WHO Drug Information

Contents

Announcement

The 15th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the State Agency for Medicines, Estonia, in collaboration with the World Health Organization

The ICDRA will take place in Tallinn, Estonia, 23 – 26 October 2012

Information and registration at:

http://www.icdra.ee

http://www.who.int/medicines/icdra

Regulatory Focus

Regulation of medicines in China

Over the past decade, China has introduced significant changes to the regulation of medicines through modernizing its legislative framework in line with international practice and by re-organizing the nation's medicines administrative agency, the State Food and Drug Administration (SFDA). Medicines regulatory agencies (MRAs) have been established at national, provincial, city and county levels and, by the end of 2010, there were 2898 administrative organs and 1076 public institutions employing human resources of 45,393 and 24,939 respectively (1). The State Food and Drug Administration (SFDA) is the responsible agency for medicines administration nationwide. The medicines regulatory agencies at provincial level are responsible for drug regulation in their administrative areas while the responsibilities of local level MRAs are legally defined or commissioned by upper level MRAs.

Administratively, mainland China consists of 31 contiguous regions at provincial level, 333 at city level and 2856 at county level (2). As of November 2010, China registered an overall population of 1339,724,852 (3) and, in 2010, the country's gross domestic product amounted to RMB 40120.2 billion (4).

This article provides insight into changes taking place in the organizational structure, legislative framework and current situation of medicines regulation in China with a focus on medicines registration, manufacturing, distribution and use, advertising, and post-market safety monitoring as well as control of narcotics and psychotropic substances*. It also draws a picture of China's pharmaceutical industry and offers a glimpse of the transformations taking place in the medicines regulatory scene set against a backdrop of international harmonization.

** This article does not focus on traditional Chinese medicine, which would merit a separate article.*

Medicines regulatory situation

The State Council of the People's Republic of China is the executive arm of the Central People's Government. It is the highest body of both state power and state administration (5). Departments under the State Council are responsible for related medicines regulatory administrative work as defined within the limits of their duties and include the National Development and Reform Commission responsible for drug pricing, the Ministry of Human Resources and Social Security responsible for formulating the *China National Formulary for Essential Medicare and Industrial Injury Insurance*, the Ministry of Agriculture responsible for supervision of raw material for narcotic drugs and the Ministry of Public Security which is responsible for monitoring the distribution of narcotic drugs and psychotropic substances.

The State Food and Drug Administration (SFDA) was established in 1998

Article by Xiaoqiong Zheng, Information Centre, State Food and Drug Administration, Beijing, China.

Table 1. State Food and Drug Administration functions

- Formulate policies and programmes on the administration of drugs, medical devices, health foods and cosmetics, as well as food safety at the consumption level (restaurant, cafeteria, etc.) and supervise implementation. Take part in drafting relevant laws, regulations and normative documents.
- Take charge of food hygiene licensing and food safety supervision at consumption level.
- Formulate good practice for food safety at the consumption stage and supervise implementation; carry out investigation and monitoring work of food safety at consumption level, and release information related to supervision on food safety at consumption level.
- Take charge of health foods, cosmetic hygiene licensing, hygiene supervision and relevant review and approval work.
- Take charge of administrative and technical supervision of medicines and medical devices, take charge of formulating good practices for medicines, medical devices in aspects of research, production, distribution and use, and supervise implementation.
- Take charge of registration and supervision of medicines and medical devices; draw up relevant national standards for medicines and medical devices, and supervise implementation; carry out adverse drug reaction (ADR) monitoring and adverse event monitoring of medical devices; be responsible for drug and medical device re-evaluation and removal. Take part in formulating the national essential medicines list and adopting the national essential medicines system. Organize implementation of a classification system for prescription and non-prescription medicines.
- Take charge in formulating regulations for traditional Chinese medicines (TCMs) and ethno-medicines, and supervise implementation, draw up quality standards for TCMs and ethno-medicines, formulating good agricultural practices for Chinese crude drugs and processing standards for prepared slices of Chinese crude drugs and supervising their implementation. Implement protection for certain TCMs.
- Supervise the quality and safety of medicines and medical devices; regulate radiopharmaceuticals, narcotics, toxics and psychotropics, and release quality and safety information on medicines and medical devices.
- Organize the investigation and take legal action against violation of laws and regulations concerning food safety at consumption level, and in research, production, distribution and use of medicines, medical devices, health food and cosmetics.
- Direct relevant local work regarding food and drug administration, emergency response, inspection and information sharing.
- Draw up and improve qualification systems for licensing pharmacists, direct and supervise the registration of licensed pharmacists.
- Carry out international information exchange and cooperation related to food and medicines regulation.
- Undertake other work assigned by the State Council and the Ministry of Health.

through the merger of medicines regulatory functions of the State Pharmaceutical Administration of China, the State Administration of Traditional Chinese Medicine of the People's Republic of China (SATCM) — also under the Ministry of Health — and the Drug Administration Department of the Ministry of Health, namely the State Drug Administration (SDA) directly under the State Council. In 2003, with additional responsibilities for food regulation, the SDA became the current SFDA. In 2008, the SFDA reverted to Ministry of Health responsibility.

The establishment of the SFDA to regulate medicines was a milestone in the history of medicines regulation in China and an important achievement in healthcare reform. From 1998 to 2011, the SFDA has been committed to public health through:

- Strengthening the science based approach to medicines evaluation.
- Promoting quality assurance systems in enterprises involved in research, production and distribution.
- Facilitating the establishment of a national essential medicines system and the classification of prescription and non-prescription medicines.
- Improving pharmacovigilance to safeguard public health.
- Ensuring the quality, safety, efficacy and accessibility of medicines.

In addition to medicines regulation, several other categories of health related products are also regulated by the SFDA (6). (Table 1.)

Regulatory responsibility and capacity
The scope of medicines regulation in China covers the whole life-cycle of medicines, including:

- Production, manufacturer licensing, provision of Internet-based pharmaceutical information, Internet pharmaceutical trading, and medical institutions producing pharmaceutical preparations, etc.
- Product approval at clinical trial, production, and import levels.
- Authorization of medicines advertising and promotion of over-the-counter (OTC) and prescription-only medicines.
- Implementation of quality assurance systems and compliance with good laboratory practice (GLP), good clinical practice (GCP), good manufacturing practice (GMP) and good distribution practice (GDP).
- Post-marketing safety surveillance through a nationwide network encompassing organization and electronic management systems for adverse drug reaction (ADR) reporting and monitoring.

The SFDA makes decisions on marketing authorizations and authorization of products for clinical trial and import. Decisions are based on reviews provided by the Centre for Drug Evaluation (CDE), an affiliated public organization providing technical support under SFDA administrative supervision. Provincial MRAs assist the drug registration process through preliminary work by verifying the original dossier application, format review and on-site inspection. Drug testing institutes established or designated by drug regulatory departments are responsible for the drug testing which is required as part of drug review and approval and for drug quality control in accordance with the law (7).

Pharmaceutical industry profile
The Chinese pharmaceutical industry has made significant progress over the past decade. According to a White Paper *The Status Quo of Drug Supervision in China* released by the Information Office of the State Council in 2008, China had the capacity to produce 1500 types of drug substance and over one billion doses a year of 41 types of vaccine against infection caused by 26 kinds of virus and

Table 2. Pharmaceutical industry profile

Indicator	January–November 2010	January–June 2011
Gross industrial output (billion yuan)	1123.9 Among these: • APIs: 215.7 • FPPs: 318.56 • Medical devices: 104.83 • TCM preparations: 317.2	714.6 Among these: • APIs: 117.8 • FPPs: 158.3 • Biological products: 59.1 • TCM preparations: 119.2
International business (billion US dollars)	54.12 Among these: • Export: 35.80 • Import: 18.32	34.55 Among these: • Export: 21.38 • Import: 13.17
R&D percentage of gross industrial output	1.82% (figure for entire year)	
Fixed assets investment (billion yuan)	175.33	110.8
Profit (billion yuan)	111.4	62.9

Source:
Department of Industry Coordination, National Development and Reform Commission at http://www.sdpc.gov.cn/jjxsfx/t20110128_393383.htm
National Development and Reform Commission at http://www.sdpc.gov.cn/zjgx/t20110323_400832.htm
National Development and Reform Commission at http://www.ndrc.gov.cn/jjxsfx/t20110829_430931.htm
National Bureau of Statistics of China. Ministry of Science and Technology of the People's Republic of China. Ministry of Finance People's Republic of China. Report on Investment in Scientific R&D, 2010, at http://www.sts.org.cn/tjbg/tjgb/document/2011/20110928.htm

pathogenic bacteria (8). By the end of 2010, China counted more than 8000 pharmaceutical enterprises — including producers of prepared Chinese crude drugs, oxygen for medical use, diagnostic agents, blood derived products and vaccines (9) — of which 4678 were producers of active pharmaceutical ingredients (APIs) and finished pharmaceutical preparations (FPPs) (1). In 2010, the gross industrial output reached 1236.827 billion yuan with annual total sales of medicinal products at 682 billion yuan (10). An overview of the Chinese pharmaceutical industry profile is set out in Table 2.

The challenges of regulating the Chinese pharmaceutical industry were highlighted in a speech given by the SFDA Deputy-Commissioner Wu Zhen at the 2011 Annual Conference on National Medicines Regulation (11). Following international economic integration, China is now the third largest pharmaceutical market in the world. This demands that the country's regulatory activities are in line with international standards. Current efforts to reform health care inside China also present challenges for capacity building and regulation, while the quality and safety of services and products provided within the essential medicines programme need to be safeguarded.

Legislative framework and regulatory status

China practises a unified, multilevel legislative system (12). The National People's Congress and its Standing Committee exercise the state's power to make laws. The State Council formulates administrative regulations and, at provincial level, the People's Congresses as well as their standing committees establish local statutes. In the area of medicines regulation, the main legislative instrument is the Drug Administration Law of the People's

Republic of China. Based on this, the legal framework of medicines regulation is established and regularly improved.

Drug Administration Law

The Drug Administration Law was issued by the National People's Congress. It was enacted in 1985, and amended in 2001. The 2001 revision has achieved better harmonization with regard to international practice and provides a modern base for control over the quality, safety and efficacy of medicines in China. The Law applies to all parties engaged in research and development, production, distribution, use, and administration. In 2002, the State Council also adopted *Regulations for Implementation of the Drug Administration Law of the People's Republic of China*.

The Drug Administration Law 2001 comprises 106 articles in ten chapters, including: General Provisions, Control of Drug Manufacturers, Control of Drug Distributors, Control of Pharmaceuticals in Medical Institutions, Control of Drugs, Control of Drug Packaging, Control of Drug Pricing and Advertising, Inspection of Drugs, Legal Liabilities, and Supplementary Provisions.

Based on the framework of the Drug Administration Law, a comprehensive legal system including regulations, provisions, and guidelines has been established.

Medicines registration

Provisions for drug registration 2007 (13) is in its fifth edition and fourth update. As the most frequently revised rule in medicines regulation, it reflects the internal and external driving forces modelling medicines regulation in China, for example:

- First released in1985 following enactment of the Drug Administration Law.
- Revised to reflect establishment of the SDA in 1998.
- Revised in response to China's membership to the World Trade Organization in 2001.
- Revised to reflect the 2001 revision of the Drug Administration Law.
- Updated following adoption of the Administrative Licensing Law of the People's Republic of China in 2004.

> Drugs/medicines refer to articles which are used in the prevention, treatment and diagnosis of human diseases and intended for the regulation of the physiological functions of human beings, for which indications, usage and dosage are established. These include Chinese crude drugs, prepared slices of Chinese crude drugs, traditional Chinese medicine preparations, chemical drug substances and their preparations, antibiotics, biochemical drugs, radiopharmaceuticals, sera, vaccines, blood products and diagnostic agents. (Article102 of the Drug Administration Law)
>
> New drugs refer to medicines which have not been marketed within the territory of the People's Republic of China. (Article 83 of the Regulation).

Under the Provisions, a series of measures relating to procedures and products have been issued, including *Supplementary provisions for TCM registration* (2008), *Provisions for on-site inspection in drug registration* (2008), *Provisions for special review and approval for new drug registration* (2009) and *Provisions for technology transfer of drugs* (2009). *Provisions for drug standards* is currently under development (14).

Applications are classified into new medicines, generic medicines, import medicines and their supplementary applications, as well as re-registration. (Article 11.12.)

The first two classifications – new medicines and generic medicines – apply to domestic applicants, whereas requests

from overseas applicants are handled according to those for imported medicines. Any application for changing a dosage form or route of administration, or claiming a new indication for marketed medicines, is submitted through the new drug application (NDA) process which covers applications for registration of medicines not previously marketed in China. (Article 12.12.)

