# WHO Drug Information

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# WHO Prequalification Programmes

## WHO Prequalification of Medicines Programme: survey of service quality provided to manufacturers

Established in 2001, the Prequalification of Medicines Programme (PQP) is a service provided by the World Health Organization (WHO) to facilitate access to quality medicines for treating priority diseases. In order to be prequalified, medicines must meet WHO-specified standards for quality, safety and efficacy. PQP is supported by various United Nations agencies (e.g., UNAIDS, UNICEF, UNFPA) and the World Bank.

WHO prequalification of medicines is a multi-step process whereby a manufacturer submits extensive information that is then evaluated by a WHO assessment team with respect to product quality, safety and efficacy, site(s) of manufacture and any clinical studies that may have been carried out during development. Products that successfully pass PQP evaluation are listed on the WHO List of Prequalified Medicinal Products (see: http://www.who.int/prequal). This list provides UN agencies with a single source of reference for quality-assured priority medicines and is also used by a variety of entities, both country-specific and international, that purchase medicines in bulk quantities.

The Prequalification of Medicines Programme has conducted a comprehensive survey among pharmaceutical manufacturers to assess its level of service. PQP assessment and inspection activities reflect those carried out by national regulatory authorities before granting marketing authorization (registration) for a medicine. The assessment review was therefore designed to maximize the diagnostic capability of the survey: to measure both the level of service provided by PQP and the levels of service expected from regulatory authorities by manufacturers. The survey included items relevant to the assessment of product dossiers and on-site inspections of manufacturing facilities in a way that separated service design (the service process) from service delivery (or the "people" aspects of service). The results of this survey provide direction for improvements to the current Programme and have implications for future strategic development.

### The survey

In administering the Prequalification of Medicines Programme (PQP), WHO interacts with a number of stakeholder groups and organizations whose objectives are dependent upon, or related to, WHO prequalification of medicines: manufacturers, government agencies (including national and regional medicines regulatory authorities) and donor organizations. In 2009, one such donor organization recommended that WHO undertake a process optimization review with respect to PQP – an exercise that would include feedback from manufacturers with experience of WHO prequalification of medicines.

To provide guidance in developing a survey of manufacturers, implementing the survey and analysing the results, PQP retained the services of a market research consulting company, Interclarity

Research & Consulting, Inc. Interclarity Research created a survey development process with both internal and external components that resulted in a survey whose contents were relevant to manufacturers and, when assessed by those manufacturers, actionable by PQP. The survey was undertaken with the clear understanding that PQP must operate in accordance with respective WHO and other relevant international technical standards. It was also understood that the results of the survey should neither serve to "lower" PQP's technical standards nor to "relax" the requirements for the sustained quality, safety and efficacy of any medicine that WHO had prequalified.

## Survey objectives

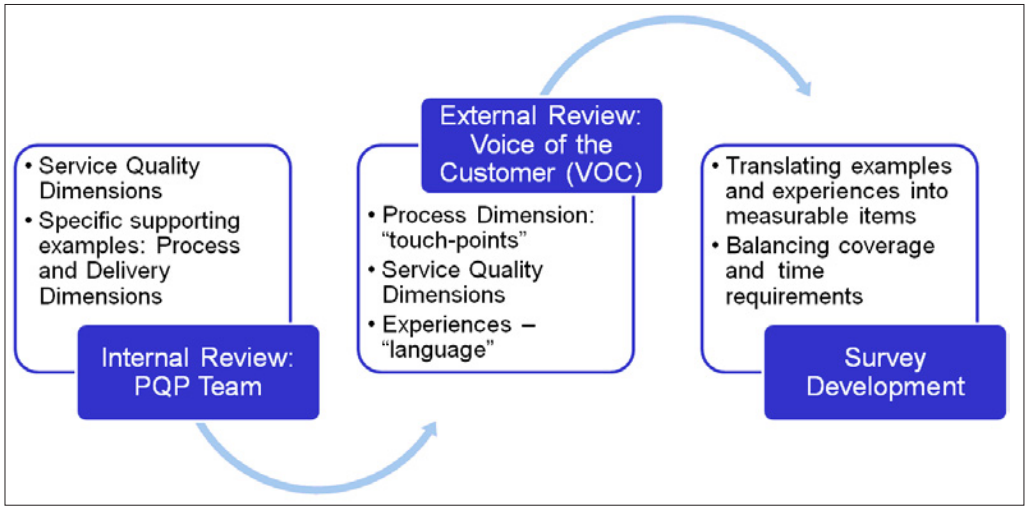
PQP identified three main objectives in designing and conducting a survey of pharmaceutical manufacturers:

- **Implement a comprehensive approach to assessing the level of service quality delivered to pharmaceutical manufacturers by PQP** by (i) incorporating aspects of both service design (process) and service delivery (people) and (ii) including services provided during both the assessment of product dossiers and on-site inspections of manufacturing facilities.
- **Maximize the diagnostic ability of the survey** by incorporating questions that use manufacturer experience with major regulatory agencies (US FDA, EMA, etc.) to measure expectations of service quality and prioritize areas for improvement.
- **Provide a unified framework for measurement.** While the intent of the initial survey of pharmaceutical manufacturers was to include only those companies that have had at least one product prequalified, PQP was also interested in developing a survey format that could be extended to companies involved for the first time (at some stage in the approval process or awaiting final approval) and companies that are considering participation.

## Survey development process

Without the benefit of previous self-assessment efforts, PQP had little to work with in terms of survey content in January

**Figure 1. Survey development**



2010. The area of service delivery is rich in both academic research and practical application [1]; the area of service design, however, is specific to the organization, application, and recipients of the service. Figure 1 on page 294 illustrates the process used by PQP to identify and codify important services related to the prequalification of medicines.

A survey development process was designed to obtain input from within the organization and from regulatory and quality assurance professionals in pharmaceutical companies. The overall aim of this process was to capture and include the knowledge and experience of PQP so that, when combined with the "voice of the customer", survey contents would be both relevant and actionable.

Interclarity Research developed topic guides and facilitated discussions, interviews and working sessions for both internal and external phases of the process. Internal working sessions, both in conference call and in-person formats, were conducted with key PQP members and groups (e.g. programme management, PQP assessors and PQP inspectors). Following the internal review, in-depth telephone interviews were conducted with industry professionals familiar with PQP. In both phases of the survey development process, the emphasis was on identifying, from a participant's point of view, important stages in the WHO prequalification process — aspects that work well and those that fall short of participant expectation. To gain greater clarity around important issues associated with service delivery, efforts were made in the "voice of the customer" to identify detailed descriptions of service delivery for both favourable and unfavourable events, as experienced by PQP manufacturer participants [2, 3].

A list of candidate survey items related to the PQP service process was developed from the findings of internal and external qualitative research. Further analysis of the qualitative findings suggested that service delivery aspects of PQP would be well-represented by items included in the SERVQUAL scale of service quality [4]. SERVQUAL is a widely-applied scale for measuring the quality of service delivery. Developed in the 1980s, it has been refined and applied over the past 25 years.

**Survey construction and deployment**
The survey was divided into four main sections:

1. Experience with PQP.

2. PQP Service Design ("process").

3. PQP Service Delivery ("people").

4. Other Aspects of PQP.

The first section includes an introduction to the survey and questions that provide indicators and measures of previous experience with PQP. Section 2 (Service Design) is "custom" to PQP – developed as a result of a process review with PQP staff and the series of interviews with pharmaceutical manufacturers. This section includes two multi-item questions on PQP aspects common to both assessment and inspection environments, and two separate multi-item questions each for regulatory affairs and quality assurance professionals respectively. In Section 3 (Service Delivery), measuring the people component with SERVQUAL requires five separate multi-item questions each for the assessment of product dossiers and on-site inspections respectively. The items in Section 4 are also custom to PQP and include measures related to the advocacy, training and compliance aspects of PQP.

Incorporating both common and application-specific items in a single survey made deploying the questionnaire on the Internet advantageous. The appropriate programming logic was developed to

display the questions common to all respondents and the application-specific questions (i.e. assessment of product dossiers and on-site inspections) only to those respondents with the relevant background and PQP experience. In addition, since a relatively large number of respondents in both the Indian and Chinese markets were anticipated, native language versions of the questionnaire for these two markets were made available, along with the English language version. An option was included in the survey introduction that allowed respondents to select a language option.

**Measurement**

WHO service performance was measured using a 7-point rating scale, where a "1" indicates "low performance" and a "7" indicates "high performance". The numbers 2 – 6 are varying degrees in between. To increase the diagnostic value of the survey results, two supplemental questions [4] were included to describe manufacturer expectations around each service item:

1. *Minimum Service Level.* The minimum level of service performance that manufacturers are willing to accept from ANY major regulatory agency.

2. *Desired Service Level.* The level of service that a regulatory agency should deliver to manufacturers.

**Data Collection**

A list of potential survey participants was compiled by PQP Staff using internal records. The list included regulatory affairs professionals (assessment of product dossiers) and quality assurance professionals (on-site inspections) who had participated in WHO prequalification of medicines during the period 2006 – 2010. Individuals on the contact list represented manufacturers of both branded and generic pharmaceutical medicines who have had a medicinal product or products prequalified by WHO. After cleaning and validation, the initial list of 75 contacts was revised to a final list of 62 prospective survey respondents. All contacts on the final list received an e-mail invitation from Interclarity Research on behalf of WHO. Each e-mail included an embedded link to the survey questionnaire on a secure web site. A total of 41 completed surveys was collected: 18 responses from regulatory affairs professionals and 23 responses from quality assurance professionals.

**Key Findings**

- Both PQP assessors and inspectors are meeting or exceeding manufacturer expectations for service delivery.

- The structure of PQP generally delivers levels of service at, or above, those expected by manufacturers. However, the service process is falling short of manufacturer expectations with respect to:

  - Review/reply time for product dossiers.
  - Opportunities for in-person communication during the assessment process.
  - Question/problem resolution during assessment.
  - Consistency of membership in the team of assessors throughout the process.
  - Local/national representation in on-site inspection teams,

- Most manufacturers view PQP GMP requirements as more stringent than those of the US Food and Drug Administration or European Medicines Agency.

- Reducing the time required to prequalify a product requires a joint effort between the manufacturer and the PQP.

## Conclusions

Overall, the findings from this survey indicate that pharmaceutical manufacturers consider PQP to be a well-designed, well-executed programme. PQP assessors and inspectors are meeting or exceeding manufacturer expectations for service delivery in the process. However, pharmaceutical manufacturer applicants place a premium on feedback, communications and problem resolution during the prequalification process – with particular emphasis on the assessment of product dossiers – and these are potential improvement areas in the service design of PQP.

Based on the survey results, WHO is now working on improvements to the Programme and these will be implemented in the coming year.

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## WHO initiates pilot prequalification of active pharmaceutical ingredients

In October 2010, the WHO Prequalification of Medicines Programme (PQP) started to pilot prequalification of selected active pharmaceutical ingredients (APIs) for products for treating HIV and related diseases, malaria and tuberculosis. Its first “Invitation to Manufacturers of Active Pharmaceutical Ingredients to Submit an Expression of Interest (EOI) for Evaluation” is available at http://who.int/prequal/

Globalization of pharmaceutical production has led to diversification of API sources and made verification of API quality more difficult. WHO’s decision to prequalify APIs responds to the increasing concern expressed by medicines regulators regarding API quality, including the manner in which APIs are manufactured.

PQP already assesses API master files (APIMFs) as part of its evaluation of finished pharmaceutical products (FPPs). This can include inspection of the manufacturing site to assess compliance with WHO good manufacturing practices (GMP), if risk assessment indicates that an on-site inspection is necessary. An API submitted for evaluation will undergo both dossier assessment and inspection of the manufacturing site.

Each prequalified API — including details of the supplier and manufacturing site(s) — will be added to the WHO List of Prequalified Active Pharmaceutical Ingredients. The List will be of great interest to FPP manufacturers seeking to ensure the good quality of APIs used in FPP production, and to national medicines regulatory authorities who wish to verify the standard of APIs that have been used to manufacture nationally registered medicines.

It is expected that the time taken to reach prequalification will be made shorter for FPPs that are manufactured using WHO-prequalified APIs, than for FPPs that are manufactured using APIs that have not previously been evaluated by WHO PQP.

An APIMF that has already been accepted by WHO in relation to the prequalification of an FPP may be included in the WHO List of Prequalified APIs without reassessment or re-inspection. This is contingent upon the APIMF meeting certain administrative criteria and the relevant manufacturing site having passed inspection by WHO or a stringent regulatory authority.

Selection of APIs for inclusion in the first Invitation was based on APIs for which APIMFs have already been submitted in connection with evaluation of an FPP. PQP anticipates that future Invitations will be expanded to incorporate additional APIs. New Invitations will be posted on the PQP web site and manufacturers are therefore encouraged to regularly access http://www.who.int/prequal.

## New on-line database for WHO prequalified vaccines

A new database for vaccines prequalified by WHO by type of vaccine, manufacturer and country of manufacture is now available on WHO's web site (1). This will enable immunization programme managers, procurement agencies, regulatory authorities, and other partners to consult summary pages for each prequalified vaccine and seek information such as date of prequalification, vaccine presentation, route of administration, shelf life, packaging, and cold chain requirements.

The ultimate goal of WHO's prequalification programme for vaccines is to ensure that all countries have access to vaccines that meet international standards of quality, safety and efficacy and are appropriate for the target population. The rigourous prequalification process includes

- review of comprehensive documentation on production methods, vaccine composition, quality control and clincial experience;
- independent testing for consistency by WHO-accredited laboratories; and
- site audits of the manufacturer to ensure that vaccine and production methods conform to international standards.

Complaints about vaccine quality and reports of adverse events following immunization are investigated by WHO. Furthermore, United Nations procurement agencies only purchase vaccines that have been prequalified by WHO.
The system is widely credited with contributing to the growing number and proportion of quality vaccines being supplied by companies in developing countries, such as Brazil, Cuba, India, Indonesia and Senegal.

The prequalification pages on WHO's web site contain sections on overall goals, principles, process and priority-setting for WHO vaccine prequalification, together with guidance documents for vaccine manufacturers.

**References**

1. Database on prequalified vaccines at http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html

2. Further information on the WHO Prequalification of Vaccines Programme at http://www.who.int/immunization_standards/vaccine_quality/vq_index/en/index.html

# Safety and Efficacy Issues

## H1N1 influenza vaccine: narcolepsy

**European Union** — The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has reviewed all available data on the suspected link between narcolepsy and Pandemrix® an H1N1 influenza vaccine. The Committee concluded that the available evidence was insufficient to determine whether there is any link between Pandemrix® and reports of narcolepsy, and that further studies were necessary to fully understand this issue.

The Committee agreed that at present the benefit-risk balance for Pandemrix® continues to be positive and that while the review is still ongoing there was no need for Europe-wide restrictions on use. Narcolepsy is a rare sleep disorder that causes a person to fall asleep suddenly and unexpectedly. Its precise cause is unknown, but it is generally considered to be triggered by a combination of genetic and environmental factors.

As per 17 September 2010, there were 81 reports from healthcare professionals suggestive of narcolepsy, all collected through spontaneous reporting systems. Of these, 34 reports come from Sweden, 30 from Finland, 10 from France, six from Norway and one from Portugal. In addition, there are a further 13 consumer reports from Sweden and two from Norway. The age range of patients is between four and 52 years.

**Reference**: *EMA Press Release*, EMA/CHMP/588294/2010, 23 September 2010 at http://www.ema. europa.eu

## Statins: interstitial lung disease

**Canada** — Interstitial lung disease (ILD) is a heterogeneous group of disorders that can be acute or chronic and may lead to pulmonary fibrosis and pulmonary insufficiency (1, 2). Signs and symptoms include difficulty breathing, nonproductive cough and diffuse crackles heard on auscultation. ILD has been reported in association with several drugs, such as amiodarone, azathioprine, carbamazepine, cyclophosphamide, methotrexate and nitrofurantoin (1, 2).

During the past 15 years, 29 cases of ILD suspected of being associated with HMG-CoA reductase inhibitors (statins) have been published (3–14). Of these, 16 describe a positive dechallenge with or without immunosuppressive treatment (3,4, 6, 8–11,14 ) and three cases described a positive rechallenge (4, 9). In some of these reports, ILD was part of systemic clinical features consistent with potential drug-induced diseases such as lupus (7), polymyositis (4, 12), dermatomyositis (5) and Churg-Strauss syndrome (14).

A systematic review of the suspected association between ILD and statins has recently been published (15). Although the mechanism of potential statin-induced ILD is unknown, some authors suggested it could be mediated by the inhibition of phospholipases; an effect of the statins on mitochondrial metabolism; or immune mediated (15).

As of 31 March 2010, Health Canada received 8 adverse reaction reports of ILD, or pathologies associated with ILD,

suspected of being associated with atorvastatin, pravastatin, rosuvastatin and simvastatin. Two of the cases received by Health Canada were published (14).

*Extracted from the Canadian Adverse Reaction Newsletter, Volume 20, Number 4, October 2010*

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## Tocilizumab: risk of fatal anaphylaxis

**Canada** — The manufacturer of tocilizumab (Actemra®) has informed healthcare professionals of important safety information.

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass with a H2L2 polypeptide structure. It is authorized for intravenous use to reduce the signs and symptoms of moderately to severely active rheumatoid arthritis in adult patients who have inadequate response to one or more disease modifying antirheumatic drugs (DMARDs) and/or tumour necrosis factor (TNF) antagonists.

A case of fatal anaphylaxis has been reported in a patient with rheumatoid arthritis treated with tocilizumab. No Canadian cases of anaphylactic reaction have been reported.

As hypersensitivity reactions can occur with the administration of tocilizumab, patients need to be closely monitored throughout the infusion for signs and symptoms of hypersensitivity.

If a hypersensitivity reaction is suspected, infusion is to be stopped immediately and appropriate treatment should be administered.

**Reference**: Communication from Hoffmann-La Roche Limited, dated 13 September 2010 at http://www.hc-sc.gc.ca/

## Pioglitazone: potential bladder cancer

**United States of America** — The Food and Drug Administration (FDA) is reviewing data from an ongoing, ten-year epidemiological study designed to evaluate whether pioglitazone (Actos®), is associated with an increased risk of bladder cancer. Findings from studies in animals and humans suggest this is a potential safety risk that needs further study. Pioglitazone is used in adults with type 2 diabetes mellitus.

Bladder cancer is estimated to occur in 20 per 100 000 persons per year in the United States and is thought to be higher in diabetics.

FDA has not concluded that pioglitazone increases the risk of bladder cancer. The Agency is reviewing information related to the safety concern and will update the public when additional information is available.

**Reference:** *FDA Drug Safety Communication,* 17 September 2010 at http://www/fda.gov

## Angiotensin receptor blockers and cancer: safety review

**United States of America** — The Food and Drug Administration (FDA) is conducting a review of the class of medications known as angiotensin receptor blockers (ARBs) after a recently published study suggested they may be associated with a small increased risk of cancer.

ARBs are used in patients with high blood pressure and other conditions. Brand names include Atacand®, Avapro®, Benicar®, Cozaar®, Diovan®, Micardis®, and Teveten®. ARBs are also sold in combination with other medications.

The Agency plans to review the available data on these medications, and evaluate additional ways to better assess a possible link between use of ARBs and cancer. FDA will update the public when this review is complete.

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1. Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *The Lancet Oncology* 2010;**11**(7), 627-36.

2. *FDA Drug Safety Communication*, 15 July 2010 at http://www/fda.gov

## GnRH agonists, diabetes and cardiovascular disease

**United States of America** — The Food and Drug Administration (FDA) has notified the manufacturers of gonadotropin-releasing hormone (GnRH) agonists of the need to add new safety information to the *Warnings and Precautions* section of drug labels. This new information warns about increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medica-

tions for the treatment of prostate cancer. This action is based on the Agency's review of several published studies (1–7), described in the Agency's ongoing safety review of GnRH agonists and possible increased risk of diabetes and certain cardiovascular diseases, issued in May 2010.

GnRH agonists are approved for palliative treatment of advanced prostate cancer. The benefits of GnRH agonist use for earlier stages of non-metastatic prostate cancer have not been established.

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8. *FDA Drug Safety Communication,* 20 October 2010 at http://www/fda.gov

## Gadolinium-based contrast agents: kidney dysfunction

**United States of America** — The Food and Drug Administration (FDA) is requiring changes to the drug labelling for gadolinium-based contrast agents (GBCAs) to minimize the risk of nephrogenic systemic fibrosis (NSF), a rare but serious condition associated with the use of GBCAs in certain patients with kidney dysfunction.

These label changes are intended to help ensure these drugs are used appropriately, and that patients at risk for NSF who receive GBCAs are actively monitored for the development of NSF. Symptoms of NSF include scaling, hardening and tightening of the skin, red or dark patches on the skin, and stiffness. NSF can also cause fibrosis of internal organs which may lead to death. There is no effective treatment for NSF.

**Reference**: *FDA Drug Safety Communication,* 9 September 2010 at http://www/fda.gov

## Lamotrigine: aseptic meningitis

**United States of America** — The Food and Drug Administration (FDA) has informed the public that lamotrigine (Lamictal®), a medication commonly used for seizures in children two years and older and bipolar disorder in adults, can cause aseptic meningitis. FDA is revising the drug label and the patient medication guide to include information about this risk.

The decision to revise the Lamictal® label is based on FDA's identification of 40 cases of aseptic meningitis in patients from December 1994 to November 2009.

**Reference**: *FDA Drug Safety Communication,* 12 August 2010 at http://www/fda.gov

## Tinzaparin sodium: renal Impairment in elderly

**Canada** — The manufacturer of tinzaparin sodium (Innohep®) has informed healthcare professionals of important safety information related to results from a clinical study that was stopped prematurely (IRIS – Innohep® in Renal Insufficiency Study) due to the observance of increased mortality. This study involved the use of therapeutic doses of tinzaparin sodium for the treatment of acute venous thromboembolism (VTE) in elderly patients with renal impairment.

Tinzaparin sodium is a low molecular weight heparin. It is authorized for the prevention of postoperative VTE in patients undergoing orthopaedic surgery and in patients undergoing general surgery who are at high risk of developing postoperative VTE; the treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE); and the prevention of clotting in indwelling intravenous lines for haemodialysis and extracorporeal circulation in patients without high bleeding risk. Based on the observations in IRIS:

- The study was halted by the Data Safety Monitoring Committee due to an interim finding of an increase in all-cause mortality in patients who received tinzaparin sodium compared to unfractionated heparin (UFH).
- Tinzaparin sodium is not recommended in elderly patients over 70 years of age with renal impairment.
- Tinzaparin sodium should be used with caution in patients with moderate to severe renal impairment and in all cases of impaired renal function patients should be closely monitored.

The IRIS study was an international, multicentre, prospective, open, centrally randomized, parallel group study comparing treatment doses of tinzaparin sodium and UFH for the initial treatment of DVT and/or PE in elderly patients with renal impairment.

**Reference**: Communication from LEO Pharma Inc., dated 14 October 2010 at http://www.hc-sc.gc.ca/

## Tamoxifen: drug interactions involving CYP2D6 genetic variants

**United Kingdom** — CYP2D6 genetic polymorphisms and concomitant use of potent CYP2D6 inhibitors may be associated with variability in clinical response in patients treated with tamoxifen for breast cancer. Therefore, concomitant use of medicines known to be potent CYP2D6 inhibitors should be avoided whenever possible in patients treated with tamoxifen. Current data for the effect of genetic polymorphisms are insufficient to support recommending genotyping of patients.

Tamoxifen is a selective oestrogen-receptor modulator indicated for palliative and adjuvant treatment of oestrogen-receptor-positive breast cancer in premenopausal and postmenopausal women. Tamoxifen is a prodrug, and the formation of the active metabolite, endoxifen, is mediated by the CYP2D6 enzyme. Several articles have recently been published regarding the potential effect of CYP2D6 genetic variants on clinical response to tamoxifen treatment in patients with breast cancer.

In patients with inherited non-functional alleles of the CYP2D6 gene ("poor metabolisers") or in patients concomi-

tantly treated with CYP2D6 enzyme inhibitors, concentrations of the tamoxifen metabolites that most strongly bind to the oestrogen receptor may be reduced.

**Reference**: *Drug Safety Update,* Volume 4, Issue 4 November 2010 at http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/index.htm

## Zoledronic acid solution: renal dysfunction

**Canada** — The manufacturer of zoledronic acid 5 mg/100 mL solution for intravenous infusion (Aclasta®) has informed healthcare professionals of important safety information. As of 30 April 2010, 265 spontaneous reports of renal impairment have been received following administration of Aclasta®, corresponding to a reporting rate of approximately 20 cases per 100 000 patient-years of exposure.

The following precautions should be taken to minimize the risk of renal adverse reactions.

- Zoledronic acid should not be used in patients with severe renal impairment.
- Zoledronic acid should be used with caution when concomitantly used with other drugs that could impact renal function.
- Creatinine clearance should be calculated before each treatment followed by periodic monitoring of serum creatinine in patients with risk factors. Transient increase in serum creatinine may be greater in patients with underlying impaired renal function.
- Patients should be appropriately hydrated, especially elderly patients and those receiving diuretic therapy.
- A single dose of Aclasta® should not exceed 5 mg and the duration of infusion should be no less than 15 minutes.

**Reference**: Communication from Novartis Pharmaceuticals Canada Inc. dated 12 October 2010 at http://www.hc-sc.gc.ca/

# Regulatory Action and News

## Influenza vaccines: 2011 southern hemisphere

**World Health Organization** — It is expected that pandemic A(H1N1), A(H3N2) and B viruses will co-circulate and the following viruses are recommended for influenza vaccines for the 2011 southern hemisphere influenza season:

- an A/California/7/2009 (H1N1)-like virus.
- an A/Perth/16/2009 (H3N2)-like virus. (A/Wisconsin/15/2009 and A/Victoria/210/2009 are A/Perth/16/2009-like viruses.)
- a B/Brisbane/60/2008-like virus.

As in previous years, national or regional control authorities approve the composition and formulation of vaccines used in each country. National public health authorities are responsible for making recommendations regarding the use of the vaccine.

**Reference**: Recommended viruses for influenza vaccines for use in the 2011 southern hemisphere influenza season. *Weekly Epidemiological Record*, **85**:401–402 (2010) at http://www.who.int/wer

## Rosiglitazone–containing antidiabetes medicines: suspension of marketing authorization

**European Union** — The European Medicines Agency has recommended suspension of the marketing authorizations for the rosiglitazone-containing antidiabetes medicines Avandia®, Avandamet® and Avaglim®.

Patients who are currently taking these medicines should make an appointment with their doctor to discuss suitable alternative treatments. Patients are advised not to stop their treatment without speaking to their doctor.

Doctors should stop prescribing rosiglitazone-containing medicines. Patients taking rosiglitazone-containing medicines should be reviewed in a timely manner to amend their treatment.

The current review of rosiglitazone by the Agency's Committee for Medicinal Products for Human Use (CHMP) was initiated on 9 July 2010 following the availability of new studies questioning the cardiovascular safety of the medicine.

Since its first authorization, rosiglitazone has been recognized to be associated with fluid retention and increased risk of heart failure and its cardiovascular safety has always been kept under close review. Consequently, the use of rosiglitazone was restricted to second-line treatment and contraindicated in patients with heart failure or a history of heart failure when it was first granted a marketing authorization as Avandia® in 2000.

Data from clinical trials, observational studies and meta analyses of existing studies that have become available over the last three years have suggested a possibly increased risk of ischaemic heart disease associated with the use of rosiglitazone. Further restrictions on the use of these medicines in patients with ischaemic heart disease were introduced. The availability of recent studies has added to the knowledge about rosiglitazone and overall, the accumulated data

support an increased cardiovascular risk of rosiglitazone.

In view of the restrictions already in place on the use of rosiglitazone, the Committee could not identify additional measures that would reduce the cardiovascular risk. The Committee therefore concluded that the benefits of rosiglitazone no longer outweigh its risks and recommended the suspension of the marketing authorization of the medicines.

**Reference**: *EMA Press Release*, EMA/585784/2010, 23 September 2010, at http://www. ema.europa.eu

## Modified-release oral opioids: suspension of marketing authorization

**European Union** — The European Medicines Agency has finalized a review of modified-release oral opioids of the WHO level III scale for the management of pain. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of most of these medicines continue to outweigh their risks, but that the existing warnings on the interaction of these medicines with alcohol should be made consistent across the class. However, for modified-release oral opioids that contain a polymethacrylate-triethylcitrate controlled-release system the Committee recommended suspension of marketing authorization until they have been reformulated to be more stable in alcohol.

Modified-release oral opioids of the WHO level III scale for the management of pain were reviewed due to concerns that they may be unstable in alcohol and that the active substance may be released too quickly when patients take them together with alcohol. This could put patients at risk of serious side effects such as respiratory depression.

**Reference**: *EMA Press Release,* EMA/463702/2010, dated 23 July 2010 at http://www.ema. europa.eu

## Human normal immunoglobulin: suspension of marketing authorization

**European Union** — The European Medicines Agency has recommended the suspension of the marketing authorizations for human normal immunoglobulin (Octagam®).

Octagam® is an intravenous solution used to strengthen the body's immune system, including people with primary immunodeficiency syndrome, or children born with acquired immune deficiency syndrome (AIDS). It is also used in people with certain immune disorders such as idiopathic thrombocytopenic purpura (ITP) and in patients who have had a bone marrow transplant.

The CHMP reviewed Octagam® because Germany and Sweden had suspended the marketing authorization of these medicines following an unexpected increase in reports of thromboembolic reactions, including stroke, myocardial infarction and pulmonary embolism in patients. This increase is thought to be related to problems with the medicine's manufacturing process.

The suspension will remain in place until the marketing authorization holder has rectified the problem.

**Reference:** *EMA Press Release,* EMA/CHMP/591722/2010, 24 September 2010 at http://www.ema. europa.eu

## Propoxyphene: recommendation against use

**United States of America —** The Food and Drug Administration (FDA) is recommending against continued prescribing

and use of the pain reliever propoxyphene because new data show that the drug can cause serious toxicity to the heart, even when used at therapeutic doses. FDA has requested that companies voluntarily withdraw propoxyphene from the United States market.

Propoxyphene is an opioid pain reliever used to treat mild to moderate pain. It is sold under various names as a single-ingredient product (e.g., Darvon®) and as part of a combination product with acetaminophen (e.g., Darvocet®).

The recommendation is based on all available data including data from a new study that evaluated the effects that increasing doses of propoxyphene have on the heart. FDA has concluded that the safety risks of propoxyphene outweigh its benefits for pain relief at recommended doses.

**Reference**: *FDA Drug Safety Communication,* 19 November 2010 at http://www/fda.gov

## Sitaxentan: worldwide withdrawal

**Australia** — The Therapeutic Goods Administration (TGA) has advised that the supply of the prescription medicine sitaxentan (Thelin®) will be suspended. The company that supplies the medicine has announced that it will withdraw Thelin® from the market globally.

Sitaxentan is a prescription-only medicine used to treat pulmonary hypertension. Patients currently taking sitaxentan should contact their physician as soon as possible to organize the supply of a different medicine but should not cease their use of sitaxentan until they have been assessed and switched to another medication.

This action has been taken in response to a review of safety data in clinical trials that showed patients were at risk of acute liver failure that in some cases was not reversible. The TGA has received 10 adverse event reports of abnormal liver function in Australian patients receiving sitaxentan.

**Reference**: *TGA Safety Alert,* 10 December 2010 at http://www.tga.gov.au/alerts/medicines/thelin-withdrawal.htm

## Sibutramine: suspension of sales

**Singapore** — The Health Sciences Authority (HSA) has taken a regulatory decision to suspend the sales of sibutramine products following a benefit-risk assessment which took into consideration the findings from the Sibutramine Cardiovascular Outcomes (SCOUT) study, use of the product in the local context and developments in other international jurisdictions.

Sibutramine is licensed in Singapore since 2001 for use as an adjunctive therapy to diet and exercise for obese patients with a body mass index (BMI) $\geq$30kg/m$^2$, or for overweight patients with a BMI $\geq$27kg/m$^2$ with other obesity-related risk factors such as Type 2 diabetes mellitus or dyslipidaemia.

The SCOUT study was a randomized, double-blind, placebo-controlled, multicentre study conducted in approximately 10 000 patients aged ≥55 who were obese or overweight and had a history of cardiovascular (CV) disease and/or type 2 diabetes with at least one other CV risk factor treated over a six year period. The study results showed that there was a 16% increase in the risk of a primary outcome event of nonfatal myocardial infarction (MI), nonfatal stroke, resuscitated cardiac arrest and CV death in the sibutramine group as compared with the placebo group. This was driven primarily by increase in rates of nonfatal MI and nonfatal stroke seen in the sibutramine group. A review of the serious adverse

events also showed that there were significantly more reports of myocardial ischaemia and ischaemic stroke in subjects taking sibutramine as compared to placebo.

The weight loss achieved in the SCOUT study was modest. At the end of 12 months, the mean weight loss achieved with sibutramine was up to 2.4 kg more than placebo. After 12 months of treatment, no additional mean weight loss was achieved and it was not clear if the effect on weight loss could be maintained when sibutramine was stopped.

Based on these findings and the overall assessment, HSA has concluded that the benefits of sibutramine do not outweigh their risks and has recommended that the sales of sibutramine be suspended. This suspension will remain in place until the company can provide sufficient data to identify a group of patients for whom sibutramine's benefits clearly outweigh its risks.

In view of the cessation of marketing of sibutramine in Singapore with immediate effect, healthcare professionals are advised to stop prescribing sibutramine, to review the therapy of existing patients who have been prescribed sibutramine and to consider suitable alternatives where appropriate.

**Reference**: *HSA Safety Alert,* 11 October 2010 at http://www.hsa.gov.sg

## Sibutramine-containing medicines: withdrawal

**Mexico** — The Federal Committee for Protection against Health Risks (COFEPRIS) has requested manufacturers of products containing sibutramine to begin withdrawal of these products from the market. Sibutramine is used for the treatment of obesity and overweight. Evidence now exists of a link to cardiovascular events.

The Committee has reminded the public of the risk incurred with self-medication of products claiming weight reduction.

**Reference**: Communication to Public and Healthcare Professionals, Comision Federal para la Proteccion contra Riesgos Sanitarios, 8 October 2010 at http://www.cofepris.gob.mx

## Testosterone transdermal patch: withdrawal of extension of indication application

**European Union** — The European Medicines Agency (EMA) has been formally notified by the manufacturer of its decision to withdraw its application for an extension of indication for the centrally authorized testosterone transdermal patch (Intrinsa®).

On 10 August 2009, the manufacturer submitted an application to extend the marketing authorization for Intrinsa® to include the treatment of hypoactive sexual desire disorder in menopausal women. Intrinsa® is currently authorized for the treatment of hypoactive sexual desire disorder in women who have had their uterus and both ovaries removed. It is used in patients already taking an oestrogen.

**Reference**: *EMA Press Release,* EMA/601877/2010, 29 September 2010 at http://www.ema. europa.eu

## Aliskiren/valsartan: withdrawal of marketing authorization application

**European Union** — The European Medicines Agency has been formally notified by the manufacturer of its decision to withdraw the application for a centralized marketing authorization for aliskiren/valsartan (Rasival®), 150/160 mg and 300/320 mg film-coated tablets.

This medicine was intended to be used for the treatment of essential hypertension as a substitution therapy in adults whose blood pressure is adequately controlled with aliskiren and valsartan, given as single components concurrently, at the same dose level as in the combination.

The company stated that its decision to withdraw the application was based on their inability to address the CHMP's requests and provide additional data within the timeframe allowed in the centralized procedure.

