance per ml and (B) 5 mg of lumefantrine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air and expose to iodine vapours until spots appear. Examine the chromatogram immediately in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B.

B. Dissolve about 20 mg, accurately weighed, in 200 ml of methanol R by sonication for about 15 minutes. Allow the solution to cool to room temperature and dilute fivefold with methanol R. The absorption spectrum (as described under method 1.6) of the diluted solution when observed between 275 and 325 nm, exhibits a maximum at about 302 nm; the specific absorbance ($A^{1\%}_{1cm}$) is between 314 and 348.

C. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from lumefantrine RS or with the *reference spectrum* of lumefantrine.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3 and determine the heavy metals content according to Method A; not more than 20 μg/g.

Sulfated ash (as described under method 2.3). Not more than 2.0 mg/g.

Loss on Drying. Dry for 3 hours at 105 °C; it loses not more than 5.0 mg/g.

Related substances
[Note from the Secretariat: The tentative method proposed below is still under investigation.]

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (12.5 cm x 4.0 mm) packed with particles of silica gel,

the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm). (Nucleosil 100 is suitable).

Use the following conditions for gradient elution:

Mobile phase A: 200 volumes of ion pair reagent, 500 volumes of water R, 250 volumes of acetonitrile R and 50 volumes of 1-propanol R.

Mobile phase B: 200 volumes of ion pair reagent, 100 volumes of water R, 650 volumes of acetonitrile R and 50 volumes of 1-propanol R.

Mobile phase C: 100 volumes of purified water, 100 volumes of acetonitrile R and 400 volumes of 1-propanol R.

Prepare the ion pair reagent by dissolving 5.65 g of sodium hexanesulfonate R and 2.75 g of sodium dihydrogen phosphate R in about 900 ml of water R. Adjust the pH to 2.3 using phosphoric acid (~105 g/l) TS, dilute to 1000 ml and filter through a 0.5 μm filter.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comments
0-14	25	75	0	Isocratic
14-19	25 to 0	75 to 100	0	Linear gradient
19-20	0	100 to 80	0 to 20	Linear gradient
20-26	0	80	20	Isocratic
26-27	0	80 to 30	20 to 70	Linear gradient
27-50	0	30	70	Isocratic
50-51	0 to 25	30 to 75	70 to 0	Linear gradient
51-56	25	75		Isocratic re-equilibration

Prepare the following solutions in acetonitrile R. For solution (1) use 0.3 mg of the test substance per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 0.3 ìg of lumefantrine per ml. For solution (3) dissolve 3 mg of lumefantrine for system suitability RS (containing lumefantrine and impurities A, B and C) in 10 ml.

[Note from the Secretariat: The availability of lumefantrine spiked with impurities A, B and C is under investigation.]

Operate with a flow rate of 2.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 265 nm.

Inject 20 μl of solution (3). The impurity peaks are eluted at the following relative retention times with reference to lumefantrine (retention time about 10 minutes): impurity A about 0.9; impurity B about 4.3 and impurity C about 4.6. The test is not valid unless the resolution factor between impurity A and lumefantrine is not less than 0.5. If necessary adjust the amount of acetonitrile in mobile phase A, or adjust the gradient programme.

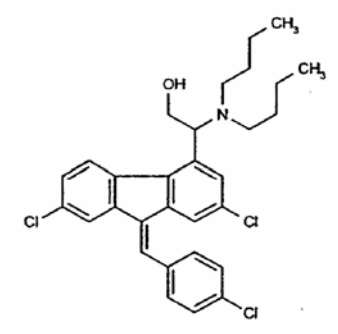
Inject alternatively 20 l each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the area of any individual peak corresponding to impurity C is not greater than 3.0 times the area of the principal peak obtained with solution (2) (0.3%). The area of any other impurity peak is not greater than the area of the principal peak obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than 3.0 times the area of the principal peak obtained with solution (2) (0.3%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (2) (0.05%) and any peak resulting from the solvent.

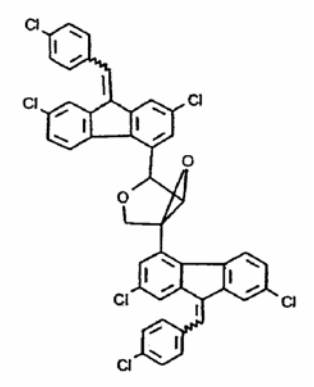
Assay
Dissolve about 0.51 g, accurately weighed, in 50 ml of glacial acetic acid R1 by stirring for about 15 minutes, and titrate with perchloric acid (0.1 mol/l) VS, determine the endpoint potentiometrically as described under 2.6 Non aqueous titration, Method A. Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 52.89 mg of $C_{30}H_{32}Cl_3NO$.

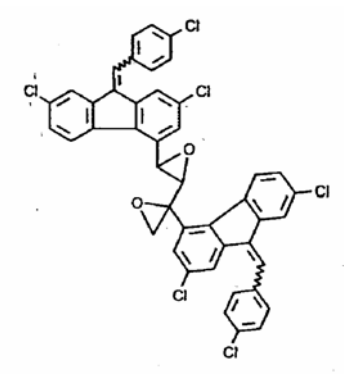
Impurities
The following list of known and potential impurities that have been shown to be controlled by the tests in this monograph is given for information.

A. 529.0 $C_{30}H_{32}Cl_3NO$



B. and C. 797.4 $C_{44}H_{24}Cl_6O_2$





The International Pharmacopoeia

Dissolution tests

Work has been carried out on developing dissolution tests for addition to certain tablet monographs of *The International Pharmacopoeia* in accordance with the approach and priorities agreed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

It is proposed to add tests to the following monographs by means of the 1st Supplement to the 4th Edition of *The International Pharmacopoeia*. The format of these tests is modelled on that used in the test that has been added to the monograph for "Phenoxymethylpenicillin potassium tablets" in the Fourth Edition. A test based on this format has also been included in the adopted monograph for "Isoniazid and Ethambutol hydrochloride tablets", the final text for which can be found at: http://www.who.int/medicines/publications/pharmacopoeia/mon_tb/en/index.html).

The method text "5.5 Dissolution test for solid oral dosage forms" from the 4th edition of *The International Pharmacopoeia* is appended to this document as Annex 1 for convenience.

Chloroquine phosphate tablets

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 10 ml of the medium through an in-line filter. Measure the absorbance of the filtered sample, suitably diluted if necessary, at the maximum at 342 nm. At the same time measure the absorbance at the maximum at 342 nm of a suitable solution of chloroquine diphosphate RS in dissolution buffer, pH 6.8, TS, using the same buffer as a blank.

For each of the six tablets tested, calculate the total amount of chloroquine phosphate, $C_{18}H_{26}Cl\,N_3$, $2H_3PO_4$, in the medium. The average amount in solution is not less than 85% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 85%.

Chloroquine sulfate tablets

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 10 ml of the medium through an in-line filter. Measure the absorbance of the filtered sample, suitably diluted if necessary, at the maximum at 342 nm. At the same time measure the absorbance at the maximum at 342 nm of a suitable solution of chloroquine sulfate RS in dissolution buffer, pH 6.8, TS, using the same buffer as a blank.

For each of the six tablets tested, calculate the total amount of chloroquine sulfate, $C_{18}H_{26}Cl\,N_3$, H_2SO_4, in the medium. The average amount in solution is not less than

85% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 85%.

Ethambutol hydrochloride tablets

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 10 ml of the medium through an in-line filter.

Either

Determine the content of ethambutol hydrochloride, $C_{10}H_{24}N_2O_2$, 2HCl, as described below under Assay.

Or

Measure the absorbance of the filtered sample, suitably diluted with copper-acetate buffer, pH 5.0, TS (new reagent) in a ratio of 1:10 or 1:20, depending on the strength of ethambutol dihydrochloride tablets tested, at the maximum at 270 nm. At the same time measure the absorbance at the maximum at 270 nm of a suitable solution of ethambutol hydrochloride RS in copper-acetate buffer, pH 5.0, TS, using the same buffer as a blank.

[Note from the Secretariat: Please comment on which of the two options for method of analysis is considered most suitable.]

For each of the six tablets tested, calculate the total amount of ethambutol hydrochloride, $C_{10}H_{24}N_2O_2$, 2HCl, in the medium. The average amount in solution is not less than 85% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 85%.

Doxycycline tablets

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 10 ml of the medium through an in-line filter.

Either

Allow the filtered sample to cool to room temperature and dilute … ml to … ml with hydrochloric acid (0.01mol/l) VS [solution (3)]. Determine the content of doxycycline, $C_{22}H_{24}N_2O_8$ as described below under Assay using solution (3) in place of solution (1).

Or

Measure the absorbance of the filtered sample, suitably diluted if necessary, at the maximum at 274 nm. At the same time measure the absorbance at the maximum at 274 nm of a suitable solution of doxycycline hyclate RS in dissolution buffer, pH 6.8, TS, using the same buffer as a blank.

[Note from the Secretariat: Please comment on which of the two options for method of analysis is considered most suitable. If the first option is used, the details of preparation for solution (3) will be given.]

For each of the six tablets tested, calculate the total amount of doxycycline, $C_{22}H_{24}N_2O_8$ in the medium from the results obtained and from the declared content of $C_{22}H_{24}N_2O_8$ in doxycycline hyclate RS. The average amount in solution is not less than 85% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 85%.

Isoniazid tablets

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 10 ml of the medium directly through an in-line filter. Measure the absorbance of the filtered sample, suitably diluted if necessary, at the maximum at 263 nm. At the same time measure the absorbance at the maximum at 263 nm of a suitable solution of isoniazid RS in dissolution buffer, pH 6.8, TS, using the same buffer as blank.

For each of the six tablets tested, calculate the total amount of isoniazid, $C_6H_7N_3O$ in the medium. The average amount in solution is not less than 85% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 85%.

Metronidazole tablets

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 10 ml of the medium directly through an in-line filter. Measure the absorbance of the filtered sample, suitably diluted if necessary, at the maximum at 319 nm. At the same time measure the absorbance at the maximum at 319 nm of a suitable solution of metronidazole RS in dissolution buffer, pH 6.8, TS, using the same buffer as blank.

For each of the six tablets tested, calculate the total amount of metronidazole, $C_6H_9N_3O_3$ in the medium. The average amount in solution is not less than 85% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 85%.

Pyrazinamide tablets

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 10 ml of the medium through an in-line filter. Determine the content of pyrazinamide, $C_5H_5N_3O$, as described below under Assay.

For each of the six tablets tested, calculate the total amount of pyrazinamide, $C_5H_5N_3O$, in the medium from the results obtained. The average amount in solution is not less than 85% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 85%.

Note: Buffers

The composition of the following dissolution buffer will be amended to:

Dissolution buffer, pH 6.8, TS

Dissolve 6.9 g of sodium dihydrogen phosphate R and 0.9 g of sodium hydroxide R in 800 ml of deionized water, adjust the pH to 6.8 with sodium hydroxide (~80g/l) TS and dilute to1000 ml with water.

A new reagent entry will be included for:

Copper-acetate buffer, pH 5.0, TS

Dissolve 55 mg Ammonium acetate R, 200 mg Copper(II)acetate R in 800 ml of water R, adjust the pH to 5.00 with Glacial acetic acid R and dilute to1000 ml with water R.

Recent Publications, Information and Events

International Pharmacopoeia: fourth edition

This new edition consolidates the texts of the five separate volumes of the third edition. In preparing this consolidated edition, a review has been undertaken of the general notices with additions and amendments to clarify interpretation and facilitate application of the requirements by the user.

Certain aspects of the layout and format have been revised. In this edition, all the monograph texts are brought together in one section and the method texts in another. Each of these major sections are divided into appropriate sub-sections and the method texts are numbered for ease of cross-reference.

New monographs for the following antiretroviral substances have been published in the Fourth edition: didanosine, indinavir sulfate, nelfinavir mesilate, nevirapine, ritonavir, saquinovir, and saquinovir mesilate. Revision of the current monograph for oral rehydration salts has been carried out to conform to the modified formula published in the 13th Model List of Essential Medicines and in the WHO Model Formulary 2004.

Method texts that have been updated to include, for example, the text on high performance liquid chromatography [HPLC]. This has been revised to clarify certain technical terms and to add advice on adjustment of chromatographic conditions.

Available from WHO Press, CH-1211 Geneva 27 • Switzerland. E-mail: bookorders@who.int or http://www.who.int/bookorders

Draft report: Specifications for Pharmaceutical Preparations

The advice and recommendations provided by this Expert Committee on Specifications for Pharmaceutical Preparations are intended to serve national and regional authorities and, in particular, drug regulatory authorities, procurement agencies, and major international bodies and organizations, such as the Global Fund, and UNICEF. The international guidelines, specifications and nomenclature developed under the aegis of the Expert Committee serve all Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, and underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme, and Stop TB. Making resources available for these activities is, therefore, very cost-effective.