The SFDA has additionally formulated *Requirements for application dossiers in CTD format for pharmaceutical products* based on the common technical document (CTD) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) taking into consideration the actual situation of drug research and development in China. The Requirements were issued in September 2010 (15).

An application for generic medicines will apply to production of medicines having an existing national medicines standard for marketing approval by the SFDA. The application process for a biological product is the same as that for an NDA. (Article 12.12.)

An application for an imported drug refers to the registration application for medicines manufactured abroad to be marketed in China. (Article 12.12.)

Special review procedures to encourage innovation also exist. Speciality products are given priority in review and approval. A specific fast track procedure applies to the following products (Article 4.12):

- Active ingredients extracted from plants, animals and minerals, etc. and their preparations not yet marketed in China. Newly discovered Chinese crude drugs and their preparations.
- Chemical drug substances and their preparations and biological products not yet approved for marketing in China or abroad.
- New drugs offering significant clinical advantage for the treatment of diseases such as AIDS, malignant tumours and rare disorders, etc.
- New drugs for the treatment of diseases for which effective therapeutic methods are not available.

Quality assurance

In China, good manufacturing practices (GMP) is a set of principles and procedures which should be followed in order to provide assurance that each medicinal product is safe and of the required quality. This comprises requirements relating to premises, equipment, personnel, documentation and quality control. These requirements are enforced through systems of factory inspection and mandatory licensing of factories which manufacture medicines.

Since its first promulgation in 1988 (16), China's *Good Manufacturing Practice for Drugs* was revised in 1992 and 1998. The latest version of GMP (2010 Revision) released by the Ministry of Health has been effective since 1 March 2011 (17). It consists of 14 chapters and 313 articles based on the concepts of quality risk management and whole process control of drug manufacturing. It attaches greater importance on the scientific nature, instructions, functions and manoeuverability consistent with WHO GMP.

Overseas manufacturers of medicines supplied to China must provide evidence that goods are manufactured to a standard of GMP equivalent to that expected of Chinese manufacturers of the same goods.

National drug standards

National drug standards in China include the *Pharmacopoeia of the People's Republic of China*, drug registration specifications, etc., published by the Ministry of Health/SFDA, including technical requirements such as testing methods

and manufacturing processes. (Article 136.12.) The 2010 edition of *The Pharmacopoeia of the People's Republic of China* is available in three volumes and contains 4567 monographs (18).

Pre-approval requirements for clinical trial applicants

- Safety evaluation in pre-clinical studies should comply with GLP (19).
- Clinical trials (including bioequivalence studies) should be conducted in compliance with GCP. (Article 30.12.)
- Drugs used for clinical trials should be manufactured in facilities in compliance with GMP. (Article 35.12.)
- A drug can be used for a clinical trial only after being tested and qualified. Vaccines, blood products and other biological products specified by the SFDA should be tested by drug testing institutes designated by the SFDA. (Article 36.12.)

All clinical trials (including bioequivalence studies) need prior SFDA approval.

- The approved clinical trial should be conducted in a certified research institution that operates in compliance with Chinese GCP.
- For overseas applicants intending to conduct an international multicentre clinical trial in China, drugs used for the clinical trial should already be approved or in phase II or III clinical trial overseas. While approving the conduct of an international multicentre clinical trial, the SFDA may require the applicant to first conduct a phase I clinical trial in China. (Article 44.12.)
- Any preventive vaccine trial not having first been registered overseas is prohibited in China. (Article 44.12.)

SFDA publishes an *Annual report on the evaluation and approval of drug registrations* (20). The report provides an overview of SFDA's work in the area of medicines registration including production, clinical trials, and other key areas.

Provisions for medicines use

Medicines use is covered by the national essential medicines system and list. This includes classification of medicines into prescription and non-prescription categories.

Essential Medicines

Over the past three decades, the concept of essential medicines has evolved in China from a list to an integrated strategy based on a national medicines policy and is a key objective of healthcare reform (21).

China released its first National Essential Medicines List in 1982 following the launch of the WHO Model List of Essential Drugs in 1975. In 2009, the National Essential Medicines Committee was established (22). The *Provision for a National Essential Medicines List (interim*) (23) and a *Position paper on implementation of the National Essential Medicines System* (24) were published in 2009. The Position Paper defines essential medicines as those which satisfy the health care needs and are available to the public at all times in adequate amounts and in appropriate dosage forms, affordable price and equitable access to the public.

The National Essential Medicines List has been regularly updated and the current 2009 edition is the Seventh edition. Coverage of products has expanded from a focus on chemical pharmaceuticals in the first edition to TCM in the second edition, and was again extended to include prepared slices of Chinese crude drugs in the current 2009 edition.

Classification of prescription and non-prescription medicines

At the National Health Conference in 1996, classification of prescription and

non-prescription medicines was identified as a key feature of the reform and development of China's healthcare system (25). In June 1999, the *Provision for classification of prescription drugs and non-prescription drugs (interim)* and the first list of non-prescription medicines (OTC) was released. In 2001, control over prescription and OTC classification management became a legal requirement under the Drug Administration Law. (Article 37.7.)

In 2004, the SFDA took a dynamic management approach to the control of OTC medicines (26). Henceforth, OTC medicines could be switched to prescription-only status as a result of any safety related issues. To further standardize information and labelling of non-prescription medicines, the SFDA revised the model insert for non-prescription drugs in 2007 (27). By the end of 2011, the SFDA had issued 5697 package inserts for non-prescription drugs, including 1170 chemical drugs and 4527 TCMs (28).

Control of narcotics and psychotropic substances

The *Regulation for control of narcotics and psychotropics* was adopted by the State Council on 26 July 2005. It consolidates and amends the former two separate regulations for narcotic drugs and psychotropic substances released in 1987 and 1988. The more stringent provisions are in line with the respective International Conventions under the principle of balancing control measures and access (29). The main points include, among others:

Coordinated supervision

Departments under the State Council involved in narcotic and psychotropic control include the SFDA, Ministry of Agriculture (MoA) and Ministry of Public Security (MPS). The MoA and SFDA hold joint responsibility for narcotics and the MPS is responsible for oversight of distribution and the medicinal plans used for narcotic medicines production (Article 5.25). MRAs above provincial level have established information monitoring networks and share information related to products (research, production, distribution, use, storage and transportation) with the public security agency at the same level. (Article 58.25.)

Clinical trials

Clinical trials of narcotics listed as a category 1 psychotropic should not be conducted in healthy subjects. (Article 13.25.)

Production

The SFDA and MoA draw up an annual cultivation plan based on production, clinical needs and national storage capacity**.** Cultivation enterprises are designated by the SFDA and MoA. (Article 14.25.)

Distributors and distribution

National wholesalers who distribute narcotic drugs and category 1 psychotropic substances among the provinces are licensed by the SFDA. (Article 24.25.) Narcotic drugs and category I psychotropic drugs are not permitted in retailing. (Article 30.25.)

Information sharing

Reports on product-related information are provided quarterly by city-level MRAs to upper level MRAs. (Article 59.25.)

Electronic distribution oversight

Real-time dynamic monitoring of production, purchase, sales, inventory and flow of narcotic drugs and category 1 psychotropic substances is realized through the Electronic Medicines Supervision and Regulation Network (30).

Control of drug promotion and advertising

Control of OTC and prescription-only medicine advertising ensures accurate content, compliance with the law and avoidance of misleading information. The legal basis for drug advertising is vested in the SFDA approved package insert/ labelling information. (Article 6.27.)

Supervision of drug advertising is the responsibility of the SFDA and the State Administration for Industry and Commerce (SAIC). The current legislative framework for medicines advertising *Provisions for drug advertisement examination* (SFDA Order 27) and *Drug advertisement examination and release standards* (SAIC Order 27) (31) was issued jointly by the two departments and became effective in May 2007.

Advertising is prohibited (Article 3.27) for:

- Narcotics, psychotropic substances, toxic medicines and radiopharmaceuticals.
- Pharmaceutical preparations produced by medical institutions.
- Products specifically for military use.
- Preparations under trial production.
- Products that have been prohibited by the SFDA for production, sale or use.

The SFDA implements a risk based regulatory approach in terms of content of advertisements and category of product (e.g., OTC or prescription-only medicines). The key points are:

- Only OTC products can be advertised directly to the consumer and all advertising materials should state that purchase and use should be made in accordance with a pharmacist's instructions or guidance. (Article 8.27.)
- Prescription medicines can only be advertised in medical or pharmaceutical journals assigned by the Ministry of Health and SFDA. The advertisement should state that it is specifically directed to medical professionals. (Article 8.27.)
- The prescription/trade name cannot be used within the advertising slogan. (Article 5.27.)
- By the end of June 2011, 544 publications had been designated by the Ministry of Health/SFDA (32).

Drug safety monitoring

Establishing a reporting system on adverse drug reactions (ADRs) is required under Article 71 of the Drug Administration Law 2001. It is a legal obligation for manufacturers, distributors and medical institutes to report serious ADRs. Improving the ADR evaluation system is also highlighted in the 2010 State Council schedule. Among the five *Priorities in the reform of the medicine and healthcare system*, an ADR evaluation system is a necessary part of the essential medicines policy (33). The *Provisions for ADR reporting and monitoring* released in 2011 by the Ministry of Health clearly define the appropriate procedure, timeframe, and responsibilities of stakeholders (34).

China's ADR monitoring work was initiated in 1989 through establishment of the ADR Monitoring Centre within the Ministry of Health. Over the past two decades, in addition to development of the appropriate legislative framework, key progress made includes formal membership of China's ADR Centre to the WHO International Drug Monitoring Programme in 1998. The first *National annual report on ADR monitoring* was released in 2009. The ADR network is expected to be expanded to 400 sub-centres nationwide with an on-line information reporting system functioning as of 2010 (35). In 2011, China signed an agreement with the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre) with the aim of enhancing data exchange from China's Adverse Drug Reaction Monitoring database and VigiBase — the WHO global database containing over 6 million ADR reports. The project agreement will also improve the *Drug Dictionary of China*, and signal detection and patient safety data mining techniques (36).

According to the *Guideline on strengthening the establishment of an ADR monitoring system* released by the SFDA in 2011, the future China ADR monito-

Roadmap for Drug Safety
National drug safety plan 2011—2015

The *Roadmap for Drug Safety* adopted on 7 December 2011 sets out the overall objectives and priorities for pharmaceutical products, which should be produced under conditions satisfying good manufacturing practices (GMP). Priorities include:

Standards improvement. Standards for chemical medicines and biological products will comply with international requirements. China should take the lead in developing international standards for traditional Chinese medicine (TCM)

Quality control capacity building. A focus will be made on strengthening improvement of quality control institutions at national level, upgrading conditions at provincial level and strengthening mobile testing capacity of institutions at county level.

Whole process oversight. Systems will be launched for quality assurance of medicines and medical devices. All marketed products will be subject to bar coding and all medicines controlled under electronic track and trace systems.

Postmarketing system. A special focus will be made on the monitoring and assessment of new drugs, TCM injectables and high risk products.

Essential medicines. The essential medicines system will be improved through ensuring safety and accessibility.

The withdrawal and recall of medicines. This will be improved and a credit rating system established for enterprises. Efforts to combat substandard and counterfeit products willl continue.

Medicines approval. An in-depth reform of the medicines administrative approval system will be carried out following strict criteria and standardized procedures. The revision and establishment of drug-related laws and regulations will be accelerated.

ring and reporting system will be based on international standards supported by information technology with an early warning capability, combined with four-level SFDA and stakeholder participation (37).

Internet-related pharmaceutical distribution and information

Internet based activities related to medicines need to be licensed by the MRAs. Under the two legal documents released by the SFDA, *Requirement for Internet-based service provision of pharmaceutical information 2004* and *Requirements for review and licensing of Internet-based pharmaceutical transactions 2005*, regulation involves two spheres:

- Regulation and authorization of information provision, whether commercial or non-commercial.
- Regulation and licensing of Internet-based medicines transactions, including third party e-commerce platform providers, business-to-business (B2B) and business-to-consumers (B2C).

References

1. State Food and Drug Administration (2011). *SFDA annual statistics report 2010.* At http://www.sfda.gov.cn/WS01/CL0108/66530.html

2. Ministry of Civil Affairs of the People's Republic of China (2011). *Statistical report on social service development in China 2010*. At http://www.mca.gov.cn/article/zwgk/mzyw/201106/20110600161364.shtml

3. National Bureau of Statistics of China (2011). *Bulletin of key figures for the 6th National Population Survey 2010.* At http://www.stats.gov.cn/tjfx/jdfx/t20110428_402722253.