**Reference**: *EMA Press Release,* EMA/583880/2010, 17 September 2010 at http://www.ema. europa.eu

## Mometasone furoate/formoterol fumarate: withdrawal of marketing authorization application

**European Union —** The European Medicines Agency has been formally notified by the manufacturer of its decision to withdraw the application for a centralized marketing authorization for mometasone furoate/formoterol fumarate (Zenhale®) 50/5, 100/5 or 200/5 mg, pressurised inhalation.

This medicine was intended to be used for long-term, twice-daily maintenance treatment of asthma, including reduction of asthma exacerbations, in adults and children aged 12 years or older.

The decision to withdraw the application was based on the manufacturer's inability to address CHMP requests to provide additional data within the timeframe allowed in the centralized procedure.

**Reference**: *EMA Press Release,* EMA/700091/2010, 9 November 2010 at http://www.ema. europa.eu

## EMA and US FDA extend confidentiality arrangements indefinitely

**European Union/United States of America** — The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have extended their confidentiality arrangements related to medicinal products for human and veterinary use, following the positive experience gained since the initial arrangements were signed in September 2003. This cooperation will now continue indefinitely without the need for further renewal.

The confidentiality arrangements allow both Agencies to exchange confidential information as part of their regulatory and scientific processes. Their aim is to promote public and animal health and to protect European and US patients. The types of information covered by the arrangements relate to scientific advice, orphan drug designation, paediatric development, good manufacturing practice (GMP) and good clinical practice (GCP) inspection planning and reports, marketing authorization procedures and subsequent changes to the marketing authorizations together with post-marketing surveillance.

**Reference**: *EMA Press Release,* EMA/579151/2010, 15 September 2010 at http://www.ema. europa.eu

# Recent Publications, Information and Events

## US Government to share patents with Medicines Patent Pool

**United States of America** — A Presidential Policy Directive on Global Development has been signed that focuses on sustainable development outcomes and places a premium on broad-based economic growth, democratic governance, game-changing innovations, and sustainable systems for meeting basic human needs. The new Policy aims to leverage innovation to solve long-standing development challenges, encourage new models for innovation and to increase developing country utilization of science and technology.

The initial contribution by the National Institutes of Health (NIH) and co-patent owner, the University of Illinois at Chicago, takes an important step toward making affordable and appropriate HIV medicines available to patients around the world. It builds on the President's previous commitment to support humanitarian licensing policies to ensure that medications developed with US taxpayer dollars are available off-patent in developing countries. The patents have previously been licensed for the HIV drug darunavir. The license to the Medicines Patent Pool stipulates that the technology will be available for the benefit of all low- and middle-income countries, as defined by the World Bank, and is royalty-free.

The Medicines Patent Pool is supported by UNITAID, an innovative global health financing mechanism that was co-founded by Brazil, Chile, France, Norway and the United Kingdom at the United Nations General Assembly in 2006. It is a voluntary mechanism through which pharmaceutical patent holders can choose to license their patents to the Pool.

**Reference**: *Fact Sheet,* 30 September 2010 at http://www.WhiteHouse.gov

## Clinical trials and global medicines development

**European Union** — In September 2010, The European Medicines Agency (EMA) held an international workshop with a broad cross section of stakeholders from around the world to discuss a way forward for a global framework of clinical trials that has at its heart the protection of the rights, safety and wellbeing of patients participating in clinical trials anywhere in the world.

The workshop was part of the consultation process on the Agency's 'Reflection Paper on Ethical and Good Clinical Practice (GCP) Aspects of Clinical Trials of Medicinal Products for Human Use Conducted in Third Countries and submitted in Marketing Authorization Applications to the EMA'.

Some 170 participants from 50 countries provided feedback on the Reflection Paper and discussed international cooperation. They represented patient organisations, health-related nongovernmental organizations, clinical trial sponsors, pharmaceutical industry, ethics committees, regulatory authorities from all continents and intergovernmental organizations.

In marketing authorization applications submitted to the Agency between 2005

and 2009, only 38.8% of patients enrolled in pivotal clinical trials, received their treatments at clinical trial sites within the EU and EEA. These trials involved more than 44 000 clinical trial sites in 89 countries. The data generated was used to support 347 marketing authorization applications as well as some applications for a variation or a line extension of the existing marketing authorization.

**References**

1. *Draft Reflection Paper on Ethical and Good Clinical Practice (GCP) Aspects of Clinical Trials of Medicinal Products for Human Use Conducted in Third Countries and submitted in Marketing Authorization Applications to the European Medicines Agency*, at http:// www.ema.europa.eu/docs/en_GB/document_ library/Regulatory_and_procedural_guideline/ 2010/06/WC500091530.pdf

2. *EMA Press Release*, EMA/559074/2010, 6 September 2010 at http:// www.ema. europa.eu

## Evaluation of future nanomedicines

**European Union** — The European Medicines Agency (EMA) has hosted the first international scientific workshop on nanomedicines in September 2010. Some 200 European and international participants from 27 countries including Australia, Canada, India, Japan and the United States discussed benefits and challenges arising from the application of nanotechnologies to medicines. Participants included representatives from patient organizations, health care professional organizations, academia, regulatory authorities and the pharmaceutical industry.

Nanotechnologies have a wide and still only partially exploited potential in the development of medicines. They provide scope for engineered nano-systems that could lead to a spectrum of useful functions such as refined drug delivery, advanced combined diagnostics/therapeutic functions, matrices and support structures for regenerative medicines. Some eighteen marketing authorization applications for nanomedicines have been reviewed by the EMA so far.

Emerging therapies give rise to questions on the appropriateness of current regulatory frameworks, the relevance and adequacy of existing requirements and guidelines, and on the availability of adequate expertise to regulators. Scientific challenges arise from the limitations of current testing methods and the reliability of novel ones, because of the 'nanosize' and the unique behaviour of such nano-systems in biological structures.

**Reference**: European public assessment reports for nanomedicines and presentations of the keynote speakers at the workshop (EMA/567306/2010) at: http://www.ema. europa.eu

## Reporting on opioid inaccessibility

Strong opioids such as morphine are rarely accessible in low- and middle-income countries, even for patients with the most severe pain. The three cases recently reported in the *Journal of Pain and Palliative Care Pharmacotherapy* from three diverse countries provide examples of the terrible and unnecessary suffering that occurs everyday when this essential, inexpensive, and safe medication is not adequately accessible by patients in pain. The reasons for this lack of accessibility are explored, and ways to resolve the problem are proposed.

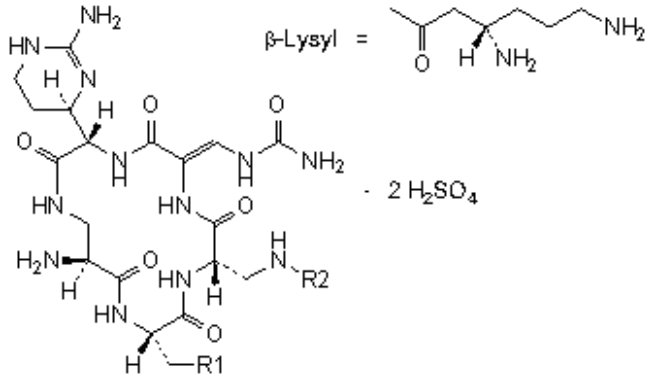
**Reference**: Krakauer EL, Wenk R, Buitrago R, Jenkins P, and Scholten W . Opioid inaccessibility and its human consequences: Reports From the Field. *Journal of Pain and Palliative Care Pharmacotherapy,* 2010;**24**(3):239–243.

# Consultation Documents

## The International Pharmacopoeia

### Capreomycini sulfas
### Capreomycin sulfate

Draft proposal for *The International Pharmacopoeia* (August 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.




| Component | $R_1$ | $R_2$ |
|---|---|---|
| Capreomycin IA | OH | -Lysyl |
| Capreomycin IB | H | -Lysyl |
| Capreomycin IIA | OH | H |
| Capreomycin IIB | H | H |

Capreomycin IA: $C_{25}H_{48}N_{14}O_{16}S_2$; Capreomycin IB: $C_{25}H_{48}N_{14}O_{15}S_2$; Capreomycin IIA: $C_{19}H_{35}N_{12}O_{15}S_2$; Capreomycin IIB: $C_{19}H_{35}N_{12}O_{14}S_2$

**Relative molecular mass.** Capreomycin IA: 864.9; Capreomycin IB: 848.9, Capreomycin IIA: 735.7; Capreomycin IIB: 719.7

**Chemical name.** Capreomycin IA: (3*S*)-3,6-diamino-N-[[(2*S*,5*S*,8Z,11*S*,15*S*)-15-amino-11-[(4*R*)-2-amino-3,4,5,6-tetrahydropyrimidin-4-yl]-8-[(carbamoylamino)

methylidene]-2-(hydroxymethyl)-3,6,9,12,16-pentaoxo-1,4,7,10,13-pentazacyclohexadec-5-yl]methyl]hexanamide; sulfuric acid.

Capreomycin IB: (3*S*)-3,6-diamino-N-[[(2*S*,5*S*,8*Z*,11*S*,15*S*)-15-amino-11-[(4*R*)-2-amino-3,4,5,6-tetrahydropyrimidin-4-yl]-8-[(carbamoylamino)methylidene]-2-methyl-3,6,9,12,16-pentaoxo-1,4,7,10,13-pentazacyclohexadec-5-yl]methyl]hexanamide; sulfuric acid.

Capreomycin IIA: [(*Z*)-[(3*S*,9*S*,12*S*,15*S*)-15-amino-9-(aminomethyl)-3-[(4*R*)-2-amino-3,4,5,6-tetrahydropyrimidin-4-yl]-12-(hydroxymethyl)-2,5,8,11,14-pentaoxo-1,4,7,10,13-pentazacyclohexadec-6-ylidene]methyl]urea; sulfuric acid.

Capreomycin IIB: [(*Z*)-[(3*S*,9*S*,12*S*,15*S*)-15-amino-9-(aminomethyl)-3-[(4*R*)-2-amino-3,4,5,6-tetrahydropyrimidin-4-yl]-12-methyl-2,5,8,11,14-pentaoxo-1,4,7,10,13-pentazacyclohexadec-6-ylidene]methyl]urea; sulfuric acid.

CAS Reg. No. 1405-37-4 (capreomycin sulfate).

**Description.** A white or almost white powder.

**Solubility.** Very soluble in water, practically insoluble in ethanol (~750 g/l) TS and in ether.

**Category.** Antituberculosis drug.

**Storage.** Capreomycin sulfate should be kept in a tightly closed container or, if sterile, in a hermetically closed container.

**Labelling.** The label states, where applicable:

(1) that the substance is free from bacterial endotoxins,
(2) that the substance is sterile.

## Requirements

**Definition.** Capreomycin sulfate is the disulfate salt of capreomycin, a polypeptide mixture produced by the growth of *Streptomyces capreolus*. It contains not less than 93.0% and not more than 102.0% of capreomycin sulfate, calculated with reference to the dried substance and taking into account the sum of capreomycins sulfate IA, IB, IIA and IIB. The content of capreomycins sulfate IA and IB is not less than 90%.

**Identity tests**
Either tests A and E or tests B, C, D and E may be applied.

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 capreomycin sulfate RS or with the *reference spectrum* of capreomycin sulfate.

B. 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 30 volumes of phenol R, 10 volumes

of water R and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 4 μl of each of the following two solutions in water R. For solution (A), use 10 mg of the test substance per ml and for solution (B), use 10 mg of capreomycin sulfate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air. Spray with triketohydrindene/methanol TS and heat the plate for 3 minutes at 120 °C. Examine the chromatogram in daylight. The spots obtained with solution A correspond in position, appearance, and intensity with those obtained with solution B.

C. The absorption spectrum of a 20 μg/ml solution in hydrochloric acid (0.1 mol/l) VS, when observed between 230 nm and 350 nm, exhibits one maximum at about 268 nm; the specific absorbance ($A^{1\%}_{1\ cm}$) is about 300.

D. The absorption spectrum of a 20 μg/ml in sodium hydroxide (0.1 mol/l) VS, when observed between 230 nm and 350 nm, exhibits a major maximum at about 287 nm; the specific absorbance ($A^{1\%}_{1\ cm}$) is about 200.

E. A 20 mg/ml solution yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

**pH value (1.3).** pH of a 30 mg/ml solution in carbon-dioxide-free water R, 4.5-7.5.

**Loss on drying.** Dry for 4 hours at 100 °C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury); it loses not more than 100 mg/g.

**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; determine the heavy metals content according to Method A; not more than 30 μg/g.

**Sulfated ash (2.3).** Not more than 10.0 mg/g.

**Bacterial endotoxins.** If intended for use in the manufacture of a parenteral dosage form, carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.35 IU of endotoxin per mg of capreomycin.

**Sterility.** If intended for use in the manufacture of either a parenteral or other sterile dosage form without a further appropriate sterilization procedure, complies with 3.2.2 Sterility testing of antibiotics, applying the membrane filtration test procedure and using the sampling plan described under 3.2.1 Test for sterility of non-injectable preparations.

**Related substances.** Carry out the test as described under 1.14.4 High performance liquid chromatography, using the conditions given under Assay, Method A.

Prepare the following solutions using water R as diluent. For solution (1) use 2.0 mg of the test substance per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 10 μg of capreomycin sulfate per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 μl of solution (1). The test is not valid unless the resolution between the two major peaks corresponding to capreomycin IA and capreomycin IB, with a relative retention of 0.89 and 1, respectively, is at least 2.0. The test is also not valid unless the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB, with a relative retention of 0.53 and 0.63, respectively, is at least 3.5.

Inject separately 20 μl each of solutions (1) and (2).

In the chromatogram obtained with solution (1), the area of any peak, other than the four major peaks corresponding to capreomycins IA, IB, IIA and IIB, is not greater than 4 times the sum of the areas of the four major peaks obtained with solution (2) (2.0%). The area of not more than one such peak is greater than twice the sum of the areas of the four major peaks obtained with solution (2) (1.0%). The sum of the areas of all peaks, other than the four major peaks, is not greater than 14 times the sum of the areas of the four major peaks obtained with solution (2) (7.0%). Disregard any peak with an area less than 0.1 times the sum of the areas of the four major peaks in the chromatogram obtained with solution (2) (0.05%).

**Assay**

Either method A or method B may be applied.

A. 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 base deactivated particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm). ( Hypersil BDS column has been found suitable).

The mobile phases for the gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 5 volumes of acetonitrile R and 95 volumes of phosphate buffer pH 2.3.
Mobile phase B: 15 volumes of acetonitrile R and 85 volumes of phosphate buffer pH 2.3.

Prepare the phosphate buffer pH 2.3 by dissolving 54.4 g of potassium dihydrogen phosphate R in 1500 ml of water R, adjust the pH to 2.3 by adding phosphoric acid (~105 g/l) TS, add 9.4 g of sodium hexanesulfonate R and dilute to 2000 ml with water R.

| Time (min) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comments |
|---|---|---|---|
| 0–25 | 55 to 52 | 45 to 48 | Linear gradient |
| 25–40 | 52 | 48 | Isocratic |
| 40–60 | 30 | 70 | Isocratic |
| 60–70 | 55 | 45 | Isocratic re-equilibration |

Prepare the following solutions using water R as diluent. For solution (1) use 2.0 mg of the test substance per ml. For solution (2) use 2.0 mg of capreomycin sulfate RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 μl of solution (1). The assay is not valid unless the resolution between the two major peaks corresponding to capreomycin IA and capreomycin IB, with a relative retention of 0.89 and 1, respectively, is at least 2.0. The assay is also not valid unless the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB, with a relative retention of 0.53 and 0.63, respectively, is at least 3.5.

Inject separately 20 μl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of capreomycin sulfate (sum of the four peaks corresponding to capreomycins IA, IB, IIA and IIB) from the declared content of capreomycin sulfate in capreomycin sulfate RS.

B. Dissolve about 40 mg, accurately weighed, in hydrochloric acid (0.1 mol/l) VS to produce 20 ml. Dilute 1 ml of this solution to 100 ml with the same solvent. Measure the absorbance of this solution in a 1-cm layer at the maximum at about 268 nm, and calculate the content of capreomycin sulfate, using the absorptivity value of 30.0 ($A^{1\%}_{1\ cm}$ = 300).

## Capreomycini add injectionem
## Capreomycin for injection

Draft proposal for *The International Pharmacopoeia* (August 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

**Description.** A white or almost white powder.

**Category.** Antituberculosis drug.

**Storage.** Capreomycin for injection should be stored in a well-closed container.

**Labelling.** The designation on the container of capreomycin for injection should state that the active ingredient is in the sulfate form, and the quantity should be indicated in terms of the equivalent amount of capreomycin.

**Additional information.** Strength in the current WHO Model List of Essential Medicines: 1 g. Strength in the current WHO Model List of Essential Medicines for children: 1 g.

The injection is reconstituted by dilution of Capreomycin powder for injections in Water for injections.

### Requirements

The powder for injection and the reconstituted injection comply with the monograph for "Parenteral preparations".

**Definition.** Capreomycin for injection is a sterile powder containing Capreomycin sulfate. It contains not less than 90.0% and not more than 115.0% of the amount of capreomycin stated on the label, taking into account the sum of capreomycins IA, IB, IIA and IIB.

**Identity tests**

Either tests A and E or tests B, C, D and E may be applied.

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 capreomycin sulfate RS or with the *reference spectrum* of capreomycin sulfate.

B. 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 30 volumes of phenol R, 10 volumes of water R and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 4 μl of each of the following two solutions in water R. For solution (A), dissolve a quantity of the powder to obtain a solution containing 10 mg of the test substance per ml. For solution (B), use 10 mg of capreomycin sulfate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air. Spray with triketohydrindene/methanol TS and heat the plate for 3 minutes at 120 °C. Examine the chromatogram in daylight.

The spots obtained with solution A correspond in position, appearance, and intensity with those obtained with solution B.

C. Dissolve a quantity of the powder in hydrochloric acid (0.1 mol/l) VS to obtain a solution containing the equivalent of 20 μg of capreomycin per ml. The absorption spectrum of this solution, when observed between 230 nm and 350 nm, exhibits one maximum at about 268 nm.

D. Dissolve a quantity of the powder in sodium hydroxide (0.1 mol/l) VS to obtain a solution containing the equivalent of 20 μg of capreomycin per ml. The absorption spectrum of this solution, when observed between 230 nm and 350 nm, exhibits a major maximum at about 287 nm.

E. A solution of the powder containing the equivalent of 20 mg of capreomycin per ml yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

**Clarity of solution.** A freshly prepared solution of the powder containing the equivalent of 1 g of capreomycin in 10 ml of carbon-dioxide-free water R is clear.

**pH value (1.3).** pH of a solution of the powder containing the equivalent of 0.3 g of capreomycin in 10 ml of carbon-dioxide-free water R, 4.5–7.5.

**Bacterial endotoxins**. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.35 IU of endotoxin per mg of capreomycin.

**Related substances.** Carry out the test as described under 1.14.4 High performance liquid chromatography, using the conditions given under Assay.

Prepare the following solutions using water R as diluent. For solution (1) dissolve a quantity of the powder to obtain a solution containing the equivalent of 2.0 mg of capreomycin per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 10 μg of capreomycin per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 μl of solution (1). The test is not valid unless the resolution between the two major peaks corresponding to capreomycin IA and capreomycin IB, with a relative retention of 0.89 and 1, respectively, is at least 2.0. The test is also not valid unless the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB, with a relative retention of 0.53 and 0.63, respectively, is at least 3.5.

Inject separately 20 μl each of solutions (1) and (2).

In the chromatogram obtained with solution (1), the area of any peak, other than the four major peaks corresponding to capreomycins IA, IB, IIA and IIB, is not greater than 4 times the sum of the areas of the four major peaks obtained with solution (2) (2.0%). The area of not more than one such peak is greater than twice the sum of the areas of the four major peaks obtained with solution (2) (1.0%). The sum of the areas of all peaks, other than the four major peaks, is not greater than 14 times the sum of the areas of the four major peaks obtained with solution (2) (7.0%). Disregard any peak with an area less than 0.1 times the sum of the areas of the four major peaks in the chromatogram obtained with solution (2) (0.05%).

**Assay**

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 base deactivated particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm). ( Hypersil BDS column has been found suitable).

The mobile phases for the gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

| | |
|---|---|
| Mobile phase A: | 5 volumes of acetonitrile R and 95 volumes of phosphate buffer pH 2.3. |
| Mobile phase B: | 15 volumes of acetonitrile R and 85 volumes of phosphate buffer pH 2.3. |

Prepare the phosphate buffer pH 2.3 by dissolving 54.4 g of potassium dihydrogen phosphate R in 1500 ml of water R, adjust the pH to 2.3 by adding phosphoric acid (~105 g/l) TS, add 9.4 g of sodium hexanesulfonate R and dilute to 2000 ml with water R.

| Time (min) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comments |
|---|---|---|---|
| 0–25 | 55 to 52 | 45 to 48 | Linear gradient |
| 25–40 | 52 | 48 | Isocratic |
| 40–60 | 30 | 70 | Isocratic |
| 60–70 | 55 | 45 | Isocratic re-equilibration |

Prepare the following solutions using water R as diluent. For solution (1) dissolve a quantity of the powder to obtain a solution containing the equivalent of 2.0 mg of capreomycin per ml. For solution (2) use an amount of capreomycin sulfate RS equivalent to 2.0 mg of capreomycin per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 l of solution (1). The assay is not valid unless the resolution between the two major peaks corresponding to capreomycin IA and capreomycin IB, with a relative retention of 0.89 and 1, respectively, is at least 2.0. The assay is also not valid unless the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB, with a relative retention of 0.53 and 0.63, respectively, is at least 3.5.

Inject separately 20 μl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of capreomycin (sum of the four peaks corresponding to capreomycins IA, IB, IIA and IIB) from the declared content of capreomycin in capreomycin sulfate RS.

*[Note from Secretariat: it is proposed that the ICRS will have its content expressed on the label in terms of capreomycin base and capreomycin sulfate]*

## Efavirenz tablets

Draft proposal for *The International Pharmacopoeia* (September 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

**Category.** Antiretroviral (Non-nucleoside Reverse Transcriptase Inhibitor).

**Storage.** Efavirenz tablets should be kept in a well-closed container, protected from light.

**Additional information.** Strengths in the current WHO Model List of Essential Medicines: 600 mg. Strengths in the current WHO Model List of Essential Medicines for Children: 600 mg.

### Requirements

Comply with the monograph for “Tablets”.

**Definition.** Efavirenz tablets contain Efavirenz. They contain not less than 90.0% and not more than 110.0% of the amount of Efavirenz ($C_{14}H_9ClF_3NO_2$) stated on the label.

### Identity tests

Either test A alone or tests B and D or tests C and D may be applied.

A. To a quantity of the powdered tablets containing 25 mg of Efavirenz, add 10 ml of methanol R, shake to dissolve and filter. Evaporate the filtrate to dryness. 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 efavirenz RS or with the *reference spectrum* of efavirenz.

If the spectra thus obtained are not concordant, repeat the test using the test residue and the residue obtained by dissolving efavirenz RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from efavirenz RS.

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

B.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 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 μl of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets containing 5 mg of Efavirenz with 5 ml, filter and use the clear filtrate. For solution (B) use 1 mg of efavirenz 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 with that obtained with solution B.

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described under test A.1 but using silica gel R5 as the coating substance. Spray the plate with basic potassium permanganate (~1 g/l) TS. Examine the chromatogram in daylight.

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

C. See the test described under Assay method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

D. The absorption spectrum of the final solution prepared for Assay method B, when observed between 210 nm and 300 nm, exhibits one maximum at about 247 nm.

**Related substances**. Prepare fresh solutions and perform the test without delay.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay Method A.

Prepare the following solutions in the dissolution solvent, a mixture of equal volumes of acetonitrile R and water R.

For solution (1) transfer a quantity of the powdered tablets containing about 25 mg of Efavirenz into about 20 ml of the dissolution solvent, sonicate for 5 minutes, allow to cool to room temperature and dilute to 25.0 ml with the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. For solution (2) dilute 1.0 ml of solution (1) to 50.0 ml with the dissolution solvent and dilute 5.0 ml of the resulting solution to 100.0 ml with the same solvent. For solution (3) dissolve about 5 mg of efavirenz RS in 5 ml of a solution prepared as follows: dissolve 1 mg of efavirenz impurity B RS in the dissolution solvent and dilute to 10 ml with the same solvent. Dilute 1 ml of the resulting solution to 25 ml with the dissolution solvent.

Inject separately 35 μl each of solutions (1), (2) and (3) 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).

In the chromatogram obtained with solution (3), the peak due to impurity B is eluted at a relative retention of about 0.9 with reference to Efavirenz (retention time about 20 minutes). The test is not valid unless the resolution factor between the peaks due to impurity B and Efavirenz is at least 3.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity B is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%), the area of any other peak, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%) and the area of not more than three such peaks is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than eight times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

*[Note from Secretariat: retention times and resolution factor to be confirmed.]*

**Assay**

Either method A or method B may be applied.

A. Carry out the assay as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm x 4.6 mm), packed with cyanopropyldimethylsilane monolayer (3.5 μm). (Zorbax® SB-CN has been found suitable.)

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 90 volumes of a 0.05% solution of trifluoroacetic acid R and 10 volumes of methanol R.
Mobile phase B: 10 volumes of a 0.05% solution of trifluoroacetic acid R and 90 volumes of methanol R.

| Time (min) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comments |
|---|---|---|---|
| 0–16 | 60 to 50 | 40 to 50 | Linear gradient |
| 16–23 | 50 to 35 | 50 to 65 | Linear gradient |
| 23–28 | 35 to 30 | 65 to 70 | Linear gradient |
| 28–29 | 30 to 20 | 70 to 80 | Linear gradient |
| 29–31 | 20 | 80 | Isocratic |
| 31–32 | 20 to 60 | 80 to 40 | Return to initial composition |
| 32–40 | 60 | 40 | Re-equilibration |

Prepare the following solutions in the dissolution solvent, a mixture of equal volumes of acetonitrile R and water R

For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 25 mg of Efavirenz, accurately weighed, into about 20 ml of the dissolution solvent, sonicate for 5 minutes, allow to cool to room temperature and dilute to 25.0 ml with the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of the resulting solution to 100.0 ml with the dissolution solvent. For solution (2) dissolve 25 mg of efavirenz RS in the dissolution solvent and dilute to 25.0 ml with the same solvent. Dilute 1.0 ml of the resulting solution to 100.0 ml with the dissolution solvent. For solution (3) dissolve about 5 mg of efavirenz RS in 5 ml of a solution prepared as follows: dissolve 1 mg of efavirenz impurity B RS in the dissolution solvent and dilute to 10 ml with the same solvent. Dilute 1 ml of the resulting solution to 25 ml with the dissolution solvent.

Operate with a flow rate of 1.5 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 250 nm.

Maintain the column temperature at 40 °C.

Inject separately 35 μl each of solutions (1), (2) and (3). In the chromatogram obtained with solution (3), the peak due to impurity B is eluted at a relative retention of about 0.9 with reference to efavirenz (retention time about 20 minutes). The assay is not valid unless the resolution factor between the peaks due to impurity B and efavirenz is at least 3.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of efavirenz ($C_{14}H_9ClF_3NO_2$) in the tablets.

*[Note from Secretariat: retention times and resolution factor to be confirmed.]*

B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 25 mg of Efavirenz, accurately weighed, to a 50-ml volumetric flask. Add about 25 ml of methanol R, sonicate for about 5 minutes, allow to cool to room temperature and make up to volume using the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of this solution to 50.0 ml with methanol R. Measure the absorbance (1.6) of a 1-cm layer of this solution at the maximum at about 247 nm. Calculate the content of efavirenz ($C_{14}H_9ClF_3NO_2$) in the tablets using an absorptivity value of 55.0 ($A^{1\%}_{1\ cm}$ = 550).

**Impurities.** The impurities limited by the requirements of this monograph include those listed in the monograph for Efavirenz.

## Efavirenz, emtricitabine and tenofovir tablets

Draft proposal for *The International Pharmacopoeia* (September 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

**Category.** Antiretroviral (Non-nucleoside/Nucleoside/Nucleotide Reverse Transcriptase Inhibitors).

**Storage.** Efavirenz, emtricitabine and tenofovir tablets should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model List of Essential Medicines: 600 mg Efavirenz, 200 mg Emtricitabine and 300 mg Tenofovir disoproxil fumarate.

### Requirements

Comply with the monograph for “Tablets”.

**Definition.** Efavirenz, emtricitabine and tenofovir tablets contain Efavirenz, Emtricitabine and Tenofovir disoproxil fumarate. They contain not less than 90.0% and not more than 110.0% of the amount of efavirenz ($C_{14}H_9ClF_3NO_2$), emtricitabine ($C_8H_{10}FN_3O_3S$) and tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$) stated on the label.

**Manufacture.** The manufacturing process and the product packaging are designed and controlled so as to minimize the moisture content of the tablets. They ensure that, if tested, the tablets would comply with a water content limit of not more than 60 mg/g when determined as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.5 g of the powdered tablets.

**Identity tests**

Either tests A and B or test 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 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 l of each of the following four solutions in methanol R. For solution (A) disperse a quantity of the powdered tablets to obtain a concentration of 5 mg of Emtricitabine per ml, filter and use the filtrate. For solution (B) use 5 mg of emtricitabine RS per ml. For solution (C) use 7.5 mg of tenofovir disoproxil fumarate RS per ml. For solution (D) use 15 mg of efavirenz RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm).
The three principal spots obtained with solution A correspond in position, appearance and intensity with those obtained with solutions B, C and D.

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Stain the plate with iodine vapour and examine the chromatogram in daylight.

The three principal spots obtained with solution A correspond in position, appearance and intensity with those obtained with solutions B, C and D.

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

B.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 50 volumes of heptane R, 30 volumes of glacial acetic acid R and 20 volumes of dichloromethane R as the mobile phase. Apply separately to the plate 5 l of each of the following two solutions in ethanol R. For solution (A) disperse a quantity of the powdered tablets to obtain a concentration of 10 mg of Tenofovir disoproxil fumarate per ml, filter and use the filtrate. For solution (B) use 2 mg of fumaric acid R per ml. Develop the plate in an unsaturated tank over a path of 10 cm. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

One of the spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test B.1 but using silica gel R5 as the coating substance. Spray lightly with a 16 g/l solution of potassium permanganate R and examine the chromatogram in daylight.

One of the spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

C. See the test described under Assay. The retention times of the principal peaks due to efavirenz, emtricitabine, tenofovir disoproxil and fumarate in the chromatogram obtained with the test solution are similar to those in the chromatogram obtained with the reference solution.

**Dissolution.** Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 1000 ml of a 2% solution of sodium dodecyl sulfate R, and rotating the paddle at 100 revolutions per minute. At 45 minutes withdraw a sample of 10 ml of the medium through an in-line filter. Allow the filtered sample to cool to room temperature and dilute if necessary [solution (1)]. Prepare solution (2) using 0.60 mg of efavirenz RS, 0.20 mg of emtricitabine RS and 0.30 mg of tenofovir disoproxil fumarate RS per ml of dissolution medium. Determine the content of efavirenz ($C_{14}H_9ClF_3NO_2$), emtricitabine ($C_8H_{10}FN_3O_3S$) and tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$) as described under Assay using solution (1) and solution (2).

For each of the six tablets tested, calculate the total amount of efavirenz ($C_{14}H_9ClF_3NO_2$), emtricitabine ($C_8H_{10}FN_3O_3S$) and tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$) in the medium from the results obtained. The amount in solution for each tablet is not less than 80% of the amount stated 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 75% and no tablet contains less than 60%.

**Tenofovir monoester.** Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay.

After preparation, keep the solutions at about 6 °C, or use an injector with cooling. Prepare the following solutions using a mixture of 20 volumes of acetonitrile R and 80 volumes of water R as a diluent. For solution (1) weigh and powder 20 tablets. Disperse a quantity of the powder containing about 100 mg of Tenofovir disoproxil fumarate, accurately weighed in 100 ml of the diluent and filter. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 5 μg of Tenofovir disoproxil fumarate per ml. For solution (3) heat carefully 1 mg of tenofovir disoproxil fumarate RS per ml of water R in a boiling water-bath for 20 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Maintain the column temperature at 35 °C.

Inject 20 μl of solution (3). The peak due to tenofovir monoester elutes at a relative retention of about 0.9 with reference to tenofovir disoproxil (retention time about 18 minutes). The test is not valid unless the resolution between these peaks is at least 5. Inject separately 20 μl each of solutions (1) and (2).

In the chromatogram obtained with solution (1), the area of any peak due to tenofovir monoester, is not greater than 7 times the area of the principal peak obtained with solution (2) (3.5%).

**Assay**

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 base-deactivated particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 m).

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 5 volumes of potassium dihydrogen phosphate (27.2 g/l) TS and 95 volumes of water R.

Mobile phase B: 70 volumes of acetonitrile R, 5 volumes of potassium dihydrogen phosphate (27.2 g/l) TS and 25 volumes of water R.

| Time (min) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comments |
|---|---|---|---|
| 0–9 | 93 | 7 | Isocratic |
| 9–15 | 93 to 0 | 7 to 100 | Linear gradient |
| 15–19 | 0 | 100 | Isocratic |
| 19–19.1 | 0 to 93 | 100 to 7 | Return to initial composition |
| 19.1–30 | 93 | 7 | Re-equilibration |

After preparation, keep the solutions at about 6 °C, or use an injector with cooling. Prepare the following solutions using a mixture of 20 volumes of acetonitrile R and 80 volumes of water R as a diluent. For solution (1) weigh and powder 20 tablets. Disperse a quantity of the powder containing about 10 mg of Tenofovir disoproxil fumarate, accurately weighed in 100 ml of the diluent and filter. For solution (2) use 0.2 mg of efavirenz RS, 0.1 mg of tenofovir disoproxil fumarate RS and 66.7 μg of emtricitabine RS per ml of diluent. For solution (c) use 0.02 mg of fumaric acid R per ml of water R.

If necessary adapt the concentration of solution (2) according to the ratio of Efavirenz, Emtricitabine and Tenofovir disoproxil fumarate in the tablets.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Maintain the column temperature at 35 °C.

Inject separately 20 μl each of solutions (1), (2) and (3).

The test is not valid unless in the chromatograms obtained with solutions (1) and (2), four principal peaks, that elute at the following retention times, are shown: fumarate (about 2.5 minutes), emtricitabine (about 9 minutes), tenofovir disoproxil (about 18 minutes) and efavirenz (about 22 minutes).

Calculate the content of efavirenz ($C_{14}H_9ClF_3NO_2$), emtricitabine ($C_8H_{10}FN_3O_3S$) and tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$) in the tablets.

## Emtricitabinum capsulae
## Emtricitabine capsules

Draft proposal for *The International Pharmacopoeia* (September 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

**Category.** Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor).

**Storage.** Emtricitabine capsules should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model List of Essential Medicines: 200 mg Emtricitabine.

### Requirements

Comply with the monograph for “Capsules”.

**Definition**. Emtricitabine capsules contain Emtricitabine. They contain not less than 90.0% and not more than 110.0% of the amount of emtricitabine ($C_8H_{10}FN_3O_3S$) stated on the label.

### Identity tests

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

A. Carry out test A.1 or, when 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 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 µl of each of the following two solutions in methanol R. For solution (A) disperse a quantity of the contents of the capsules to obtain a concentration of 5 mg of Emtricitabine per ml, filter and use the filtrate. For solution (B) use 5 mg of emtricitabine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

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

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Stain the plate with iodine vapour and examine in daylight.

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

B. Disperse the quantity of contents of the capsules containing about 50 mg of Emtricitabine with 40 ml of methanol R, dilute to 50 ml and filter. Dilute 1 ml of the filtrate to 50 ml with methanol R. The absorption spectrum (1.6) of the resulting solution, when observed between 220 and 350 nm, exhibits two maxima at about 242 nm and 284 nm.