1. The International Pharmacopoeia. Related substances tests: dosage form monographs (Annex 1)

2. List of available International Chemical Reference Substances (Annex 2)

3. General guidelines for the establishment, maintenance and distribution of chemical reference substances (Annex 3)

4. Procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies (Annex 4)

5. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (Annex 5)

6. Guidance on variations to a prequalified product dossier (Annex 6)

Available on http://www.who.int/medicines

User guide for micro, small and medium sized enterprises

A user guide has been published by the European Medicines Agency for micro, small and medium sized enterprises (SMEs) on the administrative and procedural aspects of the provisions laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs operating in the pharmaceutical sector. Its aim is to facilitate understanding of the main aspects of medicinal product legislation. The guide is structured to follow, as far as possible, the chronological stages of developing a medicinal product. A concise overview of the scientific data requirements for obtaining a marketing authorization in the European Union (EU) is provided. The regulatory procedures that are in place to optimize development and obtain an EU marketing authorization are summarized.

This initial version of the guide focuses primarily on the requirements for authorizing innovative medicinal products for human use. A chapter on veterinary medicinal product development is under preparation and will be incorporated into the next version of the guide. The scope of the guide may also be broadened at a later stage to include other aspects of interest for SMEs, such as generics, taking into account feedback received during the consultation phase which ended in March 2007.

The guide is not intended to be an exhaustive document but rather to raise SME awareness of the various more detailed sources of information available, with links throughout the text to additional information.

Pursuant to the new regulation, SMEs now have access to financial assistance (in the form of fee reductions and fee deferrals) and administrative assistance from the agency, details of which are outlined in Section 2 of the guide. To facilitate contact with the agency, an 'SME Office' has been launched that is dedicated to addressing the particular needs of smaller companies.

EMEA. User guide for micro, small and medium sized enterprises (SMEs). Doc. Ref. EMEA/206798/2006Draft, 31 January 2007.http://www.emea.europa.eu

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 57

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 (1–91) and Recommended (1–52) International Nonproprietary Names can be found in *Cumulative List No. 11, 2004* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 57

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 (1–91) et recommandées (1–52) dans la *Liste récapitulative No. 11, 2004* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 57

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 (1–91) y Recomendadas (1–52) se encuentran reunidas en *Cumulative List No. 11, 2004* (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 molecular; Fórmula desarrollada*

abagovomabum*

abagovomab — immunoglobulin G1, anti-idiotype anti-[anti-(*Homo sapiens* cancer antigen 125, CA 125, MUC-16) *Mus musculus* monoclonal antibody OC125] *Mus musculus* monoclonal antibody ACA125, clone 3D5 gamma1 heavy chain disulfide with clone 3D5 kappa light chain; (223-223'':226-226'':228-228'') trisdisulfide dimer

abagovomab — immunoglobuline G1, anti-idiotype anti-[anti-(*Homo sapiens* cancer antigen 125, CA 125, MUC-16) anticorps monoclonal murin OC125] anticorps monoclonal murin ACA125, chaîne lourde gamma1 du clone 3D5 unie par un pont disulfure à la chaîne légère kappa du clone 3D5; dimère (223-223'':226-226'':228-228'')-trisdisulfure

abagovomab — inmunoglobulina G1, anti-idiotipo anti-[anti-(*Homo sapiens* cancer antígeno 125, CA 125, MUC-16) anticuerpo monoclonal murino OC125] anticuerpo monoclonal murino ACA125, cadena pesada gamma1 del clon 3D5 unida por un puente disulfuro a la cadena ligera kappa del clon 3D5; dímero (223-223'':226-226'':228-228'')-trisdisulfuro

Heavy chain/Chaîne lourde/Cadena pesada

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QVKLQESGAE LARPGASVKL SCKASGYTFT NYWMQWVKQR PGQGLDWIGA  50
IYPGDGNTRY THKFKGKATL TADKSSSTAY MQLSSLASED SGVYYCARGE 100
GNYAWFAYWG QGTTVTVSSA KTTPPSVYPL APGSAAQTNS MVTLGCLVKG 150
YFPEPVTVTW NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT 200
CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT 250
LTPKVTCVVV DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS 300
ELPIMHQDWL NGKEFKCRVN SAAFPAPIEK TISKTKGRPK APQVYTIPPP 350
KEQMAKDKVS LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMDTDGSY 400
FVYSKLNVQK SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK         443
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Light chain/Chaîne légère/Cadena ligera

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DIELTQSPAS LSASVGETVT ITCQASENIY SYLAWHQQKQ GKSPQLLVYN  50
AKTLAGGVSS RFSGSGSGTH FSLKIKSLQP EDFGIYYCQH HYGILPTFGG 100
GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI 150
DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT 200
STSPIVKSFN RNEC                                        214
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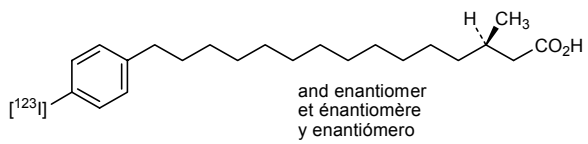
acidum iodofilticum (^{123}I)

iodofiltic acid (^{123}I) — (3*RS*)-15-[4-[^{123}I]iodophenyl]3-methylpentadecanoic acid

acide iodofiltique (^{123}I) — acide (3*RS*)-15-(4-[^{123}I]iodophényl)-3-méthylpentadécanoïque

ácido iodofíltico (^{123}I) — ácido (3*RS*)-15-(4-[^{123}I]iodofenil)-3-metilpentadecanoico

$C_{22}H_{35}{}^{123}IO_2$



and enantiomer
et énantiomère
y enantiómero

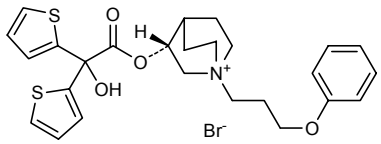
aclidinii bromidum

aclidinium bromide — (3R)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-$1\lambda^5$-azabicyclo[2.2.2]octan-1-ylium bromide

bromure d'aclidinium — bromure de (3*R*)-3-[[hydroxybis(thiophén-2-yl)acétyl]oxy]-1-(3-phénoxypropyl)-1-azoniabicyclo[2.2.2]octane

bromuro de aclidinio — bromuro de (3R)-1-(3-fenoxipropil)-3-[(hidroxi)di(tiofen-2-il)acetiloxi]-$1\lambda^5$-azabiciclo[2.2.2]octan-1-ilio

$C_{26}H_{30}BrNO_4S_2$



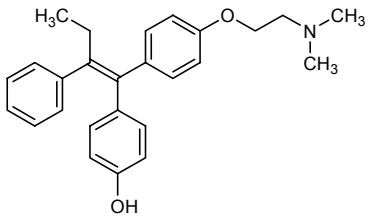
afimoxifenum

afimoxifene — 4-(1-{4-[2-(dimethylamino)ethoxy]phenyl}-2-phenylbut-1-enyl)phenol

afimoxifène — 4-[1-[4-[2-(diméthylamino)éthoxy]phényl]-2-phénylbut-1-ényl]phénol

afimoxifeno — 4-[1-[4-[2-(dimetilamino)etoxi]fenil]-2-fenilbut-1-enil]fenol

$C_{26}H_{29}NO_2$



and *Z* isomer
et l'isomère *Z*
y el isómero *Z*

afliberceptum*

aflibercept — des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 *C*-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer

aflibercept — (211-211':214-214')-bisdisulfure du dimère de la dès-432-lysine-[récepteur 1 humain du facteur de croissance endothélial vasculaire-(103-204)-peptide (contenant le domaine Ig-like C2-type 2) protéine de fusion avec le récepteur 2 humain du facteur de croissance endothélial vasculaire-(206-308)-peptide (contenant un fragment du domaine Ig-like C2-type 3) protéine de fusion avec l'immunoglobuline G1 humaine-(227 résidus *C*-terminaux)-peptide (fragment Fc)]

aflibercept

(211-211':214-214')-bisdisulfuro del dímero de la des-432-lisina-[receptor 1 humano del factor de crecimiento endotelial vascular-(103-204)-péptido (que contiene el dominio Ig-like C2-tipo 2) proteína de fusión con el receptor 2 humano del factor de crecimiento endotelial vascular-(206-308)-péptido (que contiene un fragmento del dominio Ig-like C2-tipo 3) proteína de fusión con la inmunoglobulina G1 humana-(227 restos *C*-terminales)-péptido (fragmento Fc)]

$C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$

Monomer / Monomère / Monómero

```
SDTGRPFVEM YSEIPEIIHM TEGRELVIPC RVTSPNITVT LKKFPLDTLI  50
PDGKRIIWDS RKGFIISNAT YKEIGLLTCE ATVNGHLYKT NYLTHRQTNT 100
IIDVVLSPSH GIELSVGEKL VLNCTARTEL NVGIDFNWEY PSSKHQHKKL 150
VNRDLKTQSG SEMKKFLSTL TIDGVTRSDQ GLYTCAASSG LMTKKNSTFV 200
RVHEKDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD 250
VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN 300
GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL 350
TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS 400
RWQQGNVFSC SVMHEALHNH YTQKSLSLSP G                     431
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

30-79 30'-79' 124-185 124'-185' 211-211'
214-214' 246-306 246'-306' 352-410 352'-410'

aleglitazarum

aleglitazar

(2*S*)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-benzothiophen-7-yl}propanoic acid

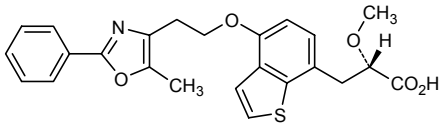
aléglitazar

acide (2*S*)-2-méthoxy-3-[4-[2-(5-méthyl-2-phényl-1,3-oxazol-4-yl)éthoxy]-1-benzothiophén-7-yl]propanoïque

aleglitazar

ácido (2*S*)-3-{4-[2-(2-fenil-1,3-oxazol-5-metil-4-il)etoxi]-1-benzotiofen-7-il}-2-metoxipropanoico

$C_{24}H_{23}NO_5S$



alferminogenum tadenovecum*

alferminogene tadenovec

recombinant human adenovirus 5 (replication-deficient, E1-deleted) containing a human fibroblast growth factor-4 cDNA sequence driven by a cytomegalovirus promoter

alferminogène tadénovec

adénovirus 5 humain recombinant (réplication-déficient, région E1-supprimée) contenant la séquence ADN-copie du facteur 4 de croissance du fibroblaste humain sous contrôle d'un promoteur de cytomégalovirus

alferminogén tadenovec

adenovirus 5 humano recombinante (replicación-deficiente, con delección E1) que contiene la secuencia DNA-copia del factor-4 de crecimiento de fibroblastos humanos controlado por un promotor de citomegalovirus

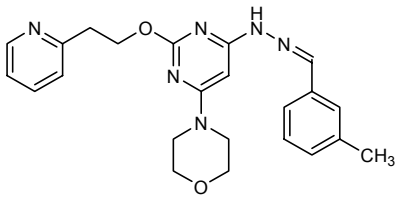
apilimodum

apilimod — 1-[(3-methylphenyl)methylidene]-2-{6-(morpholin-4-yl)-2-[2-(pyridin-2-yl)ethoxy]pyrimidin-4-yl}hydrazine

apilimod — 1-(3-méthylbenzylidène)-2-[6-(morpholin-4-yl)-2-[2-(pyridin-2-yl)=éthoxy]pyrimidin-4-yl]diazane

apilimod — 1-(3-metilbencilideno)-2-[6-(morfolin-4-il)-2-[2-(piridin-2-il)etoxi]=pirimidin-4-il]diazano

$C_{23}H_{26}N_6O_2$



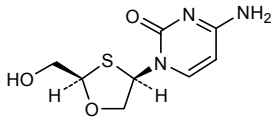
apricitabinum

apricitabine — 4-amino-1-[(2*R*,4*R*)-2-(hydroxymethyl)-1,3-oxathiolan-4-yl]pyrimidin-2(1*H*)-one

apricitabine — (-)-4-amino-1-[(2*R*,4*R*)-2-(hydroxyméthyl)-1,3-oxathiolan-4-yl]=pyrimidin-2(1*H*)-one

apricitabina — (-)-4-amino-1-[(2*R*,4*R*)-2-(hidroximetil)-1,3-oxatiolan-4-il]pirimidin-2(1*H*)-ona

$C_8H_{11}N_3O_3S$



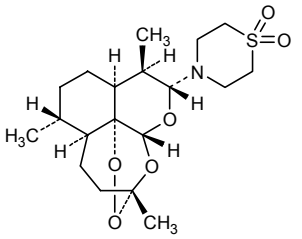
artemisonum

artemisone — 4-[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*R*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxypyrano[4,3-*j*][1,2]benzodioxepin-10-yl]=thiomorpholine-1,1-dione

artémisone — 1,1-dioxyde de 4-[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*R*,12*R*,12a*R*)-3,6,9-triméthyldécahydro-3,12-époxypyrano[4,3-*j*]-1,2-benzodioxépin-10-yl]thiomorpholine

artemisona — 1,1-dióxido de 4-[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*R*,12*R*,12a*R*)-3,6,9-trimetildecahidro-3,12-epoxipirano[4,3-*j*]-1,2-benzodioxepin-10-il]=tiomorfolina

$C_{19}H_{31}NO_6S$



ataciceptum*

atacicept — [86-serine,101-glutamic acid,196-serine,197-serine,222-aspartic acid,224-leucine][human tumor necrosis factor receptor superfamily member 13B-(30-110)-peptide (TACI fragment containing TNFR-Cys 1 and TNFR-Cys 2) fusion protein with human immunogobulin G1-(232 *C*-terminal residues)-peptide (γ1-chain Fc fragment), (92-92':95-95')-bisdisulfide dimer

atacicept — (92-92':95-95')-bisdisulfure du dimère de la [86-sérine,101-acide glutamique,196-sérine,197-sérine,222-acide aspartique, 224-leucine]-protéine de fusion du membre 13B humain de la superfamille des récepteurs du facteur de nécrose tumorale-(30-110)-peptide (portion du TACI incluant les deux régions riches en cystéine) avec l'immunoglobuline G1 humaine-(232 résidus *C*-terminaux)-peptide (fragment Fc de la chaîne γ1)

atacicept — 92-92':95-95')-bisdisulfuro del dímero de la [86-serina,101-ácido glutámico,196-serina,197-serina,222-ácido aspártico,224-leucina]-proteína de fusión del miembro 13B humano de la superfamilia de receptores del factor de necrosis tumoral-(30-110)-péptido (porción del TACI que incluye las dos regiones ricas en cisteína) con la inmunoglobulina G1 humana-(232 restos *C*-terminales)-péptido (fragmento Fc de la cadena γ1)

$C_{3104}H_{4788}N_{856}O_{950}S_{44}$

Monomer / Monomère / Monómero