4. National Bureau of Statistics of China (2011). *Preliminary verification bulletin on 2010 annual gross domestic product (GDP).* At http://www.stats.gov.cn/tjdt/zygg/sjxdtzgg/t20110907_402752625.htm

5. Constitution of the People's Republic of China (Full text after amendment on 14 March 2004). At: http://www.npc.gov.cn/englishnpc/Constitution/node_2825.htm

6. State Food and Drug Administration. *Main responsibilities of SFDA.* At http://eng.sfda.gov.cn/WS03/CL0756/

7. Order of the President of the Peoples Republic of China (No. 45). Article 6 of the Drug Administration Law of the People's Republic of China. At http://eng.sfda.gov.cn/WS03/CL0766/61638.html

8. Information Office of the State Council of the People's Republic of China (2008). *Status quo of drug supervision in China.* At http://www.gov.cn/english/2008-07/18/content_1049011.htm

9. State Food and Drug Administration (2011). *Database of Pharmaceutical manufacturers.* Official website of SFDA at http://app1.sfda.gov.cn/datasearch

10. Southern Medicine Economic Research Institute of SFDA (2011). *Medicinal Economic Newspaper.* Capital-driven time is coming. At http://www.yyjjb.com/html/2011-07/13/content_146414.htm

11. State Food and Drug Administration. Wu Zhen (2011). National Conference on Medicines Regulation. *News Release*. At http://app1.sfda.gov.cn/WS01/CL0287/68457.html

12. National People's Congress. At http://www.npc.gov.cn/pc/11_4/2007–11/20/content_1617713.htm

13. State Food and Drug Administration (2007). *Provisions for drug registration*. At http://www.sda.gov.cn/WS01/CL0053/24529.html

14. State Food and Drug Administration. Zhang Wei (2010). Latest progress in development of the Chinese pharmaceutical industry and administration of drug registration. 2010 China–Japan Symposium on Global Clinical Trials and Ethnic Factors, China. At http://www.pmda.go.jp/english/past/2010_sympo/file/201005_03.pdf

15. State Food and Drug Administration. SFDA issues *Requirements for application dossiers in CTD format for a pharmaceutical product.* News Release. 11 October 2010. At http://eng.sfda.gov.cn/WS03/CL0757/62297.html

16. State Food and Drug Administration (2011).Good manufacturing practice for drugs (2010 Revision) issued. *News Release.* At http://eng.sfda.gov.cn/WS03/CL0757/62350.html

17. State Food and Drug Administration. *Good manufacturing practice for drugs,* (2010 Revision). (MOH Decree No. 79.) At http://eng.sfda.gov.cn/WS03/CL0768/65113.html

18. State Food and Drug Administration (2010). The Third General Assembly of the Ninth Chinese Pharmacopoeia Commission and the Summing-up Conference on Compilation of The 2010 Chinese Pharmacopoeia. Beijing. *News Release.* At http://eng.sfda.gov.cn/WS03/CL0757/62334.html

19. State Food and Drug Administration. *Notice for facilitating the implementation of GLP.* Guo shi yao jian an(2006)587. At http://www.sda.gov.cn/WS01/CL0055/10619.html

21. State Food and Drug Administration (2010). *2009 Report on the evaluation and approval of drug registrations.* At http://www.sda.gov.cn/WS01/CL0236/54135.html

21. Xinhua News Agency (2009). *Deepening reform in healthcare system and establishing the county's essential medicines system.* At http://news.xinhuanet.com/politics/2009-11/15/content_12462632.htm

22. Ministry of Health (2009). *National Essential Medicines Committee established.* At http://www.moh.gov.cn/publicfiles/business/htmlfiles/wsb/pwsyw/200905/40493.htm

23. Ministry of Health, National Development and Reform Commission, Ministry of Industry and Information Technology, Ministry of Supervision, Ministry of Finance, Ministry of Human Resources and Social Security, Ministry of Commerce, State Food and Drug Administration, State Administration of Traditional Chinese Medicine (2009). *Provision for National Essential Medicines List (Interim).* At http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohbgt/s7692/200908/42512.htm

24. Ministry of Health, National Development and Reform Commission, Ministry of Industry and Information Technology, Ministry of Supervision, Ministry of Finance, Ministry of Human Resources and Social Security, Ministry of Commerce, State Food and Drug Administration, State Administration of Traditional Chinese Medicine (2009). *Position Paper on implementation of the National Essential Medicines System.* At http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohywzc/s3581/200908/42498.

25. State Drug Administration. Guo yao jian an(1999)460. *Facilitating China's classification of prescription and non-prescription medicines.* At http://www.sda.gov.cn/WS01/CL0055/9684.html

26. State Food and Drug Administration (2004). Guo shi yao jian an(2004)101, *Conducting the switch of prescription and OTC.* At http://www.sda.gov.cn/WS01/CL0055/10268.html

27. State Food and Drug Administration (2004). Guo shi yao jian zhu(2007)54. *Notification of release of the insert sheet model for over-the-counter medicines.* At http://former.sfda.gov.cn/cmsweb/webportal/W472/A64019346.html

28. State Food and Drug Administration (2011). Database of model insert for over-the-counter medicine. Official website of SFDA at http://app1.sfda.gov.cn/datasearch/face3/dir.

29. The State Council (2005). *Regulation for control of narcotics and psychotropics.* At http://www.sfda.gov.cn/WS01/CL0784/23500.html

30. State Food and Drug Administration (2007). *Notice on the establishment of a monitoring network for narcotics and psychotropics.* Guo shi yao jian ban(2007)482, 3 August,2007. At http://former.sfda.gov.cn/cmsweb/webportal/W945325/A64022736.html

31. State Food and Drug Administration. State Administration for Industry and Commerce (2007). *Drug advertisement examination and release standards.* At http://www.sfda.gov.cn/WS01/CL0053/24526.html

32. State Food and Drug Administration (2011). Online database of SFDA web sites at http://app1.sfda.gov.cn/datasearch/face3/dir.html

33. General Office of the State Council of the People's Republic of China (2010). Guo ban han (2010)67. At http://www.gov.cn/zwgk/2010-04/19/content_1586732.htm

34. Ministry of Health (2011). *Provisions for ADR reporting and monitoring*. At http://www.sfda.gov.cn/WS01/CL0053/62621.html

35. State Food and Drug Administration. Yan min. *Development of ADR reporting and monitoring in China.* 14th ICDRA, Singapore, at http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra

36. The UPPSALA Monitoring Center (2011). *SFDA in China and the UMC – Collaboration in sharing global patient safety information.* At http://www.umc-products.com/DynPage.aspx?id=75618&news=10096

37. State Food and Drug Administration (2011). *Guideline on strengthening the establishment of an ADR monitoring system.* At http://www.sfda.gov.cn/WS01/CL0844/66936

Paediatric Medicines

Better medicines for children: pharmaceutical formulations

Safe and effective pharmacotherapy in paediatric patients requires the timely development of medicines to suit the age, physiological condition and body size of the child. However, use of unlicensed and off-label medicines in children is widespread. Formulations developed specifically for children are urgently needed.

In 2007, the World Health Organization (WHO) launched the *"Make Medicines Child Size"* project. The WHO Quality Assurance Programme has contributed to the project by developing norms and standards for global application. The WHO Expert Committee on Specifications for Pharmaceutical Preparations have recently endorsed a first guideline and several monographs related to paediatric medicines.

Guideline development

A preliminary draft document *" Development of paediatric medicines: points to consider"* was discussed at the Expert Committee's Forty-second meeting in 2007. A further text was prepared based on the above draft and on *"Formulations of choice for the paediatric population"* published by the European Medicines Evaluation Agency in 2006. Preparatory work involved coordination with ongoing activities both within and outside WHO, in particular with the European Medicines Agency (EMA), UNICEF, and the WHO Essential Medicines Programme. After wide circulation for comment, *"Development of paediatric medicines: points to consider in pharmaceutical formulation"* was adopted at the Forty-sixth Expert Committee meeting in October 2011.

The guideline aims to:

- Inform regulatory authorities and manufacturers of issues that require special attention in the development of paediatric medicines taking into accounting new trends and developments as well as efforts undertaken by regulatory authorities.
- Focus on conditions and special needs in developing countries. The guideline indicates sources of detailed instructions for the development of paediatric medicine formulations. (A list of guidelines and literature appearing in the guideline are reproduced on page 19.)

The guideline covers paediatric dosage forms, dosage forms to be considered in particular, oral administration, rectal administration, parenteral administration, dermal and transdermal administration, inhalations and packaging and labelling.

Extemporaneous preparations and compounding are not within the scope of the document. However, a separate supplementary guidance document entitled *"Provision by healthcare specialists of patient-specific preparations that are not available as authorized products: points to consider"* is under preparation.

Paediatric dosage form selection

The guiding principles in selecting paediatric dosage forms should be, as for adults, the balance of risk/benefit taking into account the specific needs of the 0–18 year-old population.

Convenient, reliable administration. The administered dose should be adjusted to the age and needs of the patient and manipulation of the dose should be kept to a minimum. Paediatric medicines

Table 1. Paediatric dosage form indicators

Dosage form	Advantage	Consideration	Reference
Flexible solid dosage forms, e.g., orodispersible tablets	Priority dosage form. Suitable for both developed and developing countries May be used for various APIs Potentially for use in children > 6 months	Not suitable for medicines requiring a precise dose titration Compatibility of API and breast milk	
Oral medicines for precise dose titration	Suitable for precise dose measurement or titration	Platform technology for multiparticulate solids	WHO: QAS/11.399/Rev.1*
Parenteral formulations	For severe diseases and conditions	Requires a trained caregiver	
Rectal preparations	Severely ill children or children unable to swallow	Cultural barriers to use	

**Zhao N et al (2010). Tablet splitting: product quality assessment of metoprolol succinate extended release tablets. Working document. WHO/QAS/11.399/Rev.1*

should preferably be ready-to-use formulations. Alternatively, the dosage form should be designed to subdivide into smaller, uniform doses of appropriate size for accurate dosing.

Acceptability and palatability. The dosage form should be palatable, easy to administer and acceptable to the patient. It should also be developed to avoid any potential interactions with food and medicine or effects on bioavailability. If administration with common food or liquids is acceptable, information supported by evidence-based compatibility studies should be provided in the patient information leafet.

Dosing frequency. A minimum dosing frequency should be preferred to facilitate compliance with the dosing schedule for older children or caregivers. Instructions on the dosing frequency should be based on the pharmacokinetic and pharmacodynamic properties of the active pharmaceutical ingredient (API) but may be influenced by the design of the dosage form.

End-user needs. Paediatric medicines should be easy to use and affordable with regard to:

- Supply (e.g., ease of transportation, storage requirements).
- Access to clean water.
- Adequate product information (e.g., how to administer; compatibility and incompatibility with food ingredients).

Dosage forms

Although the most appropriate dosage form should be based on a case-by-case evaluation, in general, flexible solid dosage forms are likely to prove most suitable for global use and should be prioritized (Table 1).

Formulation design

Many items need to be considered in the design of formulations for paediatric use. Those mentioned in the *Development of paediatric medicines* document include quality, the Biopharmaceutics Classification System (BCS), excipients, colouring agents, antimicrobial preservatives,

Table 2. Paediatric formulation design indicators

Item	Consideration (key)	Selected references
1. Quality	Acceptable level of impurities in APIs Degradation products in FPPs Safety margins on APIs and FPPs Safety studies in juvenile animals FPP compliance Dissolution testing to address gastric pH of the child	WHO: QAS/10.376 ICH :Q3A(R2);Q3B;Q3C EMA: CPMP/SWP/5199/02 EMEA/CHMP/SWP/431994/2007 CPMP/SWP/QWP/4446/00 The International Pharmacopoeia FIP/AAPS guidelines
2. BCS	BCS-based API classification Transporter function and metabolic enzymes (typically CYP3A4) Excipients affecting transit time (efflux)	WHO. Technical Report Series, No.937, Annex 8.
3. Excipients	Safety profile of paediatric excipient in the target age groups Route of administration Single and daily dose of excipient Duration of treatment Acceptability for intended age group Potential alternatives Regulatory status in intended market	Breitkreutz J,Boos J (2007). Paediatric and geriatric drug delivery. Shehab N et al (2009), Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products. WHO. Technical Report Series. Evaluation of certain food additives.
4. Colouring agents	Use is generally discouraged Use may be justified in certain cases, e.g. to avoid accidental dosing errors (several strengths) Acceptable number for use is limited Azo-dyes should be avoided Risk of allergic reactions associated with natural colourants	Pollock I, Young E, Stoneham M (1989). Survey of colorings and preservatives in drugs. Pefferi G, Restani P (2003). The safety of pharmaceutical excipients.
5. Antimicrobial preservatives	Potential to cause adverse reactions in infants and neonates Avoid use whenever possible Keep to minimum concentration level Solid dosage forms do not need free-mercury-containing preservatives in ophthalmic preparations	Public statement on antimicrobial preservatives in ophthalmic preparations for human use (EMEA/622721/2009).
6. Sweetening agents	Safety in specific conditions (diabetes, fructose intolerance, phenylketonurea) Laxative effect	
7. Taste masking	Cultural differences in taste and acceptability develop taste for maximum acceptability Non-cariogenic sweeteners and flavours preferred	Ernest TB et al (2007). Developing paediatric medicines: identifying the needs and recognizing the challenges.
8. Solubility enhancers	Higher risks for parenteral preparations vs. oral preparations Children vulnerable to the effects of ethanol Toxicity on brain maturation highly probable Chronic exposure linked to dependence in adults and adolescents	

sweetening agents, taste making and solubility enhancers.