C. See the test described under Assay, Method A. The retention time of the principal peak in the chromatogram obtained with the test solution is similar to that in the chromatogram obtained with the reference solution.

**Dissolution.** Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of hydrochloric acid (~4 g/l) TS and rotating the paddle at 50 revolutions per minute. At 45 minutes withdraw a sample of 10 ml of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Measure the absorbance (1.6) of a 1-cm layer of the resulting solution, suitably diluted if necessary, at the maximum at about 280 nm. Determine the content of emtricitabine ($C_8H_{10}FN_3O_3S$) in the medium from the absorbance obtained from a solution of known concentration of emtricitabine RS.

For each of the six capsules tested, calculate the total amount of emtricitabine ($C_8H_{10}FN_3O_3S$) in the medium from the results obtained and from the declared content of $C_8H_{10}FN_3O_3S$ in emtricitabine RS. The amount in solution for each capsule is not less than 80% of the amount declared on the label. If the amount of emtricitabine obtained for one of the six capsules is less than 80%, repeat the test using a further six capsules; the average amount of emtricitabine for all 12 capsules tested is not less than 75% and no capsule contains less than 60%.

**Related substances**
Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay, Method A.

Prepare the following solutions using a mixture of 20 volumes of acetonitrile R and 80 volumes of water R as a diluent. For solution (1) weigh and mix the contents of 20 capsules and disperse a quantity containing about 50 mg of Emtricitabine in 80 ml of the diluent, dilute to 100 ml with the diluent, filter and use the filtrate. For solution (2) dilute a suitable volume of solution (1) with the diluent to obtain a concentration of 0.50 μg of Emtricitabine per ml.

For the system suitability test: prepare solution (3) using 5 ml of solution (1) and 2 ml of phosphoric acid (~105 g/l) TS, heat carefully in a boiling water-bath for 15 minutes. Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Maintain the column temperature at 35 °C.

Inject 20 μl of solution (3). The test is not valid unless the resolution between the peak due to emtricitabine (retention time about 9 minutes) and the peak with a relative retention of about 1.3 is not less than 6.

Inject separately 20 µl each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the area of any peak eluting before the principal peak is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%); the area of not more than two such peaks is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%); the area of any peak eluting after the principal peak is not greater than 7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%); the area of not more than two such peaks is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (1%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay**

Either test A or test B may be applied.

A. 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 base-deactivated particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm). (Hypersil BDS C18 has been found suitable.)
.
The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 5 volumes of potassium dihydrogen phosphate (27.2 g/l) TS and 95 volumes of water R.

Mobile phase B: 70 volumes of acetonitrile R, 5 volumes of potassium dihydrogen phosphate (27.2 g/l) TS and 25 volumes of water R.

| Time (min) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comments |
|---|---|---|---|
| 0–9 | 93 | 7 | Isocratic |
| 9–15 | 93 to 0 | 7 to 100 | Linear gradient |
| 15–19 | 0 | 100 | Isocratic |
| 19–19.1 | 0 to 93 | 100 to 7 | Return to initial composition |
| 19.1–30 | 93 | 7 | Re-equilibration |

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Maintain the column temperature at 35 °C.

Prepare the following solutions using a mixture of 20 volumes of acetonitrile R and 80 volumes of water R as a diluent. For solution (1): weigh and mix the contents of 20 capsules and disperse a quantity containing about 50 mg of Emtricitabine in 80 ml of the diluent, dilute to 100 ml with the diluent, filter and use the filtrate.

For solution (2) use 0.5 mg of emtricitabine RS per ml of the diluent.

For the system suitability test: prepare solution (3) using 5 ml of solution (1) and 2 ml of phosphoric acid (~105 g/l) TS, heat carefully in a boiling water-bath for 15 minutes. Inject 20 l of solution (3). The test is not valid unless the resolution between the peak due to emtricitabine (retention time about 9 minutes) and the peak with a relative retention of about 1.3 is not less than 6.

Inject separately 20 μl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of emtricitabine ($C_8H_{10}FN_3O_3S$).

B. Weigh and mix the contents of 20 capsules and disperse a quantity containing about 50 mg of Emtricitabine in 40 ml of methanol R, dilute to 50 ml with methanol R and filter. Dilute 1 ml of the filtrate to 50 ml with methanol R.

Measure the absorbance (1.6) of the resulting solution in a 1-cm layer at the maximum at about 284 nm.

Calculate the content of emtricitabine ($C_8H_{10}FN_3O_3S$), using the absorptivity value of 33.2 ($A_{1cm}^{1\%} = 332$).

* * *

New reagent to be added to The International Pharmacopoeia:

**Hydrochloric acid (~4 g/l) TS.**

Dilute 10 ml of hydrochloric acid (~420 g/l) TS with sufficient water to produce 1000 ml (approximately 0.1 mol/l).

## Emtricitabini et tenofoviri compressi
## Emtricitabine and tenofovir tablets

Draft proposal for *The International Pharmacopoeia* (September 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

**Category.** Antiretroviral (Nucleoside/Nucleotide Reverse Transcriptase Inhibitor).

**Storage.** Emtricitabine and tenofovir tablets should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model list of essential medicines: 200 mg Emtricitabine and 300 mg Tenofovir disoproxil fumarate.

## Requirements

Comply with the monograph for "Tablets".

**Definition.** Emtricitabine and tenofovir tablets contain Emtricitabine and Tenofovir disoproxil fumarate. They contain not less than 90.0% and not more than 110.0% of the amounts of emtricitabine ($C_8H_{10}FN_3O_3S$) and tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$) stated on the label.

**Manufacture.** The manufacturing process and the product packaging are designed and controlled so as to minimize the moisture content of the tablets. They ensure that, if tested, the tablets would comply with a water content limit of not more than 60 mg/g when determined as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.5 g of the powdered tablets.

### Identity tests

Either tests A and B or test 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 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 μl of each of the following three solutions in methanol R. For solution (A) disperse a quantity of powdered tablets to obtain a concentration of 5 mg of Emtricitabine per ml, filter and use the filtrate. For solution (B) use 5 mg of emtricitabine RS. For solution (C) use 7.5 mg of tenofovir disoproxil fumarate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

One of the two principal spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B and the other one corresponds with that obtained with solution C.

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Stain the plate with iodine vapour and examine the chromatogram in daylight.

One of the two principal spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B and the other one corresponds with that obtained with solution C.

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

B.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 50 volumes of heptane R, 30 volumes of glacial acetic acid R and 20 volumes of dichloromethane R as the mobile phase. Apply separately to the plate 5 μl of each of the following two solutions in ethanol R. For solution (A) disperse a quantity of powdered tablets to obtain a concentration of 10 mg of Tenofovir disoproxil fumarate per ml, filter and use the filtrate. For solution (B) use 2 mg of fumaric acid R per ml. Develop the plate in an unsaturated tank over a path of 10 cm. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

One of the spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test B.1 but using silica gel R5 as the coating substance. Spray lightly with a 16 g/l solution of potassium permanganate R and examine the chromatogram in daylight.

One of the spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

C. See the test described under Assay. The retention times of the principal peaks in the chromatogram obtained with the test solution are similar to those due to emtricitabine, tenofovir disoproxil and to fumarate in the chromatogram obtained with the reference solution.

**Dissolution**
Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of hydrochloric acid (~0.4 g/l) TS, and rotating the paddle at 50 revolutions per minute. At 45 minutes withdraw a sample of 10 ml of the medium and filter. Allow the filtered sample to cool to room temperature and dilute if necessary [solution (1)]. Prepare solution (2) using 0.22 mg of emtricitabine RS and 0.33 mg of tenofovir disoproxil fumarate RS per ml of dissolution medium. Determine the content of emtricitabine ($C_8H_{10}FN_3O_3S$) and tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$) as described under Assay using solution (1) and solution (2).

For each of the six tablets tested, calculate the total amount of emtricitabine ($C_8H_{10}FN_3O_3S$) and tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$) in the medium from the results obtained. For both substances, the amount in solution for each tablet is not less than 80% of the amount stated 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 75% and no tablet contains less than 60%.

**Tenofovir monoester.** Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay.

After preparation, keep the solutions at about 6 °C, or use an injector with cooling.

Prepare the following solutions using a mixture of 20 volumes of acetonitrile R and 80 volumes of water R as a diluent. For solution (1) weigh and powder 20 tablets. Disperse a quantity of the powder containing about 100 mg of Tenofovir disoproxil fumarate, accurately weighed, in 100 ml of the diluent and filter. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 5 μg of Tenofovir disoproxil fumarate per ml. For solution (3) heat carefully 1 mg of tenofovir disoproxil fumarate RS per ml of water R in a boiling water-bath for 20 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Maintain the column temperature at 35 °C.

Inject 20 μl of solution (3). The peak due to tenofovir monoester elutes at a relative retention of about 0.9 with reference to tenofovir disoproxil (retention time about 18 minutes).

Inject separately 20 μl each of solutions (1) and (2). The test is not valid unless in the chromatogram obtained with solution (1), three principal peaks are shown.

In the chromatogram obtained with solution (1), the area of any peak due to tenofovir monoester, is not greater than seven times the area of the principal peak obtained with solution (2) (3.5%).

**Assay**
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 base-deactivated particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm). (Hypersil BDS column.)

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 5 volumes of potassium dihydrogen phosphate (27.2 g/l) TS and 95 volumes of water R.

Mobile phase B: 70 volumes of acetonitrile R, 5 volumes of potassium dihydrogen phosphate (27.2 g/l) TS and 25 volumes of water R.

| Time (min) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comments |
|---|---|---|---|
| 0–9 | 93 | 7 | Isocratic |
| 9–15 | 93 to 0 | 7 to 100 | Linear gradient |
| 15–19 | 0 | 100 | Isocratic |
| 19–19.1 | 0 to 93 | 100 to 7 | Return to initial composition |
| 19.1–30 | 93 | 7 | Re-equilibration |

After preparation, keep the solutions at about 6 °C, or use an injector with cooling.

Prepare the following solutions using a mixture of 20 volumes of acetonitrile R and 80 volumes of water R as a diluent. For solution (1) weigh and powder 20 tablets. Disperse a quantity of the powder containing about 10 mg of Tenofovir disoproxil fumarate, accurately weighed in 100 ml of the diluent and filter. For solution (2) use 0.1 mg of tenofovir disoproxil fumarate RS and 66.7 μg of emtricitabine RS per ml of diluent. If necessary, adapt the concentration of solution (2) according to the ratio of Emtricitabine and Tenofovir disoproxil fumarate in the tablets. For solution (3) use 0.02 mg of fumaric acid R per ml of water R.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Maintain the column temperature at 35 °C.

Inject separately 20 μl each of solutions (1), (2) and (3).

The test is not valid unless in the chromatograms obtained with solutions (1) and (2), three principal peaks are shown and the resolution factor between those peaks is at least 5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of emtricitabine ($C_8H_{10}FN_3O_3S$) and tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$) in the tablets.

*[Note from Secretariat: a test for related substances is not available, due to the overlapping of the impurities from both APIs and the non-availability of reference substances for the impurities that would be required to allow the identification of the peaks.]*

New reagent to be added to The International Pharmacopoeia:

Hydrochloric acid (~0.4 g/l) TS.

## Levamisole tablets

Draft proposal for *The International Pharmacopoeia* (September 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

**Category.** Anthelminthic.

**Storage.** Levamisole tablets should be kept in a tightly closed container.

**Labelling.** The designation on the container of Levamisole tablets should state that the active ingredient is in the hydrochloride form and the quantity should be indicated in terms of equivalent amount of levamisole.

**Additional information.** Strengths in the current WHO Model List of Essential Medicines: 50 mg, 150 mg. Strengths in the current WHO Model List of Essential Medicines for Children: 50 mg, 150 mg

### Requirements

Comply with the monograph for “Tablets”.

**Definition.** Levamisole tablets contain Levamisole hydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of levamisole ($C_{11}H_{12}N_2S$) stated on the label.

**Identity tests**

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

A. Shake a quantity of the powdered tablets containing the equivalent of about 450 mg of levamisole with 30 ml of water R, filter. Wash the filter with 20 ml of water R and add the washings to the filtrate. To the combined filtrate add ammonia (~100 g/l) TS to make it alkaline and extract with two quantities, each of 25 ml and 15 ml, of dichloromethane R. Combine the dichloromethane extracts and evaporate to dryness. Add 0.5 ml of hydrochloride acid (~420 g/l) TS, heat on a water-bath to dryness. Dissolve the residue in 10 ml of hydrochloric acid (0.1 mol/l) VS. The optical rotation of the resulting solution is not less than -5°

B. See the test described below under Related substances using ultraviolet light (254 nm) to examine the chromatogram. The principal spot obtained with solution B corresponds in position, appearance, and intensity with that obtained with solution D.

C. See the test described below under Assay, Method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

D. Shake a quantity of the powdered tablets containing the equivalent of about 100 mg of levamisole with 40 ml of water R and filter. The filtrate yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

**Related substances**

Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as coating substance and a mixture of 60 volumes of toluene R, 40 volumes of acetone R, and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following four solutions in methanol R. For solution (A) shake a quantity of the powdered tablets containing the equivalent of about 85 mg of levamisole with 5 ml, filter, and use the filtrate. For solution (B) dilute 1 ml of solution A to 10 ml. For solution (C) dilute 1 ml of solution B to 20 ml. For solution (D) use 2.0 mg of levamisole hydrochloride RS per ml. After removing the plate from the chromatographic chamber, dry it at 105 °C for 15 minutes, and examine the chromatogram in ultraviolet light (254 nm).

Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution C (0.5%).

Expose the plate to iodine vapour in a tightly closed chamber for 15 minutes and examine the chromatogram in daylight.

Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution C (0.5%).

**Assay**

Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3 μm). (Phenomenex Gemini C18 has been found suitable.)

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: acetonitrile R

Mobile phase B: a 0.75% solution of monobasic ammonium phosphate R in water R adjusted to pH 7 with diisopropylamine R

| Time (min) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comments |
|---|---|---|---|
| 0–5 | 20 to 80 | 80 to 20 | Linear gradient |
| 5–7 | 80 | 20 | Isocratic |
| 7–8 | 80 to 20 | 20 to 80 | Return to initial composition |
| 8–12 | 20 | 80 | Re-equilibration |

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Shake a quantity of the powdered tablets containing the equivalent of about 170 mg of levamisole, accurately weighed, with 100 ml of water R, and filter. Dilute a suitable volume of the filtrate with methanol R to obtain a concentration equivalent to 0.17 mg of levamisole per ml. For solution (2) use 0.2 mg of levamisole hydrochloride RS per ml in methanol R. For solution (3) dissolve the equivalent of 17 mg of levamisole in 5 ml of a 0.1 mol/l solution of sodium hydroxide R in a test tube, and heat in a water bath at 100 °C for 5 hours. Allow to cool and dilute 1 ml of the resulting solution to 25 ml with methanol R.

Operate with a flow rate of 2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 215 nm.

Inject 10 µl of solution (3). In the chromatogram obtained with solution (3), the peak due to the major degradation product elutes at the following relative retention with reference to levamisole (retention time about 3 minutes): about 1.3. The test is not valid unless the resolution between the peak due to levamisole and the peak due to the major degradation product with a relative retention of about 1.3 is at least 6.0.

Inject separately 10 µl, each of solutions (1) and (2).

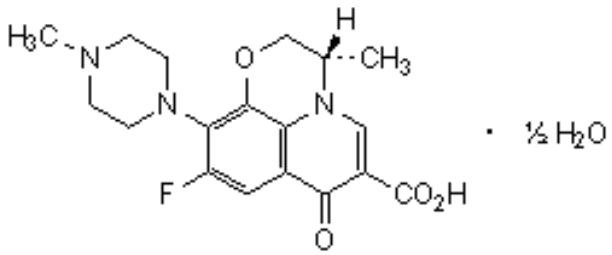
Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of levamisole ($C_{11}H_{12}N_2S$) in the tablets.

B. Weigh and powder 20 tablets. To a quantity of the powdered tablets containing the equivalent of about 170 mg of levamisole, accurately weighed, add 30 ml of water R and shake for 10 minutes. Filter, wash the filter with 20 ml of water R and add the washings to the filtrate. To the combined filtrate add ammonia (~100 g/l) TS to make it alkaline and extract with three quantities, each of 25 ml, 15 ml and 15 ml, of dichloromethane R. Filter each quantity through cotton wool covered with a layer of anhydrous sodium sulfate R and wash the filter with 15 ml of dichloromethane R. Combine the dichloromethane extracts and evaporate to dryness. Dissolve the residue in 50 ml of anhydrous glacial acetic acid R. Titrate with perchloric acid (0.1 mol/l) VS, as described under 2.6 Non-aqueous titration, Method A, using crystal violet/acetic acid TS solution as indicator.

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 20.43 mg of $C_{11}H_{12}N_2S$.

## Levofloxacin

Draft proposal for *The International Pharmacopoeia* (September 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.



$C_{18}H_{20}FN_3O_4,{}^1/_2\,H_2O$

**Relative Molecular Mass.** 370.4

**Chemical name.** (*S*)-9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid hemihydrate; CAS Reg. No. 138199-71-0.

**Description.** Yellowish white to bright yellow, crystals or crystalline powder.

**Solubility.** Slightly soluble in water, soluble in glacial acetic acid, slightly soluble or soluble in dichloromethane, slightly soluble in methanol.

**Category.** Antibacterial.

**Storage.** Levofloxacin should be kept in a tightly closed container, protected from light.

## REQUIREMENTS

**Definition.** Levofloxacin contains not less than 99.0% and not more than 101.0% of levofloxacin ($C_{18}H_{20}FN_3O_4$) calculated with reference to the anhydrous substance.

**Manufacture.** The production method is validated to ensure that the substance is the (*S*-enantiomer).

### Identity test

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

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 levofloxacin RS or with the *reference spectrum* of levofloxacin.

B. 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 10 volumes of dichloromethane R, 5 volumes of methanol R and 1 volume of ammonia solution 1% as the mobile phase. Apply separately to the plate 5 µl of each of the following two solutions in a mixture of 1 volume of methanol R and 4 volumes of dichloromethane R. For solution (A) use 5 mg of Levofloxacin per ml. For solution (B) use 5 mg of levofloxacin 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 with that obtained with solution B.

C. Transfer 25 mg of Levofloxacin to a 50-ml volumetric flask. Add about 20 ml of hydrochloric acid (~4 g/l) TS, sonicate for about 5 minutes, allow to cool to room temperature and make up to the volume using the same solvent. Filter a portion of this solution through a 0.45-µm filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of this solution to 100.0 ml using water R. The absorption spectrum (1.6) of the resulting solution, when observed between 210 and 350 nm, exhibits two maxima at about

294 nm and at about 327 nm. The specific absorbance ($A^{1\%}_{1\ cm}$) at 294 nm is between 876 and 948.

D. Determine the specific optical rotation (1.4) using a 30 mg/ml solution dissolved in a mixture of 10 volumes of methanol R and 40 volumes of dichloromethane R and calculate with reference to the anhydrous substance; $[\alpha]^{20\ °C}$ = -12° to -11°.

*[Note from Secretariat: suitability of carrying out the Optical rotation test in methanol under investigation and corresponding limits to be confirmed.]*

**Heavy metals**

*[Note from Secretariat: suitable test for heavy metals under investigation.]*

**Sulfated ash (2.3).** Not more than 1.0 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 less than 21 mg/g and not more than 27 mg/g.

**Impurity A**
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 10 volumes of glacial acetic acid R, 10 volumes of water R and 20 volumes of ethyl acetate R. Apply separately to the plate 10 l of each of the two following solutions in the dissolution solvent prepared by mixing 10 volumes of methanol R and 40 volumes of dichloromethane R. For solution (A) use 50 mg of Levofloxacin per ml. For solution (B) use 0.1 mg of levofloxacin impurity A RS per ml. After removing the plate from the chromatographic chamber, allow to dry in air. Examine the chromatogram in ultraviolet light (254 nm).

Any spot obtained with solution A corresponding impurity A is not more intense than the principal spot obtained with solution B.

**Other related substances**
Prepare fresh solutions, protected from light and perform the tests without delay. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm), packed with particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm). (Symmetry 150 x 46 mm (5 μm) is suitable.)

Maintain the column temperature at 45 °C.

Prepare the mobile phase as follows: dissolve 4.0 g of ammonium acetate R and 7.0 g of sodium perchlorate R in water R and dilute to 1300 ml; adjust to pH 2.2 with phosphoric acid R and add 240 ml of acetonitrile R.

Prepare the following solutions in the dissolution solvent prepared in mixing 10 volumes of acetonitrile R and 60 volumes of water R.

For solution (1) dissolve 10 mg of Levofloxacin in the dissolution solvent and dilute to 50.0 ml with the same solvent. For solution (2) dilute 1.0 ml of solution (1) to 50.0 ml

with the same solvent. Dilute 1.0 ml of this solution to 10.0 ml with the same solvent. For solution (3) dissolve 10 mg of levofloxacin impurity E RS in the dissolution solvent and dilute to 100.0 ml with the same solvent. Mix 10 ml with 5 ml of solution (1) and dilute to 50.0 ml with the same solvent. Dilute 1.0 ml of this solution to 50.0 ml with the same solvent.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 294 nm.

Inject 20 μl of solution (3). The test is not valid unless the resolution factor between the peaks due to impurity E and Levofloxacin is at least 2.

Inject separately 20 μl each of solutions (1), (2) and of the dissolution solvent in the chromatographic system.

In the chromatogram obtained with solution (1), the following impurity peaks, if present, are eluted at the following relative retention with reference to Levofloxacin (retention time about 17 minutes): impurity B about 0.36; impurity C about 0.57; impurity D about 0.75; impurity E about 0.91; impurity F about 1.50.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 2.6, is not greater than the area of the principal peak obtained with solution (2) (0.2%);

- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 4.2, is not greater than the area of the principal peak obtained with solution (2) (0.2%);

- the area of any peak corresponding to impurity C, E or F is not greater than the area of the principal peak obtained with solution (2) (0.2%);

- the area of any other impurity peak is not greater than 0.5 times the area of the principal peak obtained with solution (2) (0.1%);

- the sum of the areas (corrected, where necessary) of all the peaks, other than the principal peak, is not greater than 2.5 times the area of the principal peak obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.25 times the area of the principal peak obtained with solution (2) (0.05%).

*[Note from Secretariat: following information to be confirmed:*
*- correction factors for impurities B and D,*
*- limit for individual unspecified impurities,*
*- limit for total of impurities]*

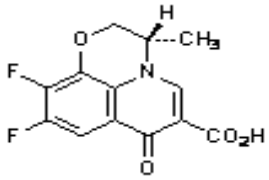
**Assay**

Dissolve about 0.300 g, accurately weighed, in 100 ml of glacial acetic acid and titrate with perchloric acid (0.1 mol/l) VS as described under 2.6. Non aqueous titrations,

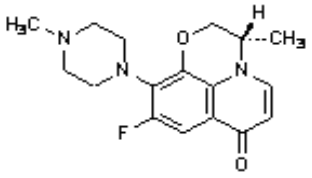
Method A determining the end point potentiometrically. Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 36.14 mg of $C_{18}H_{20}FN_3O_4$.

**Impurities**

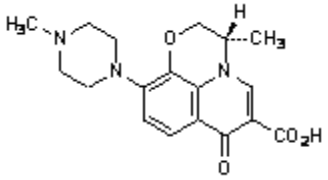
The following list of known and potential impurities that have been shown to be controlled by the tests in this monograph is given for information:



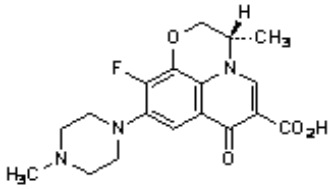
A. (3*S*)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid,



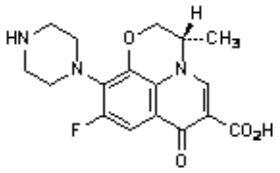
B. (3*S*)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-7-one,



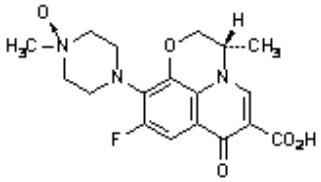
C. (3*S*)-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid,



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



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



F. 4-[(3*S*)-6-carboxy-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazin-10-yl]-1-methylpiperazine 1-oxide.

New reagent to be added to The International Pharmacopoeia:

Hydrochloric acid (~4 g/l) TS.

Dilute 10 ml of hydrochloric acid (~420 g/l) TS with sufficient water to produce 1000 ml (approximately 0.1 mol/l).

## Levofloxacin tablets

Draft proposal for *The International Pharmacopoeia* (September 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

**Category.** Antibacterial.

**Storage.** Levofloxacin tablets should be kept in a well closed container, protected from light.

**Labelling.** The designation of the container of Levofloxacin tablets should state that the active ingredient is the hemihydrate form and the quantity should be indicated in terms of the equivalent amount of Levofloxacin.

**Additional information.** Strengths in the current WHO Model List of Essential Medicines: 200 mg, 400 mg. Strengths in the current WHO Model List of Essential Medicines for Children: 200 mg, 400 mg.

### Requirements

Comply with the monograph for “Tablets”.

**Definition.** Levofloxacin tablets contain Levofloxacin. They contain not less than 90.0% and not more than 110.0% of the amount of Levofloxacin ($C_{18}H_{20}FN_3O_4$) stated on the label.

**Identity test**

Either test A alone or any two of tests B, C and D may be applied

A. To a quantity of the powdered tablets containing 100 mg of Levofloxacin, add 10 ml of acetonitrile R, shake, filter and evaporate to dryness. 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 levofloxacin RS or with the *reference spectrum* of levofloxacin.

B. 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 10 volumes of dichloromethane R, 5 volumes of methanol R and 1 volume of ammonia solution 1% as the mobile phase. Apply separately to the plate 5 μl of each of the two following solutions in a mixture of 1 volume of methanol R and 4 volumes of dichloromethane R. For solution (A) shake a quantity of the powdered tablets containing 25 mg of Levofloxacin with 5 ml, filter and use the clear filtrate. For solution (B) use 5 mg of levofloxacin 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 with that obtained with solution B.

C. See the test described under Assay method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

D. The absorption spectrum of the final solution prepared for Assay method B, when observed between 210 and 350 nm, exhibits two maxima at about 294 nm and at about 327 nm.

*[Note from Secretariat: a specific optical rotation test to differentiate levofloxacin from ofloxacin is under investigation, with the possibility to include such test under a Manufacture section.]*

**Dissolution test**

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of hydrochloric acid (~ 4 g/l) TS, and rotating the paddle at 100 revolutions per minute. At 30 minutes withdraw a sample of about 5 ml of the medium through an in-line filter. Measure the absorbance (1.6) of a 1-cm layer of the filtered sample at the maximum at about 294 nm. At the same time,

measure the absorbance at the maximum at about 294 nm of a suitable solution of levofloxacin RS in hydrochloric acid (~4 g/l) TS using hydrochloric acid (~4 g/l) TS as a blank.

For each of the six tablets, calculate the total amount of Levofloxacin ($C_{18}H_{20}FN_3O_4$), in the medium. The amount in solution for each tablet is not less than 75% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 75%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 70% and the amount obtained for no tablet is less than 55%.

*[Note from Secretariat: dissolution conditions and limits to be confirmed.]*

**Related substances**
Prepare fresh solutions and perform the tests without delay. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay, method A.

For solution (1) transfer a quantity of the powdered tablets containing about 10 mg of Levofloxacin into about 20 ml of the dissolution solvent, sonicate for 5 minutes, allow to cool to room temperature and dilute to 50.0 ml with the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. For solution (2) dilute 1.0 ml of solution (1) to 50.0 ml with the same solvent. Dilute 1.0 ml of this solution to 10.0 ml with the same solvent. For solution (3) dissolve 10 mg of levofloxacin impurity E RS in the dissolution solvent and dilute to 100.0 ml with the same solvent. Mix 10 ml with 5 ml of solution (1) and dilute to 50.0 ml with the same solvent. Dilute 1.0 ml of this solution to 50.0 ml with the same solvent.

Inject 20 μl of solution (3). The test is not valid unless the resolution factor between the peaks due to impurity E and Levofloxacin is greater than 2.

Inject separately 20 μl each of solutions (1) and (2) and of the dissolution solvent in the chromatographic system. Examine the dissolution solvent chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (1), the following impurity peaks, if present, are eluted at the following relative retention with reference to Levofloxacin (retention time about 17 minutes): impurity B about 0.36; impurity C about 0.57; impurity D about 0.75; impurity E about 0.91; impurity F about 1.50.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 2.6, is not greater than the area of the principal peak obtained with solution (2) (0.2%);

- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 4.2, is not greater than the area of the principal peak obtained with solution (2) (0.2%);

- the area of any peak corresponding to impurity C, E or F is not greater than the area of the principal peak obtained with solution (2) (0.2%);

- the area of any other impurity peak is not greater than 0.5 times the area of the principal peak obtained with solution (2) (0.1%);

- the sum of the areas (corrected, where necessary) of all the peaks, other than the principal peak, is not greater than 2.5 times the area of the principal peak obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.25 times the area of the principal peak obtained with solution (2) (0.05%).

*[Note from Secretariat: as for the API monograph, following information to be confirmed:*

*- correction factors for impurities B and D,*
*- limit for individual unspecified impurities*
*- limit for total of impurities.]*

**Assay**

Either method A or method B may be applied.

A. Prepare fresh solutions and perform the tests without delay. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm), packed with particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm). (Symmetry 150 x 46 mm (5 μm) is suitable).

Maintain the column temperature at 45 °C.

Prepare the mobile phase as follows: dissolve 4.0 g of ammonium acetateR and 7.0 g of sodium perchlorate R in water R and dilute to 1300 ml; adjust to pH 2.2 with phosphoric acid R and add 240 ml of acetonitrile R.

Prepare the following solutions in the dissolution solvent prepared by mixing 10 volumes of acetonitrile R and 60 volumes of water R.

For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 20 mg of Levofloxacin, accurately weighed, into about 20 ml of the dissolution solvent, sonicate for 5 minutes, allow to cool to room temperature and dilute to 50.0 ml with the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. Dilute 5 ml of this solution to 25 ml with the dissolution solvent.

For solution (2) dissolve 2.0 mg of ofloxacin RS in the dissolution solvent and dilute to 25.0 ml with the same solvent.

For solution (3) dissolve 10 mg of levofloxacin impurity E RS in the dissolution solvent and dilute to 100.0 ml with the same solvent. Mix 10 ml with 5 ml of solution (1) and dilute to 50.0 ml with the same solvent. Dilute 1.0 ml of this solution to 50.0 ml with the same solvent.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 294 nm.

Inject 20 μl of solution (3). The test is not valid unless the resolution factor between the peaks due to impurity E and Levofloxacin is at least 2.

Inject separately 20 μl each of solutions (1) and (2) and of the dissolution solvent in the chromatographic system.

In the chromatogram obtained with solution (1), the following peaks are eluted at the following relative retention with reference to Levofloxacin (retention time about 17 minutes): impurity B about 0.36; impurity C about 0.57; impurity D about 0.75; impurity E about 0.91; impurity F about 1.50.

Measure the areas of the peak responses in the chromatograms obtained with solutions (1) and (2). Calculate the content of Levofloxacin ($C_{18}H_{20}FN_3O_4$).

B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 25 mg of Levofloxacin, accurately weighed, to a 50-ml volumetric flask. Add about 20 ml of hydrochloric acid (~4 g/l) TS, sonicate for about 5 minutes, allow to cool to room temperature and make up to the volume using the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of this solution to 100.0 ml using water R. Measure the absorbance (1.6) of a 1-cm layer of this solution at the maximum at about 294 nm. Calculate the content of Levofloxacin in the tablets using an absorptivity value of 91.2 ( $A^{1\%}_{1\ cm}$ = 912).

**Impurities.** The impurities limited by the requirements of this monograph include impurities B to F listed in the monograph for Levofloxacin.

* * *

New reagent to be added to The International Pharmacopoeia:

**Hydrochloric acid (~4 g/l) TS.**

Dilute 10 ml of hydrochloric acid (~420 g/l) TS with sufficient water to produce 1000 ml (approximately 0.1 mol/l).

## Levonorgestrel tablets

Draft proposal for *The International Pharmacopoeia* (September 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

**Category.** Contraceptive.

**Storage.** Levonorgestrel tablets should be kept in a well-closed container, protected from light.

**Additional information.** Strength in the current WHO Model List of Essential Medicines: 30 μg, 750 μg, 1.5 mg.

### Requirements

Comply with the monograph for “Tablets”.

**Definition.** Levonorgestrel tablets contain Levonorgestrel. They contain not less than 90.0% and not more than 110.0% of the amount of levonorgestrel ($C_{21}H_{28}O_2$) stated on the label.

**Identity tests**

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

A. To a quantity of the powdered tablets containing 37.5 mg of Levonorgestrel, add 5 quantities of dichloromethane R, each of 40 ml. After each addition, stir thoroughly and filter through a sintered-glass filter (G4). Wash the residue and the filter with dichloromethane R, combine the filtrates, evaporate to dryness on a water-bath with the aid of a stream of air and allow to cool. Dissolve the residue in 5 ml of dichloromethane R and measure the optical rotation. The optical rotation of the resulting solution is not less than -0.18°.

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

B.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 7 volumes of cyclohexane R and 3 volumes of acetone R as the mobile phase. Apply separately to the plate 10 l of each of the following two solutions in acetonitrile R. For solution (A) shake a quantity of the powdered tablets containing 1.5 mg of Levonorgestrel with 5 ml, filter, and use the clear filtrate. For solution (B) use 0.30 mg of levonorgestrel 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 at 254 nm. The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described under test B.1 but using silica gel R5 as the coating substance. Spray with a mixture of equal volumes of sulfuric acid TS and ethanol (~750 g/l) TS. Heat the plate for a few minutes at 105 °C. Examine the chromatogram in daylight.

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

C. See the method described below under the test for Dextronorgestrel. The retention time of the principal peak in the chromatogram obtained with solution (2) is similar to that in the chromatogram obtained with the solution (3).

**Dissolution test**
Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of 0.1% solution of sodium dodecyl sulfate R

in hydrochloride solution (0.1 mol/l) VS, and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 ml of the medium through an in-line filter and use the filtrate. Prepare standard solution as follows: add a suitable volume of ethanol (~750 g/l) TS to dissolve a suitable amount of levonorgestrel RS, then add a suitable volume of the dissolution medium to obtain a concentration of 6 μg per ml.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the chromatographic conditions as described under Assay.

For each of the six tablets, calculate the total amount of levonorgestrel ($C_{21}H_{28}O_2$), in the medium. The amount of levonorgestrel in solution for each tablet is not less than 80% 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 75% and no tablet contains less than 60%.

*[Note from Secretariat: possible alternative dissolution method for the 30 μg tablets, which will not use sodium dodecyl sulfate is under investigation.]*

**Dextronorgestrel**
Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm). (Hypersil ODS is suitable.) As the mobile phase, use a solution prepared as follows: dissolve 5.0 g of gamma-cyclodextrin R in 500 ml of water R and dilute to 1000.0 ml with methanol R.

Prepare the following solutions in a dissolution solvent prepared by mixing 80 volumes of methanol R and 20 volumes of water R. For solution (1) transfer a quantity of powdered tablets containing about 3.0 mg of Levonorgestrel to a 25-ml volumetric flask. Add about 15 ml of the dissolution solvent Cheat in a water-bath at 60 °C for 10 minutes, shaking occasionally. Allow to equilibrate to room temperature, dilute to volume with the dissolution solvent and mix. Filter through a 0.45-μm filter. For solution (2), dilute a suitable volume of solution (1) to obtain a concentration of 6 μg of Levonorgestrel per ml. For solution (3) use 6 μg of levonorgestrel RS per ml. For solution (4), use 12 μg of norgestrel RS per ml. For solution (5), use 0.12 μg of Levonorgestrel RS per ml.