```
AMRSCPEEQY  WDPLLGTCMS  CKTICNHQSQ  RTCAAFCRSL  SCRKEQGKFY  50
DHLLRDCISC  ASICGQHPKQ  CAYFCENKLR  SEPKSSDKTH  TCPPCPAPEA  100
EGAPSVFLFP  PKPKDTLMIS  RTPEVTCVVV  DVSHEDPEVK  FNWYVDGVEV  150
HNAKTKPREE  QYNSTYRVVS  VLTVLHQDWL  NGKEYKCKVS  NKALPSSIEK  200
TISKAKGQPR  EPQVYTLPPS  RDELTKNQVS  LTCLVKGFYP  SDIAVEWESN  250
GQPENNYKTT  PPVLDSDGSF  FLYSKLTVDK  SRWQQGNVFS  CSVMHEALHN  300
HYTQKSLSLS  PGK                                            313
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
5-18   5'-18'  21-33  21'-33'  25-37  25'-37'  42-57   42'-57'  60-71
60'-71'  64-75  64'-75'  92-92'  95-95'  127-187  127'-187'  233-291  233'-291'
```

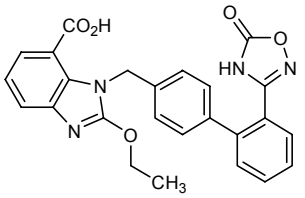
azilsartanum

azilsartan — 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-yl]methyl}-1*H*-benzimidazole-7-carboxylic acid

azilsartan — acide 2-éthoxy-1-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)=biphényl-4-yl]méthyl]-1*H*-benzimidazole-7-carboxylique

azilsartán — ácido 2-etoxi-1-{[2'-(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)bifenil-4-il]metil}-1*H*-bencimidazol-7-carboxílico

$C_{25}H_{20}N_4O_5$



bavituximabum*

bavituximab — immunoglobulin G1, anti-(phosphatidylserine) chimeric monoclonal ch3G4; gamma1 heavy chain (*Mus musculus* VH-*Homo sapiens* IGHG1) (223-214')-disulfide with kappa light chain (*Mus musculus* V-KAPPA-*Homo sapiens* IGKC); (229-229'':232-232'')-bisdisulfide dimer

bavituximab — immunoglobuline G1, anti-(phosphatidylsérine) anticorps monoclonal chimérique ch3G4; chaîne lourde gamma1 (*Mus musculus* VH-*Homo sapiens* IGHG1) (223-214')-disulfure avec la chaîne légère kappa (*Mus musculus* V-KAPPA-*Homo sapiens* IGKC); dimère (229-229'':232-232'')-bisdisulfure

bavituximab — inmunoglobulina G1, anti-(fosfatidilserina) anticuerpo monoclonal quimérico ch3G4; cadena pesada gamma1 (*Mus musculus* VH-*Homo sapiens* IGHG1) (223-214')-disulfuro con la cadena ligera kappa (*Mus musculus* V-KAPPA-*Homo sapiens* IGKC), dímero (229-229'':232-232'')-bisdisulfuro

$C_{6446}H_{9946}N_{1702}O_{2042}S_{42}$

Heavy chain / Chaîne lourde / Cadena pesada

EVQLQQSGPE	LEKPGASVKL	SCKASGYSFT	GYNMNWVKQS	HGKSLEWIGH 50
IDPYYGDTSY	NQKFRGKATL	TVDKSSSTAY	MQLKSLTSED	SAVYYCVKGG 100
YYGHWYFDVW	GAGTTVTVSS	ASTKGPSVFP	LAPSSKSTSG	GTAALGCLVK 150
DYFPEPVTVS	WNSGALTSGV	HTFPAVLQSS	GLYSLSSVVT	VPSSSLGTQT 200
YICNVNHKPS	NTKVDKKVEP	KSCDKTHTCP	PCPAPELLGG	PSVFLFPPKP 250
KDTLMISRTP	EVTCVVVDVS	HEDPEVKFNW	YVDGVEVHNA	KTKPREEQYN 300
STYRVVSVLT	VLHQDWLNGK	EYKCKVSNKA	LPAPIEKTIS	KAKGQPREPQ 350
VYTLPPSRDE	LTKNQVSLTC	LVKGFYPSDI	AVEWESNGQP	ENNYKTTPPV 400
LDSDGSFFLY	SKLTVDKSRW	QQGNVFSCSV	MHEALHNHYT	QKSLSLSPGK 450

k Chain / Chaîne k / Cadena k

DIQMTQSPSS	LSASLGERVS	LTCRASQDIG	SSLNWLQQGP	DGTIKRLIYA 50'
TSSLDSGVPK	RFSGSRSGSD	YSLTISSLES	EDFVDYYCLQ	YVSSPPTFGA 100'
GTKLELKRAD	AAPSVFIFPP	SDEQLKSGTA	SVVCLLNNFY	PREAKVQWKV 150'
DNALQSGNSQ	ESVTEQDSKD	STYSLSSTLT	LSKADYEKHK	VYACEVTHQG 200'
LSSPVTKSFN	RGEC			214'

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

22-96 22''-96'' 23'-88' 23'''-88''' 134'-194' 134'''-194''' 147-203 147''-203''
214'-223 214'''-223'' 229-229'' 232-232'' 264-324 264''-324'' 370-428 370''-428''

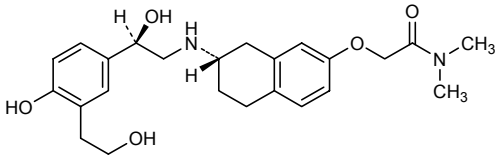
bedoradrinum

bedoradrine — 2-{[(7*S*)-7-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]=ethyl}amino)-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}-*N,N*-dimethylacetamide

bédoradrine — (-)-2-[[(7*S*)-7-[[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyéthyl)=phényl]éthyl]amino]-5,6,7,8-tétrahydronaphtalén-2-yl]oxy]-*N*,*N*-diméthylacétamide

bedoradrina — (-)-2-{[(7*S*)-7-({(2*R*)-2-hidroxi-2-[4-hidroxi-3-(2-hidroxietil)fenil]=etil}amino)-5,6,7,8-tetrahidronaftalen-2-il]oxi}-*N*,*N*-dimetilacetamida

$C_{24}H_{32}N_2O_5$



beperminogenum perplasmidum*

beperminogene perplasmid — plasmid DNA containing human hepatocyte growth factor cDNA sequence driven by a cytomegalovirus promoter

béperminogène perplasmide — ADN plasmidique contenant la séquence ADN-copie du facteur de croissance de l'hépatocyte humain sous contrôle d'un promoteur de cytomégalovirus

beperminogén perplásmido — DNA de plásmido que contiene la secuencia DNA-copia del factor de crecimiento del hepatocito humano controlado por un promotor de citomegalovirus

beroctocogum alfa*

beroctocog alfa — human blood-coagulation factor VIII-(1-740)-peptide complex with human blood-coagulation factor VIII-(1649-2332)-peptide

béroctocog alfa — combinaison du facteur VIII de coagulation humain-(1-740)-peptide (chaîne lourde du facteur VIIIa, isoforme de 92 kDa) avec le facteur VIII de coagulation humain-(1649-2332)-peptide (chaîne légère du facteur VIIIa)

beroctocog alfa — combinación del factor VIII de coagulación humano-(1-740)-péptido (cadena pesada del factor VIIIa, isoforma de 92 kDa) con el factor VIII de coagulación humano-(1649-2332)-péptido (cadena ligèra del factor VIIIa)

$C_{3821}H_{5813}N_{1003}O_{1139}S_{35} + C_{3553}H_{5400}N_{956}O_{1032}S_{35}$

Heavy chain / Chaîne lourde / Cadena pesada

```
ATRRYYLGAV  ELSWDYMQSD  LGELPVDARF  PPRVPKSFPF  NTSVVYKKTL  50
FVEFTDHLFN  IAKPRPPWMG  LLGPTIQAEV  YDTVVITLKN  MASHPVSLHA  100
VGVSYWKASE  GAEYDDQTSQ  REKEDDKVFP  GGSHTYVWQV  LKENGPMASD  150
PLCLTYSYLS  HVDLVKDLNS  GLIGALLVCR  EGSLAKEKTQ  TLHKFILLFA  200
VFDEGKSWHS  ETKNSLMQDR  DAASARAWPK  MHTVNGYVNR  SLPGLIGCHR  250
KSVYWHVIGM  GTTPEVHSIF  LEGHTFLVRN  HRQASLEISP  ITFLTAQTLL  300
MDLGQFLLFC  HISSHQHDGM  EAYVKVDSCP  EEPQLRMKNN  EEAEDYDDDL  350
TDSEMDVVRF  DDDNSPSFIQ  IRSVAKKHPK  TWVHYIAAEE  EDWDYAPLVL  400
APDDRSYKSQ  YLNNGPQRIG  RKYKKVRFMA  YTDETFKTRE  AIQHESGILG  450
PLLYGEVGDT  LLIIFKNQAS  RPYNIYPHGI  TDVRPLYSRR  LPKGVKHLKD  500
FPILPGEIFK  YKWTVTVEDG  PTKSDPRCLT  RYYSSFVNME  RDLASGLIGP  550
LLICYKESVD  QRGNQIMSDK  RNVILFSVFD  ENRSWYLTEN  IQRFLPNPAG  600
VQLEDPEFQA  SNIMHSINGY  VFDSLQLSVC  LHEVAYWYIL  SIGAQTDFLS  650
VFFSGYTFKH  KMVYEDTLTL  FPFSGETVFM  SMENPGLWIL  GCHNSDFRNR  700
GMTALLKVSS  CDKNTGDYYE  DSYEDISAYL  LSKNNAIEPR  S           741
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Light chain / Chaîne légère / Cadena ligera

```
                                                        EI  1650
TRTTLQSDQE  EIDYDDTISV  EMKKEDFDIY  DEDENQSPRS  FQKKTRHYFI  1700
AAVERLWDYG  MSSSPHVLRN  RAQSGSVPQF  KKVVFQEFTD  GSFTQPLYRG  1750
ELNEHLGLLG  PYIRAEVEDN  IMVTFRNQAS  RPYSFYSSLI  SYEEDQRQGA  1800
EPRKNFVKPN  ETKTYFWKVQ  HHMAPTKDEF  DCKAWAYFSD  VDLEKDVHSG  1850
LIGPLLVCHT  NTLNPAHGRQ  VTVQEFALFF  TIFDETKSWY  FTENMERNCR  1900
APCNIQMEDP  TFKENYRFHA  INGYIMDTLP  GLVMAQDQRI  RWYLLSMGSN  1950
ENIHSIHFSG  HVFTVRKKEE  YKMALYNLYP  GVFETVEMLP  SKAGIWRVEC  2000
LIGEHLHAGM  STLFLVYSNK  CQTPLGMASG  HIRDFQITAS  GQYGQWAPKL  2050
ARLHYSGSIN  AWSTKEPFSW  IKVDLLAPMI  IHGIKTQGAR  QKFSSLYISQ  2100
FIIMYSLDGK  KWQTYRGNST  GTLMVFFGNV  DSSGIKHNIF  NPPIIARYIR  2150
LHPTHYSIRS  TLRMELMGCD  LNSCSMPLGM  ESKAISDAQI  TASSYFTNMF  2200
ATWSPSKARL  HLQGRSNAWR  PQVNNPKEWL  QVDFQKTMKV  TGVTTQGVKS  2250
LLTSMYVKEF  LISSSQDGHQ  WTLFFQNGKV  KVFQGNQDSF  TPVVNSLDPP  2300
LLTRYLRIHP  QSWVHQIALR  MEVLGCEAQD  LY                     2332
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
153-179 528-554 1899-1903 2021-2169 2174-2326

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación
Asn-41 Asn-239 Asn-582 Asn-1810 Asn-2118

Modifications / Modificaciones
Y = 4-O-sulfotyrosyl

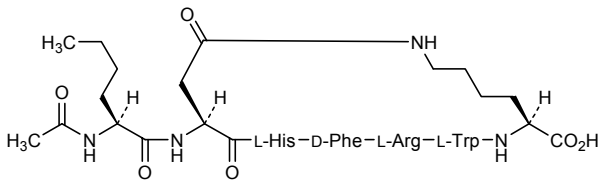
bremelanotidum

bremelanotide — 2,7-anhydro(*N*-acetyl-L-2-aminohexanoyl-L-aspartyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-L-lysine)

brémelanotide — *N*-acétyl-L-2-aminohexanoyl-L-α-aspartyl-L-histidyl-D-phénylalanyl-L-arginyl-L-tryptophyl-L-lysine-(2→7)-lactame

bremelanotida — *N*-acetil-L-2-aminohexanoil-L-α-aspartil-L-histidil-D-fenilalanil-L-arginil-L-triptofil-L-lisina-(2→7)-lactama

$C_{50}H_{68}N_{14}O_{10}$



bucelipasum alfa*

bucelipase alfa — human bile-salt-activated lipase (cholesterol esterase, EC 3.1.1.13), glycoform alfa (recombinant hBSSL)

bucélipase alfa — lipase activée par les sels biliaires humaine (cholestérol estérase, EC 3.1.1.13), glycoforme alpha (recombinante hBSSL)

bucelipasa alfa — lipasa humana activada por las sales biliares (colesterol esterasa, EC 3.1.1.13), glicoforma alfa (recombinante hBSSL)

$C_{3434}H_{5258}N_{894}O_{1041}S_{17}$