Route of administration

The common route of administration discussed in the document covers oral, rectal, parenteral, dermal and transdermal administration and inhalation. Special issues for consideration of each administration route are highlighted and relevant references are listed. (See Table 2.)

Next steps

Although development of paediatric medicines is still subject to limited knowledge in some areas, progress is rapidly being made.

Table 3. Route of administration and formulations

Administration	Special considerations	References
Oral		
liquid preparations		
• drops (microbial and chemical) • powders and granules for reconstitution • suspensions	• preferred route for paediatric patients • stabilizing agents are a major drawback • stability of multidose preparations • risks of incorrect dosing • dose-measuring device critical (drops) • stability parameters of oral suspensions	Strickly RG et al (2007). *Paediatric Drugs.* A review of commercially available oral formulations. Siewert M et al (2003). FIP/AAPS guidelines for dissolution/ in vitro release testing of novel/ special dosage forms.
Administration through nasogastric tubes	• no effects from saliva and gastric juice: may afffect bioavailability • potential absorption of API into tube material	
Solid dosage forms		Thomson SA et al (2009). Mini-tablets: new modality to deliver medicines to preschool-age children.
• powders and multiparticulate preparations	• Improved stability, good dosage uniformity, options for different doses	
• immediate-release tablets • capsules	• crushing tablets may affect bioavailability (only if allowed by manufacturer)	
• chewable tablets	• chewable tablets may be chewed or swallowed whole (dissolution test conditions same as for tablets)	Seager H (1998). Drug–delivery products and the zydis fast-dissolving dosage form.
• effervescent dosage forms	• control moisture and humidity in manufacture, packaging and storage of effervescents • effervescents: caution in renal insufficiency	
• dispersible and soluble tablets	• dispersible and soluble tablets: flexibility for water-soluble APIs	ICH E11 EMEA/622721/2009
• sustained-release formulations	• labelling instructions for sustained-release formulations (including coated tablets and matrix tablets): not to be broken or chewed	
• orodispersible dosage forms	• orodispersibles may be moisture-sensitive	
Rectal		
suppositories	• important route of administration for children severely ill or unable to swallow	
rectal liquids	• concordance and compliance of rectal preparation may be lower • cultural and regional acceptance barriers	

Table 3. Route of administration and formulations *(continued)*

Administration	Special considerations	References
Parenteral	• preferred route of administration for seriously ill children and clinically unstable term and preterm neonates (developed world setting). • limited experience of needle-free injection device use in children. • increased blood perfusion in sustained-release preparations. • safety profile of each excipient and suitability for intended use.	WHO. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (2006).
Dermal and transdermal ***Transdermal patches***	• hydration of the skin and thickness of stratum corneum in children different from adults. • unintended systemic absortion through dermis a potential risk for many APIs. • safety profile of excipients. • test for local tolerance and acceptability.	
Inhalations ***Liquids for nebulization*** ***Metered dose inhalers (MDIs)*** ***Dry powder inhalers (DPIs)***	• total lung deposition important for clinical efficacy of preparation. • small airway diameter in children, deposition by impact in upper and central airways may be significantly higher in children.	Krause J, Breitkreuts J (2008). Improving drug delivery in paediatric medicine. Dolovich M (2000). Influence of inspiratory flow rate, particle size and airway caliber in aerosolized drug delivery to the lung. Schüepp K, Jauernig J, Janssens H (2005). In vitro determination of the optimal particle size for nebulized aerosol delivery to infants.

Bibliography

1. European Medicines Agency. *Clinical Investigation of Medicinal Products in the Paediatric Population, ICH Topic E11*. January 2001 CPMP/ICH/2711/99 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.

2. World Health Organization. *Guideline on quality risk management* (working document QAS/10.376) at http://www.who.int/medicines

3. World Health Organization. Thirty-ninth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Technical Report Series,* No. 929, Annex 5. Guidelines for registration of fixed-dose combination medicinal products (2005) at http://www.who.int/medicines

4. World Health Organization. *Pharmaceutical development for multisource (generic) pharmaceutical products.* Working document QAS/08.251/Rev.1 at http://www.who.int/medicines

5. International Conference on Harmonization. Impurities in new drug substances. ICH Topic

Q3A(R2) at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2__Guideline.pdf

6. European Medicines Agency. *Impurities in new drug products, ICH Topic Q3B.* CPMP/ICH/2738/99 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002676.pdf

7. European Medicines Agency. *Impurities: guideline for residual solvents, ICH Topic Q3C.* February 2009. CPMP/ICH/283/95 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002674.pdf

8. European Medicines Agency. *Guideline on the limits of genotoxic impurities* (CPMP/SWP/5199/02). EMEA/CHMP/QWP/251344/2006 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf

9. European Medicines Agency. *Q&A on the CHMP Guideline on the limits of genotoxic impurities.* EMEA/CHMP/SWP/431994/2007 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf

10. European Medicines Agency. *Note for guidance on specification limits of residues of metal catalysts* (CPMP/SWP/QWP/4446/00). 17 December 2002. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003588.pdf

11. World Health Organization. Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Technical Report Series*, No. 937, Annex 8, Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid dosage forms (2006) at http://www.who.int/medicines

12. European Medicines Agency. *Public statement on antimicrobial preservatives in ophthalmic preparations for human use.* 8 December 2009. EMEA/622721/2009 at http://www.techtran.co.jp/techtr_j/globepharm/emea091208.pdf

13. European Medicines Agency. *Guideline on the investigation of medicinal products in the term and preterm neonate.* EMEA/566810/2008. at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003754.pdf

14. World Health Organization. Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Technical Report Series,* No. 937, Annex 7: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (2006) at http://www.who.int/medicines

References

1. Kearns GL et al. Developmental pharmacology – drug disposition, action and therapy in infants and children. *N Eng J Med* 2003;**349**(12):1157–1167.

2. European Medicines Agency. *Reflection paper: formulations of choice for the paediatric population.* (EMEA/CHMP/PEG/196810/2005) at http://www.nppg.scot.nhs.uk/misc/choicepaper0605.pdf

3. Ernest TB et al. Developing paediatric medicines: identifying the needs and recognizing the challenges. *J Pharm Pharmacol* 2007;**59**:1043–1055.

4. Krause J, Breitkreutz J. Improving drug delivery in paediatric medicine. *Pharmaceutical Medicine* 2008;**22**:41–50.

5. Allen LV. Dosage form design and development. *Clin Ther* 2008;**30**(11):2102–2111.

6. Siewert M et al. FIP/AAPS guidelines for dissolution/in vitro release testing of novel/special dosage forms. *Dissolution Technologies* 2003; February Issue, page 15.

7. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. *Expert Opin Drug Deliv* 2007;**4**(1):37–45.

8. Shehab N et al. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatric Critical Care Medicine* 2009;**10**(2):256-259.

9. “Inactive” Ingredients in Pharmaceutical Products: Update: http:/www.pediatrics.org/cgi/content/full/99/2/268

10. World Health Organization. *Technical Report Series*, Evaluation of certain food additives. List of publications: http://www.who.int/ipcs/publications/jecfa/reports/en/index.html.

11. Pollock I, Young E, Stoneham M. Survey of colourings and preservatives in drugs. *Brit. Med J* 1989;**299**:649–651.

12. Pefferi G, Restani P. The safety of pharmaceutical excipients. *Il Farmaco* 2003; **58**:541–550.

13. Mennella JA, Beauchamp GK. Optimizing oral medications for children. *Clin Ther* 2008;**30**(11):2120–2132.

14. Strickly RG et al. Paediatric drugs – A review of commercially available oral formulations. *J Pharm Sci* 2007;**97**(5):1731–1774.

15. Thomson SA et al. Mini-tablets: new modality to deliver medicines to preschool-aged children. *Paediatrics* 2009;**123**(2):e235–e238.

16. Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. *J Pharm Pharmacol*1998;**50**:375–382.

17. Dolovich M. Influence of inspiratory flow rate, particle size and airway caliber in aerosolized drug delivery to the lung. *Respiratory Care* 2000;**45**:597–608.

18. Schüepp K, Jauernig J, Janssens H. In vitro determination of the optimal particle size for nebulized aerosol delivery to infants. *J Aerosol Med* 2005;**18**(2):225–235.

Benznidazole: child-adapted dosage form approved

Brazil's National Health Surveillance Agency (ANVISA) has granted registration of a new paediatric dosage form of benznidazole, developed through a partnership between the Pernambuco State Pharmaceutical Laboratory (LAFEPE) of Brazil and the Drugs for Neglected Diseases initiative (DNDi). Registration of this formulation of benznidazole was made on 12 December 2011.

This new tablet is easier-to-administer and a safer treatment of Chagas disease in infants and young children under the age of two, as they will receive accurate dosage. Until now, benznidazole was available only as a 100 mg tablet for adults. Treatment for young children required cutting adult pills into tiny slivers — up to 12 pieces depending on the child's weight — and crushing and mixing them with water or juice, to be administered twice a day for 60 days. This difficult and inefficient method often results in improper dosing, risks of increased side-effects, ineffective treatment, or treatment stoppages.

Chagas disease affects an estimated eight to ten million people, mostly in Latin America, and kills some 12,000 people each year, making it the leading parasitic killer in the Americas. The Chagas parasite is primarily transmitted via the bite of the blood-sucking triatome bug. In addition to blood transfusion, organ transplant, or ingesting infected food, the parasite is also transmitted during pregnancy from mother to child.

This new dosage form for children represents real progress for several reasons. Children are at especially high risk of infection, with a majority of them born from infected mothers. It is known that early treatment using benznidazole in the first year of life can eliminate the parasite in more than 90% of infected newborns. Thus, babies infected with Chagas disease will benefit the most from this new paediatric tablet.

The new 12.5 mg tablet is easily dispersible and adapted for babies and children up to two years of age (20 kg body weight). Treatment is designed to use one, two, or three tablets, depending on weight (recommended dosage, 5–10 mg/kg body weight/day).

Tools to facilitate implementation of and access to the new treatment include a

Demand Forecast, a Procurement Guide, and a Tool Box providing training and educational materials for doctors, other health professionals, mothers, and caregivers regarding appropriate use of the treatment.

In 2008, DNDi and LAFEPE entered a joint development agreement for this dosage form. The new tablet will be produced by LAFEPE, a public pharmaceutical manufacturer run by the State of Pernambuco in Brazil and the sole global producer of benznidazole.

Reference: DNDi Drugs for Neglected Diseases initiative at http://www.dndi.org

Use of drugs in paediatric health conditions increasing

In the past, treatment decisions involving the use of drugs in infants, children and youth were often derived from the data in drug studies involving adults (1, 2). However, the safety and efficacy of medications may be significantly different in paediatric patients than in adult patients owing to differences in developmental physiology, disease pathophysiology, and developmental pharmacokinetics and pharmacodynamics (2). This understanding has led to the use of the phrase «children are not just small adults,» a statement that emphasizes the urgent need for evidence from high-quality trials involving paediatric patients (2).

The use of drugs to treat paediatric health conditions in Canada is increasing (3). Infants, children and youth represent nearly one-quarter of Canada's population and, on average, receive four prescriptions a year from a range of more than 1200 different drugs (3, 4). Nonetheless, data on the efficacy and safety of most medications prescribed for pediatric patients are limited (2, 3, 5).

When prescribing a medication for an «off-label» indication in infants, children or youth, health professionals may consult available sources of information, such as peer-reviewed medical literature, paediatric dosing manuals and textbooks, drug formularies at children's hospitals, community pharmacists and the relevant pharmaceutical company representatives. In the absence of experimental studies in paediatric populations, information provided by these sources may be based more on expert opinion or local practice and experience (5).