Operate with a flow rate of 1.5 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 242 nm.

Inject 20 μl of solution (3). In the chromatogram obtained with solution (3), the test is not valid unless the resolution factor between the peaks due to levonorgestrel and dextronorgestrel is at least 1.5.

Inject separately 20 μl, each of solutions (1), (2), (3), (4) and (5).

In the chromatogram obtained with solution (1) the area of the peak due to dextronorgestrel , is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

**Related substances**

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 particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm). (Spherisorb ODS 2 is suitable). As the mobile phase, use a solution prepared as follows: mix 15 volumes of methanol R, 35 volumes of acetonitrile R and 50 volumes of water R.

Prepare the following solutions in a dissolution solvent prepared by mixing equal volumes of methanol R and water R. For solution (1), transfer a quantity of powdered tablets containing about 0.18 mg of Levonorgestrel, accurately weighed, in 5 ml. Sonicate for 30 minutes, stir vigorously for 15 minutes, centrifuge and use the supernatant liquid. For solution (2), dilute a suitable volume of solution (1) to obtain a concentration of 0.36 g of Levonorgestrel per ml. For solution (3) use 4 μg of ethinylestradiol RS and 4 μg of levonorgestrel RS per ml.

Operate with a flow rate of 1.2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 30 °C.

Inject 100 μl of solution (3). Record the chromatogram for twice the retention time of levonorgestrel (retention time about 26 minutes ). The test is not valid unless, in the chromatogram obtained with solution (3), the resolution factor between the peaks due to ethinylestradiol and levonorgestrel is at least 12.

Inject separately 100 μl of each of solutions (1) and (2). Record the chromatogram for twice the retention time of levonorgestrel.

In the chromatogram obtained with solution (1) the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%). The sum of the areas of all peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

**Assay**

Use the average of the 10 individual results obtained in the test for Uniformity of content.

**Uniformity of content**

The tablets comply with the test for 5.1 Uniformity of content for single-dose preparations, using the following method of analysis.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm). (Spherisorb ODS 2 is suitable.)

As the mobile phase, use a solution prepared by mixing equal volumes of acetonitrile R and water R.

Prepare the following solutions. For solution (1), transfer one powdered tablet to a stoppered test-tubes, add 5.0 ml of the mobile phase, sonicate for 45 minutes, shake for 15 minutes, and centrifuge. Dilute a suitable volume to produce a solution containing 6 μg of Levonorgestrel per ml. For solution (2), accurately weigh 12 mg of levonorgestrel RS, dissolve in sufficient mobile phase to produce 100.0 ml, and mix. Dilute 5.0 ml of this solution to 100.0 ml with the same solvent.

Operate with a flow rate of 1.3 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Inject 25 μl, each solution (1) and (2). The retention time of levonorgestrel is about 7.9 minutes. The test is not valid unless the column efficiency, determined for the peak due to levonorgestrel using solution (2) is at least 5000. The symmetry factor of the peak due to levonorgestrel is not more than 1.6.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of levonorgestrel ($C_{21}H_{28}O_2$) in each tablet.

# International Nonproprietary Names for Pharmaceutical Substances (INN)

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

Lists of Proposed (1–101) and Recommended (1–62) International Nonproprietary Names can be found in *Cumulative List No. 13, 2009* (available in CD-ROM only). The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

# Dénominations communes internationales des Substances pharmaceutiques (DCI)

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

On trouvera d'autres listes de Dénominations communes internationales proposées (1–101) et recommandées (1–62) dans la *Liste récapitulative No. 13, 2009* (disponible sur CD-ROM seulement). Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

# Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–101) y Recomendadas (1–62) se encuentran reunidas en *Cumulative List No. 13, 2009* (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.

# Proposed International Nonproprietary Names: List 104

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for **List 104 Proposed INN not later than 31 May 2011**
**Publication date: 31 January 2011**

# Dénominations communes internationales proposées: Liste 104

Des observations ou des objections formelles à l'égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l'Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans *WHO Drug Information*, c'est à dire pour la **Liste 104 de DCI Proposées le 31 mai 2011 au plus tard.**
**Date de publication: 31 January 2011**

# Denominaciones Comunes Internacionales Propuestas: Lista 104

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en *WHO Drug Information*, es decir, para **la Lista 104 de DCI Propuestas el 30 de mayo de 2011 a más tardar.**
**Fecha de publicación: 31 de enero de 2011.**

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

**abediterolum**

abediterol

5-[(1*R*)-2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxyethyl]-8-hydroxyquinolin-2(1*H*)-one
*$\beta_2$-adrenoreceptor agonist*

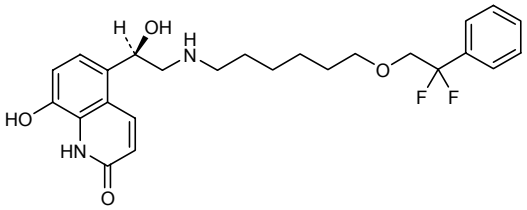
abéditérol

5-[(1*R*)-2-{[6-(2,2-difluoro-2-phényléthoxy)hexyl]amino}-1-hydroxyéthyl]-8-hydroxyquinoléin-2(1*H*)-one
*agoniste $\beta_2$-adrénergique*

abediterol

5-[(1*R*)-2-{[6-(2,2-difluoro-2-feniletoxi)hexil]amino}-1-hidroxietil]-8-hidroxiquinolin-2(1*H*)-ona
*agonista del adrenoreceptor $\beta_2$*

$C_{25}H_{30}F_2N_2O_4$ 915133-65-2



**adomiparinum natricum**

adomiparin sodium

sodium salt of a low molecular mass heparin obtained by enzymatic depolymerization of heparin from porcine intestinal mucosa; the majority of the components have a 4-deoxy-α-L-*threo*-hex-4-enopyranuronic acid or it 4-hydroxy saturated derivative at the non-reducing end and a 2-amino-2-deoxy-D-glucopyranose derivative structure at the reducing end of their chain; the relative average molecular mass range is 5,500 to 9,000 daltons and a polydispersity of less than 1.5; the degree of sulfation is about 2.6 per disaccharidic unit
*anticoagulant*

adomiparine sodique

sel sodique d'héparine de faible masse moléculaire obtenu par dépolymérisation enzymatique d'héparine de muqueuse intestinale de porc ; la majorité des composants possèdent une structure acide 4-déoxy-α-L-*thréo*-hex-4-énopyranuronique ou son dérivé saturé 4-hydroxylé à l'extrémité non réductrice de leur chaîne et une structure 2-amino-2-déoxy-D-glucopyranose à l'extrémité réductrice de leur chaîne; la masse moléculaire relative est en moyenne comprise entre 5500 et 9000 et son indice de polymolécularité est inférieure à 1,5 ; le degré de sulfatation est d'environ 2,6 par unité disaccharide.
*anticoagulant*

adomiparina sódica

sal sódica de heparina de baja masa molecular obtenida por despolimerización enzimática de heparina de mucosa intestinal de cerdo; la mayoría de cuyos componentes tienen un ácido 4-desoxi-α-L-t*reo*-hex-4-enopiranurónico o su derivado saturado 4-hidroxilado en el extremo no reductor de la cadena y una 2-amino-2-desoxi-D-glucopiranosa en el reductor; la masa molecular relativa media está comprendida entre 5500 y 9000 y su índice de polidispersión es inférior a 1,5; el grado de sulfatación es aproximadamente 2,6 par unidad de disacárido.
*anticoagulante*

9041-08-1

**aganepagum**

aganepag

5-{3-[(2*S*)-1-{4-[(1*S*)-1-hydroxyhexyl]phenyl}-5-oxopyrrolidin-2-yl]propyl}thiophene-2-carboxylic acid
*prostaglandin $E_2$ receptor agonist*

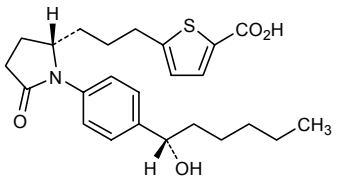
aganépag

acide 5-{3-[(2*S*)-1-{4-[(1*S*)-1-hydroxyhexyl]phényl}-5-oxopyrrolidin-2-yl]propyl}thiophène-2-carboxylique
*agoniste du récepteur de la prostaglandine $E_2$*

aganepag

ácido 5-{3-[(2*S*)-1-{4-[(1*S*)-1-hidroxihexil]fenil}-5-oxopirrolidin-2-il]propil}tiofeno-2-carboxílico
*agonista del receptor de prostaglandina $E_2$*

$C_{24}H_{31}NO_4S$ 910562-18-4



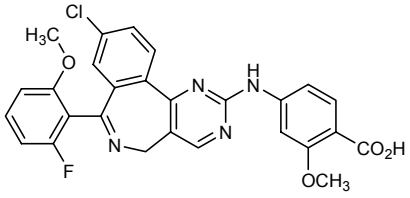
**alisertibum**

alisertib — 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-yl]amino}-2-methoxybenzoic acid
*antineoplastic*

alisertib — acide 4-{[9-chloro-7-(2-fluoro-6-méthoxyphényl)-5*H*-pyrimido[5,4-*d*][2]benzazépin-2-yl]amino}-2-méthoxybenzoïque
*antinéoplasique*

alisertib — ácido 4-{[9-cloro-7-(2-fluoro-6-metoxifenil)-5*H*-pirimido[5,4-*d*][2]benzazepin-2-il]amino}-2-metoxibenzoico
*antineoplásico*

$C_{27}H_{20}ClFN_4O_4$ 1028486-01-2



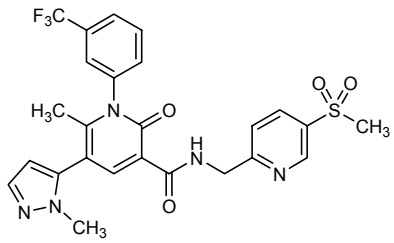
**alvelestatum**

alvelestat — *N*-{[5-(methanesulfonyl)pyridin-2-yl]methyl}-6-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide
*elastase inhibitor*

alvélestat — *N*-{[5-(méthanesulfonyl)pyridin-2-yl]méthyl}-6-méthyl-5-(1-méthyl-1*H*-pyrazol-5-yl)-2-oxo-1-[3-(trifluorométhyl)phényl]-1,2-dihydropyridine-3-carboxamide
*inhibiteur de l'élastase*

alvelestat — *N*-{[5-(metanosulfonil)piridin-2-il]metil}-6-metil-5-(1-metil-1*H*-pirazol-5-il)-2-oxo-1-[3-(trifluorometil)fenil]-1,2-dihidropiridina-3-carboxamida
*inhibidor de la elastasa*

$C_{25}H_{22}F_3N_5O_4S$ 848141-11-7



**amatuximabum #**

| | |
|---|---|
| amatuximab | immunoglobulin G1-kappa, anti-[*Homo sapiens* MSLN (mesothelin, pre-pro-megakaryocyte-potentiating factor, megakaryocyte-potentiating factor, MPF, CAK1)], chimeric monoclonal antibody; gamma1 heavy chain (1-449) [*Mus musculus* VH (IGHV1-37*01 -(IGHD)-IGHJ2*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-213')-disulfide with kappa light chain (1'-213') [*Mus musculus* V-KAPPA (IGKV4-59*01 -IGKJ4*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; (228-228'':231-231'')-bisdisulfide dimer<br>*antineoplastic* |
| amatuximab | immunoglobuline G1-kappa, anti-[*Homo sapiens* MSLN (mésothéline, facteur de potentialisation du pré-pro-mégacaryocyte, facteur de potentialisation des mégacaryocytes, MPF, CAK1)], anticorps monoclonal chimérique;<br>chaîne lourde gamma1 (1-449) [*Mus musculus* VH (IGHV1-37*01 -(IGHD)-IGHJ2*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-213')-disulfure avec la chaîne légère kappa (1'-213') [*Mus musculus* V-KAPPA (IGKV4-59*01 -IGKJ4*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dimère (228-228'':231-231'')-bisdisulfure<br>*antinéoplasique* |
| amatuximab | inmunoglobulina G1-kappa, anti-[ MSLN *de Homo sapiens* (mesotelina, factor de potenciación del pre-pro-megacariocito, factor de potenciación de megacariocitos, MPF, CAK1)], anticuerpo monoclonal quimérico;<br>cadena pesada gamma1 (1-449) [*Mus musculus* VH (IGHV1-37*01 -(IGHD)-IGHJ2*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-213')-disulfuro con la cadena ligera kappa (1'-213') [*Mus musculus* V-KAPPA (IGKV4-59*01 -IGKJ4*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dímero (228-228'':231-231'')-bisdisulfuro<br>*antineoplásico* |

931402-35-6

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQQSGPE LEKPGASVKI SCKASGYSFT GYTMNWVKQS HGKSLEWIGL  50
ITPYNGASSY NQKFRGKATL TVDKSSSTAY MDLLSLTSED SAVYFCARGG 100
YDGRGFDYWG SGTPVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DIELTQSPAI MSASPGEKVT MTCSASSSVS YMHWYQQKSG TSPKRWIYDT  50
SKLASGVPGR FSGSGSGNSY SLTISSVEAE DDATYYCQQW SKHPLTFGSG 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

```
Intra-H  22-96    146-202   263-323   369-427
         22"-96"  146"-202" 263"-323" 369"-427"
Intra-L  23'-87'  133'-193'
         23'"-87'" 133'"-193'"
Inter-H-L 222-213' 222"-213'"
Inter-H-H 228-228" 231-231"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
299, 299"

**arbaclofenum**
arbaclofen

(3*R*)-4-amino-3-(4-chlorophenyl)butanoic acid
*$GABA_B$ receptor agonist*

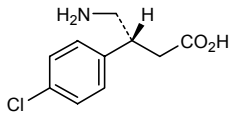
arbaclofène

(-)-acide (3*R*)-4-amino-3-(4-chlorophényl)butanoïque
*agoniste du récepteur $GABA_B$*

arbaclofeno

ácido (3*R*)-4-amino-3-(4-clorofenil)butanoico
*agonista de los receptores $GABA_B$*

$C_{10}H_{12}ClNO_2$ 69308-37-8




**asfotasum alfa #**
asfotase alfa

tissue-nonspecific alkaline phosphatase- $IgG_1$ fusion protein; human tissue-nonspecific isozyme alkaline phosphatase (AP-TNAP, EC=3.1.3.1) fusion protein with leucyl-lysyl-human immunoglobulin G1 Fc region {(6-15)-H-CH2-CH3 of IGHG1*03} fusion protein with aspartyl-isoleucyl-deca(aspartic acid), dimer (493-493':496-496')-bisdisulfide
*enzyme*

asfotase alfa

protéine de fusion phosphatase alcaline humaine isozyme tissulaire non-spécifique- IgG1;
phosphatase alcaline humaine isozyme tissulaire non-spécifique (AP-TNAP, EC=3.1.3.1) protéine de fusion avec la leucyl-lysyl-région Fc {(6-15)-H-CH2-CH3 de l'IGHG1*03} de l'immunoglobuline G1 humaine protéine de fusion avec l'aspartyl-isoleucyl-déca(acide aspartique), (493-493':496-496')-bisdisulfure du dimère
*enzyme*

asfotasa alfa

proteína de fusión fosfatasa alcalina humana isozima tisular inespecífica- IgG1;
fosfatasa alcalina humana isozima tisular inespecífica (AP-TNAP, EC=3.1.3.1) proteína de fusión con la leucil-lisil-región Fc {(6-15)-H-CH2-CH3 del IGHG1*03} de la inmunoglobulinea G1 humana proteína de fusión con aspartil-isoleucil-deca(acide aspártico), (493-493':496-496')-bisdisulfuro del diméro
*enzima*

$C_{7108}H_{11008}N_{1968}O_{2206}S_{56}$ (peptide) 1174277-80-5

Monomer / Monomère / Monómero

```
LVPEKEKDPK  YWRDQAQETL  KYALELQKLN  TNVAKNVIMF  LGDGMGVSTV  50
TAARILKGQL  HHNPGEETRL  EMDKFPFVAL  SKTYNTNAQV  PDSAGTATAY  100
LCGVKANEGT  VGVSAATERS  RCNTTQGNEV  TSILRWAKDA  GKSVGIVTTT  150
RVNHATPSAA  YAHSADRDWY  SDNEMPPEAL  SQGCKDIAYQ  LMHNIRDIDV  200
IMGGGRKYMY  PKNKTDVEYE  SDEKARGTRL  DGLDLVDTWK  SFKPRYKHSH  250
FIWNRTELLT  LDPHNVDYLL  GLFEPGDMQY  ELNRNNVTDP  SLSEMVVVAI  300
QILRKNPKGF  FLLVEGGRID  HGHHEGKAKQ  ALHEAVEMDR  AIGQAGSLTS  350
SEDTLTVVTA  DHSHVFTFGG  YTPRGNSIFG  LAPMLSDTDK  KPFTAILYGN  400
GPGYKVVGGE  RENVSMVDYA  HNNYQAQSAV  PLRHETHGGE  DVAVFSKGPM  450
AHLLHGVHEQ  NYVPHVMAYA  ACIGANLGHC  APASSLKDKT  HTCPPCPAPE  500
LLGGPSVFLF  PPKPKDTLMI  SRTPEVTCVV  VDVSHEDPEV  KFNWYVDGVE  550
VHNAKTKPRE  EQYNSTYRVV  SVLTVLHQDW  LNGKEYKCKV  SNKALPAPIE  600
KTISKAKGQP  REPQVYTLPP  SREEMTKNQV  SLTCLVKGFY  PSDIAVEWES  650
NGQPENNYKT  TPPVLDSDGS  FFLYSKLTVD  KSRWQQGNVF  SCSVMHEALH  700
NHYTQKSLSL  SPGKDIDDDD  DDDDDD                              726
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
122-184 122'-184' 472-480 472'-480' 528-588
528'-588' 634-692 634'-692' 493-493' 496-496'

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-123 Asn-123' Asn-213 Asn-213' Asn-254 Asn-254'
Asn-286 Asn-286' Asn-413 Asn-413' Asn-564 Asn-564'

**atinumabum #**
atinumab

immunoglobulin G4-kappa, anti-[*Homo sapiens* RTN4 (reticulon 4, neurite outgrowth inhibitor, NOGO), isoform A], *Homo sapiens* monoclonal antibody;
gamma4 heavy chain (1-441) [*Homo sapiens* VH (IGHV3-7*01 (93.80%) -(IGHD)-IGHJ2*01 T122>S) [8.8.7] (1-114) -IGHG4*01 (115-441)], (128-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ5*01 R123>K) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; (220-220":223-223")-bisdisulfide dimer
*immunomodulator*

atinumab

immunoglobuline G4-kappa, anti-[*Homo sapiens* RTN4 (réticulon 4, inhibiteur de la croissance des neurites, NOGO), isoforme A], *Homo sapiens* anticorps monoclonal;chaîne lourde gamma4 (1-441) [*Homo sapiens* VH (IGHV3-7*01 (93.80%) -(IGHD)-IGHJ2*01 T122>S) [8.8.7] (1-114) -IGHG4*01 (115-441)], (128-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ5*01 R123>K) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (220-220":223-223")-bisdisulfure
*immunomodulateur*

atinumab

inmunoglobulina G4-kappa, anti-[RTN4 de *Homo sapiens* (reticulón 4, inhibidor del crecimiento de las neuritas, NOGO), isoforma A], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma4 (1-441) [VH *de Homo sapiens* (IGHV3-7*01 (93.80%) -(IGHD)-IGHJ2*01 T122>S) [8.8.7] (1-114) -IGHG4*01 (115-441)], (128-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ5*01 R123>K) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (220-220":223-223")-bisdisulfuro
*inmunomodulador*

1226761-65-4

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS NYWMSWVRQA PGKGLEWVAT  50
IKQDGSQKNY VDSVKGRFTI SRDNAKNSLY LRLNSLRAED TAVYYCATEL 100
FDLWGRGSLV TVSSASTKGP SVFPLAPCSR STSESTAALG CLVKDYFPEP 150
VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL GTKTYTCNVD 200
HKPSNTKVDK RVESKYGPPC PSCPAPEFLG GPSVFLFPPK PKDTLMISRT 250
PEVTCVVVDV SQEDPEVQFN WYVDGVEVHN AKTKPREEQF NSTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK GLPSSIEKTI SKAKGQPREP QVYTLPPSQE 350
EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL 400
YSRLTVDKSR WQEGNVFSCS VMHEALHNHY TQKSLSLSLG K          441
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD  50
ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPITFGQ 100
GTKLEIKRTV 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

```
Intra-H   22-96     141-197     255-315     361-419
          22"-96"   141"-197"   255"-315"   361"-419"
Intra-L   23'-88'     134'-194'
          23'"-88'"   134'"-194'"
Inter-H-L 128-214'  128"-214'"
Inter-H-H 220-220"  223-223"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
291, 291"

**atopaxarum**

atopaxar

2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-2*H*-isoindol-2-yl)-1-[3-*tert*-butyl-4-methoxy-5-(morpholin-4-yl)phenyl]ethan-1-one
*platelet aggregation inhibitor*

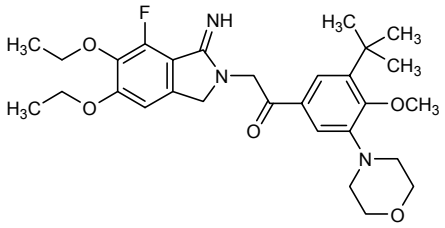
atopaxar

2-(5,6-diéthoxy-7-fluoro-1-imino-1,3-dihydro-2*H*-isoindol-2-yl)-1-[3-*tert*-butyl-4-méthoxy-5-(morpholin-4-yl)phényl]éthanone
*antiagrégant plaquettaire*

atopaxar

2-(5,6-dietoxi-7-fluoro-1-imino-1,3-dihidro-2*H*-isoindol-2-il)-1-[3-*terc*-butil-4-metoxi-5-(morfolin-4-il)fenil]etan-1-ona
*inhibidor de la agregación plaquetaria*

$C_{29}H_{38}FN_3O_5$ 751475-53-3



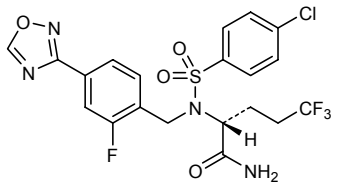
**avagacestatum**

avagacestat (2*R*)-2-(4-chloro-*N*-{[2-fluoro-4-(1,2,4-oxadiazol-3-yl)phenyl]methyl}benzenesulfonamido)-5,5,5-trifluoropentanamide
*gamma secretase inhibitor*

avagacestat (2*R*)-2-(4-chloro-*N*-{[2-fluoro-4-(1,2,4-oxadiazol-3-yl)phényl]méthyl}benzenesulfonamido)-5,5,5-trifluoropentanamide
*inhibiteur de la secrétase gamma*

avagacestat (2*R*)-2-(4-cloro-*N*-{[2-fluoro-4-(1,2,4-oxadiazol-3-yl)fenil]metil}bencenosulfonamido)-5,5,5-trifluoropentanamida
*inhibidor de la secretasa gamma*

$C_{20}H_{17}ClF_4N_4O_4S$ 1146699-66-2



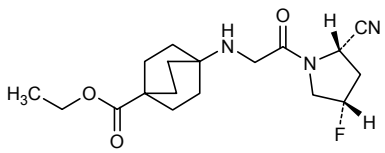
**bisegliptinum**

bisegliptin ethyl 4-({2-[(2*S*,4*S*)-2-cyano-4-fluoropyrrolidin-1-yl]-2-oxoethyl}amino)bicyclo[2.2.2]octane-1-carboxylate
*antidiabetic*

biségliptine 4-({2-[(2*S*,4*S*)-2-cyano-4-fluoropyrrolidin-1-yl]-2-oxoéthyl}amino)bicyclo[2.2.2]octane-1-carboxylate d'éthyle
*antidiabétique*

bisegliptina 4-({2-[(2*S*,4*S*)-2-ciano-4-fluoropirrolidin-1-il]-2-oxoetil}amino)biciclo[2.2.2]octano-1-carboxilato de etilo
*hipoglucemiante*

$C_{18}H_{26}FN_3O_3$ 862501-61-9



**burixaforum**

burixafor

(2-{4-[6-amino-2-({[(1*r*,4*r*)-4-({[3-(cyclohexylamino)propyl]amino}methyl)cyclohexyl]methyl}amino)pyrimidin-4-yl]piperazin-1-yl}ethyl)phosphonic acid
*chemokine CXCR 4 receptor antagonist*

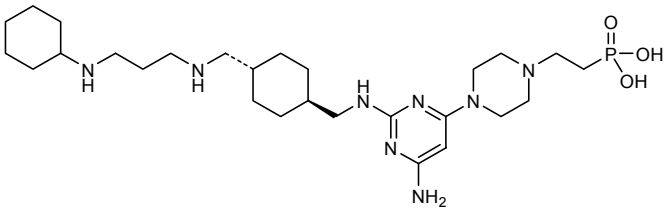
burixafor

acide (2-{4-[6-amino-2-({[(1*r*,4*r*)-4-({[3-(cyclohexylamino)propyl]amino}méthyl)cyclohexyl]méthyl}amino)pyrimidin-4-yl]pipérazin-1-yl}éthyl)phosphonique
*antagoniste du récepteur de chimiokine CXCR4*

burixafor

ácido (2-{4-[6-amino-2-({[(1*r*,4*r*)-4-({[3-(ciclohexilamino)propil]amino}metil)ciclohexil]metil}amino)pirimidin-4-il]piperazin-1-il}etil)fosfónico
*antagonista del receptor (CXCR4) de quimiokina*

$C_{27}H_{51}N_8O_3P$ 1191448-17-5



**cadazolidum**

cadazolid

1-cyclopropyl-6-fluoro-7-[4-({2-fluoro-4-[(5*R*)-5-(hydroxymethyl)-2-oxo-1,3-oxazolidin-3-yl]phenoxy}methyl)-4-hydroxypiperidin-1-yl]-4-oxo-1,4-dihydroquinolin-3-carboxylic acid
*antibacterial*

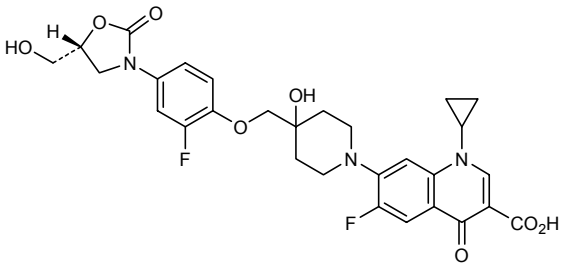
cadazolid

acide 1-cyclopropyl-6-fluoro-7-[4-({2-fluoro-4-[(5*R*)-5-(hydroxyméthyl)-2-oxo-1,3-oxazolidin-3-yl]phénoxy}méthyl)-4-hydroxypipéridin-1-yl]-4-oxo-1,4-dihydroquinoléine-3-carboxylique
*antibactérien*

cadazolid

ácido 1-ciclopropil-6-fluoro-7-[4-({2-fluoro-4-[(5*R*)-5-(hidroximetil)-2-oxo-1,3-oxazolidin-3-il]fenoxi}metil)-4-hidroxipiperidin-1-il]-4-oxo-1,4-dihidroquinolin-3-carboxílico
*antibacteriano*

$C_{29}H_{29}F_2N_3O_8$ 1025097-10-2



**carlumabum #**

carlumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* CCL2 (chemokine (C-C motif) ligand 2, C-C motif chemokine 2, monocyte chemoattractant protein-1, MCP-1, monocyte chemotactic and activating factor, MCAF, small inducible cytokine A2, SCYA2, HC11)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-449) [*Homo sapiens* VH (IGHV1-69*01 (99.00%) -(IGHD)-IGHJ4*01 [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-216')-disulfide with kappa light chain (1'-216') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (94.50%) -IGKJ1*01) [7.3.10] (1'-109') -IGKC*01 (110'-216')]; (228-228'':231-231'')-bisdisulfide dimer
*immunomodulator*

carlumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* CCL2 (chimiokine (C-C motif) ligand 2, C-C motif chimiokine 2, protéine 1 chimioattractante du monocyte, MCP-1, facteur activateur et chimiotactique du monocyte, MCAF, SCYA2, HC11)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-449) [*Homo sapiens* VH (IGHV1-69*01 (99.00%) -(IGHD)-IGHJ4*01 [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-216')-disulfure avec la chaîne légère kappa (1'-216') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (94.50%) -IGKJ1*01) [7.3.10] (1'-109') -IGKC*01 (110'-216')]; dimère (228-228'':231-231'')-bisdisulfure
*immunomodulateur*

carlumab — inmunoglobulina G1-kappa, anti-[*Homo sapiens* CCL2 (quimiokina (C-C motif) ligando 2, C-C motif quimiokina 2, proteìna 1 quimiotàctica de monocito, MCP-1, factor activador y quimiotàctico de monocito, MCAF, SCYA2, HC11)], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma1 (1-449) [*Homo sapiens* VH (IGHV1-69*01 (99.00%) -(IGHD)-IGHJ4*01 [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-216')-disulfuro con la cadena ligera kappa (1'-216') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (94.50%) -IGKJ1*01) [7.3.10] (1'-109') -IGKC*01 (110'-216')]; dìmero (228-228'':231-231'')-bisdisulfuro
*inmunomodulador*

915404-94-3

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYGISWVRQA PGQGLEWMGG  50
IIPIFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARYD 100
GIYGELDFWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSLSPGERAT LSCRASQSVS DAYLAWYQQK PGQAPRLLIY  50
DASSRATGVP ARFSGSGSGT DFTLTISSLE PEDFAVYYCH QYIQLHSFTF 100
GQGTKVEIKR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW 150
KVDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH 200
QGLSSPVTKS FNRGEC                                      216
```