```
AKLGAVYTEG  GFVEGVNKKL  GLLGDSVDIF  KGIPFAAPTK  ALENPQPHPG  50
WQGTLKAKNF  KKRCLQATIT  QDSTYGDEDC  LYLNIWVPQG  RKQVSRDLPV  100
MIWIYGGAFL  MGSGHGANFL  NNYLYDGEEI  ATRGNVIVVT  FNYRVGPLGF  150
LSTGDANLPG  NYGLRDQHMA  IAWVKRNIAA  FGGDPNNITL  FGESAGGASV  200
SLQTLSPYNK  GLIRRAISQS  GVALSPWVIQ  KNPLFWAKKV  AEKVGCPVGD  250
AARMAQCLKV  TDPRALTLAY  KVPLAGLEYP  MLHYVGFVPV  IDGDFIPADP  300
INLYANAADI  DYIAGTNNMD  GHIFASIDMP  AINKGNKKVT  EEDFYKLVSE  350
FTITKGLRGA  KTTFDVYTES  WAQDPSQENK  KKTVVDFETD  VLFLVPTEIA  400
LAQHRANAKS  AKTYAYLFSH  PSRMPVYPKW  VGADHADDIQ  YVFGKPFATP  450
TGYRPQDRTV  SKAMIAYWTN  FAKTGDPNMG  DSAVPTHWEP  YTTENSGYLE  500
ITKKMGSSSM  KRSLRTNFLR  YWTLTYLALP  TVTDQEATPV  PPTGDSEATP  550
VPPTGDSETA  PVPPTGDSGA  PPVPPTGDSG  APPVPPTGDS  GAPPVPPTGD  600
SGAPPVPPTG  DSGAPPVPPT  GDSGAPPVPP  TGDSGAPPVP  PTGDAGPPPV  650
PPTGDSGAPP  VPPTGDSGAP  PVTPTGDSET  APVPPTGDSG  APPVPPTGDS  700
EAAPVPPTDD  SKEAQMPAVI  RF                                  722
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
64-80 246-257

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación
Asn-187 Thr-538 Thr-549 Thr-559 Thr-576 Thr-587
Thr-598 Thr-609 Thr-620 Thr-631 Thr-642

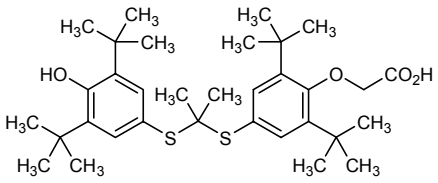
camobucolum

camobucol — 4-{4-[(2-{[3,5-di(*tert*-butyl)-4-hydroxyphenyl]sulfanyl}propan-2-yl)=sulfanyl]-2,6-di(*tert*-butyl)phenoxy}acetic acid

camobucol — acide 4-{4-[(2-{[3,5-di(*tert*-butyl)-4-hydroxyphényl]sulfanyl}propan-2-yl)sulfanyl]-2,6-di(*tert*-butyl)phénoxy}acétique

camobucol — ácido 4-{4-[(2-{[3,5-di(*terc*-butil)4-hidroxifenil]sulfanil}propan-2-il)=sulfanil]-2,6-di(*terc*-butil)fenoxi}acético

$C_{33}H_{50}O_4S_2$



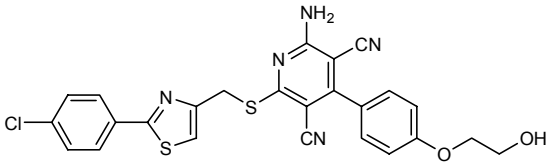
capadenosonum

capadenoson — 2-amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-4-[4-(2-hydroxyethoxy)phenyl]pyridine-3,5-dicarbonitrile

capadénoson — 2-amino-6-[[[2-(4-chlorophényl)-1,3-thiazol-4-yl]méthyl]sulfanyl]-4-[4-(2-hydroxyéthoxy)phényl]pyridine-3,5-dicarbonitrile

capadenosón — 2-amino-6-({[2-(4-clorofenil)-1,3-tiazol-4-il]metil}sulfanil)-4-[4-(2-hidroxietoxi)fenil]piridina-3,5-dicarbonitrilo

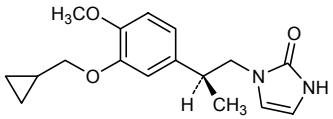
$C_{25}H_{18}ClN_5O_2S_2$



catramilastum

catramilast	1-{(2*S*)-2-[3-(cyclopropylmethoxy)-4-methoxyphenyl]propyl}-1,3-dihydro-2*H*-imidazol-2-one
catramilast	1-[(2*S*)-2-[3-(cyclopropylméthoxy)-4-méthoxyphényl]propyl]-1,3-dihydro-2*H*-imidazol-2-one
catramilast	1-{(2*S*)-2-[3-(ciclopropilmetoxi)-4-metoxifenil]propil}-1,3-dihidro-2*H*-imidazol-2-ona

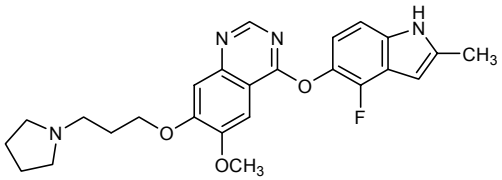
$C_{17}H_{22}N_2O_3$



cediranibum

cediranib	4-[(4-fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline
cédiranib	4-[(4-fluoro-2-méthyl-1*H*-indol-5-yl)oxy]-6-méthoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline
cediranib	4-[(4-fluoro-2-metil-1*H*-indol-5-il)oxi]-6-metoxi-7-[3-(pirrolidin-1-il)=propoxi]quinazolina

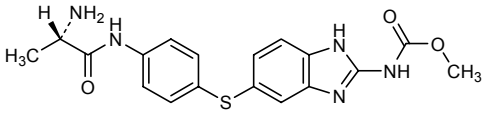
$C_{25}H_{27}FN_4O_3$



denibulinum

denibulin	methyl [5-({4-[(2*S*)-2-aminopropanamido]phenyl}sulfanyl)-1*H*-benzimidazol-2-yl]carbamate
dénibuline	[5-[[4-[[(2*S*)-2-aminopropanamido]phenyl]sulfanyl]-1*H*-benzimidazol-2-yl]carbamate de méthyle
denibulina	[5-({4-[(2*S*)-2-aminopropanamido]fenil}sulfanil)-1*H*-bencimidazol-2-il]carbamato de metilo

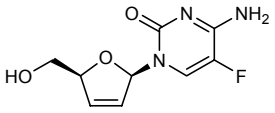
$C_{18}H_{19}N_5O_3S$



dexelvucitabinum

dexelvucitabine	4-amino-5-fluoro-1-[(2*R*,5*S*)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl]pyrimidin-2(1*H*)-one
dexelvucitabine	(+)-4-amino-5-fluoro-1-[(2*R*,5*S*)-5-(hydroxyméthyl)-2,5-dihydrofuran-2-yl]pyrimidin-2(1*H*)-one
dexelvucitabina	(+)-4-amino-5-fluoro-1-[(2*R*,5*S*)-5-(hidroximetil)-2,5-dihidrofuran-2-il]pirimidin-2(1*H*)-ona

$C_9H_{10}FN_3O_3$



efungumabum*

efungumab	immunoglobulin scFv fragment, anti-(heat shock protein 90 homolog from *Candida albicans* (yeast)), methionylalanyl-[human monoclonal HSP90mab VH domain (120 residues)]-tris[(tetraglycyl)seryl]-[human monoclonal HSP90mab V-KAPPA domain (107 residues)]-[arginyl-trialanyl-leucyl-glutamyl]-hexahistidine
éfungumab	immunoglobuline fragment scFv, anti-(homologue de la protéine de choc thermique 90 de *Candida albicans* (levure)), methionylalanyl-[domaine VH (120 residus) de l'anticorps monoclonal humain HSP90mab]-tris[(tetraglycyl)seryl]-[domaine V-KAPPA (107 residus) de l'anticorps monoclonal humain HSP90mab]-[arginyl-trialanyl-leucyl-glutamyl]-hexahistidine
efungumab	inmunoglobulina fragmento scFv, anti-(homólogo de la proteína de choc térmico 90 de *Candida albicans*), metionilalanil-[dominio VH (120 restos) del anticuerpo monoclonal humano HSP90mab]-tris[(tetraglicil)seril]-[dominio V-KAPPA (107 restos) del anticuerpo monoclonal humano HSP90mab]-[arginil-trialanil-leucil-glutamil]-hexahistidina

```
 MAEVQLVES GAEVKKPGES LRISCKGSGC IISSYWISWV RQMPGKGLEW
MGKIDPGDSY INYSPSFQGH VTISADKSIN TAYLQWNSLK ASDTAMYYCA
RGGRDFGDSF DYWGQGTLVT VSSGGGGSGG GGSGGGGSDV VMTQSPSFLS
AFVGDRITIT CRASSGISRY LAWYQQAPGK APKLLIYAAS TLQTGVPSRF
SGSGSGTEFT LTINSLQPED FATYYCQHLN SYPLTFGGGT KVDIKRAAA
LEhhhhhh
```

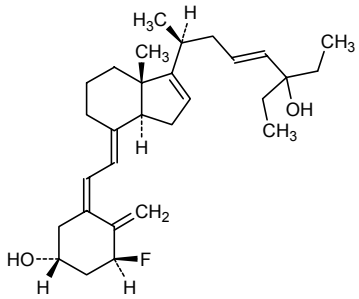
elocalcitolum

elocalcitol — (1*S*,3*R*,5*Z*,7*E*,23*E*)-1-fluoro-26,27-dihomo-9,10-secocholesta-5,7,10(19),16,23-pentaene-3,25-diol