Drug investigations in paediatric populations can be faced with multiple challenges. Some examples include:

- Defining appropriate ethical adaptations of clinical trials for studies involving infants, children and youth (1).
- Ensuring adequate sample sizes (1, 2).
- Choosing objective, clinically relevant endpoints that can be measured in a valid and reliable manner (1, 2).
- Overcoming technical difficulties, such as the need for frequent blood sampling (1).
- Improving pharmacoepidemiologic and pharmacovigilance practices aimed to coordinate the development of reliable information about drug benefits and harms to reduce uncertainties about the use of drugs in paediatric populations.
- Expanding the availability of age-appropriate product formulations (e.g., liquid formulations).

Health Canada, like other regulatory authorities around the world, recognizes the need to strengthen information related to paediatric health. In pursuit of this objective, some of its key activities include:

- Coordinating the development of paediatric information through the regulatory system and other means.
- Coordinating how this information is made available and accessible.
- Raising awareness of child health needs and safety issues related to the development and use of health products and food.
- Promoting conditions that enable informed decisions about the health and nutrition of infants, children and youth.

To help improve safety data about health products for the paediatric population, it is important for healthcare providers to continue to report adverse reactions in both paediatric and adult populations.

Extracted from Canadian Adverse Reaction Newsletter, Volume 22, Issue 1, January 2012

References

1. Matsui D, Kwan C, Steer E, et al. The trials and tribulations of doing drug research in children. *CMAJ* 2003;**169**(10):1033–4.

2. Klassen TP, Hartling L, Craig JC, et al. Children are not just small adults: the urgent need for high-quality trial evidence in children. *PLoS Medicine* 2008;**5**(8):1180–2.

3. Abi Khaled L, Ahmad F, Brogan T, et al. Prescription medicine use by one million Canadian children. *Paediatr Child Health* 2003;**8**(A):6A–56A.

4. Junker A. Canadian pediatric clinical trials activity 2005-2009. *Maternal Infant Child Youth Res Network* 2010;Aug:1–19.

5. Matsui D, Jardine M, Steer V, et al. Where physicians look for information on drug prescribing for children. *Paediatr Child Health* 2003;**8**(4):219–21.

Safety and Efficacy Issues

Bevacizumab: severe infectious endophthalmitis and blindness

Canada — Health Canada has informed healthcare professionals of new safety information regarding unauthorized use of bevacizumab (Avastin®) when repackaged for intra-vitreal injection.

Three clusters of serious ocular complications, including acute ocular inflammation, endophthalmitis, and infectious endoph-thalmitis resulting in blindness, have been recently reported in California, Florida and Tennessee. Although these clusters continue to be investigated, it is possible that the events of blindness from streptococcal endophthalmitis in Florida were due to repackaging of bevacizumab without proper aseptic technique.

Bevacizumab is a recombinant humanized monoclonal antibody that is directed against vascular endothelial growth factor (VEGF). It is authorized for intravenous administration in the following indications:

- First-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine-based chemotherapy.
- Treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer in combination with carboplatin/paclitaxel chemotherapy regimen.
- Treatment of patients with glioblastoma after relapse or disease progression, following prior therapy.

Reference: Communication from Hoffmann-La Roche dated 2 December 2011 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2011/avastin_8_hpc-cps-eng.php

Ursodeoxycholic acid: serious hepatic events

Canada — Ursodeoxycholic acid (Ursodiol®) is indicated for the management of cholestatic liver diseases. Canadian Product Monographs for ursodiol® products have been updated in October, 2011 to reflect data from a long-term clinical trial in primary sclerosing cholangitis (PSC) finding an increase in serious liver adverse events in patients taking an unapproved ursodiol dose (twice the recommended dose).

- The recommended ursodiol dose is 13–15 mg/kg/day for adults with cholestatic disease.
- In a clinical trial in patients with PSC, long-term use of twice the recommended dose of ursodiol® was associated with improvement in serum liver tests but did not improve survival, and was associated with higher rates of serious adverse events (including death or liver transplantation) compared to placebo.
- Improved serum liver tests do not always correlate with improved liver disease status.

Reference: Communication from Aptalis Pharma Canada dated 1 December 2011 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2011/avastin_8_hpc-cps-eng.php

Simvastatin with amiodarone: dosage review

United States of America — The Food and Drug Administration (FDA) has advised of a dose limitation for simvastatin from 10 mg to 20 mg when co-administered with the cardiac drug amiodarone. In June 2011, the FDA previously recommended that the dose limitation for

simvastatin be decreased from 20 mg to 10 mg, and has now reconsidered that recommendation. Unlike other interacting drugs, there were no pharmacokinetic or clinical trial data to support the simvastatin dose reduction approved with amiodarone. Therefore FDA has determined that the simvastatin dose limitation, when taken with amiodarone, should be restored to 20 mg.

In patients who are taking both simvastatin and amiodarone, the dose of simvastatin should not exceed 20 mg per day. The simvastatin drug labels (Zocor® and generics, Vytorin®) have been updated to reflect this correction.

Reference: *FDA Drug Safety Communication,* 15 December 2011 at http://www.fda.gov/Drugs/DrugSafety/ucm283137.htm

Fenofibric acid: the ACCORD lipid trial

United States of America — The Food and Drug Administration (FDA) has advised that the cholesterol-lowering medicine fenofibric acid (Trilipix®) may not lower a patient's risk of having a heart attack or stroke. This is based on data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial, which evaluated the efficacy and safety of fenofibrate plus simvastatin combination therapy versus simvastatin alone in patients with type 2 diabetes mellitus. FDA reviewed this trial as part of its ongoing investigation of the safety and efficacy of Trilipix®.

In the ACCORD Lipid trial, there was no significant difference in the risk of experiencing a major adverse cardiac event between the group treated with fenofibrate plus simvastatin compared with simvastatin alone. In addition, a subgroup analysis showed that relative to treatment in men, there was an increase in the risk for major adverse cardiac events in women receiving the combination therapy versus simvastatin alone.

Reference: *FDA Drug Safety Communication,* 9 November 2011 at http://www.fda.gov/Drugs/DrugSafety/ucm278837.htm

BCG vaccine: lymphadenitis

Singapore — The Health Sciences Authority (HSA) has updated healthcare professionals on suspected reports of lymphadenitis following the administration of the Bacillus Calmette-Guérin (BCG) Vaccine Staten Serum Institute (SSI)®. This observation arose from the active surveillance and monitoring of vaccine adverse events (VAEs) at the sentinel site at KK Women's and Children's Hospital (KKH).

In 2009, HSA collaborated with KKH to initiate active surveillance for VAEs related to H1N1 vaccines in pregnant women and children. This was subsequently expanded to include all VAEs following childhood immunization.

In Singapore, BCG vaccine is routinely given to newborns as part of the National Childhood Immunization Schedule. Since June 2003, the BCG vaccine manufactured by SSI is the sole BCG vaccine registered in Singapore. BCG Vaccine SSI® contains an attenuated strain of *Mycobacterium bovis* (BCG), Danish strain 1331.

In 2009, there were 26 reports of BCG-associated lymphadenitis of which 23 cases (88%) presented as suppurative lymphadenitis. Of these, 22 cases required surgical intervention such as excision or incision and drainage. In 2010, there were 25 reports of lymphadenitis. Sixteen cases (64%) presented as suppurative lymphadenitis which required surgical intervention. From January 2011 to October 2011, the reports of lymphadenitis increased to 53.

An increase in the number of suspected reports of BCG-associated suppurative lymphadenitis has also been identified in some countries such as Ireland and Latvia in recent years. However, the

overall rate and pattern of VAEs remain consistent with the expected frequency of occurrence listed in the package insert of BCG Vaccine SSI®.

Reference: *Health Sciences Authority (HSA) Safety Announcement* at http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/safety_alerts_2011/reports_of_lymphadenitis.html

Dabigatran etexilate mesylate: bleeding events

United States of America — The Food and Drug Administration (FDA) has evaluated post-marketing reports of serious bleeding events in patients taking dabigatran etexilate mesylate (Pradaxa®). Dabigatran etexilate mesylate is a direct thrombin inhibitor used to reduce the risk of stroke in patients with non-valvular atrial fibrillation, the most common type of heart rhythm abnormality.

Bleeding that may lead to serious or even fatal outcomes is a well-recognized complication of all anticoagulant therapies and the Pradaxa® drug label contains a warning about significant and sometimes fatal bleeding.

Reference: *FDA Drug Safety Communication,* 7 December 2011 at http://www.fda.gov/Drugs/DrugSafety/ ucm282724.htm

Dabigatran etexilate: caution in the elderly and renally impaired

Singapore — The Health Sciences Authority (HSA) has alerted healthcare professionals to serious cases of bleeding associated with the use of dabigatran and reminded them to closely monitor patients who are prescribed this medication, especially the elderly and those with renal impairment.

Dabigatran (Pradaxa®) has been licensed locally since August 2009 for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or total knee replacement surgery. In June 2011, the indication for Pradaxa® was extended to include the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Bleeding is a known side-effect for dabigatran as it is an extension of its pharmacological effect. Based on clinical evidence, the risk of major or severe bleeding from dabigatran is rare, even though life-threatening or even fatal outcomes may occur. The local package insert of Pradaxa® currently carries warnings of this risk, including the recommendation to monitor for signs of bleeding or anaemia (1). Additionally, the local package insert recommends dose adjustments in the elderly and those with impaired renal function as well as close clinical surveillance in patients with low body weight (<50kg) and high body weight (>110kg). Dabigatran is contraindicated in patients with severe renal impairment.

To date, HSA has received seven suspected adverse reaction reports associated with dabigatran. These included one case of bleeding, one case of deep vein thrombosis and blood clot in the heart and one case of stroke, all occurring in patients between 77 and 86 years of age. The time to onset of these cases were a few months after initiation of dabigatran. No concomitant medicines were reported and none of these cases had a fatal outcome.

Reference: The Health Sciences Authority (HSA). *Safety Announcement,* at http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information

Dabigatran: risk of bleeding

Australia — Dabigatran (Pradaxa®) is a potent short-acting anticoagulant for which there is no antidote or reversal agent. As with warfarin, bleeding events can occur. Clinicians are urged to give careful consideration to the suitability of

patients for dabigatran particularly with regard to recognized risks of bleeding.

Dabigatran is a potent oral anticoagulant. It is a direct thrombin inhibitor that inhibits free and clot-bound thrombin. It has a mean half-life of 12–17 hours. It is renally excreted and the rate of elimination is related to renal function. There is a close correlation between plasma dabigatran levels and anticoagulant effect.

Dabigatran may be considered an alternative to warfarin and it carries similar risks of bleeding. In clinical trials the risk of bleeding per year of treatment with dabigatran was 16.6% when taking 150 mg twice daily, and 14.7% taking 110 mg twice daily compared with 18.4% for warfarin.

In April 2011, the Therapeutic Goods Administration (TGA) approved dabigatran for use for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one risk factor for stroke. Since then, the TGA has received an increase in the number of bleeding-related adverse events reports for dabigatran (see table).

The analysis of these reports shows that some of the bleeding adverse events occurred during the transition from warfarin to dabigatran; many of the adverse events are occurring in patients on the reduced dosage regimen; and the most common site of serious bleeding for dabigatran is the gastrointestinal tract, whereas for warfarin it is intracranial.

Australian experts are currently developing guidelines for the management of bleeding in patients taking dabigatran. In the meantime clinicians are referred to the New Zealand guidelines (1).

It is strongly recommended that clinicians read the Product Information before prescribing dabigatran. The Product Information is available from the TGA web site (2). For more detailed information regarding the considerations of the TGA in approving dabigatran please see the Australian Public Assessment Report (AusPAR) (3).

Adverse events reported to the TGA for dabigatran June 2009 – October 2011

Type of adverse event	Number
Total adverse events	297
Serious adverse events	196
Serious bleeding adverse events	70
Serious gastrointestinal bleeding	48
Serious intracranial bleeding	6
Events in patients aged 75 years or older:	
Total adverse events	166
Serious adverse events	108

References

1. Guidelines for management of bleeding with dabigatran. New Zealand: *PHARMAC*; 2011.

2. Pradaxa Product Information. Boehringer Ingelheim Pty Limited. August 2011.

3. Dabigatran etexilate mesilate-AusPAR. Therapeutic Goods Administration. 14 May 2011 at http://www.tga.gov.au

Pneumovax 23®: revaccination recommendations

Australia — Pneumovax 23® vaccination is used to prevent life-threatening infections by pneumococcal bacteria.