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

```
Intra-H  22-96    146-202   263-323   369-427
         22"-96"  146"-202" 263"-323" 369"-427"
Intra-L  23'-89'   136'-196'
         23'"-89'" 136'"-196'"
Inter-H-L  222-216' 222"-216'"
Inter-H-H  228-228" 231-231"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
299, 299"

**cenisertibum**

cenisertib

(1*S*,2*S*,3*R*,4*R*)-3-{[5-fluoro-2-({3-methyl-4-(4-methylpiperazin-1-yl)phenyl}amino)pyrimidin-4-yl]amino}bicyclo[2.2.1]hept-5-ene-2-carboxamide
*antineoplastic*

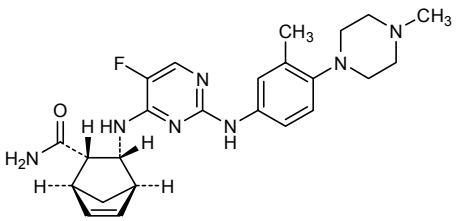
cénisertib

(1*S*,2*S*,3*R*,4*R*)-3-[(5-fluoro-2-{[3-méthyl-4-(4-méthylpipérazin-1-yl)phényl]amino}pyrimidin-4-yl)amino]bicyclo[2.2.1]hept-5-ène-2-carboxamide
*antinéoplasique*

cenisertib

(1*S*,2*S*,3*R*,4*R*)-3-{[5-fluoro-2-({3-metil-4-(4-metilpiperazin-1-il)fenil}amino)pirimidin-4-il]amino}biciclo[2.2.1]hept-5-eno-2-carboxamida
*antineoplásico*

$C_{24}H_{30}FN_7O$ 871357-89-0



**crolibulinum**

crolibulin

(4*R*)-2,7,8-triamino-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-chromene-3-carbonitrile
*antineoplastic*

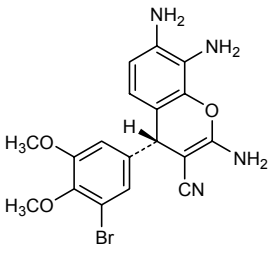
crolibuline

(4*R*)-2,7,8-triamino-4-(3-bromo-4,5-diméthoxyphényl)-4*H*-chromène-3-carbonitrile
*antinéoplasique*

crolibulina

(4*R*)-2,7,8-triamino-4-(3-bromo-4,5-dimetoxifenil)-4*H*-cromeno-3-carbonitrilo
*antineoplásico*

$C_{18}H_{17}BrN_4O_3$ 1000852-17-4



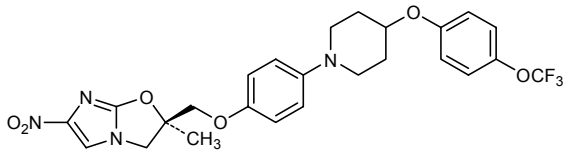
**delamanidum**

delamanid (2*R*)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole
*antibacterial*

délamanid (2*R*)-2-méthyl-6-nitro-2-[(4-{4-[4-(trifluorométhoxy)phénoxy]pipéridin-1-yl}phénoxy)méthyl]-2,3-dihydroimidazo[2,1-*b*]oxazole
*antibactérien*

delamanid (2*R*)-2-metil-6-nitro-2-[(4-{4-[4-(trifluorometoxi)fenoxi]piperidin-1-il}fenoxi)metil]-2,3-dihidroimidazo[2,1-*b*][1,3]oxazol
*antibacteriano*

$C_{25}H_{25}F_3N_4O_6$ 681492-22-8



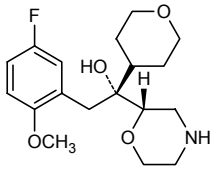
**edivoxetinum**

edivoxetine (1*R*)-2-(5-fluoro-2-methoxyphenyl)-1-[(2*S*)-morpholin-2-yl]-1-(oxan-4-yl)ethan-1-ol
*antidepressant*

édivoxétine (1*R*)-2-(5-fluoro-2-méthoxyphényl)-1-[(2*S*)-morpholin-2-yl]-1-(oxan-4-yl)éthan-1-ol
*antidépresseur*

edivoxetina (1*R*)-2-(5-fluoro-2-metoxifenil)-1-[(2*S*)-morfolin-2-il]-1-(oxan-4-il)etan-1-ol
*antidepresivo*

$C_{18}H_{26}FNO_4$ 1194508-25-2



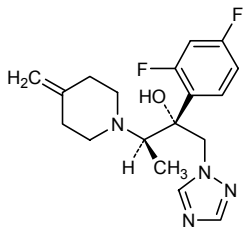
**efinaconazolum**

efinaconazole (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1*H*-1,2,4-triazin-1-yl)butan-2-ol
*antifungal*

éfinaconazole (2*R*,3*R*)-2-(2,4-difluorophényl)-3-(4-méthylènepipéridin-1-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol
*antifongique*

efinaconazol (2*R*,3*R*)-2-(2,4-difluorofenil)-3-(4-metilenopiperidin-1-il)-1-(1*H*-1,2,4-triazin-1-il)butan-2-ol
*antifúngico*

$C_{18}H_{22}F_2N_4O$ 164650-44-6



**egaptivonum pegolum**

egaptivon pegol

a pegylated aptamer which binds von Willebrand factor; 5'-*O*-{[6-(carboxyamino)hexyl]hydroxyphosphoryl}-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→3')-thymidine, carbamate ester with monomethyl ether of polyethylene gycol (20 kDa)
*anti-von Willebrand factor*

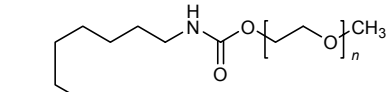
egaptivon pégol

aptamère pégylé qui se lie au facteur de von Willebrand; ester carbamique entre l'éther monométhylique du polyéthylèneglycol (macrogol 20 kDa) et le 5'-*O*-{[6-(carboxyamino)hexyl]hydroxyphosphoryl}-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-déoxyguanylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxyadénylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxyguanylyl-(3'→5')-2'-déoxyguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→3')-thymidine
*anti-facteur Von Willebrand*

egaptivón pegol

aptámero pegilado que se une al factor de von Willebrand;
éster carbámico entre el éter monometílico del polietilenglicol (macrogol 20 kDa) y el 5'-*O*-{[6-(carboxiamino)hexil]hidroxifosforil}-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-desoxiguanilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-timidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiguanilil-(3'→5')-2'-desoxiguanilil-(3'→5')-timidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-*O*-mtiladenilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilcitidilil-(3'→3')-timidina
*inhibidor del factor Von Willebrand*

$C_{413}H_{546}N_{144}O_{275}P_{40}S\ (C_2H_4O)_n$ 934868-74-3



(3'-5')( p−Gm−Cm−Gm−Um−dG−dC−dA−Gm−Um−Gm−Cm−Cm−Um−Cm−Gm−Gm−Cm−dC−Gm−sp−dT−Gm−dC−dG−dG−dT−Gm−Gm−Cm−dC−Um−dC−dC−Gm−Um−dC−Am−Cm−Gm−Cm3'−3'dT)

**elobixibatum**

elobixibat

[(2*R*)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1λ$^6$,5-benzothiazepin-8-yl]oxy}acetamido)-2-phenylacetamido]acetic acid
*ileal bile acid transporter inhibitor*

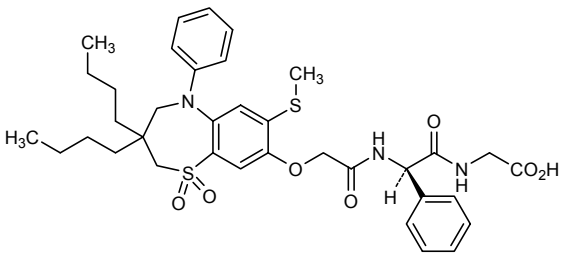
élobixibat

acide [(2*R*)-2-(2-{[3,3-dibutyl-7-(méthylsulfanyl)-1,1-dioxo-5-phényl-2,3,4,5-tétrahydro-1*H*-1λ$^6$,5-benzothiazépin-8-yl]oxy}acétamido)-2-phénylacétamido]acétique
*inhibiteur du transporteur iléal d'acides biliaires*

elobixibat

ácido [(2*R*)-2-(2-{[3,3-dibutil-5-fenil-7-(metilsulfanil)-1,1-dioxo-2,3,4,5-tetrahidro-1*H*-1λ$^6$,5-benzotiazepin-8-il]oxi}acetamido)-2-fenilacetamido]acético
*inhibidor del transportador ilíaco de ácidos biliares*

$C_{36}H_{45}N_3O_7S_2$ 439087-18-0



**elsiglutidum**

elsiglutide — [2-glycine(A>G),3-glutamic acid(D>E),8-serine(D>S),10-leucine(M>L),11-serine(N>S),16-alanine(N>A),24-alanine(N>A),28-alanine(Q>A)]human glucagon-like peptide 2 (GLP-2) fusion protein with hexalysinamide
*antidiarrhoeal*

elsiglutide — [2-glycine(A>G),3-acide glutamique(D>E),8-sérine(D>S),10-leucine(M>L),11-sérine(N>S),16-alanine(N>A),24-alanine(N>A),28-alanine(Q>A)]peptide 2 semblable au glucagon humain (GLP-2) protéine de fusion avec l'hexalysinamide
*antidiarrhéique*

elsiglutida — [2-glicina(A>G),3-acide glutámico(D>E), 8-serina(D>S),10-leucina(M>L),11-serina(N>S),16-alanina(N>A),24-alanina(N>A),28-alanina(Q>A)]péptido 2 similar al glucagón humano(GLP-2) proteína de fusión con hexalisinamida
*antidiarréico*

$C_{196}H_{323}N_{53}O_{56}$ 914009-84-0

HGEGSFSSEL STILDALAAR DFIAWLIATK ITDKKKKK<u>K</u> 39

Modified residue / Résidu modifié / Residuo modificado
<u>K</u> lysinamide

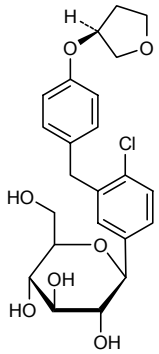
**empagliflozinum**

empagliflozin — (1*S*)-1,5-anhydro-1-*C*-{4-chloro-3-[(4-{[(3*S*)-oxan-3-yl]oxy}phenyl)methyl]phenyl}-D-glucitol
*antidiabetic*

empagliflozine — (1*S*)-1,5-anhydro-1-*C*-{4-chloro-3-[(4-{[(3*S*)-oxan-3-yl]oxy]}phényl)méthyl]phényl}-D-glucitol
*antidiabétique*

empagliflozina — (1*S*)-1,5-anhidro-1-*C*-{4-cloro-3-[(4-{[(3*S*)-oxan-3-il]oxi}fenil)metil]fenil}-D-glucitol
*hipoglucemiante*

$C_{23}H_{27}ClO_7$ 864070-44-0



**enavatuzumabum #**

| | |
|---|---|
| enavatuzumab | immunoglobulin G1-kappa, anti-[*Homo sapiens* TNFRSF12A (tumor necrosis factor receptor superfamily member 12A, fibroblast growth factor (FGF)-inducible 14 kDa protein, Fn14, TNF-like weak inducer of apoptosis (Tweak) receptor, Tweak receptor, TweakR, CD266], humanized monoclonal antibody;<br>gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV3-7*01 (86.70%) -(IGHD)-IGHJ6*01 T123>L (114)) [8.10.10] (1-119) -*Homo sapiens* IGHG1*01 CH3 D12>E (358), L14>M (360) (120-449)], (222-218')-disulfide with kappa light chain (1'-218') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (84.80%) - IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; (228-228":231-231")-bisdisulfide dimer<br>*antineoplastic* |
| énavatuzumab | immunoglobuline G1-kappa, anti-[*Homo sapiens* TNFRSF12A (membre 12A de la superfamille des récepteurs du facteur de nécrose tumorale, protéine de 14 kDa induite par le facteur de croissance du fibroblaste (FGF), Fn14, TNF-like faible inducteur d'apoptose (Tweak), récepteur de Tweak, CD266], anticorps monoclonal humanisé;<br>chaîne lourde gamma1 (1-449) [VH humanisé (*Homo sapiens* IGHV3-7*01 (86.70%) -(IGHD)-IGHJ6*01 T123>L (114)) [8.10.10] (1-119) -*Homo sapiens* IGHG1*01 CH3 D12>E (358), L14>M (360) (120-449)], (222-218')-disulfure avec la chaîne légère kappa (1'-218') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (84.80%) - IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; dimère (228-228":231-231")-bisdisulfure<br>*antinéoplasique* |
| enavatuzumab | inmunoglobulina G1-kappa, anti-[TNFRSF12A de *Homo sapiens* (miembro 12A de la superfamilia de receptores del factor de necrosis tumoral, proteína de 14 kDa inducida por el factor de crecimiento de fibroblastos (FGF), Fn14, TNF-like débil inductor de apoptosis (Tweak), receptor de Tweak, CD266], anticuerpo monoclonal humanizado;<br>cadena pesada gamma1 (1-449) [VH humanizada (*Homo sapiens* IGHV3-7*01 (86.70%) -(IGHD)-IGHJ6*01 T123>L (114)) [8.10.10] (1-119) -*Homo sapiens* IGHG1*01 CH3 D12>E (358), L14>M (360) (120-449)], (222-218')-disulfuro con la cadena ligera kappa (1'-218') [V-KAPPA humanizada (*Homo sapiens* IGKV1-39*01 (84.80%) - IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; dímero (228-228":231-231")-bisdisulfuro<br>*antineoplásico* |

62149-33-0

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAE  50
IRLKSDNYAT HYAESVKGRF TISRDDSKNS LYLQMNSLRA EDTAVYYCTG 100
YYADAMDYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASQSVS TSSYSYMHWY QQKPGKAPKL  50
LIKYASNLES GVPSRFSGSG SGTDFTLTIS SLQPEDFATY YCQHSWEIPY 100
TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV 150
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV 200
THQGLSSPVT KSFNRGEC                                    218
```

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

```
Intra-H  22-98    146-202    263-323    369-427
         22"-98"  146"-202"  263"-323"  369"-427"
Intra-L  23'-92'   138'-198'
         23'"-92'" 138'"-198'"
Inter-H-L  222-218'  222"-218'"
Inter-H-H  228-228"  231-231"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
299, 299"

**enokizumabum #**

enokizumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* IL9 (interleukin 9, IL-9, T cell growth factor p40)], humanized monoclonal antibody; gamma1 heavy chain (1-452) [humanized VH (*Homo sapiens* IGHV1-69*11 (87.80%) -(IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG1*03 (123-452)], (225-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (83.20%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (231-231":234-234")-bisdisulfide dimer
*antiasthmatic*

énokizumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* IL9 (interleukine 9, IL-9, facteur de croissance p40 des cellules T)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-452) [VH humanisé (*Homo sapiens* IGHV1-69*11 (87.80%) -(IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG1*03 (123-452)], (225-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (83.20%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (231-231":234-234")-bisdisulfure
*antiasthmatique*

enokizumab — inmunoglobulina G1-kappa, anti-[IL9 de *Homo sapiens* (interleukina 9, IL-9, factor de crecimiento p40 de células T)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-452) [VH humanizada (*Homo sapiens* IGHV1-69*11 (87.80%) -(IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG1*03 (123-452)], (225-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizada (*Homo sapiens* IGKV1-39*01 (83.20%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (231-231":234-234")-bisdisulfuro
*antiasmático*

909875-08-7

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGSSVKV SCKASGGTFS YYWIEWVRQA PGQGLEWMGE  50
ILPGSGTTNP NEKFKGRVTI TADESTSTAY MELSSLRSED TAVYYCARAD 100
YYGSDYVKFD YWGQGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
QTYICNVNHK PSNTKVDKRV EPKSCDKTHT CPPCPAPELL GGPSVFLFPP 250
KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ 300
YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE 350
PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 400
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 450
GK                                                      452
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCKASQHVI THVTWYQQKP GKAPKLLIYG  50
TSYSYSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ FYEYPLTFGG 100
GTKVEIKRTV 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

Intra-H 22-96 149-205 266-326 372-430
22"-96" 149"-205" 266"-326" 372"-430"
Intra-L 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L 225-214' 225"-214'"
Inter-H-H 231-231" 234-234"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
302, 302"

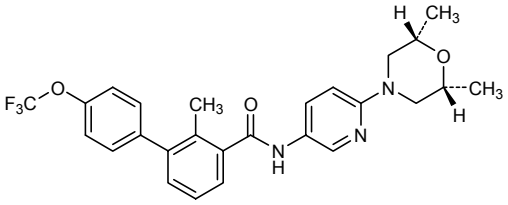
**erismodegibum**

erismodegib — *N*-{6-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]pyridin-3-yl}-2-methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-carboxamide
*antineoplastic*

érismodégib — *N*-{6-[(2*R*,6*S*)-2,6-diméthylmorpholin-4-yl]pyridin-3-yl}-2-méthyl-4'-(trifluorométhoxy)-[1,1'-biphényl]-3-carboxamide
*antinéoplasique*

erismodegib — *N*-{6-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]piridin-3-il}-2-metil-4'-(trifluorometoxi)-[1,1'-bifenil]-3-carboxamida
*antineoplásico*

$C_{26}H_{26}F_3N_3O_3$ 956697-53-3



**erteberelum**

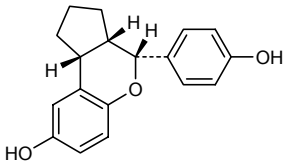
erteberel — (3a*S*,4*R*,9b*R*)-4-(4-hydroxyphenyl)-1,2,3,3a,4,9b-hexahydrocyclopenta[*c*]chromen-8-ol
*beta estrogen receptor agonist*

ertébérel — (3a*S*,4*R*,9b*R*)-4(4-hydroxyphényl)-1,2,3,3a,4,9b-hexahydrocyclopenta[*c*][1]chromén-8-ol
*agoniste des récepteurs oestrogéniques beta*

erteberel

(3a*S*,4*R*,9b*R*)-4-(4-hidroxifenil)-1,2,3,3a,4,9b-hexahidrociclopenta[*c*]cromen-8-ol
*agonista de los receptores estrogénicos beta*

$C_{18}H_{18}O_3$ 533884-09-2




**etrolizumabum #**

etrolizumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* integrins ITGA4_ITGB7 (integrin alpha4 (CD49d)_beta7, integrin α4β7, lymphocyte Peyer's patch adhesion molecule 1, LPAM-1) and ITGAE_ITGB7 (integrin alphaE (CD103, alphaIEL)_beta7, integrin αEβ7, HML-1], humanized monoclonal antibody;
gamma1 heavy chain (1-446) [humanized VH (*Homo sapiens* IGHV3-66*01 (81.40%) -(IGHD)-IGHJ4*01) [8.7.11] (1-117) -*Homo sapiens* IGHG1*01 CH3 D12>E (356), L14>M (358), K130>del (118-446)], (220-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (85.30%) -IGKJ1*01) [6.4.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (226-226":229-229")-bisdisulfide dimer
*immunomodulator*

étrolizumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* intégrines ITGA4_ITGB7 (intégrine alpha4 (CD49d)_bêta7, intégrine α4β7, récepteur d'adressage spécifique des plaques de Peyer, LPAM-1) et ITGAE_ITGB7 (intégrine alphaE (CD103, alphaIEL)_bêta7, intégrine αEβ7, HML1)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-446) [VH humanisé (*Homo sapiens* IGHV3-66*01 (81.40%) -(IGHD)-IGHJ4*01) [8.7.11] (1-117) -*Homo sapiens* IGHG1*01 CH3 D12>E (356), L14>M (358), K130>del (118-446)], (220-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (85.30%) -IGKJ1*01) [6.4.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (226-226":229-229")-bisdisulfure
*immunomodulateur*

etrolizumab

immunoglobuline G1-kappa, anti-[integrinas ITGA4_ITGB7 de *Homo sapiens* (integrina alfa4 (CD49d)_beta7, integrina α4β7, molécula de adhesión específica de linfocitos de las placas de Peyer, LPAM-1) e ITGAE_ITGB7 (integrina alfaE (CD103, alfaIEL)_beta7, integrina αEβ7, HML1)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-446) [VH humanizada (*Homo sapiens* IGHV3-66*01 (81.40%) -(IGHD)-IGHJ4*01) [8.7.11] (1-117) -*Homo sapiens* IGHG1*01 CH3 D12>E (356), L14>M (358), K130>del (118-446)], (220-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (85.30%) -IGKJ1*01) [6.4.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (226-226":229-229")-bisdisulfuro
*inmunomodulador*

1044758-60-2

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFFIT NNYWGWVRQA PGKGLEWVGY  50
ISYSGSTSYN PSLKSRFTIS RDTSKNTFYL QMNSLRAEDT AVYYCARTGS 100
SGYFDFWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG     446
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASESVD DLLHWYQQKP GKAPKLLIKY  50
ASQSISGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GNSLPNTFGQ 100
GTKVEIKRTV 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

Intra-H 22-95 144-200 261-321 367-425
22"-95" 144"-200" 261"-321" 367"-425"
Intra-L 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L 220-214' 220"-214'"
Inter-H-H 226-226" 229-229"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
297, 297"

**florbenazinum ($^{18}$F)**

florbenazine ($^{18}$F)

(2*R*,3*R*,11b*R*)-9-(3-[$^{18}$F]fluoropropoxy)-10-methoxy-3-(2-methylpropyl)-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ol
*diagnostic aid*

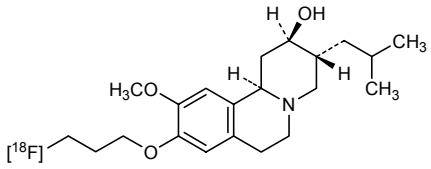
florbénazine ($^{18}$F)

(2*R*,3*R*,11b*R*)-9-(3-[$^{18}$F]fluoropropoxy)-10-méthoxy-3-(2-méthylpropyl)-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinoléin-2-ol
*produit à usage diagnostique*

florbenazina ($^{18}$F)

(2*R*,3*R*,11b*R*)-9-(3-[$^{18}$F]fluoropropoxi)-3-(2-metilpropil)-10-metoxi-1,3,4,6,7,11b-hexahidro-2*H*-pirido[2,1-*a*]isoquinolin-2-ol
*agente de diagnóstico*

$C_{21}H_{32}{}^{18}FNO_3$ 956903-29-0



**forigerimodum**
forigerimod — $O^{3,140}$-phosphono(human U1 small nuclear ribonucleoprotein 70 kDa (snRNP70))-(131-151)-peptide
*immunomodulator*

forigérimod — $O^{3,140}$-phosphono(petite ribonucléoprotéine nucléaire U1 humaine de 70 kDa (snRNP70))-(131-151)-peptide
*immunomodulateur*

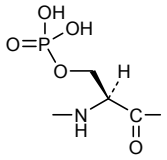
forigerimod — $O^{3,140}$-fosfono(pequeña ribonucleoproteína nuclear U1 humana de 70 kDa (snRNP70))-(131-151)-péptido
*inmunomodulador*

$C_{117}H_{181}N_{34}O_{32}PS$ 497156-60-2

RIHMVYSKRS GKPRGYAFIE Y 21

Modified residues / Résidus modifiés / Residuos modificados

S
10
O3,10-phosphono
(phosphoserine)



**fulranumabum #**
fulranumab — immunoglobulin G2-kappa, anti-[*Homo sapiens* NGF (nerve growth factor, nerve growth factor beta polypeptide, NGFB, beta-NGF)], *Homo sapiens* monoclonal antibody;
gamma2 heavy chain (1-449) [*Homo sapiens* VH (IGHV3-48*02 (92.90%) -(IGHD)-IGHJ4*01) [8.8.16] (1-123) -IGHG2*01 (124-449)], (137-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-13*02 (100.00%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; (225-225'':226-226':229-229'':232-232''')-tetrakisdisulfide dimer
*nerve growth factor inhibitor*

fulranumab — immunoglobuline G2-kappa, anti-[*Homo sapiens* NGF (facteur de croissance du nerf, facteur de croissance du nerf polypeptide bêta, NGFB, bêta-NGF)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma2 (1-449) [*Homo sapiens* VH (IGHV3-48*02 (92.90%) -(IGHD)-IGHJ4*01) [8.8.16] (1-123) -IGHG2*01 (124-449)], (137-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-13*02 (100.00%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (225-225'':226-226':229-229'':232-232''')-tétrakisdisulfure
*inhibiteur du facteur de croissance des cellules nerveuses*

fulranumab — inmunoglobulina G2-kappa, anti-[NGF de *Homo sapiens* (factor de crecimiento de nervios, factor de crecimiento de nervios polipétido beta, NGFB, beta-NGF)], anticuerpo monoclonal de *Homo sapiens*; cadena pesada gamma2 (1-449) [*Homo sapiens* VH (IGHV3-48*02 (92.90%) -(IGHD)-IGHJ4*01) [8.8.16] (1-123) -IGHG2*01 (124-449)], (137-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-13*02 (100.00%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (225-225'':226-226':229-229'':232-232''')-tetrakisdisulfuro
*inhibidor del factor de crecimiento de células nerviosas*

902141-80-4

Heavy chain / Chaîne lourde / Cadena pesada
```
EVQLVESGGG LVQPGGSLRL SCAASGFTLR SYSMNWVRQA PGKGLEWVSY  50
ISRSSHTIFY ADSVKGRFTI SRDNAKNSLY LQMDSLRDED TAMYYCARVY 100
SSGWHVSDYF DYWGQGILVT VSSASTKGPS VFPLAPCSRS TSESTAALGC 150
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSNFG 200
TQTYTCNVDH KPSNTKVDKT VERKCCVECP PCPAPPVAGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVQFNWY VDGVEVHNAK TKPREEQFNS 300
TFRVVSVLTV VHQDWLNGKE YKCKVSNKGL PAPIEKTISK TKGQPREPQV 350
YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPML 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera
```
AIQLTQSPSS LSASVGDRVT ITCRASQGIS SALAWYQQKP GKAPKLLIYD  50
ASSLESGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ FNSYPLTFGG 100
GTKVEIKRTV 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
Intra-H 22-96 150-206 263-323 369-427
22"-96" 150"-206" 263"-323" 369"-427"
Intra-L 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L 137-214' 137"-214'"
Inter-H-H 225-225" 226-226" 229-229" 232-232"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
299, 299"

**gaxilosum**
gaxilose

4-*O*-β-D-galactopyranosyl-D-xylose
*diagnostic aid*

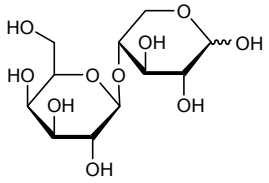
gaxilose

4-*O*-β-D-galactopyranosyl-D-xylose
*produit à usage diagnostique*

gaxilosa

4-*O*-β-D-galactopiranosil-D-xilosa
*agente de diagnostico*

$C_{11}H_{20}O_{10}$ 14087-31-1




**gevokizumabum #**
gevokizumab

immunoglobulin G2-kappa, anti-[*Homo sapiens* IL1B (interleukin 1 beta, 1L1F2, IL-1B)], humanized monoclonal antibody; gamma2 heavy chain (1-445) [humanized VH (*Homo sapiens* IGHV2-5*10 (72.70%) -(IGHD)-IGHJ5*01) [10.7.12] (1-120) -*Homo sapiens* IGHG2*02 CH3 K130>del (121-445)], (134-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (82.10%) -IGKJ1*01 V124>L (104')) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (222-222":223-223":226-226":229-229")-tetrakisdisulfide dimer
*interleukin-1 β antagonist*

gévokizumab

immunoglobuline G2-kappa, anti-[*Homo sapiens* IL1B (interleukine 1 bêta, 1L1F2, IL-1B)], anticorps monoclonal humanisé;
chaîne lourde gamma2 (1-445) [VH humanisé (*Homo sapiens* IGHV2-5*10 (72.70%) -(IGHD)-IGHJ5*01) [10.7.12] (1-120) -*Homo sapiens* IGHG2*02 CH3 K130>del (121-445)], (134-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (82.10%) -IGKJ1*01 V124>L (104')) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (222-222":223-223":226-226":229-229")-tétrakisdisulfure
*antagoniste de l'interleukine-1β*

gevokizumab

inmunoglobulina G2-kappa, anti-[IL1B *de Homo sapiens* (interleukina 1 beta, 1L1F2, IL-1B)], anticuerpo monoclonal humanizado;
cadena pesada gamma2 (1-445) [VH humanizada (*Homo sapiens* IGHV2-5*10 (72.70%) -(IGHD)-IGHJ5*01) [10.7.12] (1-120) -*Homo sapiens* IGHG2*02 CH3 K130>del (121-445)], (134-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (82.10%) -IGKJ1*01 V124>L (104')) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (222-222":223-223":226-226":229-229")-tetrakisdisulfuro
*antagonista de la interleukina-1β*

1129435-60-4

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQESGPG LVKPSQTLSL TCSFSGFSLS TSGMGVGWIR QPSGKGLEWL  50
AHIWWDGDES YNPSLKSRLT ISKDTSKNQV SLKITSVTAA DTAVYFCARN 100
RYDPPWFVDW GQGTLVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK 150
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VTSSNFGTQT 200
YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSHEDP EVQFNWYVDG MEVHNAKTKP REEQFNSTFR 300
VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP IEKTISKTKG QPREPQVYTL 350
PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPMLDSD 400
GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPG      445
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSTSS LSASVGDRVT ITCRASQDIS NYLSWYQQKP GKAVKLLIYY  50
TSKLHSGVPS RFSGSGSGTD YTLTISSLQQ EDFATYFCLQ GKMLPWTFGQ 100
GTKLEIKRTV 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

Intra-H 22-97 147-203 260-320 366-424
22"-97" 147"-203" 260"-320" 366"-424"
Intra-L 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L 134-214' 134"-214'"
Inter-H-H 222-222" 223-223" 226-226" 229-229"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
296, 296"

**granotapidum**

granotapide

diethyl 2-({2-[3-(dimethylcarbamoyl)-4-{4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamido}phenyl]acetyloxy}methyl)-2-phenylpropanedioate
*antihyperlipidaemic*

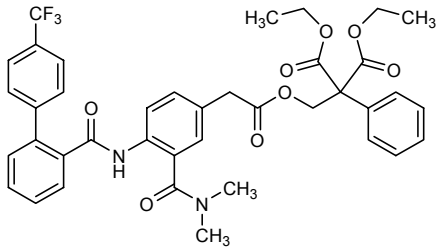
granotapide

2-[({2-[3-(diméthylcarbamoyl)-4-({[4'-(trifluorométhyl)-[1,1'-biphényl]-2-yl-carboxamido)phényl]acétyl}oxy)méthyl]-2-phénylpropanedioate de diéthyle
*antihyperlipidémiant*

granotapida

2-({2-[3-(dimetilcarbamoil)-4-{4'-(trifluorometil)-[1,1'-bifenil]-2-carboxamido}fenil]acetiloxi}metil)-2-fenilpropanodioato de dietilo
*antihiperlipémico*

$C_{39}H_{37}F_3N_2O_8$ 594842-13-4



**icrucumabum #**

icrucumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* FLT1 (fms-related tyrosine kinase 1, vascular endothelial growth factor receptor 1, VEGFR-1, VEGFR, FLT, FRT, vascular permeability factor receptor)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-456) [*Homo sapiens* VH (IGHV3-33*01 (93.90%) -(IGHD)-IGHJ6*01 [8.8.19] (1-126) -IGHG1*03 (127-456)], (229-215')-disulfide with kappa light chain (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (100.00%) -IGKJ4*01) [7.3.9] (1'-108') -IGKC1*01 (109'-215')]; (235-235'':238-238'')-bisdisulfide dimer
*antineoplastic*

icrucumab

immunoglobuline G1 kappa, anti-[*Homo sapiens* FLT1 (tyrosine kinase 1 apparentée au fms, récepteur 1 du facteur de croissance endothélial vasculaire, VEGFR-1, VEGFR, FLT, FRT, récepteur du facteur de perméabilité vasculaire)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-456) [*Homo sapiens* VH (IGHV3-33*01 (93.90%) -(IGHD)-IGHJ6*01 [8.8.19] (1-126) -IGHG1*03 (127-456)], (229-215')-disulfure avec la chaîne légère kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (100.00%) -IGKJ4*01) [7.3.9] (1'-108') -IGKC1*01 (109'-215')]; dimère (235-235'':238-238'')-bisdisulfure
*antinéoplasique*

icrucumab

inmunoglobulina G1 kappa, anti-[*Homo sapiens* FLT1 (tirosin kinasa 1 emparentada con el fms, receptor 1 del factor de crecimiento endotelial vascular, VEGFR-1, VEGFR, FLT, FRT, receptor del factor de permeabilidad vascular)], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma1 (1-456) [*Homo sapiens* VH (IGHV3-33*01 (93.90%) -(IGHD)-IGHJ6*01 [8.8.19] (1-126) -IGHG1*03 (127-456)], (229-215')-disulfuro con la cadena ligera kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (100.00%) -IGKJ4*01) [7.3.9] (1'-108') -IGKC1*01 (109'-215')]; dímero (235-235":238-238")-bisdisulfuro
*antineoplásico*

1024603-92-6

Heavy chain / Chaîne lourde / Cadena pesada

```
QAQVVESGGG VVQSGRSLRL SCAASGFAFS SYGMHWVRQA PGKGLEWVAV  50
IWYDGSNKYY ADSVRGRFTI SRDNSENTLY LQMNSLRAED TAVYYCARDH 100
YGSGVHHYFY YGLDVWGQGT TVTVSSASTK GPSVFPLAPS SKSTSGGTAA 150
LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS 200
SLGTQTYICN VNHKPSNTKV DKRVEPKSCD KTHTCPPCPA PELLGGPSVF 250
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP 300
REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG 350
QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY 400
KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL 450
SLSPGK                                                  456
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY  50
GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPLTFG 100
GGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK 150
VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ 200
GLSSPVTKSF NRGEC                                        215
```

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

| | | | | |
|---|---|---|---|---|
| Intra-H | 22-96 | 153-209 | 270-330 | 376-434 |
| | 22"-96" | 153"-209" | 270"-330" | 376"-434" |
| Intra-L | 23'-89' | 135'-195' | | |
| | 23'"-89'" | 135'"-195'" | | |
| Inter-H-L | 229-215' | 229"-215'" | | |
| Inter-H-H | 235-235" | 238-238" | | |

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
306, 306"

**irosustatum**

irosustat

6-oxo-6,7,8,9,10,11-hexahydrocyclohepta[*c*]chromen-3-yl sulfamate
*antineoplastic*

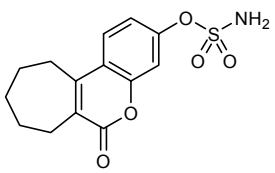
irosustat

sulfamate de 6-oxo-6,7,8,9,10,11-hexahydrocyclohepta[*c*]chromèn-3-yle
*antinéoplasique*

irosustat

sulfamato de 6-oxo-6,7,8,9,10,11-hexahidrociclohepta[*c*]cromen-3-ilo
*antineoplásico*

$C_{14}H_{15}NO_5S$ 288628-05-7



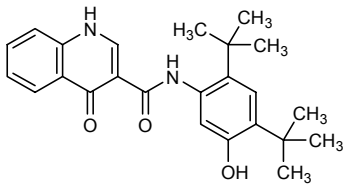
**ivacaftorum**

ivacaftor — *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
*CFTR (Cystic fibrosis Transmembrane Regulator) channel activator*

ivacaftor — *N*-[2,4-di-*tert*-butyl-5-hydroxyphényl]-4-oxo-1,4-dihydroquinoléine-3-carboxamide
*activateur de la protéine régulatrice de la perméabilité transmembrainre impliquée dans la mucoviscidose*

ivacaftor — *N*-(2,4-di-*terc*-butil-5-hidroxifenil)-4-oxo-1,4-dihidroquinolina-3-carboxamida
*activateur del canal CFTR (regulador de la conductancia transmembrana de la fibrosis quística)*

$C_{24}H_{28}N_2O_3$ 873054-44-5



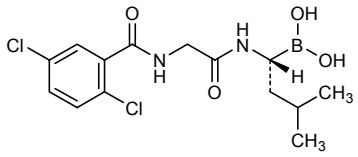
**ixazomibum**

ixazomib — {(1*R*)-1-[(2,5-dichlorobenzamido)acetamido]-3-methylbutyl}boronic acid
*antineoplastic*

ixazomib — acide [(1*R*)-1-{[*N*-(2,5-dichlorobenzoyl)glycyl]amino}-3-méthylbutyl]boronique
*antinéoplasique*

ixazomib — acido {(1*R*)-1-[(2,5-diclorobenzamido)acetamido]-3-metilbutil]borónico
*antineoplásico*

$C_{14}H_{19}BCl_2N_2O_4$ 1072833-77-2



**lenvatinibum**

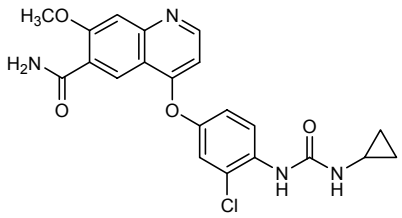
lenvatinib — 4-{3-chloro-4-[(cyclopropylcarbamoyl)amino]phenoxy}-7-methoxyquinoline-6-carboxamide
*antineoplastic*

lenvatinib — 4-{3-chloro-4-[(cyclopropylcarbamoyl)amino]phénoxy}-7-méthoxyquinoléine-6-carboxamide
*antinéoplasique*

lenvatinib

4-{3-cloro-4-[(ciclopropilcarbamoil)amino]fenoxi}-7-metoxiquinolina-6-carboxamida
*antineoplásico*

$C_{21}H_{19}ClN_4O_4$ 417716-92-8



**letaxabanum**

letaxaban

1-(1-{(2*S*)-3-[(6-chloronaphthalen-2-yl)sulfonyl]-2-hydroxypropanoyl}piperidin-4-yl)tetrahydropyrimidin-2(1*H*)-one
*blood coagulation factor Xa inhibitor*

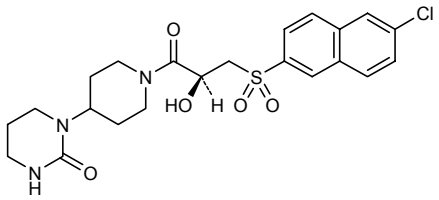
létaxaban

1-(1-{(2*S*)-3-[(6-chloronaphtalén-2-yl)sulfonyl]-2-hydroxypropanoyl}pipéridin-4-yl)tétrahydropyrimidin-2(1*H*)-one
*inhibiteur du facteur Xa de coagulation*

letaxabán

1-(1-{(2*S*)-3-[(6-cloronaftalen-2-il)sulfonil]-2-hidroxipropanoil}piperidin-4-il)tetrahidropirimidin-2(1*H*)-ona
*inhibidor del factor Xa de coagulación*

$C_{22}H_{26}ClN_3O_5S$ 870262-90-1



**letermovirum**

letermovir

(4*S*)-2-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid
*antiviral*

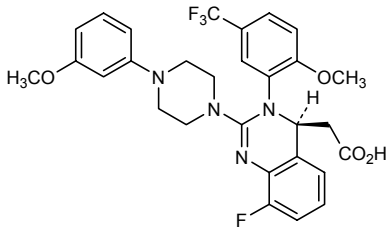
létermovir

acide {(4*S*)-8-fluoro-2-[4-(3-méthoxyphényl)pipérazin-1-yl]-3-[2-méthoxy-5-(trifluorométhyl)phényl]-3,4-dihydroquinazolin-4-yl}acétique
*antiviral*

letermovir

ácido (4*S*)-2-{8-fluoro-2-[4-(3-metoxifenil)piperazin-1-il]-3-[2-metoxi-5-(trifluorometil)fenil]-3,4-dihidroquinazolin-4-il}acético
*antiviral*

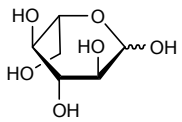
$C_{29}H_{28}F_4N_4O_4$ 917389-32-3



**levoglucosum**

| | |
|---|---|
| levoglucose | L-glucose<br>*diagnostic aid* |
| lévoglucose | L-glucose<br>*produit à usage diagnostique* |
| levoglucosa | L-glucosa<br>*agente de diagnóstico* |

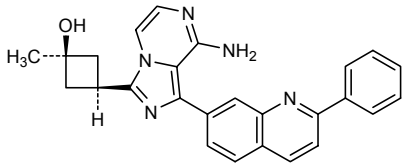
$C_6H_{12}O_6$ 921-60-8



**linsitinibum**

| | |
|---|---|
| linsitinib | (1*s*,3*r*)-3-[8-amino-1-(2-phenylquinolin-7-yl)imidazo[1,5-*a*]pyrazin-3-yl]-1-methylcyclobutan-1-ol<br>*antineoplastic* |
| linsitinib | (1*s*,3*r*)-3-[8-amino-1-(2-phénylquinoléin-7-yl)imidazo[1,5-*a*]pyrazin-3-yl]-1-méthylcyclobutan-1-ol<br>*antinéoplasique* |
| linsitinib | (1*s*,3*r*)-3-[8-amino-1-(2-fenilquinolin-7-il)imidazo[1,5-*a*]pirazin-3-il]-1-metilciclobutan-1-ol<br>*antineoplásico* |

$C_{26}H_{23}N_5O$ 867160-71-2



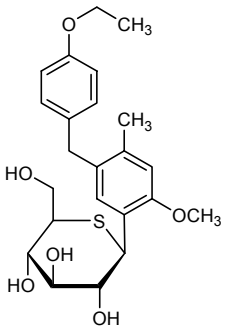
**luseogliflozinum**

luseogliflozin (2*S*,3*R*,4*R*,5*S*,6*R*)-2-{5-[(4-ethoxyphenyl)methyl]-2-methoxy-4-methylphenyl}-6-(hydroxymethyl)thiane-3,4,5-triol
*antidiabetic*

luséogliflozine (2*S*,3*R*,4*R*,5*S*,6*R*)-2-{5-[(4-éthoxyphényl)méthyl]-2-méthoxy-4-méthylphényl}-6-(hydroxyméthyl)thiane-3,4,5-triol
*antidiabétique*

luseogliflozina (2*S*,3*R*,4*R*,5*S*,6*R*)-2-{5-[(4-etoxifenil)metil]-4-metilfenil-2-metoxi}-6-(hidroximetil)tiano-3,4,5-triol
*hipoglucemiante*

$C_{23}H_{30}O_6S$ 898537-18-3



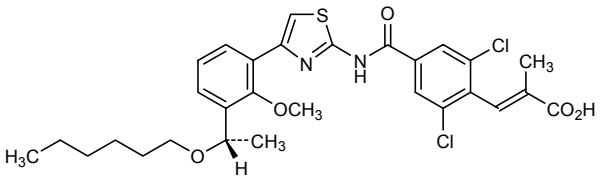
**lusutrombopagum**

lusutrombopag (2*E*)-3-{2,6-dichloro-4-[(4-{3-[(1*S*)-1-(hexyloxy)ethyl]-2-methoxyphenyl}-1,3-thiazol-2-yl)carbamoyl]phenyl}-2-methylprop-2-enoic acid
*thrombopoietin receptor agonist*

lusutrombopag acide (2*E*)-3-{2,6-dichloro-4-[(4-{3-[(1*S*)-1-(hexyloxy)éthyl]-2-méthoxyphényl}-1,3-thiazol-2-yl)carbamoyl]phényl}-2-méthylprop-2-énoïque
*agoniste du récepteur de la thrombopoïétine*

lusutrombopag ácido (2*E*)-3-{2,6-dicloro-4-[(4-{3-[(1*S*)-1-(hexiloxi)etil]-2-metoxifenil}-1,3-tiazol-2-il)carbamoil]fenil}-2-metilprop-2-enoico
*agonista de los receptores de trombopoyetina*

$C_{29}H_{32}Cl_2N_2O_5S$ 1110766-97-6



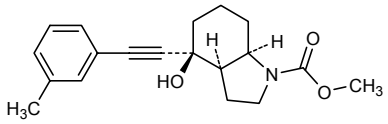
**mavoglurantum**

mavoglurant — methyl (3a*R*,4*S*,7a*R*)-4-hydroxy-4-[2-(3-methylphenyl)ethynyl]octahydro-1*H*-indole-1-carboxylate
*glutamate receptor antagonist*

mavoglurant — (3a*R*,4*S*,7a*R*)-4-hydroxy-4-[2-(3-méthylphényl)éthynyl]octahydro-1*H*-indole-1-carboxylate de méthyle
*antagoniste des récepteurs au glutamate*

mavoglurant — (3a*R*,4*S*,7a*R*)-4-hidroxi-4-[2-(3-metilfenil)etinil]octahidro-1*H*-indol-1-carboxilato de metil
*antagonista del receptor de glutamato*

$C_{19}H_{23}NO_3$ 543906-09-8



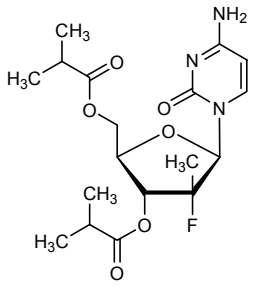
**mericitabinum**

mericitabine — (2'*R*)-2'-deoxy-2'-fluoro-2'-methyl-2',3'-bis-*O*-(2-methylpropanoyl)cytidine
*antiviral*

méricitabine — 3',5'-bis(2-méthylpropanoate) de (2'*R*)-2'-déoxy-2'-fluoro-2'-méthylcytidine
*antiviral*

mericitabina — (2'*R*)-2'-desoxi-2'-fluoro-2'-metil-2',3'-bis-*O*-(2-metilpropanoil)citidina
*antiviral*

$C_{18}H_{26}FN_3O_6$ 940908-79-2



**mogamulizumabum #**

mogamulizumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* CCR4 (chemokine (C-C motif) receptor 4, CC chemokine receptor 4, CCR-4, CKR4, k5-5, CD194)], humanized monoclonal antibody;
gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV3-21*01 (83.70%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2-29*02 (81.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (228-228":231-231")-bisdisulfide dimer
*immunomodulator*

mogamulizumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* CCR4 (récepteur 4 de chimiokine (C-C motif), récepteur 4 de chimiokine CC, CCR-4, CKR4, k5-5, CD194)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-449) [VH humanisé (*Homo sapiens* IGHV3-21*01 (83.70%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV2-29*02 (81.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimère (228-228":231-231")-bisdisulfure
*immunomodulateur*

mogamulizumab

inmunoglobulina G1-kappa, anti-[CCR4 de *Homo sapiens* (receptor 4 de quimiokina (C-C motif), receptor 4 de quimiokina CC, CCR-4, CKR4, k5-5, CD194)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-449) [VH humanizada (*Homo sapiens* IGHV3-21*01 (83.70%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizada (*Homo sapiens* IGKV2-29*02 (81.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dímero (228-228":231-231")-bisdisulfuro
*inmunomodulador*

1159266-37-1

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGD LVQPGRSLRL SCAASGFIFS NYGMSWVRQA PGKGLEWVAT  50
ISSASTYSYY PDSVKGRFTI SRDNAKNSLY LQMNSLRVED TALYYCGRHS 100
DGNFAFGYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DVLMTQSPLS LPVTPGEPAS ISCRSSRNIV HINGDTYLEW YLQKPGQSPQ  50
LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCFQGSLLP 100
WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200
VTHQGLSSPV TKSFNRGEC                                   219
```