élocalcitol — (1*R*,5*S*)-3-[(1*Z*)-2-[(3a*S*,4*E*,7a*S*)-1-[(1*S*,3*E*)-5-éthyl-5-hydroxy-1-méthylhept-3-ényl]-7a-méthyl-3,3a,5,6,7,7a-hexahydro-4*H*-indén-4-ylidène]éthylidène]-5-fluoro-4-méthylidènecyclohexanol

elocalcitol — (1*S*,3*R*,5*Z*,7*E*,23*E*)-1-fluoro-26,27-dihomo-9,10-secocolesta-5,7,10(19),16,23-pentaeno-3,25-diol

$C_{29}H_{43}FO_2$



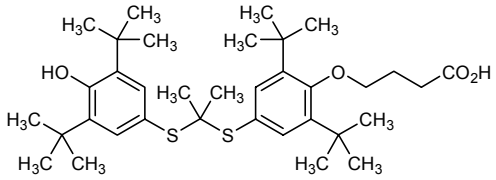
elsibucolum

elsibucol — 4-{4-[(2-{[3,5-di-*tert*-butyl-4-hydroxyphenyl]sulfanyl}propan-2-yl)=sulfanyl]-2,6-di-*tert*-butylphenoxy}butanoic acid

elsibucol — acide 4-[4-[[1-[[3,5-bis(1,1-diméthyléthyl)-4-hydroxyphényl]sulfanyl]-1-méthyléthyl]sulfanyl]-2,6-bis(1,1-diméthyléthyl)phénoxy]butanoïque

elsibucol — ácido 4-{4-[(2-{[3,5-di-*terc*-butil-4-hidroxifenil]sulfanil}propan-2-il)=sulfanil]-2,6-di-*terc*-butilfenoxi}butanoico

$C_{35}H_{54}O_4S_2$



epoetinum theta

epoetin theta — human erythropoietin-(1-165)-peptide, glycoform θ

époétine thêta — érythropoïétine humaine-(1-165)-peptide, glycoforme θ

epoetina zeta — eritropoyetina humana-péptido-(1-165), glicoforma θ

$C_{809}H_{1301}N_{229}O_{240}S_5$

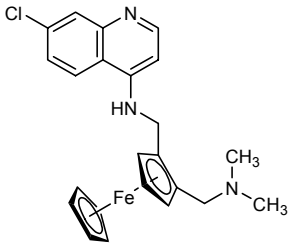
ferroquinum

ferroquine — *N'*-(7-chloroquinolin-4-yl)-*N*,*N*-dimethyl-*C*,*C'*-(ferrocene-1,2-diyl)= dimethanamine

ferroquine — *N'*-(7-chloroquinoléin-4-yl)-*N*,*N*-diméthyl-*C*,*C'*-(férrocène-1,2-diyl)= diméthanamine

ferroquina — *N'*-(7-cloroquinolin-4-il)-*N*,*N*-dimetil-*C*,*C'*-(ferroceno-1,2-diil)= dimetanamina

$C_{23}H_{24}ClFeN_3$



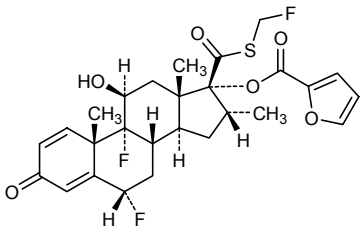
fluticasonum furoas

fluticasone furoate — 6α,9-difluoro-17{[(fluoromethyl)sulfanyl]carbonyl}-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate

furoate de fluticasone — furane-2-carboxylate de 6α,9-difluoro-17-[[(fluorométhyl)sulfanyl]= carbonyl]-11β-hydroxy-16α-méthyl-3-oxoandrosta-1,4-dién-17α-yle

furoato de fluticasona — furano-2-carboxilato de 6α,9-difluoro-17-[[(fluorometil)sulfanil]= carbonil]-11β-hidroxi-16α-metil-3-oxoandrosta-1,4-dien-17α-ilo

$C_{27}H_{29}F_3O_6S$



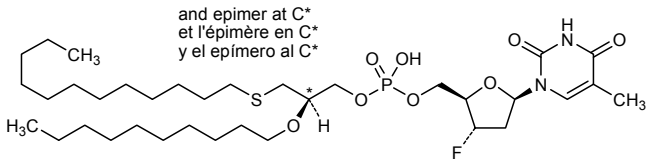
fosalvudinum tidoxilum

fosalvudine tidoxil — (2*RS*)-2-(decyloxy)-3-[(dodecyl)sulfanyl]propyl [(2*R*,3*S*,5*R*)-3-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl]methyl hydrogen phosphate

fosalvudine tidoxil — hydrogénophosphate de (2*RS*)-2-(décyloxy)-3-(dodécylsulfanyl)= propyle et de [(2*R*,3*S*,5*R*)-3-fluoro-5-(5-méthyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tétrahydrofuran-2-yl]méthyle

fosalvudina tidoxilo — hidrógenofosfato de (2*RS*)-2-(deciloxi)-3-[(dodecil)sulfanil]propilo y [(2*R*,3*S*,5*R*)-3-fluoro-5-(5-metil-2,4-dioxo-3,4-dihidropirimidin-1(2*H*)-il)tetrahidrofuran-2-il]metilo

$C_{35}H_{64}FN_2O_8PS$



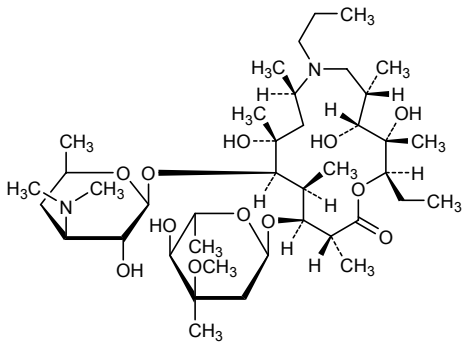
gamithromycinum

gamithromycin — (2*R*,3*S*,4*R*,5*S*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-7-propyl-11-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-1-oxa-7-azacylopentadecan-15-one

gamithromycin — (2*R*,3*S*,4*R*,5*S*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-didésoxy-3-*C*-méthyl-3-*O*-méthyl-α-L-*ribo*-hexopyranosyl)oxy]-2-éthyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexaméthyl-7-propyl-11-[[3,4,6-tridésoxy-3-(diméthylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-7-azacyclopentadécan-15-one

gamitromicina — (2*R*,3*S*,4*R*,5*S*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-didesoxi-3-*C*-metil-3-*O*-metil-α-L-*ribo*-hexopiranosil)oxi]-2-etil-3,4,10-trihidroxi-3,5,8,10,12,14-hexametil-7-propil-11-{[3,4,6-tridesoxi-3-(dimetilamino)-β-D-*xylo*-hexopiranosil]oxi}-1-oxa-7-azaciclopentadecan-15-ona

$C_{40}H_{76}N_2O_{12}$



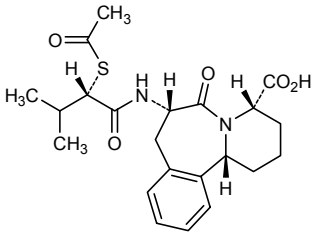
ilepatrilum

ilepatril — (4*S*,7*S*,12b*R*)-7-[(2*S*)-2-(acetylsulfanyl)-3-methylbutanamido]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-*a*][2]benzazepine-4-carboxylic acid

ilépatril — acide (4*S*,7*S*,12b*R*)-7-[[(2*S*)-2-(acétylsulfanyl)-3-méthylbutanoyl]=amino]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]=benzazépine-4-carboxylique

ilepatrilo — ácido (4*S*,7*S*,12b*R*)-7-{[(2*S*)-2-(acetilsulfanil)-3-metilbutanoil]amino}-6-oxo-1,2,3,4,6,7,8,12b-octahidropirido[2,1-*a*][2]benzazepina-4-carboxílico

$C_{22}H_{28}N_2O_5S$



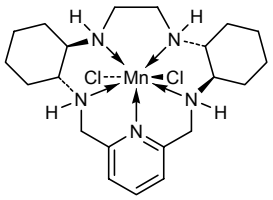
imisopasemum manganum

imisopasem manganese — (*PBPY*-7-11-2344'3')-dichloro[(4a*R*,13a*R*,17a*R*,21a*R*)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-icosahydro-7,11-(azeno)dibenzo[*b,h*][1,4,7,10]=tetraazacycloheptadecine-$\kappa^4N^5,N^{13},N^{18},N^{21},N^{22}$]manganese

imisopasem manganèse — (*PBPY*-7-11-2344'3')-dichloro[(4a*R*,13a*R*,17a*R*,21a*R*)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-icosahydro-11,7-nitrilo-7*H*-dibenzo[*b,h*][1,4,7,10]=tétraazacycloheptadécine-$\kappa N^5,\kappa N^{13},\kappa N^{18},\kappa N^{21},\kappa N^{22}$]manganèse

imisopasem manganeso — (*PBPY*-7-11-2344'3')-dicloro[(4a*R*,13a*R*,17a*R*,21a*R*)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-icosahidro-7,11-(azeno)dibenzo[*b,h*][1,4,7,10]=tetraazaciclohepta decino-$\kappa^4N^5,N^{13},N^{18},N^{21},N^{22}$]manganeso

$C_{21}H_{35}Cl_2MnN_5$



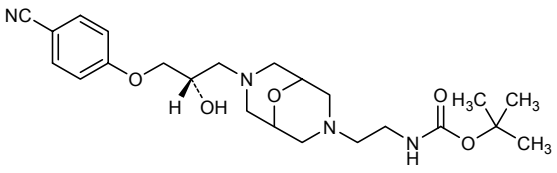
inakalantum

inakalant — *tert*-butyl (2-{7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl}ethyl)carbamate

inakalant — [2-[7-[(2S)-3-(4-cyanophénoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]éthyl]carbamate de 1,1-diméthyléthyle

inakalant — (2-{7-[(2*S*)-3-(4-cianofenoxi)-2-hidroxipropil]-9-oxa-3,7-diazabiciclo=[3.3.1]nonan-3-il}etil)carbamato de *terc*-butilo

$C_{23}H_{34}N_4O_5$



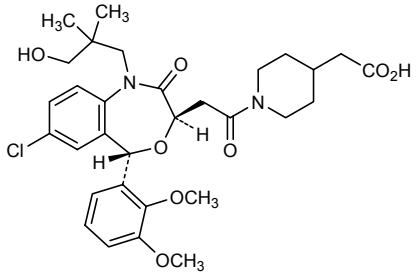
lapaquistatum

lapaquistat — (1-{[(3*R*,5*S*)-1-(3-hydroxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}piperidin-4-yl)acetic acid

lapaquistat — acide (1-{[(3*R*,5*S*)-1-(3-hydroxy-2,2-diméthylpropyl)-7-chloro-5-(2,3-diméthoxyphényl)-2-oxo-1,2,3,5-tétrahydro-4,1-benzoxazépin-3-yl]acétyl}pipéridin-4-yl)acétique

lapaquistat — ácido (1-{(3*R*,5*S*)-1-[3-hidroxi-2,2-dimetilpropil)]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}piperidin-4-il)acético

$C_{31}H_{39}ClN_2O_8$



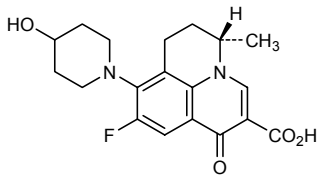
levonadifloxacinum

levonadifloxacin — (5*S*)-9-fluoro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid

lévonadifloxacine — (-)-acide (5*S*)-9-fluoro-8-(4-hydroxypipéridin-1-yl)-5-méthyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylique

levonadifloxacino — ácido (5*S*)-9-fluoro-8-(4-hidroxipiperidin-1-il)-5-metil-1-oxo-6,7-dihidro-1*H*,5*H*-benzo[*ij*]quinolizina-2-carboxílico

$C_{19}H_{21}FN_2O_4$



lexatumumabum*

lexatumumab — immunoglobulin G1, anti-[human tumor necrosis factor receptor superfamily member 10B (TNFRSF10B, death receptor 5, TNF-related apoptosis-inducing ligand receptor 2, TRAIL-R2, CD262)] human monoclonal HGS-ETR2; gamma1 heavy chain (*Homo sapiens* VH-IGHG1) (224-213')-disulfide with lambda light chain (*Homo sapiens* V-LAMBDA- IGLC2); (230-230":233-233")-bisdisulfide dimer

lexatumumab

immunoglobuline G1, anti-[membre 10B de la superfamille des récepteurs du facteur de nécrose tumorale humain (TNFRSF10B, death receptor 5, TRAIL-R2, CD262)] anticorps monoclonal humain HGS-ETR2; chaîne lourde gamma1 (*Homo sapiens* VH-IGHG1) (224-213')-disulfure avec la chaîne légère lambda (*Homo sapiens* V-LAMBDA- IGLC2); dimère (230-230'':233-233'')-bisdisulfure

lexatumumab

inmunoglobulina G1, anti-[miembro 10B de la superfamilia de receptores del factor de necrosis tumoral humano (TNFRSF10B, death receptor 5, TRAIL-R2, CD262)] anticuerpo monoclonal humano HGS-ETR2; cadena pesada gamma1 (*Homo sapiens* VH-IGHG1) (224-213')-disulfuro con la cadena ligera lambda (*Homo sapiens* V-LAMBDA- IGLC2); dímero (230-230'':233-233'')-bisdisulfuro