In March 2011, a cluster of seven severe local injection site reactions was reported to the Therapeutic Goods Administration (TGA) by NSW Health and as a result a recall of the batch of Pneumovax® implicated in these reactions was ordered by the TGA on 25 March 2011.

In April 2011, as a result of a continued increase in severe injection site reaction reports, the TGA issued advice to health professionals not to administer a second or subsequent dose of Pneumovax 23® vaccine pending the outcome of a review, which has now been completed.

Laboratory analysis of the recalled batch (N3336) did not detect any problems related to vaccine manufacture or handling. The TGA has now determined that the adverse events were not a batch-related problem. The TGA considers that the increased numbers of reports of severe reactions were a result of:

- The known high rates of local reactions, including severe injection site reactions, which occur more commonly after a repeat dose of Pneumovax 23®.
- The increased number of people having a repeat dose following the inclusion of Pneumovax 23® vaccine in the National Immunization Programme in 2005 with revaccination after five years.
- The increased reporting that followed the publicity of the batch recall.

The TGA is advising that revaccination with Pneumovax 23® can be undertaken in accordance with the approved Product Information (PI). In summary, revaccination should:

- not be given routinely to immunocompetent individuals (that is, those with a healthy immune system).
- be considered for patients at a high risk of serious pneumococcal disease, provided that at least five years has passed since the previous dose of Pneumovax 23®.

Reference: Pneumovax 23®: updated revaccination recommendations. 23 December 2011 at http://www.tga.gov.au/safety/alerts-medicine-pneumovax-111223.htm

Somatropin-containing medicines: positive benefit-risk balance

European Union — Following a review of somatropin-containing medicines, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has confirmed that the benefit-risk balance of these medicines remains positive. However, the CHMP wished to remind prescribers to strictly follow the approved indications and doses and to carefully consider the warnings and precautions for somatropin-containing medicines.

Somatropin is a human growth hormone, manufactured using recombinant DNA technology. It promotes growth during childhood and adolescence, and also affects the way the body handles proteins, fat and carbohydrates. It is used to treat a number of conditions associated with impaired growth and short stature. These include children who fail to grow adequately due to a lack of growth hormone, Turner syndrome or chronic renal insufficiency and short children born small for gestational age.

Reference: *EMA Press Release,* EMA/CHMP/965945/2011, 15 December 2011 at http://www.ema.europa.eu

Pholcodine-containing cough medicines

European Union — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has confirmed that the benefits of pholcodine-containing cough medicines outweigh their risks and that these medicines should remain available for the treatment of non-productive (dry) cough in children and adults.

The review of pholcodine-containing medicines was initiated because of concerns that there could be cross-sensitisation between pholcodine and neuromuscular blocking agents (NMBAs). It was suspected that this in turn could lead to anaphylactic reactions in some patients receiving NMBAs during emergency surgery who had previously taken pholcodine-containing cough medicines.

Following a thorough review of all available data on the safety and efficacy of pholcodine-containing cough medicines, the Committee found no firm evidence to substantiate the hypothesis of cross-

sensitization between pholcodine and NMBAs and a subsequent increased risk of anaphylactic reactions during surgery.

Reference: *EMA Press Release,* EMA/CHMP/898043/2011, 18 November 2011 at http://www.ema.europa.eu

Antipsychotics in children and adolescents: cardiometabolic reactions

Canada — Health Canada has received 29 reports of cardiometabolic adverse reactions suspected of being associated with second-generation antipsychotics (SGAs) in children and adolescents under 18 years of age. In Canada, no SGAs are authorized for use in children or adolescents, with one recent exception authorized for use only in adolescents 15 to 17 years old for the treatment of schizophrenia.

Excess weight and obesity in the population are increasing problems throughout the Western world, and this rise has also been observed in children and adolescents (1). Weight gain and obesity are known to be associated with diabetes, dyslipidaemia and hypertension (2). In addition, weight gain is a well-established adverse reaction to second-generation antipsychotics (SGAs) (1).

In Canada, there are seven marketed second-generation antipsychotics: clozapine, risperidone, olanzapine, quetiapine, paliperidone, ziprasidone and aripiprazole. Recently, aripiprazole (Abilify®) was authorized for the treatment of schizophrenia in adolescents 15 to 17 years old (3).

Previously, there were no authorized indications for the use of SGAs in children or adolescents under 18 years of age in Canada. Paediatric drug use, in many circumstances, has been based primarily on information extrapolated from studies involving adults, as well as from other types of scientific evidence, including case reports, open studies of clinical experience and controlled clinical trials (4, 5). Second-generation antipsychotics have been prescribed for children and adolescents with mental health problems such as schizophrenia, bipolar I disorder, autism, pervasive developmental disorder, disruptive behaviour disorders (including conduct disorder and attention-deficit hyperactivity disorder), developmental disabilities and Tourette syndrome (6). Use of these drugs in the paediatric population has increased substantially over the last decade (6–8). According to one estimate, antipsychotic drug prescriptions for children and youth in Canada increased by 114% from 2005 to 2009 (4). Despite this increased use, data regarding their safety are limited (2).

The cardiometabolic effects of SGAs in pediatric patients, including age-inappropriate weight gain, obesity, hypertension, and lipid and glucose abnormalities, are of concern (8). Furthermore, children and adolescents with mental health problems often have multiple cardiovascular risk factors, including poor nutrition, inadequate exercise, substance abuse and lack of adequate healthcare monitoring (2, 9). Some studies have shown that youth using antipsychotic agents may be at a higher risk of weight gain and metabolic effects than adults who use the same drugs (2, 7, 10). If weight gain is established in youth, it tends to persist into adulthood (10).

Because of differences in absorption, distribution and metabolism of antipsychotics in the paediatric population, higher doses per weight are required than in adults to achieve similar efficacy (2). Cardiometabolic effects are problematic during childhood because they tend to be predictors of adult obesity, metabolic syndrome, hypertension, cardiovascular morbidity and malignant disease (2, 7, 8).

Adverse effects such as weight gain have been found to vary significantly by SGA agent. Clozapine and olanzapine seem

to be associated with the highest risk of clinically significant weight gain in children and adults (1, 2, 7). Risperidone and quetiapine generally show modest risk, whereas ziprasidone and aripiprazole are associated with the lowest risk. Limited data are available for paliperidone (4). The risk of lipid elevation and increased blood sugar appears to be greatest with olanzapine (11).

Extracted from Canadian Adverse Reaction Newsletter, Volume 22, Issue 1, January 2012

References

1. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 2005;**19**(Suppl 1):1–93.

2. De Hert M, Dobbelaere M, Sheridan EM, et al. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systemic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry* 2011;**26**:144–58.

3. Abilify® (aripiprazole) [product monograph]. Montréal (QC): Bristol-Myers Squibb Canada; 2011.

4. Pringsheim T, Panagiotopoulos C, Davidson J, et al. Evidence-based recommendations for monitoring safety of second generation antipsychotics in children and youth. *J Can Acad Child Adolesc Psychiatry* 2011;**20**(3):218–33.

5. Zito JM, Derivan AT, Kratochvil CJ, et al. Off-label psychopharmacologic prescribing for children: history supports close clinical monitoring. *Child Adolesc Psychiatry Mental Health* 2008;**2**(24):1–11.

6. Panagiotopoulos C, Ronsley R, Elbe D, et al. First do no harm: promoting an evidence-based approach to atypical antipsychotic use in children and adolescents. *J Can Acad Child Adolesc Psychiatry* 2010;**19**(2):124–37.

7. Correll CU. Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents. *J Clin Psychiatry* 2008;**69**(Suppl 4):26–36.

8, Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 2009;**302**(16):1765–73.

9. Varley CK, McClellan J. Implications of marked weight gain associated with atypical antipsychotic medications in children and adolescents. *JAMA* 2009;**302**(16):1811–2.

10. Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. *J Am Acad Child Adolesc Psychiatry* 2002;**41**(3):337–43.

11. Ho J, Panagiotopoulos C, McCrindle B, et al. Management recommendations for metabolic complications associated with second generation antipsychotic use in children and youth. *J Can Acad Child Adolesc Psychiatry* 2011;**20**(3):234–41.

Citalopram hydrobromide: dose-dependent QT prolongation

Canada — Health Canada has informed healthcare professionals that the antidepressant citalopram hydrobromide (Celexa®, also marketed as generics), should no longer be used at doses greater than 40 mg per day due to study results indicating a dose-dependent potential for QT prolongation. Previously, the Canadian Product Monograph stated that certain patients may require 60 mg per day.

Citalopram hydrobromide is a selective serotonin reuptake inhibitor (SSRI) indicated for the symptomatic relief of depressive illness available as 20 mg and 40 mg tablets.

A thorough QT study, conducted according to international standards, assessing the effects of citalopram 20 mg per day and 60 mg per day on the QT interval has shown that citalopram causes dose-dependent QT prolongation. Patients at particular risk for developing prolongation of the QT interval include those with

underlying heart conditions and those who are predisposed to low blood levels of potassium and magnesium. Hypokalaemia and hypomagnesaemia should be corrected before administering citalopram hydrobromide.

Reference: *Safety Alert – Medeffect.* 25 January 2012 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/celexa_2_hpc-cps-eng.php

Brentuximab vedotin: new warning and contraindication

United States of America — The Food and Drug Administration (FDA) has advised that two additional cases of progressive multifocal leukoencephalopathy (PML) have been reported with the lymphoma drug brentuximab vedotin (Adcetris®). Due to the serious nature of PML, a new boxed warning has been added to the drug label.

Brentuximab vedotin is used to treat Hodgkin lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. It is an antibody-drug conjugate, allowing the antibody to direct the drug to a target on CD30 lymphoma cells.

In addition, a new contraindication warning against use of brentuximab vedotin with the cancer drug bleomycin due to increased risk of pulmonary (lung) toxicity has been added to the drug label. A clinical trial compared the combination of Adcetris® plus Adriamycin® (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD) to the combination of Adcetris® plus Adriamycin® (doxorubicin), vinblastine, and dacarbazine (AVD) as front-line therapy for HL. An excessive number of patients in the Adcetris plus® ABVD treatment group experienced non-infectious pulmonary toxicity.

- Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity.
- John Cunningham virus (JCV) infection resulting in progressive multifocal leukoencephalopathy (PML) and death has been reported in Adcetris®-treated patients. The factors leading to reactivation of latent JC virus are not fully understood.

Healthcare professionals should instruct patients to report changes in mood or unusual behavior, confusion, loss of memory, changes in walking or talking, decreased strength or weakness on one side of the body, or changes in vision.

Reference: *FDA Drug Safety Communication,* 13 January 2012 at http://www.fda.gov/Drugs/DrugSafety/

Quetiapine: information updated

United Kingdom — The manufacturer of quetiapine and quetiapine prolonged release has informed healthcare professionals of an update to the special warnings and precautions section of the summary of product characteristics concerning weight gain, hyperglycaemia and metabolic risk.

Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate in accordance with antipsychotic guidelines.

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor.

Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Given the observed changes in weight, blood glucose and lipids seen in clinical studies, there may be possible worsening of the metabolic risk profile in individual patients, which should be managed as clinically appropriate.

Reference: Medicines and Healthcare Products Regulatory Agency (MHRA). Communication from AstraZeneca UK at http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/index.htm

Aliskiren: cardiovascular and renal events

United Kingdom — The manufacturer of aliskiren (Rasilez®) has informed healthcare professionals of new safety information following the interim results from the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE). Analyses of these data are ongoing. However, as a precautionary measure, it is advised that routine (non-urgent) review is carried out for patients taking Aliskiren-containing medicines.

Additionally, aliskiren or aliskiren-containing fixed combination products should not be used in patients with diabetes in combination with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). As a consequence:

- Healthcare professionals should stop aliskiren-containing treatment in patients who are diabetic and also taking an ACE inhibitor or an ARB. Alternative antihypertensive treatment should be considered as necessary.
- Aliskiren-containing products should not be initiated in diabetic patients who are also taking either an ACE inhibitor or ARB.

The ALTITUDE study was conducted in type 2 diabetic patients at high risk of fatal and non-fatal cardiovascular and renal events. In most patients arterial blood pressure was adequately controlled at baseline. Aliskiren 300 mg was given in addition to standard of care, including an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

A higher incidence of adverse events related to non-fatal stroke, renal complications, hyperkalaemia and hypotension were observed in this high-risk population.