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

```
Intra-H   22-96    146-202   263-323   369-427
          22"-96"  146"-202" 263"-323" 369"-427"
Intra-L   23'-93'    139'-199'
          23'"-93'"  139'"-199'"
Inter-H-L 222-219' 222"-219'"
Inter-H-H 228-228" 231-231"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
299, 299"

**namilumabum #**
namilumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* CSF2 (*Homo sapiens* colony stimulating factor 2 (granulocyte-macrophage), granulocyte-macrophage colony stimulating factor, GM-CSF)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-449) [*Homo sapiens* VH (IGHV1-2*02 (89.80%) -(IGHD)-IGHJ4*01 L123>M (114)) [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-39*01 (88.40%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; (228-228":231-231")-bisdisulfide dimer
*immunomodulator*

namilumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* CSF2 (*Homo sapiens* facteur 2 stimulant de colonies (granulocyte-macrophage), facteur stimulant des colonies de granulocytes et macrophages, GM-CSF)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-449) [*Homo sapiens* VH (IGHV1-2*02 (89.80%) -(IGHD)-IGHJ4*01 L123>M (114)) [8.8.12] (1-119) - IGHG1*01 (120-449)], (222-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-39*01 (88.40%) - IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (228-228":231-231")-bisdisulfure
*immunomodulateur*

namilumab

inmunoglobulina G1-kappa, anti-[CSF2 de *Homo sapiens* (*Homo sapiens* factor 2 estimulante de colonias (granulocito-macrófago), factor estimulante de colonias de granulocitos y macrófagos, GM-CSF)], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma1 (1-449) [*Homo sapiens* VH (IGHV1-2*02 (89.80%) -(IGHD)-IGHJ4*01 L123>M (114)) [8.8.12] (1-119) - IGHG1*01 (120-449)], (222-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-39*01 (88.40%) - IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (228-228":231-231")-bisdisulfuro
*inmunomodulador*

1206681-39-1

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKAFGYPFT DYLLHWVRQA PGQGLEWVGW  50
LNPYSGDTNY AQKFQGRVTM TRDTSISTAY MELSRLRSDD TAVYYCTRTT 100
LISVYFDYWG QGTMVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS VSASVGDRVT IACRASQNIR NILNWYQQRP GKAPQLLIYA  50
ASNLQSGVPS RFSGSGSGTD FTLTINSLQP EDFATYYCQQ SYSMPRTFGG 100
GTKLEIKRTV 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

```
Intra-H   22-96    146-202    263-323    369-427
          22"-96"  146"-202"  263"-323"  369"-427"
Intra-L   23'-88'  134'-194'
          23'"-88'" 134'"-194'"
Inter-H-L 222-214' 222"-214'"
Inter-H-H 228-228" 231-231"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
299, 299"

**naronapridum**

naronapride

(3*R*)-1-azabicyclo[2.2.2]octan-3-yl 6-[(3*S*,4*R*)-4-(4-amino-5-chloro-2-methoxybenzamido)-3-methoxypiperidin-1-yl]hexanoate
*dopamine receptor antagonist*

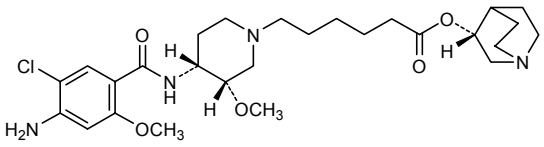
naronapride

6-{(3*S*,4*R*)-4-(4-amino-5-chloro-2-méthoxybenzamido)-3-méthoxypipéridin-1-yl}hexanoate de (3*R*)-1-azabicyclo[2.2.2]oct-3-yl
*antagoniste des récepteurs dopaminergiques*

naronaprida

6-[(3*S*,4*R*)-4-(4-amino-5-cloro-2-metoxibenzamido)-3-metoxipiperidin-1-il]hexanoato de (3*R*)-1-azabiciclo[2.2.2]octan-3-ilo
*antagonista de los receptores de la dopamina*

$C_{27}H_{41}ClN_4O_5$ 860174-12-5



**onartuzumabum #**

onartuzumab

immunoglobulin G1-kappa monovalent Fab-Fc, anti-[*Homo sapiens* MET (met proto-oncogene, hepatocyte growth factor receptor, HGFR, scatter factor receptor, HGF/SF receptor, receptor tyrosine-protein kinase c-Met, papillary renal cell carcinoma 2, RCCP2)], humanized monoclonal antibody;
gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV3-74*01 (77.30%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 CH3 D12>E (358), L14>M (360), T22>S (368), L24>A (370), Y86>V (409) (120-449)], (222-220')-disulfide with kappa light chain (1'-220') [humanized V-KAPPA (*Homo sapiens* IGKV4-1*01 (80.20%) -IGKJ1*01) [12.3.9] (1'-113') -*Homo sapiens* IGKC*01 (114'-220')], (228-6":231-9")-bisdisulfide with truncated gamma1 chain consisting of partial hinge-CH2-CH3 (1"-227") [*Homo sapiens* IGHG1*01 hinge 6-15(1"-10")-CH2(11"-120")-CH3(121"-227") CH3 D12>E (136"), L14>M (138"), T22>W (146")]
*antineoplastic*

onartuzumab

immunoglobuline G1-kappa monovalent Fab-Fc, anti-[*Homo sapiens* MET (proto-oncogène met, récepteur du facteur de croissance hépatocytaire, HGFR, récepteur du facteur de dispersion, récepteur de l'HGF/SF, récepteur protéine-tyrosine kinase c-Met, carcinome papillaire à cellules rénales 2, RCCP2)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-449) [VH humanisé (*Homo sapiens* IGHV3-74*01 (77.30%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 CH3 D12>E (358), L14>M (360), T22>S (368), L24>A (370), Y86>V (409) (120-449)], (222-220')-disulfure avec la chaîne légère kappa (1'-220') [V-KAPPA humanisé (*Homo sapiens* IGKV4-1*01 (80.20%) -IGKJ1*01) [12.3.9] (1'-113') -*Homo sapiens* IGKC*01 (114'-220')], (228-6":231-9")-bisdisulfure avec la chaîne gamma1 tronquée comprenant charnière partielle-CH2-CH3 (1"-227") [*Homo sapiens* IGHG1*01 charnière 6-15(1"-10")-CH2(11"-120")-CH3(121"-227") CH3 D12>E (136"), L14>M (138"), T22>W (146")]
*antinéoplasique*

onartuzumab

inmunoglobulina G1-kappa monovalente Fab-Fc, anti-[*Homo sapiens* MET (protooncogén met, receptor del factor de crecimiento hepatocitario, HGFR, receptor del factor de dispersión, receptor de l'HGF/SF, receptor de tirosina proteín-kinasa c-Met, carcinoma papilar de cèlulas renales 2, RCCP2)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-449) [VH humanizada (*Homo sapiens* IGHV3-74*01 (77.30%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 CH3 D12>E (358), L14>M (360), T22>S (368), L24>A (370), Y86>V (409) (120-449)], (222-220')-disulfuro con la cadena ligera kappa (1'-220') [V-KAPPA humanizada (*Homo sapiens* IGKV4-1*01 (80.20%) -IGKJ1*01) [12.3.9] (1'-113') -*Homo sapiens* IGKC*01 (114'-220')], (228-6":231-9")-bisdisulfuro con la cadena gamma1 truncada que comprende parte de la bisagra-CH2-CH3 (1"-227") [*Homo sapiens* IGHG1*01 bisagra 6-15(1"-10")-CH2(11"-120")-CH3(121"-227") CH3 D12>E (136"), L14>M (138"), T22>W (146")]
*antineoplásico*

1133766-06-9

Heavy chain / Chaîne lourde / Cadena pesada (H)
```
EVQLVESGGG LVQPGGSLRL SCAASGYTFT SYWLHWVRQA PGKGLEWVGM  50
IDPSNSDTRF NPNFKDRFTI SADTSKNTAY LQMNSLRAED TAVYYCATYR 100
SYVTPLDYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSREEM TKNQVSLSCA VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLVS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera (L)
```
DIQMTQSPSS LSASVGDRVT ITCKSSQSLL YTSSQKNYLA WYQQKPGKAP  50
KLLIYWASTR ESGVPSRFSG SGSGTDFTLT ISSLQPEDFA TYYCQQYYAY 100
PWTFGQGTKV EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA 150
KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC 200
EVTHQGLSSP VTKSFNRGEC                                  220
```

Hinge-CH2-CH3 / Charnière-CH2-CH3/ Bisagra-CH2-CH3 (H")
```
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED  50
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK 100
CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLWCLVK 150
GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG 200
NVFSCSVMHE ALHNHYTQKS LSLSPGK                          227
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-96 146-202 263-323 369-427
Intra-H" 41"-101" 147"-205"
Intra-L 23'-94' 140'-200'
Inter-H-L 222-220'
Inter-H-H" 228-6" 231-9"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
299, 77" unglycosylated as expressed in *Escherichia coli*

**ordopidinum**

ordopidine

1-ethyl-4-[2-fluoro-3-(methanesulfonyl)phenyl]piperidine
*antiparkinsonian*

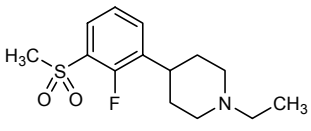
ordopidine

1-éthyl-4-[2-fluoro-3-(méthylsulfonyl)phényl]pipéridine
*antiparkinsonien*

ordopidina

1-etil-4-[2-fluoro-3-(metanosulfonil)fenil]piperidina
*antiparkinsoniano*

$C_{14}H_{20}FNO_2S$ 871351-60-9



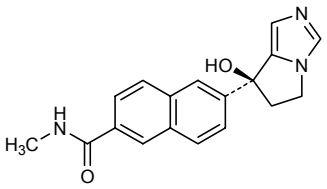
**orteronelum**

orteronel 6-[(7*S*)-7-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl]-*N*-methylnaphthalene-2-carboxamide
*antiandrogen*

ortéronel 6-[(7*S*)-7-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl]-*N*-méthylnaphtalène-2-carboxamide
*antiandrogène*

orteronel 6-[(7*S*)-7-hidroxi-6,7-dihidro-5*H*-pirrolo[1,2-*c*]imidazol-7-il]-*N*-metilnaftaleno-2-carboxamida
*antiandrógeno*

$C_{18}H_{17}N_3O_2$ 566939-85-3



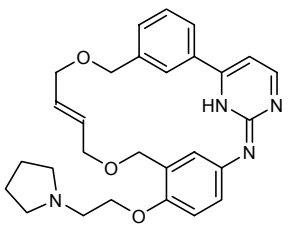
**pacritinibum**

pacritinib ((2*E*,16*E*)-11-[2-(pyrrolidin-1-yl)ethoxy]-14,19-dioxa-5,7,27-triazatetracyclo[19.3.1.1$^{2,6}$.1$^{8,12}$]heptacosa-1(25),2,4,6,8,10,12(26),16,21,23-decaene
*antineoplastic*

pacritinib (16*E*)-11-[2-(pyrrolidin-1-yl)éthoxy]-14,19-dioxa-5,7,27-triazatétracyclo[19.3.1.1$^{2,6}$.1$^{8,12}$]heptacosa-1(24),2,4,6,8,10,12(26),16,21(25),22-décaène
*antinéoplasique*

pacritinib ((2*E*,16*E*)-11-[2-(pirrolidin-1-il)etoxi]-14,19-dioxa-5,7,27-triazatetraciclo[19.3.1. 1$^{2,6}$.1$^{8,12}$]heptacosa 1(25),2,4,6,8,10,12(26),16,21,23-decaeno
*antineoplásico*

$C_{28}H_{32}N_4O_3$ 937272-79-2



**plecanatidum**

plecanatide — [3-glutamic acid(D>E)]human uroguanylin (UGN)
*gastrointestinal agent*

plécanatide — [3-acide glutamique(D>E)]uroguanyline humaine (UGN)
*agent gastro-intestinal*

plecanatida — [3-ácido glutámico(D>E)]uroguanilina humana (UGN)
*agente gastrointestinal*

$C_{65}H_{104}N_{18}O_{26}S_4$ 467426-54-6

NDECELCVNV ACTGCL 16

Disulfide bridges location / Position des ponts disulfure/ Posiciones de los puentes disulfuros
4-12 7-15

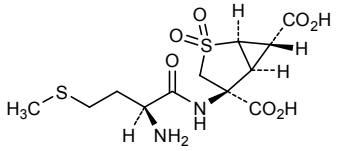
**pomaglumetadum methionilum**

pomaglumetad methionil — (1*R*,4*S*,5*S*,6*S*)-4-(L-methionylamino)-2,2-dioxo-2λ$^6$-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid
*antipsychotic*

pomaglumétad méthionil — acide (1*R*,4*S*,5*S*,6*S*)-4-(L-méthionylamino)-2,2-dioxo-2λ$^6$-thiabicyclo[3.1.0]hexane-4,6-dicarboxylique
*antipsychotique*

pomaglumetad metionilo — ácido (1*R*,4*S*,5*S*,6*S*)-4-(L-metionilamino)-2,2-dioxo-2λ$^6$-tiabiciclo[3.1.0]hexano-4,6-dicarboxílico
*antipsicótico*

$C_{12}H_{18}N_2O_7S_2$ 635318-55-7



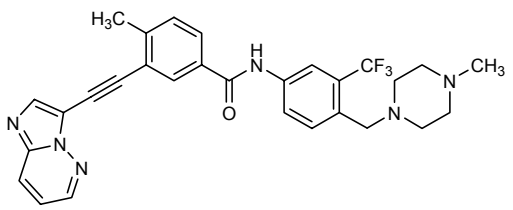
**ponatinibum**

ponatinib — 3-[2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl]-4-methyl-*N*-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide
*antineoplastic*

ponatinib — 3-[2-(imidazo[1,2-*b*]pyridazin-3-yl)éthynyl]-4-méthyl-*N*-{4-[(4-méthylpipérazin-1-yl)méthyl]-3-(trifluorométhyl)phényl}benzamide
*antinéoplasique*

ponatinib — 3-[2-(imidazo[1,2-*b*]piridazin-3-il)etinil]-4-metil-*N*-{4-[(4-metilpiperazin-1-il)metil]-3-(trifluorometil)fenil}benzamida
*antineoplásico*

$C_{29}H_{27}F_3N_6O$ 943319-70-8



**ponezumabum #**

ponezumab — immunoglobulin G2-kappa, anti-[*Homo sapiens* amyloid beta (A beta) peptide Aβ40], humanized monoclonal antibody; gamma2 heavy chain (1-442) [humanized VH (*Homo sapiens* IGHV1-46*02 (84.50%) -(IGHD)-IGHJ6*01) [8.8.9] (1-116) -*Homo sapiens* IGHG2*01 CH2 A115>S (325), P116>S (326) (117-442)], (130-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2-30*01 (89.00%) -IGKJ5*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (218-218":219-219":222-222":225-225")-tetrakisdisulfide dimer
*human β-amyloid fibrils depository inhibitor*

ponezumab — immunoglobuline G2-kappa, anti-[*Homo sapiens* peptide amyloïde bêta (A bêta) Aβ40], anticorps monoclonal humanisé; chaîne lourde gamma2 (1-442) [VH humanisé (*Homo sapiens* IGHV1-46*02 (84.50%) -(IGHD)-IGHJ6*01) [8.8.9] (1-116) -*Homo sapiens* IGHG2*01 CH2 A115>S (325), P116>S (326) (117-442)], (130-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV2-30*01 (89.00%) -IGKJ5*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimère (218-218":219-219":222-222":225-225")-tétrakisdisulfure
*inhibiteur de la déposition de fibrilles β-amyloïdes humaines*

ponezumab — inmunoglobulina G2-kappa, anti-[péptido amiloide beta de *Homo sapiens* (A beta) Aβ40], anticuerpo monoclonal humanizado; cadena pesada gamma2 (1-442) [VH humanizada (*Homo sapiens* IGHV1-46*02 (84.50%) -(IGHD)-IGHJ6*01) [8.8.9] (1-116) -*Homo sapiens* IGHG2*01 CH2 A115>S (325), P116>S (326) (117-442)], (130-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizada (*Homo sapiens* IGKV2-30*01 (89.00%) -IGKJ5*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dímer (218-218":219-219":222-222":225-225")-tetrakisdisulfuro
*inhibidor del depósito de fibrillas β-amiloides humanas*

1178862-65-1

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKASGYYTE AYYIHWVRQA PGQGLEWMGR  50
IDPATGNTKY APRLQDRVTM TRDTSTSTVY MELSSLRSED TAVYYCASLY 100
SLPVYWGQGT TVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN 200
VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR 250
TPEVTCVVVD VSHEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV 300
LTVVHQDWLN GKEYKCKVSN KGLPSSIEKT ISKTKGQPRE PQVYTLPPSR 350
EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PMLDSDGSFF 400
LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK         442
```

Light chain / Chaîne légère / Cadena ligera

```
DVVMTQSPLS LPVTLGQPAS ISCKSSQSLL YSDAKTYLNW FQQRPGQSPR  50
RLIYQISRLD PGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCLQGTHYP 100
VLFGQGTRLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200
VTHQGLSSPV TKSFNRGEC                                   219
```

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

| | | | | |
|---|---|---|---|---|
| Intra-H | 22-96 | 143-199 | 256-316 | 362-420 |
| | 22"-96" | 143"-199" | 256"-316" | 362"-420" |
| Intra-L | 23'-93' | 139'-199' | | |
| | 23'"-93'" | 139'"-199'" | | |
| Inter-H-L | 130-219' | 130"-219'" | | |
| Inter-H-H | 218-218" | 219-219" | 222-222" | 225-225" |

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
292, 292"

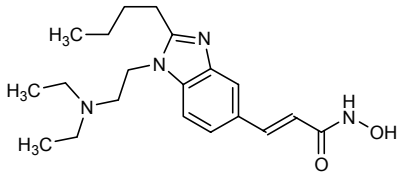
**pracinostatum**

pracinostat — (2*E*)-3-{2-butyl-1-[2-(dimethylamino)ethyl]-1*H*-benzimidazol-5-yl}-*N*-hydroxyprop-2-enamide
*antineoplastic*

pracinostat — (2*E*)-3-{2-butyl-1-[2-(diéthylamino)éthyl]-1*H*-benzimidazol-5-yl]-*N*-hydroxyprop-2-énamide
*antinéoplasique*

pracinostat — (2*E*)-3-{2-butil-1-[2-(dimetilamino)etil]-1*H*-bencimidazol-5-il}-*N*-hidroxyprop-2-enamida
*antineoplásico*

$C_{20}H_{30}N_4O_2$ 929016-96-6



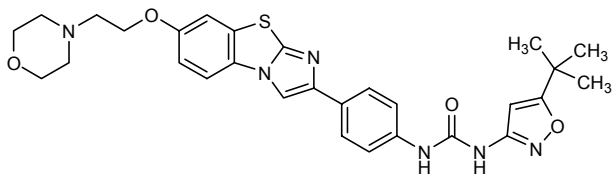
**quizartinibum**

quizartinib — 1-(5-*tert*-butyl-1,2-oxazol-3-yl)-3-(4-{7-[2-(morpholin-4-yl)ethoxy]imidazo[2,1-*b*][1,3]benzothiazol-2-yl}phenyl)urea
*antineoplastic*

quizartinib — *N*-[5-*tert*-butyl-1,2-oxazol-3-yl]-*N*'-(4-{7-[2-(morpholin-4-yl)éthoxy]imidazo[2,1-*b*][1,3]benzothiazol-2-yl}phényl)urée
*antinéoplasique*

quizartinib — 1-(5-*terc*-butil-1,2-oxazol-3-il)-3-(4-{7-[2-(morfolin-4-il)etoxi]imidazo[2,1-*b*][1,3]benzotiazol-2-il}fenil)urea
*antineoplásico*

$C_{29}H_{32}N_6O_4S$ 950769-58-1



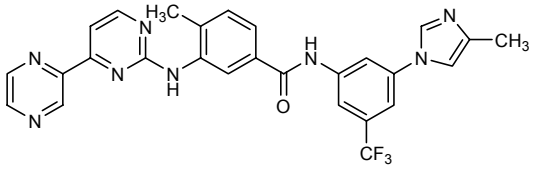
**radotinibum**

radotinib — 4-methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-{[4-(pyrazin-2-yl)pyrimidin-2-yl]amino}benzamide
*antineoplastic*

radotinib — 4-méthyl-*N*-[3-(4-méthyl-1*H*-imidazol-1-yl)-5-(trifluorométhyl)phényl]-3-{[4-(pyrazin-2-yl)pyrimidin-2-yl]amino}benzamide
*antinéoplasique*

radotinib — 4-metil-*N*-[3-(4-metil-1*H*-imidazol-1-il)-5-(trifluorometil)fenil]-3-{[4-(pirazin-2-il)pirimidin-2-il]amino}benzamida
*antineoplásico*

$C_{27}H_{21}F_3N_8O$ 926037-48-1



**radretumabum #**

radretumab — immunoglobulin scFv-CH dimer, anti-[*Homo sapiens* fibronectin extra domain B (ED-B)], *Homo sapiens* monoclonal antibody fragment dimer of single chain (scFv) fused with the IGHE CH4; scFv-CH (1-357) [*Homo sapiens* VH (IGHV3-23*01 (94.90%) -(IGHD)-IGHJ4*01) [8.8.14] (1-116)-12-mer linker (117-128)- *Homo sapiens* V-KAPPA (IGKV3-20*01 (94.80%) -IGKJ1*01) [7.3.9] (129-236)-5-mer linker (237-241)- *Homo sapiens* IGHE*01 CH4 (242-349)-8-mer linker (350-357)]; (357:357') disulfide dimer
*antineoplastic*

radrétumab — immunoglobuline scFv-CH dimère, anti-[*Homo sapiens* extra domaine B (ED-B) de la fibronectine], *Homo sapiens* anticorps monoclonal fragment dimère de scFv fusionné au CH4 de l'IGHE; scFv-CH (1-357) [*Homo sapiens* VH (IGHV3-23*01 (94.90%) -(IGHD)-IGHJ4*01) [8.8.14] (1-116)-12-mer linker (117-128)- *Homo sapiens* V-KAPPA (IGKV3-20*01 (94.80%) -IGKJ1*01) [7.3.9] (129-236)-5-mer linker (237-241)- *Homo sapiens* IGHE*01 CH4 (242-349)-8-mer linker (350-357)]; dimère (357:357')
*antinéoplasique*

radretumab — inmunoglobulina scFv-CH dímero, anti-[*Homo sapiens* extra dominio B (ED-B) de la fibronectina], fragmento de anticuerpo monoclonal de *Homo sapiens* dímero de scFv fusionado con el CH4 del IGHE; scFv-CH (1-357) [*Homo sapiens* VH (IGHV3-23*01 (94.90%) -(IGHD)-IGHJ4*01) [8.8.14] (1-116)-dodecámero de conexión (117-128)- *Homo sapiens* V-KAPPA (IGKV3-20*01 (94.80%) -IGKJ1*01) [7.3.9] (129-236)-pentámero de conexión (237-241)- *Homo sapiens* IGHE*01 CH4 (242-349)-octámero de conexión (350-357)]; dímero (357:357') disulfuro
*antineoplásico*

1253180812

scFv-CH chain / Chaîne scFv-CH / Cadena scFv-CH

```
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SFSMSWVRQA PGKGLEWVSS  50
ISGSSGTTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKPF 100
PYFDYWGQGT LVTVSSGDGS SGGSGGASEI VLTQSPGTLS LSPGERATLS 150
CRASQSVSSS FLAWYQQKPG QAPRLLIYYA SSRATGIPDR FSGSGSGTDF 200
TLTISRLEPE DFAVYYCQQT GRIPPTFGQG TKVEIKSGGS GGPRAAPEVY 250
AFATPEWPGS RDKRTLACLI QNFMPEDISV QWLHNEVQLP DARHSTTQPR 300
KTKGSGFFVF SRLEVTRAEW EQKDEFICRA VHEAASPSQT VQRAVSVNPE 350
SSRRGGC                                                 357
```

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

Intra-chain 22-96 151-217 268-328
22'-96' 151'-217' 268'-328'
Inter-chain 357-357'

**ravatirelinum**

ravatirelin

(4*S*,5*S*)-5-methyl-*N*-{(2*S*)-1-[(2*R*)-2-methylpyrrolidin-1-yl]-1-oxo-3-[(1,3-thiazol-4-yl)methyl]propan-2-yl}-2-oxo-1,3-oxazolidine-4-carboxamide
*growth hormone release-stimulating peptide*

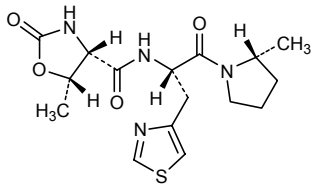
ravatiréline

(4*S*,5*S*)-5-méthyl-*N*-{(2*S*)-1-[(2*R*)-2-méthylpyrrolidin-1-yl]-1-oxo-3-[(1,3-thiazol-4-yl)méthyl]propan-2-yl}-2-oxo-1,3-oxazolidine-4-carboxamide
*peptide de stimulation de la libération de l'hormone de croissance*

ravatirelina

(4*S*,5*S*)-5-metil-*N*-{(2*S*)-1-[(2*R*)-2-metilpirrolidin-1-il]-1-oxo-3-[(1,3-tiazol-4-il)metil]propan-2-il}-2-oxo-1,3-oxazolidina-4-carboxamida
*péptido estimulante de la liberación de la hormona del crecimiento*

$C_{16}H_{22}N_4O_4S$ 204386-76-5



**ronomilastum**

ronomilast

*N*-(3,5-dichloropyridin-4-yl)-2-{1-[(4-fluorophenyl)methyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-2-oxoacetamide
*phosphodiesterase IV inhibitor*

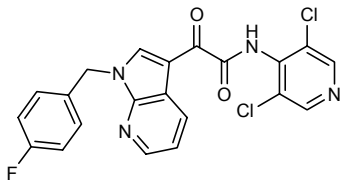
ronomilast

*N*-(3,5-dichloropyridin-4-yl)-2-{1-[(4-fluorophényl)méthyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}-2-oxoacétamide
*inhibiteur de la phosphodiesterase IV*

ronomilast

*N*-(3,5-dicloropiridin-4-il)-2-{1-[(4-fluorofenil)metil]-1*H*-pirrolo[2,3-*b*]piridin-3-il}-2-oxoacetamida
*inhibidor de la fosfodiesterasa IV*

$C_{21}H_{13}Cl_2FN_4O_2$ 418794-42-0



**selurampanelum**

selurampanel

*N*-[6-(1-methyl-1*H*-pyrazol-5-yl)-7-(propan-2-yl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]methanesulfonamide
*AMPA receptor antagonist*

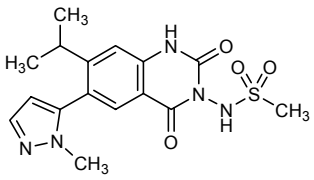
sélurampanel

*N*-[6-(1-méthyl-1*H*-pyrazol-5-yl)-7-(propan-2-yl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl]méthanesulfonamide
*antagoniste des récepteurs de l'AMPA*

selurampanel

*N*-[6-(1-metil-1*H*-pirazol-5-il)-7-(propan-2-il)-2,4-dioxo-1,4-dihidroquinazolin-3(2*H*)-il]metanosulfonamida
*antagonista de los receptores del AMPA*

$C_{16}H_{19}N_5O_4S$ 912574-69-7



**seridopidinum**

seridopidine

1-ethyl-4-[3-fluoro-5-(methanesulfonyl)phenyl]piperidine
*antipsychotic*

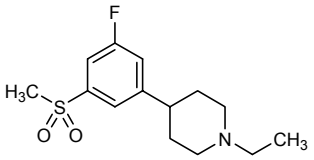
séridopidine

1-éthyl-4-[3-fluoro-5-(méthylsulfonyl)phényl]pipéridine
*antipsychotique*

seridopidina

1-etil-4-[3-fluoro-5-(metanosulfonil)fenil]piperidina
*antipsicótico*

$C_{14}H_{20}FNO_2S$ 883631-51-4



**setipiprantum**

setipiprant

[8-fluoro-2-(naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-5*H*-pyrido[4,3-*b*]indol-5-yl]acetic acid
*prostanoid $D_2$ receptor antagonist*

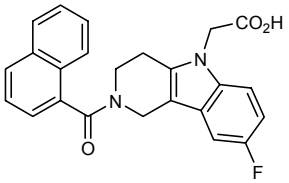
sétipiprant

acide 2-[8-fluoro-2-(naphtalén-1-ylcarbonyl)-1,2,3,4-tétrahydro-5*H*-pyrido[4,3-*b*]indol-5-yl]acétique
*antagoniste du récepteur $D_2$ prostanoïde*

setipiprant

ácido {8-fluoro-2-(naftalen-1-carbonil)-1,2,3,4-tetrahidro-5*H*-pirido[4,3-*b*]indol-5-il}acético
*antagonista del receptor de prostanoide $D_2$*

$C_{24}H_{19}FN_2O_3$ 866460-33-5



**simoctocogum alfa #**

simoctocog alfa

B-domain deleted human coagulation factor VIII; [749-glutamine,750-alanine-751-tyrosine-753-tyrosine-754-arginine-755-arginine-756-glycine]human coagulation factor VIIIa heavy chain-(1-756)-peptide (containing F5/8 type A 1 and A 2 domains) fusion protein with human coagulation factor VIIIa light chain, glycosylated
*blood coagulation factor*

simoctocog alfa

facteur VIII de coagulation humain dont le domaine B a été supprimé; [749-glutamine,750-alanine-751-tyrosine-753-tyrosine-754-arginine-755-arginine-756-glycine]chaîne lourde du facteur VIIIa de coagulation humain-(1-756)-peptide (contenant les domaines F5/8 type A 1 and A 2) protéine de fusion avec la chaîne légère du facteur VIIIa de coagulation humain glycosylé
*facteur de coagulation sanguine*

simoctocog alfa

factor VIII de coagulación humano cuyo dominio B se ha suprimido; [749-glutamina,750-alanina-751-tirosina-753-tirosina-754-arginina-755-arginina-756-glicina]cadena pesada del factor VIIIa de coagulación humano-(1-756)-péptido (contiene los dominios F5/8 tipo A 1 y A 2) proteína de fusión con la cadena ligera del factor VIIIa de coagulación humano glicosilado
*factor de coagulación sanguínea*

$C_{7459}H_{11338}N_{1992}O_{2188}S_{68}$ (peptide) 1219013-68-9