$C_{6346}H_{9832}N_{1720}O_{2002}S_{42}$

Heavy chain / chaîne lourde / cadena pesada

```
EVQLVQSGGG  VERPGGSLRL  SCAASGFTFD  DYGMSWVRQA  PGKGLEWVSG  50
INWNGGSTGY  ADSVKGRVTI  SRDNAKNSLY  LQMNSLRAED  TAVYYCAKIL  100
GAGRGWYFDL  WGKGTTVTVS  SASTKGPSVF  PLAPSSKSTS  GGTAALGCLV  150
KDYFPEPVTV  SWNSGALTSG  VHTFPAVLQS  SGLYSLSSVV  TVPSSSLGTQ  200
TYICNVNHKP  SNTKVDKRVE  PKSCDKTHTC  PPCPAPELLG  GPSVFLFPPK  250
PKDTLMISRT  PEVTCVVVDV  SHEDPEVKFN  WYVDGVEVHN  AKTKPREEQY  300
NSTYRVVSVL  TVLHQDWLNG  KEYKCKVSNK  ALPAPIEKTI  SKAKGQPREP  350
QVYTLPPSRE  EMTKNQVSLT  CLVKGFYPSD  IAVEWESNGQ  PENNYKTTPP  400
VLDSDGSFFL  YSKLTVDKSR  WQQGNVFSCS  VMHEALHNHY  TQKSLSLSPG  450
K
```

Lambda chain / chaîne lambda / cadena lambda

```
SSELTQDPAV  SVALGQTVRI  TCQGDSLRSY  YASWYQQKPG  QAPVLVIYGK  50
NNRPSGIPDR  FSGSSSGNTA  SLTITGAQAE  DEADYYCNSR  DSSGNHVVFG  100
GGTKLTVLGQ  PKAAPSVTLF  PPSSEELQAN  KATLVCLISD  FYPGAVTVAW  150
KADSSPVKAG  VETTTPSKQS  NNKYAASSYL  SLTPEQWKSH  RSYSCQVTHE  200
GSTVEKTVAP  TECS
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
22-96    22'-87'    22''-96''   22'''-87'''  136'-195'  136'''-195'''  148-204  148''-204''
213'-224 213'''-224'' 230-230''  233-233''   265-325    265''-325''    371-429  371''-429''
```

lificiguatum

lificiguat

[5-(1-benzyl-1*H*-indazol-3-yl)furan-2-yl]methanol

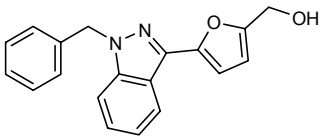
lificiguat

[5-(1-benzyl-1*H*-indazol-3-yl)furan-2-yl]méthanol

lificiguat

[5-(1-bencil-1*H*-indazol-3-il)furan-2-il]metanol

$C_{19}H_{16}N_2O_2$



lobeglitazonum

lobeglitazone

(5*RS*)-5{[4-(2-{[6-(4-methoxyphenoxy)pyrimidin-4-yl]methylamino}=ethoxy)phenyl]methyl}-1,3-thiazolidine-2,4-dione

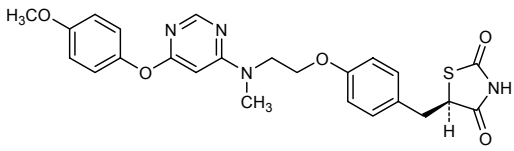
lobéglitazone

(5*RS*)-5-[4-[2-[[6-(4-méthoxyphénoxy)pyrimidin-4-yl]méthylamino]=éthoxy]benzyl]thiazolidine-2,4-dione

lobeglitazona

(5*RS*)-5-[4-(2-{[6-(4-metoxifenoxi)pirimidin-4-il]metilamino}etoxi)=bencil]-1,3-tiazolidina-2,4-diona

$C_{24}H_{24}N_4O_5S$



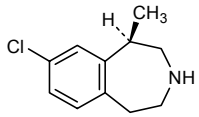
lorcaserinum

lorcaserin (1*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

lorcasérine (1*R*)-8-chloro-1-méthyl-2,3,4,5-tétrahydro-1*H*-3-benzazépine

lorcaserina (1*R*)-8-cloro-1-metil-2,3,4,5-tetrahidro-1*H*-3-benzazepina

$C_{11}H_{14}ClN$



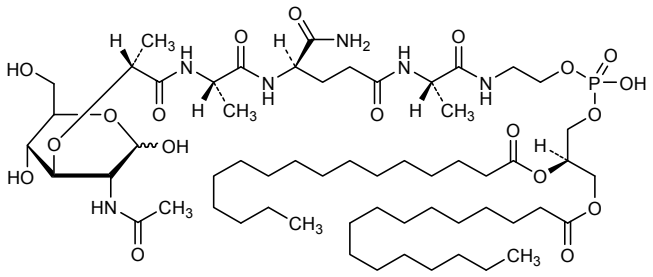
mifamurtidum

mifamurtide 2-[(*N*-{(2*R*)-[(2-acetamido-2,3-dideoxy-D-glucopyranos-3-yl)oxy]= propanoyl}-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexadecanoyloxy)propyl hydrogen phosphate

mifamurtide hydrogénophosphate de 2-[[*N*-[(2*R*)-2-[(3*R*,4*R*,5*S*,6*R*)-3-(acétylamino)-2,5-dihydroxy-6-(hydroxyméthyl)tétrahydro-2*H*-pyran-4-yloxy]propanoyl]-L-alanyl-D-isoglutaminyl-L-alanyl]amino]éthyle et de (2*R*)-2,3-bis(hexanoyloxy)propyle

mifamurtida hidrógenofosfato de 2-[[*N*-[(2*R*)-2-[(3*R*,4*R*,5*S*,6*R*)-3-(acetilamino)-2,5-dihidroxi-6-(hidroximetil)tetrahidro-2*H*-piran-4-iloxi]propanoil]-L-alanil-D-isoglutaminil-L-alanil]amino]etilo y de (2*R*)-2,3-bis(hexanoiloxi)propilo

$C_{59}H_{109}N_6O_{19}P$



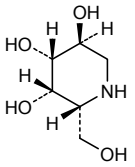
migalastatum

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

migalastat (+)-(2*R*,3*S*,4*R*,5*S*)-2-(hydroxyméthyl)pipéridine-3,4,5-triol

migalastat (2*R*,3*S*,4*R*,5*S*)-2-(hidroximetil)piperidina-3,4,5-triol

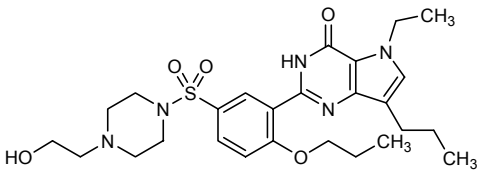
$C_6H_{13}NO_4$



mirodenafilum

mirodenafil	5-ethyl-2-(5-{[4-(2-hydroxyethyl)piperazin-1-yl]sulfonyl}-2-propoxyphenyl)-7-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one
mirodénafil	5-éthyl-2-[5-[[4-(2-hydroxyéthyl)pipérazin-1-yl]sulfonyl]-2-propoxyphenyl]-7-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one
mirodenafilo	5-etil-2-(5-{[4-(2-hidroxietil)piperazin-1-il]sulfonil}-2-propoxifenil)-7-propil-3,5-dihidro-4*H*-pirrolo[3,2-*d*]pirimidin-4-ona

$C_{26}H_{37}N_5O_5S$



motavizumabum*

motavizumab	immunoglobulin G1, anti-(human respiratory syncytial virus glycoprotein F) humanized monoclonal MEDI-524; gamma1 heavy chain [humanized VH (*Homo sapiens* FR/*Mus musculus* CDR)-*Homo sapiens* IGHG1] (223-213')-disulfide with kappa light chain [humanized V-KAPPA (*Homo sapiens* FR/*Mus musculus* CDR)-*Homo sapiens* IGKC]; (229-229":232-232")-bisdisulfide dimer
motavizumab	immunoglobuline G1, anti-(glycoprotéine de fusion du virus syncytial respiratoire humain) anticorps monoclonal humanisé MEDI-524; chaîne lourde gamma1 [VH humanisé (*Homo sapiens* FR/*Mus musculus* CDR)- *Homo sapiens* IGHG1] (223-213')-disulfure avec la chaîne légère kappa [V-KAPPA humanisé (*Homo sapiens* FR/*Mus musculus* CDR)-*Homo sapiens* IGKC]; dimère (229-229":232-232")-bisdisulfure
motavizumab	inmunoglobulina G1, anti-(glicoproteína de fusión del virus sincitial respiratorio humano) anticuerpo monoclonal humanizado MEDI-524; cadena pesada gamma1 [VH humanizada (*Homo sapiens* FR/*Mus musculus* CDR)- *Homo sapiens* IGHG1] (223-213')-disulfuro con la cadena ligera kappa [V-KAPPA humanizada (*Homo sapiens* FR/*Mus musculus* CDR)- *Homo sapiens* IGKC]; (229-229":232-232")-bisdisulfide dimer

$C_{6476}H_{10014}N_{1706}O_{2008}S_{48}$

γ-1-Chain / Chaîne γ-1 / Cadena γ-1

QVTLRESGPA	LVKPTQTLTL	TCTFSGFSLS	TAGMSVGWIR	QPPGKALEWL	50
ADIWWDDKKH	YNPSLKDRLT	ISKDTSKNQV	VLKVTNMDPA	DTATYYCARD	100
MIFNFYFDVW	GQGTTVTVSS	ASTKGPSVFP	LAPSSKSTSG	GTAALGCLVK	150
DYFPEPVTVS	WNSGALTSGV	HTFPAVLQSS	GLYSLSSVVT	VPSSSLGTQT	200
YICNVNHKPS	NTKVDKRVEP	KSCDKTHTCP	PCPAPELLGG	PSVFLFPPKP	250
KDTLMISRTP	EVTCVVVDVS	HEDPEVKFNW	YVDGVEVHNA	KTKPREEQYN	300
STYRVVSVLT	VLHQDWLNGK	EYKCKVSNKA	LPAPIEKTIS	KAKGQPREPQ	350
VYTLPPSREE	MTKNQVSLTC	LVKGFYPSDI	AVEWESNGQP	ENNYKTTPPV	400
LDSDGSFFLY	SKLTVDKSRW	QQGNVFSCSV	MHEALHNHYT	QKSLSLSPGK	450

κ Chain / Chaîne κ/ Cadena κ

DIQMTQSPST	LSASVGDRVT	ITCSASSRVG	YMHWYQQKPG	KAPKLLIYDT	50'
SKLASGVPSR	FSGSGSGTEF	TLTISSLQPD	DFATYYCFQG	SGYPFTFGGG	100'
TKVEIKRTVA	APSVFIFPPS	DEQLKSGTAS	VVCLLNNFYP	REAKVQWKVD	150'
NALQSGNSQE	SVTEQDSKDS	TYSLSSTLTL	SKADYEKHKV	YACEVTHQGL	200'
SSPVTKSFNR	GEC				213'

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

22-97 22''-97'' 23'-87' 23'''-87''' 133'-193' 133'''-193''' 147-203 147''-203''
213'-223 213'''-223'' 229-229'' 232-232'' 264-324 264''-324'' 370-428 370''-428''

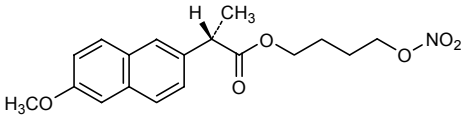
naproxcinodum

naproxcinod — 4-(nitrooxy)butyl (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate

naproxcinod — (2*S*)-2-(6-méthoxynaphtalén-2-yl)propanoate de 4-(nitrooxy)butyle

naproxcinod — (2*S*)-2-(6-metoxinaftalen-2-il)propanoato de 4-(nitrooxi)butilo

$C_{18}H_{21}NO_6$



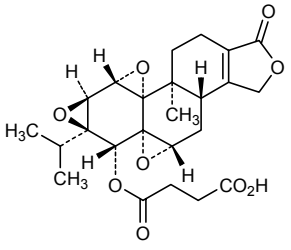
omtriptolidum

omtriptolide — 4-{[(3b*S*,4a*S*,5a*R*,6*R*,6a*S*,7a*S*,7b*S*,8a*S*,8b*S*)-8b-methyl-6a-(propan-2-yl)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahydrotrisoxireno=[4b,5:6,7:8a,9]phenanthro[1,2-*c*]furan-6-yl]oxy}-4-oxobutanoic acid

omtriptolide — acide 4-[[(3b*S*,4a*S*,5a*R*,6*R*,6a*S*,7a*S*,7b*S*,8a*S*,8b*S*)-8b-méthyl-6a-(1-méthyléthyl)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodécahydrotrisoxiréno[4b,5:6,7:8a,9]phénanthro[1,2-*c*]furan-6-yl]=oxy]-4-oxobutanoïque

omtriptolida — ácido 4-{[(3b*S*,4a*S*,5a*R*,6*R*,6a*S*,7a*S*,7b*S*,8a*S*,8b*S*)-8b-metil-6a-(propan-2-il)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahidrotrisoxireno[4b,5:6,7:8a,9]fenantro[1,2-*c*]furan-6-il]oxi}-4-oxobutanoico