Reference: Medicines and Healthcare Products Regulatory Agency (MHRA). Communication from Novartis dated 23 December 2011 at http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/index.htm

Natalizumab: progressive multifocal leukoencephalopathy

United States of America — The Food and Drug Administration (FDA) has advised that testing positive for anti-John Cunningham virus (JCV) antibodies has been identified as a risk factor for progressive multifocal leukoencephalopathy (PML). PML is a rare but serious brain infection associated with use of natalizumab (Tysabri®) for the treatment of multiple sclerosis or Crohn disease.

Natalizumab has been approved for the treatment of relapsing forms of multiple sclerosis since November 2004 and for the treatment of moderately to severely active Crohn disease since January 2008.

Patients with three known risk factors have an estimated risk of PML of 11/1,000 users. The risk factors are:

- Presence of anti-JCV infection antibodies.
- Longer duration of Tysabri® treatment, especially beyond 2 years.
- Prior treatment with an immunosuppressant medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil).

Reference: *FDA Drug Safety Communication,* 20 January 2012 at http://www.fda.gov/Drugs/DrugSafety

Boceprevir: HIV protease inhibitor interactions

United States of America — The Food and Drug Administration (FDA) has notified healthcare professionals of drug interactions between the hepatitis C virus (HCV) protease inhibitor boceprevir (Victrelis®) and certain ritonavir-boosted human immunodeficiency virus (HIV) protease inhibitors (atazanavir, lopinavir, darunavir) which can potentially reduce the effectiveness of these medicines when used together.

Boceprevir is a hepatitis C virus (HCV) protease inhibitor used with the medicines peginterferon alfa and ribavirin to treat chronic hepatitis C infection in adults who have not been treated before or who have failed previous treatment. Ritonavir is an HIV protease inhibitor used to "boost" other HIV protease inhibitors, increasing their levels in the blood and making them more effective.

A drug interaction study showed that taking boceprevir (Victrelis®) with ritonavir (Norvir®) in combination with atazanavir (Reyataz®) or darunavir (Prezista®), or with lopinavir/ritonavir (Kaletra®) reduced blood levels of the HIV medicines and boceprevir in the body.

Drug interactions between boceprevir and ritonavir-boosted atazanavir, lopinavir, and darunavir can potentially reduce the effectiveness of these medicines when co-administered.

Reference: *FDA Drug Safety Communication,* 8 February 2012 at http://www.fda.gov/Drugs/DrugSafety/ucm291119.htm

Bortezomib: fatal if given intrathecally

Canada — Health Canada has alerted healthcare professionals to the risk of fatal outcome associated with the inadvertent intrathecal administration of the antineoplastic drug bortezomib (Velcade®).

Since the first global approval of bortezomib in May 2003, three cases of inadvertent intrathecal administration with fatal outcome have been reported worldwide; these occurred in France and Italy. Each case occurred when an intrathecal oncology chemotherapy was scheduled at the same time as bortezomib intravenous administration. Health Canada has not received any Canadian reports involving inadvertent intrathecal administration.

Bortezomib should only be administered via the approved intravenous (IV) route; Bortezomib is fatal if given intrathecally. Healthcare professionals are encouraged:

- To administer chemotherapy intended via the intrathecal route at a different time than other parenteral chemotherapy.
- To use different connectors for medicinal products to be administered via the intrathecal or intravenous route.
- To clearly label syringes with the name of the medicinal product and route of administration to be used and ensure procedures are in place to enforce a double check of syringe labelling before administration.

Reference: *Safety Alert – Medeffect.* 26 January 2012 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/velcade_hpc-cps-eng.php

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

Regulatory Action and News

Bevacizumab: suspension for metastatic breast cancer

Canada — Health Canada has taken the decision to suspend authorization of bevacizumab (Avastin®) for use in the treatment of metastatic breast cancer.

This decision does not affect Health Canada's authorization of bevacizumab for other types of cancer. Bevacizumab remains authorized in Canada for use in the treatment of metastatic colon, rectal, and lung cancers, as well as in the treatment of glioblastoma.

Reference: *Information Update 2011–59,* 28 November 2011 at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2011/avastin_8_hpc-cps-eng.php

Drotrecogin alfa: withdrawal

United States of America — The Food and Drug Administration (FDA) has announced the worldwide voluntary market withdrawal of drotrecogin alfa (activated) [Xigris®] by the manufacturer.

In a recently completed clinical trial (PROWESS-SHOCK trial), drotrecogin alfa failed to show a survival benefit. In this trial of 1696 patients, 851 patients were enrolled in the drotrecogin alfa arm and 845 patients were enrolled in the placebo arm. Results based on preliminary analyses that were submitted to the FDA showed a 28-day all cause mortality rate of 26.4% (223/846) in Xigris®-treated patients compared to 24.2% (202/834) in placebo-treated patients.

Reference: *FDA Drug Safety Communication*, 25 October 2011 at http://www.fda.gov/Drugs/DrugSafety

Buflomedil-containing medicines: suspension

European Union — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded, following a review of the safety and efficacy of buflomedil, that the risks of these medicines, particularly the risks of severe cardiological and neurological adverse reactions, do not outweigh their limited benefits in the treatment of patients with chronic peripheral arterial occlusive disease (PAOD). The Committee therefore recommended that the marketing authorizations of all buflomedil-containing medicines be suspended in all European Union (EU) Member States where they are currently authorized.

The review of buflomedil was initiated following the suspension of the marketing authorization in France by the French regulatory authority in February 2011.

Reference: *EMA Press Release,* EMA/CHMP/570796/2011, 17 November 2011 at http://www.ema.europa.eu

Dextropropoxyphene-containing analgesics cancelled

Australia — The Therapeutic Goods Administration (TGA) has cancelled all pain-killers containing dextropropoxyphene (Capadex®, Di-Gesic®, Doloxene® and Paradex®) from the Australian Register of Therapeutic Goods (ARTG), as of 1 March 2012.

Following a review of the available evidence, the TGA found that the safety risks of using analgesics containing dextropropoxyphene outweighed the benefits. Cancellation from the ARTG means

that these prescription medicines can no longer be supplied by their Australian sponsors.

Dextropropoxyphene has recently been shown to increase the risk of serious arrhythmias. This effect is more pronounced with high doses or overdoses. An extensive review of the safety and efficacy of dextropropoxyphene has been conducted by the TGA which has determined that the overall risk of serious adverse reactions outweighs any benefits that may be provided by these medicines. This position is consistent with medicine regulators in Europe, New Zealand, USA and elsewhere, where dextropropoxyphene-containing medicines have been removed from the market.

Reference: *Therapeutic Goods Administration Safety Announcement,* 2 December 2011 at http://www.tga.gov.au/newsroom/media-2011-dextropropoxyphene-111122.htm

Vemurafenib approved for metastatic or unresectable melanoma

European Union — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a marketing authorization for a novel protein-kinase inhibitor to treat patients suffering from metastatic or unresectable melanoma with BRAF V600 mutations.

In Europe, doctors diagnose almost 60 000 new cases of melanoma per year and approximately 8300 men and 7600 women die from this type of cancer annually. In the pivotal clinical trial, vemurafenib (Zelboraf®) was compared to the standard first-line treatment of dacarbazine. The medicine was shown to improve progression-free survival by about four months and overall survival by about three months in patients who tested positive for BRAF V600 mutations.

Reference: *EMA Press Release,* EMA/CHMP/975685/2011, 16 December 2011 at http://www.ema.europa.eu

Ecallantide: marketing authorization application withdrawal

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw the application for ecallantide (Kalbitor®), 10 mg/ml solution for injection. Ecallantide was intended to be used for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents 16 years of age and older.

The company stated that they were unable to provide sufficient information to address the outstanding clinical issues identified during the evaluation of their application.

Reference: *EMA Press Release,* EMA/891024/2011, 15 November 2011 at http://www.ema.europa.eu

Sitagliptin and pioglitazone: marketing authorization application withdrawal

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw the application for sitagliptin and pioglitazone (Janacti® and related trade names)100/30 mg and 100/45 mg fixed-dose combination tablets.

Janacti® was intended to be used for the treatment of adult patients with type 2 diabetes mellitus.

The company stated that they are withdrawing the application following a review of the regulatory and commercial prospects for the fixed-dose combination product. There are currently no ongoing clinical trials with Janacti®.

Reference: *EMA Press Release,* EMA/887576/2011, 14 November 2011 at http://www.ema.europa.eu

Voclosporin: marketing authorization application withdrawal

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw the application for voclosporin (Luveniq®), 10 mg soft capsules.

Voclosporin was intended to be used for the treatment of patients with chronic non-infectious uveitis involving the posterior or intermediate segments of the eyes as characterized by a high degree of inflammation and in whom corticosteroids are inappropriate, do not provide adequate control, or cannot be tapered below 10 mg/day. Voclosporin was designated an orphan medicinal product on 14 September 2007.

The company stated that they were unable to demonstrate to the satisfaction of the CHMP an overwhelming effect showing that the benefits of Luveniq® outweigh its risks, and thus would qualify for a recommendation for authorization with one pivotal study only.

Reference: *EMA Press Release,* EMA/833913/2011, 18 October 2011 at http://www.ema.europa.eu

Desloratadine: marketing authorization application withdrawal

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw the application for desloratadine (Desloratadine Krka®), 5 mg film coated tablets.

Desloratadine Krka® was intended to be used for the relief of symptoms associated with allergic rhinitis and urticaria. Desloratadine Krka® is a generic of Aerius® which has been authorized in the European Union since 15 January 2001.

In its official letter, the company stated that their marketing strategy is the reason for withdrawal.

Reference: *EMA Press Release,* EMA/840073/2011, 19 October 2011 at http://www.ema.europa.eu

Electronic CTD implementation

Saudi Arabia — The Saudi Food and Drug Authority (SFDA) has informed pharmaceutical companies and their agents to prepare for implemention of the electronic common technical document (eCTD) when submitting product files for evaluation.

The timeframe determined for implementing the eCTD is as follows.

- As of 20 December 2011: non- eCTD electronic submission (NeeS) can be submitted according to *Guidance for Registration* (version 3).
- As of 1 September 2012, the NeeS will be mandatory and the SFDA will not accept any other format.
- Starting 5 January 2013, either eCTD or NeeS can be submitted.
- As of 4 January 2014, the NeeS will be accepted but submissions in eCTD are preferred
- Starting from 3 January 2015, only eCTD will be accepted.

More information about the difference between eCTD and NeeS is available in *Guidance for Registration* and the *GCC Module 1 Specifications guideline* which are available from sdr.drug@sfda.gov.sa and at www.sfda.gov.sa. In addition, the SFDA will conduct workshops to assist pharmaceutical companies in following these technical requirements.

Reference: Saudi Food and Drug Authority. News Release dated 14 Jaunary 2012. At http://www.sfda.gov.sa/En/Drug/News/1122-en-14-1.htm

ATC/DDD Classification

ATC/DDD Classification (Temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2011. Comments or objections to the decisions should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. The new ATC codes and DDDs will be considered final and be included in the January 2013 issue of the ATC Index. The inclusion of a substance in the lists does not imply any recommendation for use in medicine or pharmacy.