```
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 SFSQNSRHQA 750
YRYRRGEITR TTLQSDQEEI DYDDTISVEM KKEDFDIYDE DENQSPRSFQ 800
KKTRHYFIAA VERLWDYGMS SSPHVLRNRA QSGSVPQFKK VVFQEFTDGS 850
FTQPLYRGEL NEHLGLLGPY IRAEVEDNIM VTFRNQASRP YSFYSSLISY 900
EEDQRQGAEP RKNFVKPNET KTYFWKVQHH MAPTKDEFDC KAWAYFSDVD 950
LEKDVHSGLI GPLLVCHTNT LNPAHGRQVT VQEFALFFTI FDETKSWYFT 1000
ENMERNCRAP CNIQMEDPTF KENYRFHAIN GYIMDTLPGL VMAQDQRIRW 1050
YLLSMGSNEN IHSIHFSGHV FTVRKKEEYK MALYNLYPGV FETVEMLPSK 1100
AGIWRVECLI GEHLHAGMST LFLVYSNKCQ TPLGMASGHI RDFQITASGQ 1150
YGQWAPKLAR LHYSGSINAW STKEPFSWIK VDLLAPMIIH GIKTQGARQK 1200
FSSLYISQFI IMYSLDGKKW QTYRGNSTGT LMVFFGNVDS SGIKHNIFNP 1250
PIIARYIRLH PTHYSIRSTL RMELMGCDLN SCSMPLGMES KAISDAQITA 1300
SSYFTNMFAT WSPSKARLHL QGRSNAWRPQ VNNPKEWLQV DFQKTMKVTG 1350
VTTQGVKSLL TSMYVKEFLI SSSQDGHQWT LFFQNGKVKV FQGNQDSFTP 1400
VVNSLDPPLL TRYLRIHPQS WVHQIALRME VLGCEAQDLY          1440
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Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
153-179 248-329 528-554 630-711 940-966 1007-1011 1129-1277 1282-1434

Sulfated residues (Y) / Résidus sulfatés (Y) / Reioduos sulfatados (Y)
Tyr-346 Tyr-718 Tyr-719 Tyr-723 Tyr-772 Tyr-788

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-41 Asn-239 Asn-918 Asn-1226

**solithromycinum**

solithromycin

(3a*R*,4*R*,7*S*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-1-{4-[4-(3-aminophenyl)-1*H*-1,2,3-triazol-1-yl]butyl}-4-ethyl-7-fluoro-11-methoxy-3a,7,9,11,13,15-hexamethyl-10-{[trideoxy-(dimethylamino)-β-D-hexopyranosyl]oxy}octahydro-2*H*-oxacyclotetradecino[4,3-*b*][1,3]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetraone
*antibiotic*

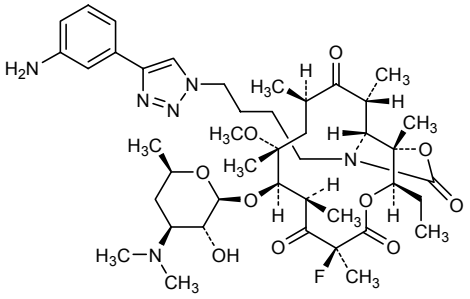
solithromycine

(3a*S*,4*R*,7*S*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-1-{4-[4-(3-aminophényl)-1*H*-1,2,3-triazol-1-yl]butyl}-4-éthyl-7-fluoro-11-méthoxy-3a,7,9,11,13,15-hexaméthyl-10-{[3,4,6-tridéoxy-3-(diméthylamino)-β-D-*xylo*-hexopyranosyl]oxy}octahydro-2*H*-oxacyclotétradécino[4,3-*d*]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tétrone
*antibiotique*

solitromicina

(3a*R*,4*R*,7*S*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-1-{4-[4-(3-aminofenil)-1*H*-1,2,3-triazol-1-il]butil}-4-etil-7-fluoro-3a,7,9,11,13,15-hexametil-11-metoxi-10-{[tridesoxi-(dimetilamino)-β-D-hexopiranosil]oxi}octahidro-2*H*-oxaciclotetradecino[4,3-*b*][1,3]oxazol-2,6,8,14(1*H*,7*H*,9*H*)-tetraona
*antibiótico*

$C_{43}H_{65}FN_6O_{10}$ 760981-83-7



**talimogenum laherparepvecum #**

talimogene laherparepvec

recombinant replicating *Herpes simplex* type -1 virus vector, with ICP47 and both copies of ICP34.5 genes deleted, expressing human granulocyte macrophage colony stimulating factor (hGM-CSF) in the ICP34.5 loci
*gene therapy product (antineoplastic)*

talimogène laherparépvec

vecteur viral *Herpes simplex* type 1 répliquant avec délétion du gène ICP47 et des deux copies du gène ICP34.5, exprimant le facteur humain de développement des polynucléaires et des macrophages (hGM-CSF) dans les loci ICP34.5
*produit de thérapie génique (antinéoplasique)*

talimogén laherparepvec

vector virus del *Herpes simplex* tipo-1 replicante recombinante con delección del gen ICP47 y las dos copias del gen ICP34.5, que expresa el factor humano estimulante de colonias de granulocitos y macrógafos (hGM-CSF) in los loci ICP34.5
*producto para terapia génica (antineoplásico)*

1187560-31-1

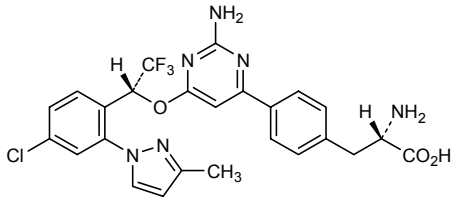
**telotristatum**

telotristat — 4-(2-amino-6-{(1*R* -1-[4-chloro-2-(3-methyl-1*H*-pyrazol-1-yl) phenyl])-2,2,2-trifluoroethoxy}pyrimidin-4-yl)-L-phenylalanine
*tryptophan hydroxylase inhibitor*

télotristat — 4-(2-amino-6-{(1*R*)-1-[4-chloro-2-(3-méthyl-1*H*-pyrazol-1-yl)phényl]-2,2,2-trifluoroéthoxy}pyrimidin-4-yl)-L-phénylalanine
*inhibiteur de l'hydroxylase du tryptophane*

telotristat — 4-(2-amino-6-{(1*R* -1-[4-cloro-2-(3-metil-1*H*-pirazol-1-il)fenil])-2,2,2-trifluoroetoxi}pirimidin-4-il)-L-fenilalanina
*inhibidor de la hidroxilasa de triptófano*

$C_{25}H_{22}ClF_3N_6O_3$ 1033805-28-5



**tregalizumabum #**

tregalizumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* CD4 (T cell surface antigen T4/Leu-3, p55)], humanized monoclonal antibody;
gamma1 heavy chain (1-454) [humanized VH (*Homo sapiens* IGHV3-15*06 (77.80%) -(IGHD)-IGHJ5*01) [8.10.15] (1-124) -*Homo sapiens* IGHG1*01 (125-454)], (227-218')-disulfide with kappa light chain (1'-218') [humanized V-KAPPA (*Homo sapiens* IGKV4-1*01 (80.20%) -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; (233-233":236-236")-bisdisulfide dimer
*immunomodulator*

trégalizumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* CD4 (antigène de surface T4/Leu-3 de cellule T, p55)], anticorps monoclonal humanisé;
chaîne lourde gamma1(1-454) [VH humanisé (*Homo sapiens* IGHV3-15*06 (77.80%) -(IGHD)-IGHJ5*01) [8.10.15] (1-124) -*Homo sapiens* IGHG1*01 (125-454)], (227-218')-disulfure avec la chaîne légère kappa (1'-218') [V-KAPPA humanisé (*Homo sapiens* IGKV4-1*01 (80.20%) -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; dimère (233-233":236-236")-bisdisulfure
*immunomodulateur*

tregalizumab — inmunoglobulina G1-kappa, anti-[CD4 de *Homo sapiens* (antígeno de superficie T4/Leu-3 de célula T, p55)], anticuerpo monoclonal humanizado;
cadena pesada gamma1(1-454) [VH humanizada (*Homo sapiens* IGHV3-15*06 (77.80%) -(IGHD)-IGHJ5*01) [8.10.15] (1-124) -*Homo sapiens* IGHG1*01 (125-454)], (227-218')-disulfuro con la cadena ligera kappa (1'-218') [V-KAPPA humanizada (*Homo sapiens* IGKV4-1*01 (80.20%) -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; dimero (233-233":236-236")-bisdisulfuro
*inmunomodulador*

1207446-68-1

Heavy chain / Chaîne lourde / Cadena pesada

```
EEQLVESGGG LVKPGGSLRL SCAASGFSFS DCRMYWLRQA PGKGLEWIGV  50
ISVKSENYGA NYAESVRGRF TISRDDSKNT VYLQMNSLKT EDTAVYYCSA 100
SYYRYDVGAW FAYWGQGTLV TVSSASTKGP SVFPLAPSSK STSGGTAALG 150
CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL 200
GTQTYICNVN HKPSNTKVDK KVEPKSCDKT HTCPPCPAPE LLGGPSVFLF 250
PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE 300
EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP 350
REPQVYTLPP SRDELTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT 400
TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL 450
SPGK                                                    454
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPDS LAVSLGERAT INCRASKSVS TSGYSYIYWY QQKPGQPPKL  50
LIYLASILES GVPDRFSGSG SGTDFTLTIS SLQAEDVAVY YCQHSRELPW 100
TFGQGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV 150
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV 200
THQGLSSPVT KSFNRGEC                                    218
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-98 151-207 268-328 374-432
22"-98" 151"-207" 268"-328" 374"-432"
Intra-L 23'-92' 138'-198'
23'"-92'" 138'"-198'"
Inter-H-L 227-218' 227"-218'"
Inter-H-H 233-233" 236-236"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
304, 304"

**turoctocogum alfa #**

turoctocog alfa — human coagulation factor VIII-(1-750)-(1638-2332)-peptide, glycosylated
*blood coagulation factor*

turoctocog alfa — facteur VIII de coagulation humain-(1-750)-(1638-2332)-peptide glycosylé
*facteur de coagulation sanguine*

turoctocog alfa — factor VIII de coagulación humano-(1-750)-(1638-2332)-péptido glicosilado
*factor de coagulación sanguínea*

$C_{7480}H_{11379}N_{1999}O_{2194}S_{68}$ (peptide) 1192451-26-5

```
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 SFSQNSRHPS 750
QNPPVLKRHQ REITRTTLQS DQEEIDYDDT ISVEMKKEDF DIYDEDENQS 800
PRSFQKKTRH YFIAAVERLW DYGMSSSPHV LRNRAQSGSV PQFKKVVFQE 850
FTDGSFTQPL YRGELNEHLG LLGPYIRAEV EDNIMVTFRN QASRPYSFYS 900
SLISYEEDQR QGAEPRKNFV KPNETKTYFW KVQHHMAPTK DEFDCKAWAY 950
FSDVDLEKDV HSGLIGPLLV CHTNTLNPAH GRQVTVQEFA LFFTIFDETK 1000
SWYFTENMER NCRAPCNIQM EDPTFKENYR FHAINGYIMD TLPGLVMAQD 1050
QRIRWYLLSM GSNENIHSIH FSGHVFTVRK KEEYKMALYN LYPGVFETVE 1100
MLPSKAGIWR VECLIGEHLH AGMSTLFLVY SNKCQTPLGM ASGHIRDFQI 1150
TASGQYGQWA PKLARLHYSG SINAWSTKEP FSWIKVDLLA PMIIHGIKTQ 1200
GARQKFSSLY ISQFIIMYSL DGKKWQTYRG NSTGTLMVFF GNVDSSGIKH 1250
NIFNPPIIAR YIRLHPTHYS IRSTLRMELM GCDLNSCSMP LGMESKAISD 1300
AQITASSYFT NMFATWSPSK ARLHLQGRSN AWRPQVNNPK EWLQVDFQKT 1350
MKVTGVTTQG VKSLLTSMYV KEFLISSSQD GHQWTLFFQN GKVKVFQGNQ 1400
DSFTPVVNSL DPPLLTRYLR IHPQSWVHQI ALRMEVLGCE AQDLY      1445
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
153-179 248-329 528-554 630-711 945-971 1012-1016 1134-1282 1287-1439

Sulfated residues (Y) / Résidus sulfatés (Y) / Residuos sulfatados(Y)
Tyr-346 Tyr-718 Tyr-719 Tyr-723 Tyr-777 Tyr-793

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-41 Asn-239 Asn-923 Asn-1231

**ublituximabum #**

ublituximab — immunoglobulin G1-kappa, anti-[*Homo sapiens* MS4A1 (membrane-spanning 4-domains subfamily A member 1, B lymphocyte surface antigen B1, leukocyte surface antigen Leu-16, Bp35, CD20], chimeric monoclonal antibody;
gamma1 heavy chain (1-448) [*Mus musculus* VH (IGHV1-12*01 -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*01 (119-448)], (221-213')-disulfide with kappa light chain (1'-213') [*Mus musculus* V-KAPPA (IGKV4-72*01 -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; (227-227":230-230")-bisdisulfide dimer
*antineoplastic*

ublituximab — immunoglobuline G1-kappa, anti-[*Homo sapiens* MS4A1 (membre 1 de la sous-famille A avec 4 transmembrane regions, antigène de surface B1 des lymphocytes B, antigène de surface Leu-16 des leucocytes, Bp35, CD20], anticorps monoclonal chimérique;
chaîne lourde gamma1 (1-448) [*Mus musculus* VH (IGHV1-12*01 -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*01 (119-448)], (221-213')-disulfure avec la chaîne légère kappa (1'-213') [*Mus musculus* V-KAPPA (IGKV4-72*01 -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dimère (227-227":230-230")-bisdisulfure
*antinéoplasique*

ublituximab — inmunoglobulina G1-kappa, anti-[MS4A1 de *Homo sapiens* (miembro 1 de la subfamilia A con 4 regiones , transmembrana , antígeno de superficie B1 de linfocitos B, antígeno de superficie Leu-16 de leucocitos, Bp35, CD20], anticuerpo monoclonal quimérico;
cadena pesada gamma1 (1-448) [*Mus musculus* VH(IGHV1-12*01 -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*01 (119-448)], (221-213')-disulfuro con la cadena ligera kappa (1'-213') [*Mus musculus* V-KAPPA (IGKV4-72*01 -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dímero (227-227":230-230")-bisdisulfuro
*antineoplásico*

1174014-05-1

Heavy chain / Chaîne lourde / Cadena pesada

```
QAYLQQSGAE LVRPGASVKM SCKASGYTFT SYNMHWVKQT PRQGLEWIGG  50
IYPGNGDTSY NQKFKGKATL TVGKSSSTAY MQLSSLTSED SAVYFCARYD 100
YNYAMDYWGQ GTSVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI 200
CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD 250
TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST 300
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY 350
TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK   448
```

Light chain / Chaîne légère / Cadena ligera

```
QIVLSQSPAI LSASPGEKVT MTCRASSSVS YMHWYQQKPG SSPKPWIYAT  50
SNLASGVPAR FSGSGSGTSY SFTISRVEAE DAATYYCQQW TFNPPTFGGG 100
TRLEIKRTVA 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

| | | | | |
|---|---|---|---|---|
| Intra-H | 22-96 | 145-201 | 262-322 | 368-426 |
| | 22"-96" | 145"-201" | 262"-322" | 368"-426" |
| Intra-L | 23'-87' | 133'-193' | | |
| | 23'"-87"' | 133'"-193"' | | |
| Inter-H-L | 221-213' | 221"-213'" | | |
| Inter-H-H | 227-227" | 230-230" | | |

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
298, 298"

**urelumabum #**

urelumab

immunoglobulin G4-kappa, anti-[*Homo sapiens* TNFRSF9 (tumor necrosis factor receptor superfamily member 9, 4-1BB, T cell antigen ILA, CD137)], *Homo sapiens* monoclonal antibody;
gamma4 heavy chain (1-448) [*Homo sapiens* VH (IGHV4-34*01 (92.80%) -(IGHD)-IGHJ2*01) [8.7.15] (1-121) -IGHG4*01 hinge S10>P (229) (122-448)], (135-216')-disulfide with kappa light chain (1'-216') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ4*01 G119>C) [6.3.11] (1'-109') -IGKC1*01 (110'-216')]; (227-227'':230-230'')-bisdisulfide dimer
*immunomodulator*

urélumab

immunoglobuline G4-kappa, anti-[*Homo sapiens* TNFRSF9 (membre 9 de la superfamille des récepteurs du facteur de nécrose tumorale, 4-1BB, antigène ILA de lymphocyte T, CD137)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma4 (1-448) [*Homo sapiens* VH (IGHV4-34*01 (92.80%) -(IGHD)-IGHJ2*01) [8.7.15] (1-121) -IGHG4*01 charnière S10>P (229) (122-448)], (135-216')-disulfure avec la chaîne légère kappa (1'-216') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ4*01 G119>C) [6.3.11] (1'-109') -IGKC1*01 (110'-216')]; dimère (227-227'':230-230'')-bisdisulfure
*immunomodulateur*

urelumab

inmunoglobulina G4-kappa, anti-[TNFRSF9 de *Homo sapiens* (miembro 9 de la superfamilia de receptores del factor de necrosis tumoral, 4-1BB, antígeno ILA de linfocito T, CD137)], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma4 (1-448) [*Homo sapiens* VH (IGHV4-34*01 (92.80%) -(IGHD)-IGHJ2*01) [8.7.15] (1-121) -IGHG4*01 bisagra S10>P (229) (122-448)], (135-216')-disulfuro con la cadena ligera kappa (1'-216') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ4*01 G119>C) [6.3.11] (1'-109') -IGKC1*01 (110'-216')]; dímero (227-227'':230-230'')-bisdisulfuro
*inmunomodulador*

934823-49-1

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQQWGAG LLKPSETLSL TCAVYGGSFS GYYWSWIRQS PEKGLEWIGE  50
INHGGYVTYN PSLESRVTIS VDTSKNQFSL KLSSVTAADT AVYYCARDYG 100
PGNYDWYFDL WGRGTLVTVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV 150
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTK 200
TYTCNVDHKP SNTKVDKRVE SKYGPPCPPC PAPEFLGGPS VFLFPPKPKD 250
TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST 300
YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY 350
TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD 400
SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK   448
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD  50
ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPALTF 100
CGGTKVEIKR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW 150
KVDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH 200
QGLSSPVTKS FNRGEC                                       216
```

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

| | | | | |
|---|---|---|---|---|
| Intra-H | 22-95 | 148-204 | 262-322 | 368-426 |
| | 22''-95'' | 148''-204'' | 262''-322'' | 368''-426'' |
| Intra-L | 23'-88' | 136'-196' | | |
| | 23'''-88''' | 136'''-196''' | | |
| Inter-H-L | 135-216' | 135''-216''' | | |
| Inter-H-H | 227-227'' | 230-230'' | | |

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
298, 298''

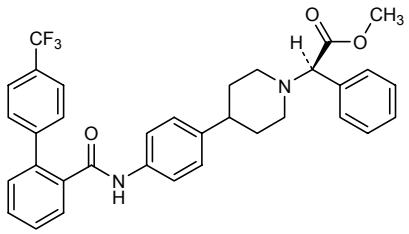
**usistapidum**

usistapide — methyl (2*S*)-2-phenyl-2-[4-(4-{4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamido}phenyl)piperidin-1-yl]acetate
*antihyperlipidaemic*

usistapide — (+)-(2*S*)-2-phényl-2-{4-[4-({[4'-(trifluorométhyl)-[1,1'-biphényl]-2-yl]carbonyl}amino)phényl]pipéridin-1-yl}acétate de méthyle
*antihyperlipidémiant*

usistapida — (2*S*)-2-fenil-2-[4-(4-{4'-(trifluorometil)-[1,1'-bifenil]-2-carboxamido}fenil)piperidin-1-il]acetato de metilo
*antihiperlipémico*

$C_{34}H_{31}F_3N_2O_3$ 403989-79-7



**vesencumabum #**

vesencumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* NRP1 (neuropilin 1, NRP, vascular endothelial cell growth factor 165 receptor, VEGF165 receptor, VEGF165R, CD304) extracellular domain], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-453) [*Homo sapiens* VH (IGHV3-23*04 (90.80%) -(IGHD)-IGHJ6*01) [8.8.16] (1-123) -IGHG1*01 CH3 D12>E (362), L14>M (364) (124-453)], (226-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-39*01 (89.50%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; (232-232'':235-235'')-bisdisulfide dimer
*antineoplastic*

vésencumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* NRP1 (neuropiline 1, NRP, récepteur de l'isoforme 165 du facteur de croissance des cellules endothéliales vasculaires, récepteur du VEGF165, VEGF165R, CD304) domaine extracellulaire], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-453) [*Homo sapiens* VH (IGHV3-23*04 (90.80%) -(IGHD)-IGHJ6*01) [8.8.16] (1-123) -IGHG1*01 CH3 D12>E (362), L14>M (364) (124-453)], (226-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-39*01 (89.50%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (232-232'':235-235'')-bisdisulfure
*antinéoplasique*

vesencumab

inmunoglobulina G1-kappa, anti-[NRP1 de *Homo sapiens* (neuropilina 1, NRP, receptor de la isoforma 165 del factor de crecimiento de células endoteliales vasculares, receptor de VEGF165, VEGF165R, CD304) dominio extracelular], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma1 (1-453) [VH de *Homo sapiens* (IGHV3-23*04 (90.80%) -(IGHD)-IGHJ6*01) [8.8.16] (1-123) -IGHG1*01 CH3 D12>E (362), L14>M (364) (124-453)], (226-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-39*01 (89.50%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (232-232":235-235")-bisdisulfuro
*antineoplásico*