$C_{24}H_{28}O_9$



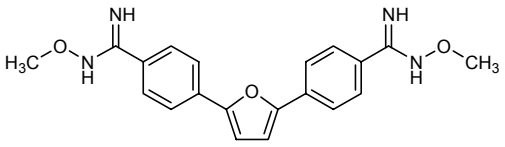
pafuramidinum

pafuramidine — 4,4'-(furan-2,5-diyl)bis(*N*-methoxybenzenecarboximidamide)

pafuramidine — 4,4'-(furane-2,5-diyl)bis(*N*-méthoxybenzènecarboximidamide)

pafuramidina — 4,4'-(furano-2,5-diil)bis(*N*-metoxibencenocarboximidamida)

$C_{20}H_{20}N_4O_3$



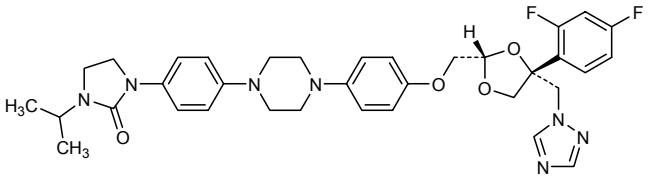
pramiconazolum

pramiconazole — 1-(4-{4-[4-({(2*S*,4*R*)-4-(2,4-difluorophenyl)-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-2-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-3-(propan-2-yl)imidazolidin-2-one

pramiconazole — (+)-1-[4-[4-[4-[[(2*S*,4*R*)-4-(2,4-difluorophényl)-4-[(1*H*-1,2,4-triazol-1-yl)méthyl]-1,3-dioxolan-2-yl]méthoxy]phényl]pipérazin-1-yl]phényl]-3-(1-méthyléthyl)imidazolidin-2-one

pramiconazol — 1-(4-{4-[4-({(2*S*,4*R*)-4-(2,4-difluorofenil)-4-[(1*H*-1,2,4-triazol-1-il)metil]-1,3-dioxolan-2-il}metoxi)fenil]piperazin-1-il}fenil)-3-(propan-2-il)imidazolidin-2-ona

$C_{35}H_{39}F_2N_7O_4$



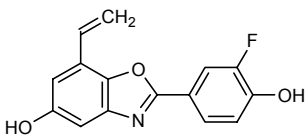
prinaberelum

prinaberel — 7-ethenyl-2-(3-fluoro-4-hydroxyphenyl)-1,3-benzoxazol-5-ol

prinabérel — 7-éthényl-2-(3-fluoro-4-hydroxyphényl)-1,3-benzoxazol-5-ol

prinaberel — 7-etenil-2-(3-fluoro-4-hidroxifenil)-1,3-benzoxazol-5-ol

$C_{15}H_{10}FNO_3$



rilonaceptum*

rilonacept — [653-glycine][human interleukin-1 receptor accessory protein-(1-339)-peptide (extracellular domain fragment) fusion protein with human type 1 interleukin-1 receptor-(5-316)-peptide (extracellular domain fragment) fusion protein with human immunoglobulin G1-(229 *C*-terminal residues)-peptide (Fc fragment)], (659-659':662-662')-bisdisulfide dimer

rilonacept — (659-659':662-662')-bisdisulfure du dimère de la [653-glycine][protéine accessoire du récepteur de l'interleukine-1 humaine-(1-339)-peptide (fragment du domaine extracellulaire) protéine de fusion avec le récepteur de type I humain de l'interleukine-1-(5-316)-peptide (fragment du domaine extracellulaire) protéine de fusion avec l'immunoglobuline G1 humaine-(229 résidus *C*-terminaux)-peptide (fragment Fc)]

rilonacept — (659-659':662-662')-bisdisulfuro del dímero de la [653-glicina][proteína accesoria del receptor de la interleukina-1 humana-(1-339)-péptido (fragmento del dominio extracelular) proteína de fusión con el receptor de tipo I humano de la interleukina-1-(5-316)-péptido (fragmento del dominio extracelular) proteína de fusión con la inmunoglobulina G1 humana-(229 restos *C*-terminales)-péptido (fragmento Fc)]

$C_{9030}H_{13932}N_{2400}O_{2670}S_{74}$

Monomer / Monomère / Monómero

SERCDDWGLD	TMRQIQVFED	EPARIKCPLF	EHFLKFNYST	AHSAGLTLIW 50
YWTRQDRDLE	EPINFRLPEN	RISKEKDVLW	FRPTLLNDTG	NYTCMLRNTT 100
YCSKVAFPLE	VVQKDSCFNS	PMKLPVHKLY	IEYGIQRITC	PNVDGYFPSS 150
VKPTITWYMG	CYKIQNFNNV	IPEGMNLSFL	IALISNNGNY	TCVVTYPENG 200
RTFHLTRTLT	VKVVGSPKNA	VPPVIHSPND	HVVYEKEPGE	ELLIPCTVYF 250
SFLMDSRNEV	WWTIDGKKPD	DITIDVTINE	SISHSRTEDE	TRTQILSIKK 300
VTSEDLKRSY	VCHARSAKGE	VAKAAKVKQK	VPAPRYTVEK	CKEREEKIIL 350
VSSANEIDVR	PCPLNPNEHK	GTITWYKDDS	KTPVSTEQAS	RIHQHKEKLW 400
FVPAKVEDSG	HYYCVVRNSS	YCLRIKISAK	FVENEPNLCY	NAQAIFKQKL 450
PVAGDGGLVC	PYMEFFKNEN	NELPKLQWYK	DCKPLLLDNI	HFSGVKDRLI 500
VMNVAEKHRG	NYTCHASYTY	LGKQYPITRV	IEFITLEENK	PTRPVIVSPA 550
NETMEVDLGS	QIQLICNVTG	QLSDIAYWKW	NGSVIDEDDP	VLGEDYYSVE 600
NPANKRRSTL	ITVLNISEIE	SRFYKHPFTC	FAKNTHGIDA	AYIQLIYPVT 650
NSGDKTHTCP	PCPAPELLGG	PSVFLFPPKP	KDTLMISRTP	EVTCVVVDVS 700
HEDPEVKFNW	YVDGVEVHNA	KTKPREEQYN	STYRVVSVLT	VLHQDWLNGK 750
EYKCKVSNKA	LPAPIEKTIS	KAKGQPREPQ	VYTLPPSRDE	LTKNQVSLTC 800
LVKGFYPSDI	AVEWESNGQP	ENNYKTTPPV	LDSDGSFFLY	SKLTVDKSRW 850
QQGNVFSCSV	MHEALHNHYT	QKSLSLSPGK		880

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

4-102 4'-102' 27-94 27'-94' 117-161 117'-161' 140-192 140'-192' 246-312 246'-312' 341-422 341'-422' 362-414 362'-414' 339-482 339'-482' 460-514 460'-514' 566-630 566'-630' 659-659' 662-662' 694-754 694'-754' 800-858 800'-858'

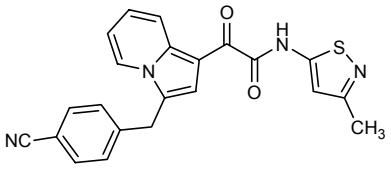
rosabulinum

rosabulin — 2-{3-[(4-cyanophenyl)methyl]indolizin-1-yl}-*N*-(3-methyl-1,2-thiazol-5-yl)-2-oxoacetamide

rosabuline — 2-[3-(4-cyanobenzyl)indolizin-1-yl]-*N*-(3-méthylisothiazol-5-yl)-2-oxoacétamide

rosabulina — 2-{3-[(4-cianofenil)metil]indolizin-1-il}-*N*-(3-metilisotiazol-5-il)-2-oxoacetamida

$C_{22}H_{16}N_4O_2S$



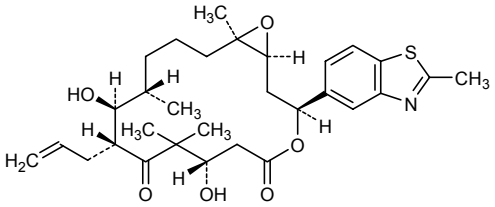
sagopilonum

sagopilone — (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihydroxy-8,8,12,16-tetramethyl-3-(2-methyl-1,3-benzothiazol-5-yl)-10-(prop-2-enyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

sagopilone — (-)-(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihydroxy-8,8,12,16-tétraméthyl-3-(2-méthyl-1,3-benzothiazol-5-yl]-10-(prop-2-ényl)-4,17-dioxabicyclo[14.1.0]heptadécane-5,9-dione

sagopilona — (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihidroxi-8,8,12,16-tetrametil-3-(2-metil-1,3-benzotiazol-5-il)-10-(prop-2-enil)-4,17-dioxabiciclo[14.1.0]heptadecano-5,9-diona

$C_{30}H_{41}NO_6S$



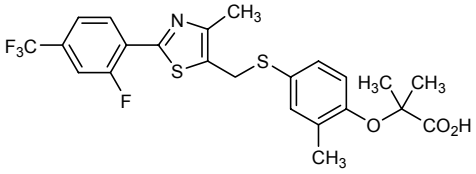
sodelglitazarum

sodelglitazar — 2-{4-[({2-[2-fluoro-4-(trifluromethyl)phenyl]-4-methyl-1,3-thiazol-5-yl}methyl)sulfanyl]-2-methylphenoxy}-2-methylpropanoic acid

sodelglitazar — acide 2-[4-[[[2-[2-fluoro-4-(trifluorométhyl)phényl]-4-méthyl-1,3-thiazol-5-yl]méthyl]sulfanyl]-2-méthylphénoxy]-2-méthylpropanoïque

sodelglitazar — ácido 2-{4-[({2-[2-fluoro-4-(trifluorometil)fenil]-4-metil-1,3-tiazol-5-il}metil)sulfanil]-2-metilfenoxi}-2-metilpropanoico

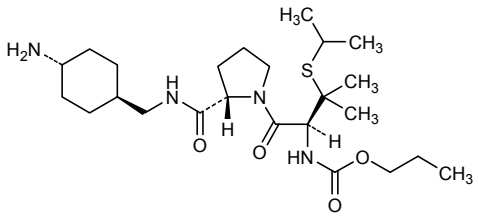
$C_{23}H_{21}F_4NO_3S_2$



sofigatranum

sofigatran	propyl {(1*S*)-1-{(2*S*)-2-[(*trans*-4-aminocyclohexylmethyl)carbamoyl]= pyrrolidine-1-carbonyl}-2-methyl-2-[(propan-2-yl)sulfanyl]propyl}= carbamate
sofigatran	[(1*S*)-1-[[(2*S*)-2-[[(*trans*-4-aminocyclohexyl)méthyl]carbamoyl]= pyrrolidin-1-yl]carbonyl]-2-méthyl-2-[(1-méthyléthyl)sulfanyl]propyl]= carbamate de propyle
sofigatrán	[(1*S*)-1-[[(2*S*)-2-[[(*trans*-4-aminociclohexil)metil]carbamoil]pyrrolidin-1-il]carbonil]-2-metil-2-[(propan-2-il)sulfanil]propil]carbamato de propilo

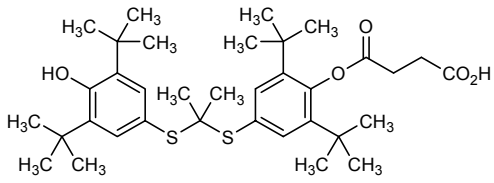
$C_{24}H_{44}N_4O_4S$



succinobucolum

succinobucol	4-{4-[(2-{[3,5-di(*tert*-butyl)-4-hydroxyphenyl]sulfanyl}propan-2-yl)= sulfanyl]-2,6-di(*tert*-butyl)phenoxy}-4-oxobutanoic acid
succinobucol	acide 4-[4-[[1-[[3,5-bis(1,1-diméthyléthyl)-4-hydroxyphényl]sulfanyl]-1-méthyléthyl]sulfanyl]-2,6-bis(1,1-diméthyléthyl)phénoxy]-4-oxobutanoïque
succinobucol	ácido 4-{4-[(2-{[3,5-di(*terc*-butil)4-hidroxifenil]sulfanil}propan-2-il)= sulfanil]-2,6-di(*terc*-butil)fenoxi}-4-oxobutanoico

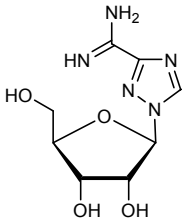
$C_{35}H_{52}O_5S_2$



taribavirinum

taribavirin	1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboximidamide
taribavirine	1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboximidamide
taribavirina	1-β-D-ribofuranosil-1*H*-1,2,4-triazol-3-carboximidamida

$C_8H_{13}N_5O_4$



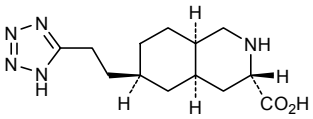
tezampanelum

tezampanel (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid

tézampanel (-)-acide (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*-tétrazol-5-yl)éthyl]= décahydroisoquinoléine-3-carboxylique

tezampanel (-)-ácido (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*-tetrazol-5-il)etil]= decahidroisoquinolina-3-carboxílico

$C_{13}H_{21}N_5O_2$



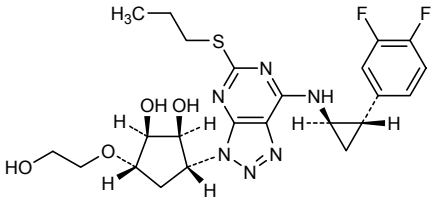
ticagrelorum

ticagrelor (1*S*,2*S*,3*R*,5*S*)-3-(7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]= amino}-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

ticagrélor (1*S*,2*S*,3*R*,5*S*)-3-[7-[[(1*R*,2*S*)-2-(3,4-difluorophényl)cyclopropyl]= amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyéthoxy)cyclopentane-1,2-diol

ticagrelor (1*S*,2*S*,3*R*,5*S*)-3-(7-{[(1*R*,2*S*)-2-(3,4-difluorofenil)ciclopropil]amino}-5-(propilsulfanil)-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-3-il)-5-(2-hidroxietoxi)ciclopentano-1,2-diol

$C_{23}H_{28}F_2N_6O_4S$



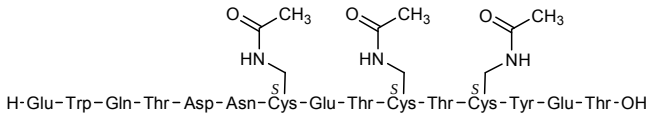
tigapotidum

tigapotide — L-glutamyl-L-tryptophyl-L-glutaminyl-L-threonyl-L-aspartyl-L-asparaginyl-*S*-[(acetamido)methyl]-L-cysteinyl-L-glutamyl-L-threonyl-*S*-[(acetamido)methyl]-L-cysteinyl-L-threonyl-*S*-[(acetamido)methyl]-L-cysteinyl-L-tyrosyl-L-glutamyl-L-threonine

tigapotide — S^{37}-S^{40},S^{42}-tris[(acétylamino)méthyl]bêta-microséminoprotéine humaine (protéine PSP94 sécrétée par la prostate)-(31-45)-peptide

tigapotida — S^{37}-S^{40},S^{42}-tris[(aceltilamino)metil]beta-microseminoproteína humana (proteína PSP94 secretada por la próstata)-(31-45)-péptido

$C_{82}H_{119}N_{21}O_{34}S_3$



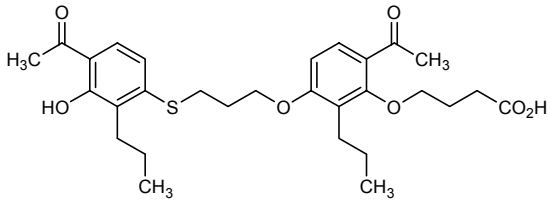
tipelukastum

tipelukast — 4-(6-acetyl-3-{3-[(4-acetyl-3-hydroxy-2-propylphenyl)sulfanyl]=propoxy}-2-propylphenoxy)butanoic acid

tipélukast — acide 4-[6-acétyl-3-[3-[(4-acétyl-3-hydroxy-2-propylphényl)sulfanyl]=propoxy]-2-propylphénoxy]butanoïque

tipelukast — ácido 4-[6-acetil-3-[3-[(4-acetil-3-hidroxi-2-propilfenil)sulfanil]=propoxi]-2-propilfenoxi]butanoico

$C_{29}H_{38}O_7S$



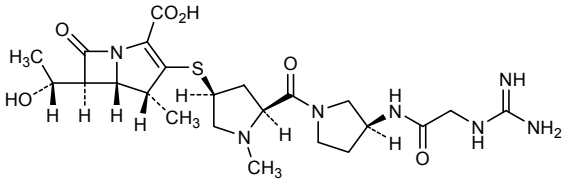
tomopenemum

tomopenem — (4*R*,5*S*,6*S*)-3-({(3*S*,5*S*)-5-[(3*S*)-3-(carbamimidamidoacetamido)=pyrrolidine-1-carbonyl]-1-methylpyrrolidin-3-yl}sulfanyl)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

tomopénem — (-)-acide (4*R*,5*S*,6*S*)-3-[[(3*S*,5*S*)-5-[[(3*S*)-3-[[(carbamimidoylamino)=acétyl]amino]pyrrolidin-1-yl]carbonyl]-1-méthylpyrrolidin-3-yl]=sulfanyl]-6-[(1*R*)-1-hydroxyéthyl]-4-méthyl-7-oxo-1-azabicyclo[3.2.0]=hept-2-ène-2-carboxylique

tomopenem — ácido (4*R*,5*S*,6*S*)-3-{[(3*S*,5*S*)-5-({(3*S*)-3-(carbamimidamidoacetamido)pirrolidin-1-il}carbonil)-1-metilpirrolidin-3-il]sulfanil}-6-[(1*R*)-1-hidroxietil]-4-metil-7-oxo-1-azabiciclo[3.2.0]=hept-2-eno-2-carboxílico

$C_{23}H_{35}N_7O_6S$



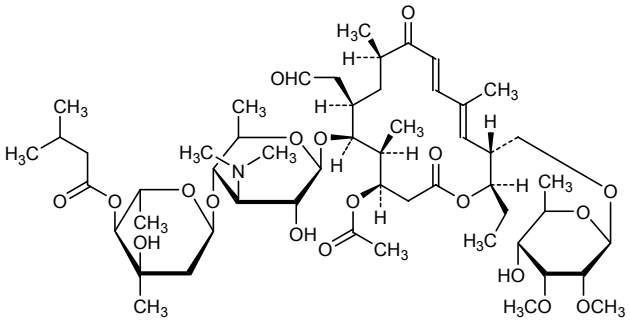
tylvalosinum

tylvalosin — (4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-{[(6-deoxy-2,3-di-*O*-methyl-β-D-allopyranosyl)oxy]methyl}-6-({3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl}oxy)-16-ethyl-5,9,13-trimethyl-2,10-dioxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-4-yl acetate

tylvalosine — (-)-acétate de (4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-[[(6-désoxy-2,3-di-*O*-méthyl-β-D-allopyranosyl)oxy]méthyl]-6-[[3,6-didésoxy-4-*O*-[2,6-didésoxy-3-*C*-méthyl-4-*O*-(3-méthylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(diméthylamino)-β-D-glucopyranosyl]oxy]-16-éthyl-5,9,13-triméthyl-2,10-dioxo-7-(2-oxoéthyl)oxacyclohexadéca-11,13-dién-4-yle

tilvalosina — (-)-acetato de (4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-[[(6-desoxi-2,3-di-*O*-metil-β-D-alopiranosil)oxi]metil]-6-[[3,6-didesoxi-4-*O*-[2,6-didesoxi-3-*C*-metil-4-*O*-(3-metilbutanoil)-α-L-*ribo*-hexopiranosil]-3-(dimetilamino)-β-D-glucopiranosil]oxi]-16-etil-5,9,13-trimetil-2,10-dioxo-7-(2-oxoetil)oxaciclohexadeca-11,13-dien-4-ilo

$C_{53}H_{87}NO_{19}$



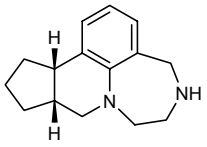
vabicaserinum

vabicaserin — (9a*R**,12a*S**)-4,5,6,7,9,9a,10,11,12,12a-decahydrocyclopenta[*c*][1,4]diazepino[6,7,1-*ij*]quinoline

vabicasérine — (-)-(9a*R**,12a*S**)-4,5,6,7,9,9a,10,11,12,12a-décahydrocyclopenta[*c*][1,4]diazepino[6,7,1-*ij*]quinoléine

vabicaserina — (-)-(9a*R**,12a*S**)-4,5,6,7,9,9a,10,11,12,12a-decahidrociclopenta[*c*][1,4]diazepino[6,7,1-*ij*]quinolina

$C_{15}H_{20}N_2$

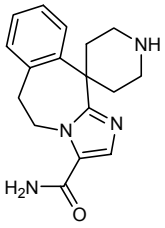


or enantiomer, (-)-isomer
ou énantiomère, (-)-isomère
o enantiómero, (-)-isómero

vapitadinum

vapitadine	5,6-dihydrospiro(imidazo[2,1-*b*][3]benzazepine-11,4'-piperidine)-3-carboxamide
vapitadine	5,6-dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazépine-11,4'-pipéridine]-3-carboxamide
vapitadina	5,6-dihidrospiro(11*H*-imidazo[2,1-*b*][3]benzazepina-11,4'-piperidina)-3-carboxamida

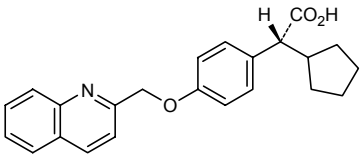
$C_{17}H_{20}N_4O$



veliflaponum

veliflapon	(2*R*)-cyclopentyl{4-[(quinolin-2-yl)methoxy]phenyl}acetic acid
véliflapon	(+)-acide (2*R*)-cyclopentyl[4-(quinoléin-2-ylméthoxy)phényl]acétique
veliflapón	(+)-ácido (2*R*)-ciclopentil[4-(quinolin-2-ilmetoxi)fenil]acético

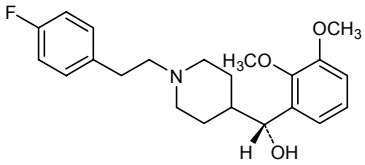
$C_{23}H_{23}NO_3$



volinanserinum

volinanserin	(*R*)-(2,3-dimethoxyphenyl){1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}=methanol
volinansérine	(+)-(*R*)-(2,3-diméthoxyphényl)[1-[2-(4-fluorophényl)éthyl]pipéridin-4-yl]méthanol
volinanserina	(+)-(*R*)-(2,3-dimetoxifenil)[1-[2-(4-fluorofenil)etil]piperidin-4-il]metanol

$C_{22}H_{28}FNO_3$



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

Recommended International Non Proprietary Names (Rec. INN): List 53
Dénominations communes internationales recommandées (DCI Rec.): Liste 53
Denominaciones Comunes Internacionales recomendadas (DCI Rec.): Lista 53
(WHO Drug Information, Vol. 19, No. 1, 2005)

p. 80	*delete/supprimer/suprímase*	*insert/insérer/insertése*
	gantacurium chloridum	gantacurii chloridum

p. 88 **panitumumabun**

panitumumab	*replace the molecular formula by the following*
panitumumab	*remplacer la formule brute par la suivante*
panitumumab	*sustitúyase la fórmula molecular por la siguiente*

$C_{6398}H_{9878}N_{1694}O_{2016}S_{48}$

p. 88 **pelitinibum**

pelitinib	*sustitúyase el nombre químico por el siguiente:*
	(2*E*)-*N*-[3-ciano-4-[(3-cloro-4-fluorofenil)amino]-7-etoxiquinolin-6-il]-4-(dimetilamino)-2-butenamina

Recommended International Non Proprietary Names (Rec. INN): List 55
Dénominations communes internationales recommandées (DCI Rec.): Liste 55
Denominaciones Comunes Internacionales recomendadas (DCI Rec.): Lista 55
(WHO Drug Information, Vol. 20, No. 1, 2006)

p. 45	*suprimáse*	*insértese*
	nebicapone	nebicapona

* Electronic structure available on Mednet: http://mednet.who.int/
* Structure électronique disponible sur Mednet: http://mednet.who.int/
* Estructura electrónica disponible en Mednet: http://mednet.who.int/

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 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 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 las listas de DCI propuestas.