1205533-60-3

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSQ  50
ISPAGGYTNY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARGE 100
LPYYRMSKVM DVWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC 150
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG 200
TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP 250
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE 300
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR 350
EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT 400
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS 450
PGK                                                     453
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASQYFS SYLAWYQQKP GKAPKLLIYG  50
ASSRASGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YLGSPPTFGQ 100
GTKVEIKRTV 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

```
Intra-H  22-96    150-206    267-327    373-431
         22"-96"  150"-206"  267"-327"  373"-431"
Intra-L  23'-88'   134'-194'
         23'"-88'" 134'"-194'"
Inter-H-L  226-214'  226"-214'"
Inter-H-H  232-232"  235-235"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
303, 303"

**vidupiprantum**

vidupiprant

{4-[4-(*tert*-butylcarbamoyl)-2-(2-chloro-4-cyclopropylbenzenesulfonamido)phenoxy]-5-chloro-2-fluorophenyl}acetic acid
*antiasthmatic*

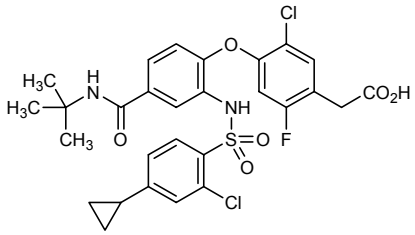
vidupiprant

acide {4-[4-(*tert*-butylcarbamoyl)-2-(2-chloro-4-cyclopropylbenzènesulfonamido)phénoxy]-5-chloro-2-fluorophényl}acétique
*antiasthmatique*

vidupiprant

ácido {4-[4-(*terc*-butilcarbamoil)-2-(2-cloro-4-ciclopropilbencenosulfonamido)fenoxi]-5-cloro-2-fluorofenil}acético
*antiasmático*

$C_{28}H_{27}Cl_2FN_2O_6S$ 1169483-24-2



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

**Proposed International Non Proprietary Names (Prop. INN): List 14**
***(WHO Chronicle, Vol. 18, No. 11, 1964)***
**Denominations communes internationales proposées (DCI Prop.): Liste 14**
***(Chronique OMS, Vol. 18, No. 11, 1964)***

| | | |
|---|---|---|
| | **dalanatum insulinum** | |
| p. 435 | dalanated insulin | *replace the description by the following* |
| | | an insuline derivative prepared by the removal of the *C*-terminal alanine from the B chain of insulin |
| p. 461 | insuline dalanatée | *remplacer la description par la suivante* |
| | | dérivé de l'insuline préparé par déplacement de l'alanine terminale *C* de la chaîne B de l'insuline |

**Proposed International Non Proprietary Names (Prop. INN): List 64**
**Denominations communes internationales proposées (DCI Prop.): Liste 64**
**Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 64**
***(WHO Drug Information, Vol. 4, No. 4, 1990)***

| | | |
|---|---|---|
| p. 22 | *delete/supprimer/suprimáse* | *insert/insérer/insertese* |
| | **suplatastum tosilas** | **suplatasti tosilas** |

**Proposed International Non Proprietary Names (Prop. INN): List 100**
**Denominations communes internationales proposées (DCI Prop.): Liste 100**
**Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 100**
***(WHO Drug Information, Vol. 22, No. 4, 2008)***

| | | |
|---|---|---|
| p. 348 | *delete/supprimer/suprimáse* | *insert/insérer/insertese* |
| | **voreloxinum** | **vosaroxinum** |
| | voreloxin | vosaroxin |
| | voréloxine | vosaroxine |
| | voreloxina | vosaroxina |

**Proposed International Non Proprietary Names (Prop. INN): List 101**
**Denominations communes internationales proposées (DCI Prop.): Liste 101**
**Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 101**
***(WHO Drug Information, Vol. 23, No. 2, 2009)***

p. 146 **fonturacetamum**

| | |
|---|---|
| fonturacetam | *replace the chemical name by the following* |
| fonturacétam | *remplacer le nom chimique par le suivant* |
| fonturacetam | *sustitúyase el nombre químico por el siguiente* |
| | *rac*-2-(2-oxo-4-phenylpyrolidin-1-yl)acetamide |
| | *rac*-2-(2-oxo-4-phénylpyrolidin-1-yl)acétamide |
| | *rac*-2-(4-fenil-2-oxopirolidin-1-il)acetamida |

p. 165 **sifalimumabum**

| | |
|---|---|
| sifalimumab | *replace the description by the following* |
| sifalimumab | *remplacer la description par la suivante* |
| sifalimumab | *sustitúyase la descripción por la siguiente* |
| | immunoglobulin G1-kappa, anti-[*Homo sapiens* interferon alpha (IFN-alpha)], *Homo sapiens* monoclonal antibody;<br>gamma1 heavy chain (1-446) [*Homo sapiens* VH (IGHV1-18*01 (95.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) –IGHG1*03 CH1 R120>K (213) (117-446)], (219-213')-disulfide with kappa light chain (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (99.00%) –IGKJ1*01) [7.3.9] (1'-108') -IGKC*01 (109'-215')]; (225-225'':228-228'')-bisdisulfide dimer |
| | immunoglobuline G1-kappa, anti-[*Homo sapiens* interféron alpha (IFN-alpha)], *Homo sapiens* anticorps monoclonal;<br>chaîne lourde gamma1 (1-446) [*Homo sapiens* VH (IGHV1-18*01 (95.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) –IGHG1*03 CH1 R120>K (213) (117-446)], (219-215')-disulfure avec la chaîne légère kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (99.00%) –IGKJ1*01) [7.3.9] (1'-108') -IGKC*01 (109'-215')]; dimère (225-225'':228-228'')-bisdisulfure |
| | inmunoglobulina G1-kappa, anti-[interferón alfa (IFN-alfa) de *Homo sapiens*], anticuerpo monoclonal de *Homo sapiens*;<br>cadena pesada gamma1 (1-446) [*Homo sapiens* VH (IGHV1-18*01 (95.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) –IGHG1*03 CH1 R120>K (213) (117-446)], (219-215')-disulfuro con la cadena ligera kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (99.00%) –IGKJ1*01) [7.3.9] (1'-108') -IGKC*01 (109'-215')]; dímero (225-225'':228-228'')-bisdisulfuro |

p. 169

| *delete/supprimer/suprimáse* | *insert/insérer/insertese* |
|---|---|
| **tanexabanum** | **darexabanum** |
| tanexaban | darexaban |
| tanexaban | darexaban |
| tanexabán | darexabán |

| p. 172 | *delete/supprimer/suprimáse* | *insert/insérer/insertese* |
|---|---|---|
| | **torezolidum** | **tedizolidum** |
| | torezolid | tedizolid |
| | torézolid | tédizolid |
| | torezolid | tedizolid |

**Proposed International Non Proprietary Names (Prop. INN): List 102**
**Denominations communes internationales proposées (DCI Prop.): Liste 102**
**Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 102**
***(WHO Drug Information, Vol. 23, No. 4, 2009)***

p. 321 **afatinibum**

| | |
|---|---|
| afatinib | *replace the chemical name by the following* |
| afatinib | *remplacer le nom chimique par le suivant* |
| afatinib | *sustitúyase el nombre químico por el siguiente* |
| | (2*E*)-*N*-[4-(3-chloro-4-fluoroanilino)-7-{[(3*S*)-oxolan-3-yl]oxy}quinazolin-6-yl]-4-(dimethylamino)but-2-enamide |
| | (2*E*)-*N*-[4-(3-chloro-4-fluoroanilino]-7-{[(3*S*)-oxolan-3-yl]oxy}quinazolin-6-y]-4-(diméthylamino)but-2-énamide |
| | (2*E*)-*N*-[4-(3-cloro-4-fluoroanilino)-7-{[(3*S*)-oxolan-3-il]oxi}quinazolin-6-il]-4-(dimetilamino)but-2-enamida |

p. 343 **sotaterceptum**

| | |
|---|---|
| sotatercept | *replace the description by the following* |
| sotatercept | *remplacer la description par la suivante* |
| sotatercept | *sustitúyase la descripción por la siguiente* |
| | fusion protein for immune applications (FPIA) comprising *Homo sapiens* ACVR2A (activin receptor type 2A, activin receptor type IIA) fragment fused with *Homo sapiens* immunoglobulin G1 Fc fragment;<br>*Homo sapiens* ACVR2A, 21-135 precursor fragment (1-115) -threonyl-triglycyl linker (116-119) -gamma1 chain H-CH2-CH3 fragment (120-344) [*Homo sapiens* IGHG1*03 hinge (120-127), CH2, A115>V (227) (128-237), CH3 (238-344)]; (123-123':126-126')-bisdisulfide dimer |
| | protéine de fusion pour applications immunitaires (FPIA) comprenant un fragment d'*Homo sapiens* ACVR2A (récepteur type 2A de l'activine, récepteur type IIA de l'activine) fusionné au fragment Fc de l'*Homo sapiens* immunoglobuline G1;<br>fragment précurseur 21-135 de *Homo sapiens* ACVR2A (1-115) -linker thréonyl-triglycyl (116-119) -fragment H-CH2-CH3 de chaîne gamma1 (120-344) [*Homo sapiens* IGHG1*03 charnière (120-127), CH2, A115>V (227) (128-237), CH3 (238-344)]; dimère (123-123':126-126')-bisdisulfure |

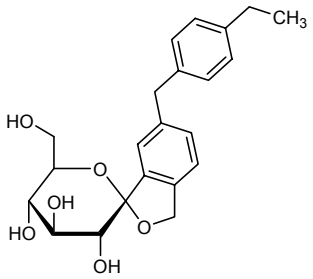
proteína de fusión para aplicaciones inmunitarias (FPIA) que comprende un fragmento de ACVR2A (receptor tipo 2A de la activina, receptor tipo IIA de la activina) de *Homo sapiens* fusionado al fragmento Fc de la inmunoglobulina G1 de *Homo sapiens*;
fragmento precursor 21-135 de ACVR2A de *Homo sapiens* (1-115)-conector treonil-triglicil (116-119) -fragmento H-CH2-CH3 de cadena gamma1 (120-344) [*Homo sapiens* IGHG1*03 bisagra(120-127), CH2, A115>V (128-237), CH3 (238-344)]; dímero (123-123':126-126')-bisdisulfuro

**Proposed International Non Proprietary Names (Prop. INN): List 103**
**Denominations communes internationales proposées (DCI Prop.): Liste 103**
**Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 103**
***(WHO Drug Information Vol. 24, No. 2, 2010)***

| | | |
|---|---|---|
| p. 154 | *supprimer* | *insérer* |
| | nonacog bêta pegol | nonacog bêta pégol |
| p. 167 | *supprimer* | *insérer* |
| | somatropine pegol | somatropine pégol |

p. 172 **tofogliflozinum**

| | |
|---|---|
| tofogliflozin | *replace the structure by the following* |
| tofogliflozine | *remplacer la structure par la suivante* |
| tofogliflozina | *sustitúyase la estructura por la siguiente* |




| | | |
|---|---|---|
| p. 180 | *delete/supprimer/suprimáse* | *insert/insérer/insertese* |
| | **trifenas** | **trifenatas** |
| | trifenate | trifenatate |
| | trifénate | trifénatate |
| | trifenato | trifenatato |

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

ANNEX 1

# PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES[1]

The following procedure shall be followed by the World Health Organization (hereinafter also referred to as "WHO") in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with resolution WHA3.11 of the World Health Assembly, and in the substitution of such names.

*Article 1* - Proposals for recommended international nonproprietary names and proposals for substitution of such names shall be submitted to WHO on the form provided therefore. The consideration of such proposals shall be subject to the payment of an administrative fee designed only to cover the corresponding costs of the Secretariat of WHO ("the Secretariat"). The amount of this fee shall be determined by the Secretariat and may, from time to time, be adjusted.

*Article 2* - Such proposals shall be submitted by the Secretariat to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, such designated members hereinafter referred to as "the INN Expert Group", for consideration in accordance with the "General principles for guidance in devising International Nonproprietary Names for Pharmaceutical Substances", annexed to this procedure[2]. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

*Article 3* - Subsequent to the examination provided for in article 2, the Secretariat shall give notice that a proposed international nonproprietary name is being considered.

a) Such notice shall be given by publication in *WHO Drug Information*[3] and by letter to Member States and to national and regional pharmacopoeia commissions or other bodies designated by Member States.

i) Notice shall also be sent to the person who submitted the proposal ("the original applicant") and other persons known to be concerned with a name under consideration.

b) Such notice shall:

i) set forth the name under consideration;

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

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

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

v) state the authority under which WHO is acting and refer to these rules of procedure.

c) In forwarding the notice, the Secretariat shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by WHO.

*Article 4* - Comments on the proposed name may be forwarded by any person to WHO within four months of the date of publication, under article 3, of the name in *WHO Drug Information*.

[1] See Annex 1 in WHO Technical Report Series, No. 581, 1975. The original text was adopted by the Executive Board in resolution EB15.R7 and amended in resolutions EB43.R9 and EB115.R4.

[2] See Annex 2.

[3] Before 1987, lists of international nonproprietary names were published in the *Chronicle of the World Health Organization*.

*Article 5* - A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in *WHO Drug Information.*

Such objection shall:

i) identify the person objecting;

ii) state his or her interest in the name;

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

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

*Article 7* - Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Secretariat shall give notice in accordance with subsection (a) of article 3 that the name has been selected by WHO as a recommended international nonproprietary name.

*Article 8* - In forwarding a recommended international nonproprietary name to Member States under article 7, the Secretariat shall:

a) request that it be recognized as the nonproprietary name for the substance; and

b) request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name and to prohibit registration of the name as a trademark or trade name.

*Article 9*
a) In the extraordinary circumstance that a previously recommended international nonproprietary name gives rise to errors in medication, prescription or distribution, or a demonstrable risk thereof, because of similarity with another name in pharmaceutical and/or prescription practices, and it appears that such errors or potential errors cannot readily be resolved through other interventions than a possible substitution of a previously recommended international nonproprietary name, or in the event that a previously recommended international nonproprietary name differs substantially from the nonproprietary name approved in a significant number of Member States, or in other such extraordinary circumstances that justify a substitution of a recommended international nonproprietary name, proposals to that effect may be filed by any interested person. Such proposals shall be submitted on the form provided therefore and shall:

i) identify the person making the proposal;

ii) state his or her interest in the proposed substitution; and

iii) set forth the reasons for the proposal; and

iv) describe, and provide documentary evidence regarding the other interventions undertaken in an effort to resolve the situation, and the reasons why these other interventions were inadequate.

Such proposals may include a proposal for a new substitute international nonproprietary name, devised in accordance with the General principles, which takes into account the pharmaceutical substance for which the new substitute international nonproprietary name is being proposed.

The Secretariat shall forward a copy of the proposal, for consideration in accordance with the procedure described in subsection (b) below, to the INN Expert Group and the original applicant or its successor (if different from the person bringing the proposal for substitution and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations).

In addition, the Secretariat shall request comments on the proposal from:

i) Member States and national and regional pharmacopoeia commissions or other bodies designated by Member States (by including a notice to that effect in the letter referred to in article 3(a), and

ii) any other persons known to be concerned by the proposed substitution.

The request for comments shall:

i) state the recommended international nonproprietary name that is being proposed for substitution (and the proposed substitute name, if provided);

ii) identify the person who submitted the proposal for substitution (if so requested by such person);

iii) identify the substance to which the proposed substitution relates and reasons put forward for substitution;

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

v) state the authority under which WHO is acting and refer to these rules of procedure.

Comments on the proposed substitution may be forwarded by any person to WHO within four months of the date of the request for comments.

b) After the time period for comments referred to above has elapsed, the Secretariat shall forward any comments received to the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution. If, after consideration of the proposal for substitution and the comments received, the INN Expert Group, the person bringing the proposal for substitution and the original applicant or its successor all agree that there is a need to substitute the previously recommended international nonproprietary name, the Secretariat shall submit the proposal for substitution to the INN Expert Group for further processing.
Notwithstanding the foregoing, the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed for substitution.

In the event that a proposal for substitution shall be submitted to the INN Expert Group for further processing, the INN Expert Group will select a new international nonproprietary name in accordance with the General principles referred to in article 2 and the procedure set forth in articles 3 to 8 inclusive. The notices to be given by the Secretariat under article 3 and article 7, respectively, including to the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), shall in such event indicate that the new name is a substitute for a previously recommended international nonproprietary name and that Member States may wish to make transitional arrangements in order to accommodate existing products that use the previously recommended international nonproprietary name on their label in accordance with national legislation.

If, after consideration of the proposal for substitution and the comments received in accordance with the procedure described above, the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution do not agree that there are compelling reasons for substitution of a previously recommended international nonproprietary name, this name shall be retained (provided always that the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event that the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed to be substituted). In such an event, the Secretariat shall advise the person having proposed the substitution, as well as the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), Member States, national and regional pharmacopoeia commissions, other bodies designated by Member States, and any other persons known to be concerned by the proposed substitution that, despite a proposal for substitution, it has been decided to retain the previously recommended international nonproprietary name (with a description of the reason(s) why the proposal for substitution was not considered sufficiently compelling).

ANNEX 2

# GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES[1]

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

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

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

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

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

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.
For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

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

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

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

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

| ***Latin*** | ***English*** | |
|---|---|---|
| *-acum* | *-ac* | anti-inflammatory agents, ibufenac derivatives |
| *-adolum* | *-adol }* | analgesics |
| *-adol-* | *-adol-}* | |
| *-astum* | *-ast* | antiasthmatic, antiallergic substances not acting primarily as antihistaminics |
| *-astinum* | *-astine* | antihistaminics |
| *-azepamum* | *-azepam* | diazepam derivatives |
| *bol* | *bol* | steroids, anabolic |
| *-cain-* | *-cain-* | class I antiarrhythmics, procainamide and lidocaine derivatives |
| *-cainum* | *-caine* | local anaesthetics |

[1] In its Twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, INN in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves the use of a characteristic “stem” indicative of a common property of the members of a group. The reason for, and the implications of, the change are fully discussed.
The guiding principles were updated during the 13th consultation on nonproprietary names for pharmaceutical substances (Geneva, 27-29 April 1983) (PHARM S/NOM 928 13 May 1983, revised 18 August 1983).

[2] A more extensive listing of stems is contained in the working document WHO/EMP/QSM/2009.3 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.

| | | |
|---|---|---|
| *cef-* | *cef-* | antibiotics, cefalosporanic acid derivatives |
| *-cillinum* | *-cillin* | antibiotics, 6-aminopenicillanic acid derivatives |
| *-conazolum* | *-conazole* | systemic antifungal agents, miconazole derivatives |
| *cort* | *cort* | corticosteroids, except prednisolone derivatives |
| *-coxibum* | *-coxib* | selective cyclo-oxygenase inhibitors |
| *-entanum* | *-entan* | endothelin receptor antagonists |
| *gab* | *gab* | gabamimetic agents |
| *gado-* | *gado-* | diagnostic agents, gadolinium derivatives |
| *-gatranum* | *-gatran* | thrombin inhibitors, antithrombotic agents |
| *gest* | *gest* | steroids, progestogens |
| *gli* | *gli* | antihyperglycaemics |
| *io-* | *io-* | iodine-containing contrast media |
| *-metacinum* | *-metacin* | anti-inflammatory, indometacin derivatives |
| *-mycinum* | *-mycin* | antibiotics, produced by *Streptomyces* strains |
| *-nidazolum* | *-nidazole* | antiprotozoal substances, metronidazole derivatives |
| *-ololum* | *-olol* | β-adrenoreceptor antagonists |
| *-oxacinum* | *-oxacin* | antibacterial agents, nalidixic acid derivatives |
| *-platinum* | *-platin* | antineoplastic agents, platinum derivatives |
| *-poetinum* | *-poetin* | erythropoietin type blood factors |
| *-pril(at)um* | *-pril(at)* | angiotensin-converting enzyme inhibitors |
| *-profenum* | *-profen* | anti-inflammatory substances, ibuprofen derivatives |
| *prost* | *prost* | prostaglandins |
| *-relinum* | *-relin* | pituitary hormone release-stimulating peptides |
| *-sartanum* | *-sartan* | angiotensin II receptor antagonists, antihypertensive (non-peptidic) |
| *-vaptanum* | *-vaptan* | vasopressin receptor antagonists |
| *vin-* | *vin- }* | vinca-type alkaloids |
| *-vin-* | *-vin-}* | |

ANNEXE 1

## PROCEDURE A SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDEES POUR LES SUBSTANCES PHARMACEUTIQUES[1]

L'Organisation mondiale de la Santé (également désignée ci-après sous l'appellation « OMS ») observe la procédure exposée ci-dessous pour l'attribution de dénominations communes internationales recommandées pour les substances pharmaceutiques, conformément à la résolution WHA3.11 de l'Assemblée mondiale de la Santé, et pour le remplacement de telles dénominations.

*Article 1* - Les propositions de dénominations communes internationales recommandées et les propositions de remplacement de telles dénominations sont soumises à l'OMS sur la formule prévue à cet effet. L'examen de telles propositions est soumis au paiement d'une taxe administrative destinée uniquement à couvrir les coûts correspondants assumés par le Secrétariat de l'OMS (« le Secrétariat »). Le montant de cette taxe est déterminé par le Secrétariat et peut être modifié de temps à autre.

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

[1] Voir annexe 1 dans OMS, Série de Rapports techniques, N° 581, 1975. Le texte original a été adopté par le Conseil exécutif dans sa résolution EB15.R7 et amendé dans ses résolutions EB43.R9 et EB115.R4.

[2] Voir annexe 2.

*Article 3* - Après l'examen prévu à l'article 2, le Secrétariat notifie qu'un projet de dénomination commune internationale est à l'étude.

a) Cette notification est faite par une insertion dans *WHO Drug Information*[1] et par l'envoi d'une lettre aux Etats Membres et aux commissions nationales et régionales de pharmacopée ou autres organismes désignés par les Etats Membres.

i) Notification est également faite à la personne qui a soumis la proposition (« le demandeur initial ») et à d'autres personnes portant à la dénomination mise à l'étude un intérêt notoire.

b) Cette notification contient les indications suivantes :

i) dénomination mise à l'étude;

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

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

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

v) mention des pouvoirs en vertu desquels agit l'OMS et référence au présent règlement.

c) En envoyant cette notification, le Secrétariat demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l'étude par l'OMS.

*Article 4* - Des observations sur la dénomination proposée peuvent être adressées à l'OMS par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans *WHO Drug Information* (voir l'article 3).

*Article 5* - Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans *WHO Drug Information* (voir l'article 3).

Cette objection doit s'accompagner des indications suivantes :

i) nom de l'auteur de l'objection ;

ii) intérêt qu'il ou elle porte à la dénomination en cause ;

iii) raisons motivant l'objection contre la dénomination proposée.

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

*Article 7* - Lorsqu'il n'est formulé aucune objection en vertu de l'article 5, ou que toutes les objections présentées ont été levées, le Secrétariat fait une notification conformément aux dispositions du paragraphe a) de l'article 3, en indiquant que la dénomination a été choisie par l'OMS en tant que dénomination commune internationale recommandée.

*Article 8* - En communiquant aux Etats Membres, conformément à l'article 7, une dénomination commune internationale recommandée, le Secrétariat :
a) demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée ; et
b) demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur cette dénomination et interdire le dépôt de cette dénomination comme marque ou appellation commerciale.

[1] Avant 1987, les listes de dénominations communes internationales étaient publiées dans la *Chronique de l'Organisation mondiale de la Santé*.

*Article 9 -*
a) Dans le cas exceptionnel où une dénomination commune internationale déjà recommandée donne lieu à des erreurs de médication, de prescription ou de distribution ou en comporte un risque démontrable, en raison d'une similitude avec une autre appellation dans la pratique pharmaceutique et/ou de prescription, et où il apparaît que ces erreurs ou ces risques d'erreur ne peuvent être facilement évités par d'autres interventions que le remplacement éventuel d'une dénomination commune internationale déjà recommandée, ou dans le cas où une dénomination commune internationale déjà recommandée diffère sensiblement de la dénomination commune approuvée dans un nombre important d'Etats Membres, ou dans d'autres circonstances exceptionnelles qui justifient le remplacement d'une dénomination commune internationale recommandée, toute personne intéressée peut formuler une proposition dans ce sens. Cette proposition est présentée sur la formule prévue à cet effet et doit s'accompagner des indications suivantes :

i) nom de l'auteur de la proposition ;

ii) intérêt qu'il ou elle porte au remplacement proposé ;

iii) raisons motivant la proposition ; et

iv) description, faits à l'appui, des autres interventions entreprises pour tenter de régler le problème et exposé des raisons pour lesquelles ces interventions ont échoué.

Les propositions peuvent comprendre une proposition de nouvelle dénomination commune internationale de remplacement, établie conformément aux Directives générales, compte tenu de la substance pharmaceutique pour laquelle la nouvelle dénomination commune internationale de remplacement est proposée.

Le Secrétariat transmet une copie de la proposition pour examen, conformément à la procédure exposée plus loin au paragraphe b), au Groupe d'experts des DCI et au demandeur initial ou à son successeur (s'il s'agit d'une personne différente de celle qui a formulé la proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles).

De plus, le Secrétariat demande aux entités et personnes ci-après de formuler des observations sur la proposition :

i) les Etats Membres et les commissions nationales et régionales de pharmacopée ou d'autres organismes désignés par les Etats Membres (en insérant une note à cet effet dans la lettre mentionnée à l'article 3.a), et

ii) toutes autres personnes portant au remplacement proposé un intérêt notoire.

La demande d'observations contient les indications suivantes :

i) dénomination commune internationale recommandée pour laquelle un remplacement est proposé (et la dénomination de remplacement proposée, si elle est fournie) ;

ii) nom de l'auteur de la proposition de remplacement (si cette personne le demande) ;

iii) définition de la substance faisant l'objet du remplacement proposé et raisons avancées pour le remplacement ;

iv) délai pendant lequel seront reçus les commentaires et nom et adresse de la personne habilitée à recevoir ces commentaires ; et

v) mention des pouvoirs en vertu desquels agit l'OMS et référence au présent règlement.

Des observations sur la proposition de remplacement peuvent être communiquées par toute personne à l'OMS dans les quatre mois qui suivent la date de la demande d'observations.

b) Une fois échu le délai prévu ci-dessus pour la communication d'observations, le Secrétariat transmet les observations reçues au Groupe d'experts des DCI, au demandeur initial ou à son successeur et à l'auteur de la proposition de remplacement. Si, après avoir examiné la proposition de remplacement et les observations reçues, le Groupe d'experts des DCI, l'auteur de la proposition de remplacement et le demandeur initial ou son successeur reconnaissent tous qu'il est nécessaire de remplacer la dénomination commune internationale déjà recommandée, le Secrétariat soumet la proposition de remplacement au Groupe d'experts des DCI pour qu'il y donne suite.

Nonobstant ce qui précède, le demandeur initial ou son successeur n'est pas habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu'il porte un intérêt durable à la dénomination commune internationale recommandée qu'il est proposé de remplacer.

Dans le cas où une proposition de remplacement est soumise au Groupe d'experts des DCI pour qu'il y donne suite, le Groupe choisit une nouvelle dénomination commune internationale conformément aux Directives générales mentionnées à l'article 2 et selon la procédure décrite dans les articles 3 à 8 inclus. La notification faite par le Secrétariat en vertu de l'article 3 et de l'article 7, respectivement, y compris au demandeur initial ou à son successeur (si ce n'est pas la même personne que celle qui a proposé le remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles), doit dans un tel cas indiquer que la nouvelle dénomination remplace une dénomination commune internationale déjà recommandée et que les Etats Membres peuvent souhaiter prendre des mesures transitoires pour les produits existants qui utilisent la dénomination commune internationale déjà recommandée sur leur étiquette conformément à la législation nationale.

Si, après examen de la proposition de remplacement et des observations communiquées conformément à la procédure exposée plus haut, le Groupe d'experts des DCI, le demandeur initial ou son successeur et l'auteur de la proposition de remplacement ne s'accordent pas sur le fait qu'il y a des raisons impératives de remplacer une dénomination commune internationale déjà recommandée, cette dernière est conservée (étant entendu toujours que le demandeur initial ou son successeur n'est pas habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu'il porte un intérêt durable à la dénomination commune internationale recommandée qu'il est proposé de remplacer). Dans un tel cas, le Secrétariat informe l'auteur de la proposition de remplacement, ainsi que le demandeur initial ou son successeur (s'il s'agit d'une personne différente de celle qui a formulé la proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles), les Etats Membres, les commissions nationales et régionales de pharmacopée, les autres organismes désignés par les Etats Membres et toutes autres personnes portant un intérêt notoire au remplacement proposé que, malgré une proposition de remplacement, il a été décidé de conserver la dénomination commune internationale déjà recommandée (avec une brève description de la ou des raisons pour lesquelles la proposition de remplacement n'a pas été jugée suffisamment impérative).

## ANNEXE 2

## DIRECTIVES GENERALES POUR LA FORMATION DE DENOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES[1]

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

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

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

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

[1] Dans son vingtième rapport (OMS, Série de Rapports techniques, N° 581, 1975), le Comité OMS d'experts des Dénominations communes pour les Substances pharmaceutiques a examiné les directives générales pour la formation des dénominations communes internationales et la procédure à suivre en vue de leur choix, compte tenu de l'évolution du secteur pharmaceutique au cours des dernières années. La modification la plus importante a été l'extension aux substances de synthèse de la pratique normalement suivie pour désigner les substances tirées ou dérivées de produits naturels. Cette pratique consiste à employer des syllabes communes ou groupes de syllabes communes (segments-clés) qui sont caractéristiques et indiquent une propriété commune aux membres du groupe des substances pour lequel ces segments-clés ont été retenus. Les raisons et les conséquences de cette modification ont fait l'objet de discussions approfondies. Les directives ont été mises à jour lors de la treizième consultation sur les dénominations communes pour les substances pharmaceutiques (Genève, 27-29 avril 1983) (PHARM S/NOM 928, 13 mai 1983, révision en date du 18 août 1983).

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

5. Les DCI pour les substances utilisées sous forme de sels devront en général s'appliquer à la base active (ou à l'acide actif). Les dénominations pour différents sels ou esters d'une même substance active ne différeront que par le nom de l'acide inactif (ou de la base inactive).
En ce qui concerne les substances à base d'ammonium quaternaire, la dénomination s'appliquera de façon appropriée au cation et à l'anion en tant qu'éléments distincts d'une substance quaternaire. On évitera de choisir une désignation évoquant un sel aminé.

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

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

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

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

| **Latin** | **Français** | |
|---|---|---|
| *-acum* | *-ac* | substances anti-inflammatoires du groupe de l'ibufénac |
| *-adolum* | *-adol* } | analgésiques |
| *-adol-* | *-adol-* } | |
| *-astum* | *-ast* | antiasthmatiques, antiallergiques n'agissant pas principalement en tant qu'antihistaminiques |
| *-astinum* | *-astine* | antihistaminiques |
| *-azepamum* | *-azépam* | substances du groupe du diazépam |
| *bol* | *bol* | stéroïdes anabolisants |
| *-cain-* | *-caïn-* | antiarythmiques de classe I, dérivés du procaïnamide et de la lidocaïne |
| *-cainum* | *-caïne* | anesthésiques locaux |
| *cef-* | *céf-* | antibiotiques, dérivés de l'acide céphalosporanique |
| *-cillinum* | *-cilline* | antibiotiques, dérivés de l'acide 6-aminopénicillanique |
| *-conazolum* | *-conazole* | agents antifongiques systémiques du groupe du miconazole |
| *cort* | *cort* | corticostéroïdes, autres que les dérivés de la prednisolone |
| *-coxibum* | *-coxib* | inhibiteurs sélectifs de la cyclo-oxygénase |
| *-entanum* | *-entan* | antagonistes du récepteur de l'endothéline |
| *gab* | *gab* | gabamimétiques |
| *gado-* | *gado-* | agents diagnostiques, dérivés du gadolinium |
| *-gatranum* | *-gatran* | antithrombines, antithrombotiques |
| *gest* | *gest* | stéroïdes progestogènes |
| *gli* | *gli* | antihyperglycémiants |
| *io-* | *io-* | produits de contraste iodés |
| *-metacinum* | *-métacine* | substances anti-inflammatoires du groupe de l'indométacine |
| *-mycinum* | *-mycine* | antibiotiques produits par des souches de *Streptomyces* |
| *-nidazolum* | *-nidazole* | substances antiprotozoaires du groupe du métronidazole |
| *-ololum* | *-olol* | antagonistes des récepteurs β-adrénergiques |
| *-oxacinum* | *-oxacine* | substances antibactériennes du groupe de l'acide nalidixique |
| *-platinum* | *-platine* | antinéoplasiques, dérivés du platine |
| *-poetinum* | *-poétine* | facteurs sanguins de type érythropoïétine |
| *-pril(at)um* | *-pril(ate)* | inhibiteurs de l'enzyme de conversion de l'angiotensine |
| *-profenum* | *-profène* | substances anti-inflammatoires du groupe de l'ibuprofène |
| *prost* | *prost* | prostaglandines |

[1] Une liste plus complète de segments-clés est contenue dans le document de travail WHO/EMP/QSM/2009.3 qui est régulièrement mis à jour et qui peut être demandé auprès du programme des DCI, OMS, Genève.

| | | | |
|---|---|---|---|
| *-relinum* | *-réline* | | peptides stimulant la libération d'hormones hypophysaires |
| *-sartanum* | *-sartan* | | antagonistes d'un récepteur de l'angiotensine II, antihypertenseurs (non peptidiques) |
| *-vaptanum* | *-vaptan* | | antagonistes du récepteur de la vasopressine |
| *vin-* | *vin-* | } | alcaloïdes du type vinca |
| *-vin-* | *-vin-* | } | |

ANEXO 1

## PROCEDIMIENTO DE SELECCIÓN DE DENOMINACIONES COMUNES INTERNACIONALES RECOMENDADAS PARA SUSTANCIAS FARMACÉUTICAS[1]

La Organización Mundial de la Salud (OMS) seguirá el procedimiento que se expone a continuación tanto para seleccionar denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11, como para sustituir esas denominaciones.

*Artículo 1* - Las propuestas de denominaciones comunes internacionales recomendadas y las propuestas de sustitución de esas denominaciones se presentarán a la OMS en los formularios que se proporcionen a estos efectos. El estudio de estas propuestas estará sujeto al pago de una tasa destinada a sufragar los costos de administración que ello suponga para la Secretaría de la OMS («la Secretaría»). La Secretaría establecerá la cuantía de esa tasa y podrá ajustarla periódicamente.

*Artículo 2* - Estas propuestas serán sometidas por la Secretaría a los miembros del Cuadro de Expertos en Farmacopea Internacional y Preparaciones Farmacéuticas encargados de su estudio, en adelante designados como «el Grupo de Expertos en DCI», para que las examinen de conformidad con los «Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas», anexos a este procedimiento.[2] A menos que haya poderosas razones en contra, la denominación aceptada será la empleada por la persona que haya descubierto o fabricado y comercializado por primera vez esa sustancia farmacéutica.

*Artículo 3* - Tras el examen al que se refiere el artículo 2, la Secretaría notificará que está en estudio un proyecto de denominación internacional.

*a*) Esa notificación se hará mediante una publicación en *Información Farmacéutica OMS*[3] y el envío de una carta a los Estados Miembros y a las comisiones nacionales y regionales de las farmacopeas u otros organismos designados por los Estados Miembros.

*i*) La notificación será enviada también a la persona que haya presentado la propuesta («el solicitante inicial») y a otras personas que tengan un interés especial en una denominación objeto de estudio.

*b*) En esa notificación se incluirán los siguientes datos:

*i*) la denominación sometida a estudio;

*ii*) la identidad de la persona que ha presentado la propuesta de denominación de la sustancia, si lo pide esa persona;

*iii*) la identidad de la sustancia cuya denominación está en estudio;

*iv*) el plazo fijado para recibir observaciones y objeciones, así como el nombre y la dirección de la persona a quien deban dirigirse; y

*v*) los poderes conferidos para el caso a la OMS y una referencia al presente procedimiento.

[1] Véase el anexo 1 en OMS, Serie de Informes Técnicos, Nº 581, 1975. El texto vigente fue adoptado por el Consejo Ejecutivo en su resolución EB15.R7 y modificado en las resoluciónes EB43.R9 y EB115.R4..

[2] Véase el anexo 2.

[3] Hasta 1987 las listas de DCI se publicaban en la *Crónica de la Organización Mundial de la Salud*.

*c*) Al enviar esa notificación, la Secretaría solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de patente sobre la denominación propuesta, durante el periodo en que la OMS la tenga en estudio.

*Artículo 4* - Toda persona puede formular a la OMS observaciones sobre la denominación propuesta dentro de los cuatro meses siguientes a su publicación en *Información Farmacéutica OMS*, conforme a lo dispuesto en el artículo 3.

*Artículo 5* - Toda persona interesada puede presentar una objeción formal a una denominación propuesta dentro de los cuatro meses siguientes a su publicación en *Información Farmacéutica OMS*, conforme a lo dispuesto en el artículo 3. Esa objeción deberá acompañarse de los siguientes datos:

*i*) la identidad de la persona que formula la objeción;

*ii*) las causas que motivan su interés por la denominación; y

*iii*) las causas que motivan su objeción a la denominación propuesta.

*Artículo 6* - Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la OMS podrá reconsiderar el nombre propuesto o utilizar sus buenos oficios para intentar lograr que se retire la objeción. La OMS no seleccionará como denominación común internacional una denominación a la que se haya hecho una objeción formal, presentada según lo previsto en el artículo 5, que no haya sido retirada, todo ello sin perjuicio de que la Organización examine otra denominación o denominaciones sustitutivas.

*Artículo 7* - Cuando no se haya formulado ninguna objeción en la forma prevista en el artículo 5, o cuando todas las objeciones presentadas hayan sido retiradas, la Secretaría notificará, conforme a lo dispuesto en el párrafo *a*) del artículo 3, que la denominación ha sido seleccionada por la OMS como denominación común internacional recomendada.

*Artículo 8* - Al comunicar a los Estados Miembros una denominación común internacional, conforme a lo previsto en el artículo 7, la Secretaría:

*a*) solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate; y

*b*) solicitará a los Estados Miembros que adopten todas las medidas necesarias para impedir la adquisición de derechos de patente sobre la denominación, y prohíban que sea registrada como marca de fábrica o como nombre comercial.

*Artículo 9*
*a*) En el caso excepcional de que, debido a su semejanza con otra denominación utilizada en las prácticas farmacéuticas y/o de prescripción, una denominación común internacional recomendada anteriormente ocasione errores de medicación, prescripción o distribución, o suponga un riesgo manifiesto de que esto ocurra, y parezca que tales errores o potenciales errores no sean fácilmente subsanables con otras medidas que no sean la posible sustitución de esa denominación común internacional recomendada anteriormente; en el caso de que una denominación común internacional recomendada anteriormente difiera considerablemente de la denominación común aprobada en un número importante de Estados Miembros, o en otras circunstancias excepcionales que justifiquen el cambio de una denominación común internacional recomendada, cualquier persona interesada puede presentar propuestas en este sentido. Esas propuestas se presentarán en los formularios que se proporcionen a estos efectos e incluirán los siguientes datos:

i) la identidad de la persona que presenta la propuesta;

ii) las causas que motivan su interés en la sustitución propuesta;

iii) las causas que motivan la propuesta; y

iv) una descripción, acompañada de pruebas documentales, de las otras medidas que se hayan adoptado con el fin de resolver la situación y de los motivos por los cuales dichas medidas no han sido suficientes.

Entre esas propuestas podrá figurar una relativa a una nueva denominación común internacional sustitutiva, formulada con arreglo a los Principios generales y que tenga en cuenta la sustancia farmacéutica para la que se proponga la nueva denominación común internacional sustitutiva.

La Secretaría enviará al Grupo de Expertos en DCI y al solicitante inicial o a su sucesor (en el caso de que sea una persona diferente de la que ha presentado la propuesta de sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones

industriales) una copia de la propuesta, para que sea examinada de conformidad con el procedimiento descrito en el párrafo *b*) *infra*.
Además, la Secretaría solicitará observaciones sobre la propuesta:

*i*) a los Estados Miembros y a las comisiones nacionales y regionales de las farmacopeas u otros organismos designados por los Estados Miembros (ello se hará incluyendo una notificación a tal efecto en la carta a la que se refiere el párrafo *a*) del artículo 3), y

*ii*) a cualquier persona que tenga un interés especial en la sustitución propuesta.

Al solicitar que se formulen estas observaciones se facilitarán los siguientes datos:

*i*) la denominación común internacional recomendada que se propone sustituir (y la denominación sustitutiva propuesta, si se ha facilitado);

*ii*) la identidad de la persona que ha presentado la propuesta de sustitución (si lo pide esa persona);

*iii*) la identidad de la sustancia a la que se refiere la sustitución propuesta y las razones para presentar la propuesta de sustitución;

*iv*) el plazo fijado para recibir observaciones, así como el nombre y la dirección de la persona a quien deban dirigirse; y

*v*) los poderes conferidos para el caso a la OMS y una referencia al presente procedimiento.

Toda persona puede formular a la OMS observaciones sobre la sustitución propuesta dentro de los cuatro meses siguientes a la fecha en que se realizó la solicitud de observaciones.

*b*) Una vez agotado el mencionado plazo para la formulación de observaciones, la Secretaría enviará todos los comentarios recibidos al Grupo de Expertos en DCI, al solicitante inicial o a su sucesor, y a la persona que haya presentado la propuesta de sustitución. Si después de examinar la propuesta de sustitución y las observaciones recibidas, el Grupo de Expertos en DCI, la persona que haya presentado la propuesta de sustitución y el solicitante inicial, o su sucesor, están de acuerdo en la necesidad de sustituir la denominación común internacional recomendada anteriormente, la Secretaría remitirá la propuesta de sustitución al Grupo de Expertos en DCI para que la tramite.
No obstante lo anterior, el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone.

En caso de que la propuesta de sustitución sea presentada al Grupo de Expertos en DCI para que la tramite, este grupo seleccionará una nueva denominación común internacional de conformidad con los Principios generales a los que se refiere el artículo 2 y al procedimiento establecido en los artículos 3 a 8 inclusive. En ese caso, en las notificaciones que la Secretaría ha de enviar con arreglo a los artículos 3 y 7, respectivamente, incluida la notificación al solicitante inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), se indicará que la nueva denominación sustituye a una denominación común internacional recomendada anteriormente y que los Estados Miembros podrán, si lo estiman oportuno, adoptar disposiciones transitorias aplicables a los productos existentes en cuya etiqueta se utilice, con arreglo a la legislación nacional, la denominación común internacional recomendada anteriormente que se haya sustituido.

En caso de que, después de haber estudiado la propuesta de sustitución y los comentarios recibidos de conformidad con el procedimiento descrito anteriormente, el Grupo de Expertos en DCI, el solicitante inicial o su sucesor y la persona que haya presentado la propuesta de sustitución no lleguen a un acuerdo sobre la existencia de razones poderosas para sustituir una denominación común internacional recomendada anteriormente, esta denominación se mantendrá (siempre en el entendimiento de que el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone). En ese caso, la Secretaría comunicará a la persona que haya propuesto la sustitución, así como al solicitante inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), a los Estados Miembros, a las comisiones nacionales y regionales de las farmacopeas o a otros organismos designados por los Estados Miembros y a cualquier otra persona que tenga interés en la sustitución

propuesta, que, pese a la presentación de una propuesta de sustitución, se ha decidido mantener la denominación común internacional recomendada anteriormente (con una descripción de la o las razones por las que se ha considerado que la propuesta de sustitución no estaba respaldada por razones suficientemente poderosas).

ANEXO 2

## PRINCIPIOS GENERALES DE ORIENTACIÓN PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACÉUTICAS[1]

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

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse las denominaciones que puedan tener connotaciones anatómicas, fisiológicas, patológicas o terapéuticas para el paciente.

*Estos principios primarios se pondrán en práctica utilizando los siguientes principios secundarios:*

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de poder formar DCI convenientes para las sustancias emparentadas que se agreguen al nuevo grupo.

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

5. Las DCI para las sustancias que se usan en forma de sal deberán en general aplicarse a la base activa o al ácido activo. Las denominaciones para diferentes sales o esteres de la misma sustancia activa solamente deberán diferir en el nombre del ácido o de la base inactivos.
En los compuestos de amonio cuaternario, el catión y el anión deberán denominarse adecuadamente por separado, como componentes independientes de una sustancia cuaternaria y no como sales de una amina.

6. Deberá evitarse el empleo de letras o números aislados; también es indeseable el empleo de guiones.

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

8. Siempre que las denominaciones propuestas estén de acuerdo con estos principios, recibirán una consideración preferente las denominaciones propuestas por la persona que haya descubierto las sustancias, o que fabrique y comercialice por primera vez una sustancia farmacéutica, así como las denominaciones ya adoptadas oficialmente en cualquier país.

9. El parentesco entre sustancias del mismo grupo se pondrá de manifiesto en las DCI (véase el Principio 2) utilizando una partícula común. En la lista que figura a continuación se indican ejemplos de partículas para grupos de sustancias, en particular para grupos nuevos. Existen muchas otras partículas que se usan habitualmente.[2] Cuando una partícula aparece sin guión alguno, puede utilizarse en cualquier lugar de la palabra.

[1] En su 20º informe (OMS, Serie de Informes Técnicos, Nº 581, 1975), el Comité de Expertos de la OMS en Denominaciones Comunes para las Sustancias Farmacéuticas revisó los Principios generales para formar denominaciones comunes internacionales (DCI), y su procedimiento de selección, a la luz de las novedades registradas en los últimos años en materia de compuestos farmacéuticos. El cambio más importante había consistido en hacer extensivo a la denominación de sustancias químicas sintéticas el método utilizado hasta entonces para las sustancias originadas en productos naturales o derivadas de éstos. Dicho método conlleva la utilización de una «partícula» característica que indica una propiedad común a los miembros de un grupo. En el citado informe se examinan en detalle las razones y consecuencias de este cambio.
Los Principios generales de orientación se actualizaron durante la 13ª consulta sobre denominaciones comunes para sustancias farmacéuticas (Ginebra, 27 a 29 de abril de 1983) (PHARM S/NOM 928, 13 de mayo de 1983, revisado el 18 de agosto de 1983).

[2] En el documento de trabajo WHO/EMP/QSM/2009.3, que se actualiza periódicamente y puede solicitarse al Programa sobre Denominaciones Comunes Internacionales, OMS, Ginebra, figura una lista más amplia de partículas.

| **Latin** | **Español** | |
|---|---|---|
| *-acum* | *-aco* | antiinflamatorios derivados del ibufenaco |
| *-adolum* | *-adol* ) | analgésicos |
| *-adol-* | *-adol- )* | |
| *-astum* | *-ast* | antiasmáticos, sustancias antialérgicas cuya acción principal no es la antihistamínica |
| *-astinum* | *-astina* | antihistamínicos |
| *-azepamum* | *-azepam* | derivados del diazepam |
| *bol* | *bol* | esteroides anabolizantes |
| *-cain-* | *-caína-* | antiarrítmicos de clase I, derivados de procainamida y lidocaína |
| *-cainum* | *-caína-* | anestésicos locales |
| *cef-* | *cef-* | antibióticos, derivados del ácido cefalosporánico |
| *-cillinum* | *- cilina* | antibióticos derivados del ácido 6-aminopenicilánico |
| *-conazolum* | *-conazol* | antifúngicos sistémicos derivados del miconazol |
| *cort* | *cort* | corticosteroides, excepto derivados de prednisolona |
| *-coxibum* | *-coxib* | inhibidores selectivos de ciclooxigenasa |
| *-entanum* | *-entán* | antagonistas del receptor de endotelina |
| *gab* | *gab* | gabamiméticos |
| *gado-* | *gado-* | agentes para diagnóstico derivados de gadolinio |
| *-gartranum* | *-gatrán* | inhibidores de la trombina antitrombóticos |
| *gest* | *gest* | esteroides progestágenos |
| *gli* | *gli* | hipoglucemiantes, antihiperglucémicos |
| *io-* | *io-* | medios de contraste iodados |
| *-metacinum* | *-metacina* | antiinflamatorios derivados de indometacina |
| *-mycinum* | *-micina* | antibióticos producidos por cepas de *Streptomyces* |
| *-nidazolum* | *-nidazol* | antiprotozoarios derivados de metronidazol |
| *-ololum* | *-olol* | antagonistas de receptores β-adrenérgicos |
| *-oxacinum* | *-oxacino* | antibacterianos derivados del ácido nalidíxico |
| *-platinum* | *-platino* | antineoplásicos derivados del platino |
| *-poetinum* | *-poetina* | factores sanguíneos similares a la eritropoyetina |
| *-pril(at)um* | *-pril(at)* | inhibidores de la enzima conversora de la angiotensina |
| *-profenum* | *-profeno* | antiinflamatorios derivados del ibuprofeno |
| *prost* | *prost* | prostaglandinas |
| *-relinum* | *-relina* | péptidos estimulantes de la liberación de hormonas hipofisarias |
| *-sartanum* | *-sartán* | antihipertensivos (no peptídicos) antagonistas del receptorde angiotensina II |
| *-vaptanum* | *-vaptán* | antagonistas del receptor de vasopresina |
| *vin-* | *vin- )* | alcaloides de la vinca |
| *-vin-* | *-vin- )* | |