ATC level	INN Common name	ATC code
New ATC 5th level codes:		
	aclidinium bromide	R03BB05
	alcaftadine	S01GX11
	alendronic acid and alfacalcidol, sequential	M05BB06
	apixaban	B01AF02
	atorvastatin and ezetimibe	C10BA05
	boseprevir	J05AE12
	cefuroxime	S01AA27
	ciclesonide	R01AD13
	cobicistat	V03AX03
	dextromethorphan, combinations	N07XX59
	electrolytes in combination with other drugs	B05BB04
	elvitegravir	J05AX11
	emtricitabine, tenofovir disoproxil, elvitegravir and cobicistat	J05AR09
	faropenem	J01DI03
	fidaxomicin	A07AA12
	florbetapir (18F)	V09AX05
	fluoxetine and psycholeptics	N06CA03
	flutemetamol (18F)	V09AX04
	glycopyrronium bromide	R03BB06
	ingenol mebutate	D06BX02
	ivacaftor	R07AX02
	lomitapide	C10AX12
	meningococcus A, purified polysaccharide antigen conjugated	J07AH10

ATC level	INN Common name	ATC code
	mirabegron	G04BD12
	nafcillin	J01CF06
	ormeloxifen	G03XC04
	pioglitazone and sitagliptin	A10BD12
	ridaforolimus	L01XE19
	rubidium (82Rb) chloride	V09GX04
	simvastatin and fenofibrate	C10BA04
	sitagliptin and simvastatin	A10BH51
	technetium (99mTc) ethyl-enedicysteine	V09CA06

New ATC level codes (other than 5th level):

Direct factor Xa inhibitors	B01AF
Fluoroquinolones	S01AE

ATC code changes:

INN Common name	Previous ATC	New ATC
besifloxacin	S01AX23	S01AE08
ciprofloxacin	S01AX13	S01AE03
diamorphine	N02AA09	N07BC06
droperidol	N01AX01	N05AD08*
gatifloxacin	S01AX21	S01AE06
histrelin	H01CA03	L02AE05
levofloxacin	S01AX19	S01AE05
lomefloxacin	S01AX17	S01AE04
lopinavir and ritonavir **	J05AE06	J05AR10
moxifloxacin	S01AX22	S01AE07
norfloxacin	S01AX12	S01AE02
ofloxacin	S01AX11	S01AE01
rivaroxaban	B01AX06	B01AF01

** Existing code*
*** New ATC level name (previous name: lopinavir)*

ATC name changes:

Previous	New	ATC code
Other cephalosporins	Other cephalosporins and penems	J01DI

New DDDs:

	DDD	Unit	Adm.R	ATC code
abiraterone	1	g	O	L02BX03
amifampridine	40	mg	O	N07XX05
apixaban	5	mg	O	B01AF02
belatacept	12.5	mg	P	L04AA28
belimumab	25	mg	P	L04AA26
boceprevir	2.4	g	O	J05AE12

New DDDs *(continued)*

	DDD	Unit	Adm.R	ATC code
ciclesonide	0.2	mg	N	R01AD13
collagenase clostridium histolyticum	0.9	mg	P	M09AB02
delavirdine	1.2	g	O	J05AG02
dextromethorpen, combinations	40	mg[1]	O	N07XX59
exenatide	0.286	mg	P depot inj.	A10BX04
fidaxomicin	0.4	g	O	A07AA12
histamine dihydrochloride	0.5	mg	P	L03AX14
inosine pranobex	3	g	O	J05AX05
leuprorelin	0.134	mg	P depot implant	L02AE02
lorazepam	2.5	mg	P	N05BA06
nabiximols	42	mg	SL	N02BG10
naproxen and esomeprazole	0.5	g[2]	O	M01AE52
pyrvinium	0.35	g	O	P02CX01
retigabine	0.9	g	O	N03AX21
rifaximin	0.6	g	O	A07AA11
telaprevir	2.25	g	O	J05AE11
tobramycin	0.112	g	Inhal. powder	J01GB01
triptorelin	0.1	mg	P	L02AE04
vinpocetine	15	mg	O	N06BX18
von Willebrand factor	6	TU	P	B02BD10

[1] expressed as dextromethorphan
[2] refers to naproxen

Herbal medicinal products*

ATC level	INN Common name	ATC code
New ATC 5th level codes:		
	Agni casti fructus	G02CX03
	Cimicifugae rhizoma	G02CX04

** Assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data (e.g. the well-established use procedure in EU).*

ATC/DDD Classification

ATC/DDD Classification (Final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in March 2011. They have been included in the January 2012 version of the ATC Index. The inclusion of a substance in the lists does not imply any recommendation for use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no.

	INN Common name	ATC code
New ATC 5th level codes:		
	aclidinium bromide	R03BB05
	abiraterone	L02BX03
	aflibercept	S01LA05
	axitinib	L01XE17
	bosutinib	L01XE14
	brentuximab vedotin	L01XC12
	catridecacog	B02BD11
	crizotinib	L01XE16$
	dapagliflozin	A10BX09
	dexlansoprazole	A02BC06
	levomethadone	N07BC05
	losartan and amlodipine	C09DB06
	meloxicam, combinations	M01AC56
	mipomersen	C10AX11
	naproxen and misoprostol	M01AE56
	pasireotide	H01CB05
	perampanel	N03AX22
	ruxolitinib	L01XE18
	sipuleucel-T	L03AX17
	tafamidis	N07XX08
	telaprevir	J05AE11
	tesamorelin	H01AC06
	vemurafenib	L01XE15

ATC name changes:

Previous	New	ATC code
Antigrowth hormones	Somatostatin and analogues	H01CB
Calcium, combinations with other drugs	Calcium, combinations with vitamin D and/or other drugs	A12AX
Enzyme inhibitors	Aromatase inhibitors	L02BG

New DDDs:

	DDD	Unit	Adm.R	ATC code
aspoxicillin	4	g	P	J01CA19
aztreonam	0.225	g	Inhal. solution	J01DF01
bekanamycin	0.6	g	P	J01GB13
carumonam	2	g	P	J01DF02
cefbuperazone	2	g	P	J01DC13
cefminox	4	g	P	J01DC12
conestat alfa	3.5	TU	P	B06AC04
desvenlafaxine	50	mg	O	N06AX23
fingolimod	0.5	mg	O	L04AA27
flomoxef	2	g	P	J01DC14
histrelin	0.137	mg*	implant	H01CA03
isepamicin	0.4	g	P	J01GB11
ribostamycin	1	g	P	J01GB10
tapentadol	0.4	g	O	N02AX06
ticagrelor	0.18	g	O	B01AC24
vernakalant	0.2	g	P	C01BG11

** DDD assigned according to the total content of the implant.*

Herbal medicinal products*

ATC level	INN Common name	ATC code
New ATC 5th level codes:		
	Hyperici herba	N06AX25

** Assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data (e.g. the well-established use procedure in EU).*

Recent Publications, Information and Events

Pharmacovigilance Toolkit

The World Health Organization has announced the launch of a Pharmacovigilance Toolkit. This has been developed by the WHO Collaborating Centre for Pharmacovigilance Training and Advocacy, Ghana, in collaboration with the WHO Advisory Committee on Safety of Medicinal Products, the Uppsala Monitoring Centre, Sweden, and the WHO Quality and Safety of Medicines Programme, Geneva.

The Toolkit brings together existing resources that are used in the practice of pharmacovigilance. Its main objective is to bring current information, guidelines and practical advice to all pharmacovigilance practitioners.

In addition to a dedicate web site, the Toolkit is available on a USB key in a similar format for use in areas with poor internet connectivity. The Toolkit is currently available in English but efforts are underway to have it translated into other languages.

Reference: The Pharmacovigilance Toolkit. At www.pvtoolkit.org

Uppsala Monitoring Centre signals document: increased availability

Among the objectives of the WHO Programme for International Drug Monitoring is the early identification of international drug safety problems not identified in clinical trials, known as signals. These signals are published in the Uppsala Monitoring Centre's (UMC) SIGNAL document, and represent varying levels of suspicions derived from examination of the data in the WHO Global Individual case safety reports database — also known as VigiBase(®) — which contains over seven million such reports. After receiving a signal, national regulatory authorities may consider possible action — for instance further evaluation of source data, or a study for the testing of a hypothesis.

In 2011, the WHO Advisory Committee on the Safety of Medicinal Products recommended that signal articles be made public. A first step in making UMC signals publicly available will be taken in early 2012 when, for the first time, they will be included in *WHO Pharmaceuticals Newsletter* which is issued every second month. Currently, 450 professionals receive the restricted signal document, mainly staff at national pharmacovigilance centres. The new arrangement with allow for a wider audience

References

1. Uppsala Monitoring Centre/WHO Collaborating Centre for International Drug Monitoring, Sweden, at http://www.who-umc.org

2. World Health Organization. *WHO Pharmaceuticals Newsletter.* At http://www.who.int/medicines

Learning module: selective serotonin reuptake inhibitors

The United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) has just launched a learning module on selective serotonin reuptake inhibitors (SSRI) for clinical practitioners.

SSRIs form the most widely prescribed class of antidepressants. This module identifies the most important hazards of SSRIs and informs on actions that health professionals should take in order to minimize and manage the risks. For each adverse effect, the package outlines:

- The main features of the adverse effect.
- Factors that increase the risk.
- How the risk can be reduced.
- Specific treatment for the adverse effect.

A self-assessment exercise, together with full feedback, complements the learning material which is suitable for doctors, pharmacists and nurses involved in the care of patients with depression. Clinicians starting out in psychiatry will find it especially valuable.

Used in conjunction with authoritative guidelines on disease management, this module will help maximize the benefits of SSRI treatment.

Reference: Healthcare products Regulatory Agency (MHRA). *SSRI learning module*. At http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/Reducingmedicinerisk/SSRIlearningmodule/index.htm

Medicines access survey

A team of researchers at the National Institute of Public Health in Mexico have conducted an analysis of availability, affordability and prices of medicines in Mexico City during 2009/2010 using the Health Action International (HAI)/WHO suggested methodology.

The analysis showed that in the public sector medicines included in the sample were unavailable in more than 50% of those health establishments visited. In the private sector, originator product prices were on average 4.5 times higher than their corresponding interchangeable generics (e.g., the originator product, fluoxetin, was 172 times more expensive than its generic counterpart). Almost 50% of all treatments analysed were unaffordable.

Reference: Mexico: Medicines access survey. At http://www.haiweb.org/medicineprices/surveys.php

ATC/DDD methodology course

The WHO Collaborating Centre for Drug Statistics Methodology will organize its annual course in ATC/DDD methodology in Oslo from 7 to 8 June 2012. The course gives an introduction to the Anatomical Therapeutic Chemical (ATC) classification system and the technical unit of measurement, the Defined Daily Dose (DDD). The purpose of the ATC/DDD and how to use the methodology is also covered in the course which consists of lectures, discussions and working groups. The course is open for all interested parties. However, basic knowledge in common medical terminology is recommended.

The Centre also arranges courses on request from countries which plan to start using the ATC/DDD methodology. For example, courses have previously been arranged in Ecuador, Japan and Morocco.

Lectures will cover the following topics:

- Background, overview and development of the ATC/DDD methodology
- The main principles for establishing new ATC codes and assigning DDDs
- Procedures for applications (ATC codes, DDDs and changes).

The second day will focus on application of the ATC/DDD methodology in drug consumption statistics. Working group sessions will address various ATC/DDD problems and points to consider related to the application of the methodology in drug consumption statistics.

Reference: WHO Collaborating Centre for Drug Statistics Methodology. At http://www.whocc.no/courses/

Access and Control Newsletter

The Access and Control Newsletter provides the latest news from WHO on access to medicines controlled under

the international drug treaties. It aims to provide information on improving access for medical use and evaluation of the dependence-producing properties of substances and medicines made from these substances.

The current number includes:

- Roundtable in Bosnia and Herzegovina.
- Serbian National WHO Counterpart for pain treatment — access to opioids.
- Psychiatrists are stakeholders in improving access to controlled medicines.
- Prequalification of morphine and methadone.
- ATOME Project: workshops on improving access to controlled medicines.
- Life Before Death: Short movies on the global crisis of pain treatment.

Reference: WHO Access and Control Newsletter, No 9, January 2012 at http://www.who.int/medicines/areas/quality_safety/Access_Contr_Newsletter/en/index.html

Managing access to medicines and health technologies

Managing Drug Supply is the leading reference on how to manage essential medicines in developing countries. *Managing Drug Supply* was originally published in 1982. It was revised in 1997 with over 10,000 copies distributed in over 60 countries worldwide. The third edition, *Managing Access to Medicines and other Health Technologies* reflects the dramatic changes in politics, public health priorities, advances in science and medicine, greater focus on health care systems, increased donor funding, and the advent of information technology that have profoundly affected access to essential medicines over the past 14 years.

The revised edition has many new areas that have been added or enhanced, including six new chapters:

- Intellectual property and access to medicines
- Traditional and complementary medicines policy
- Pharmaceutical pricing policy
- Pharmaceutical benefits in insurance programmes
- Drug seller initiatives
- Pharmacovigilance

Reference: Management Sciences for Health. *Managing Access to Medicines and other Health Technologies.* At http://www.msh.org/resource-center/managing-drug-supply-digital-edition.cfm

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 67

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9); Resolution EB115.R4 (EB115/2005/REC/1)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.
Lists of Proposed (1–105) and Recommended (1–66) International Nonproprietary Names can be found in *Cumulative List No. 14, 2011* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 67

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9); résolution EB115.R4 (EB115/2005/REC/1)] les dénominations ci-dessous sont choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.
On trouvera d'autres listes de Dénominations communes internationales proposées (1–105) et recommandées (1–66) dans la *Liste récapitulative No. 14, 2011* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 67

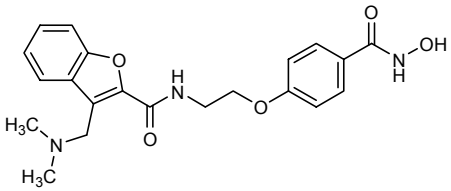
De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, **60**, 3 (Resolución EB15.R7); 1969, **173**, 10 (Resolución EB43.R9); Résolution EB115.R4 (EB115/2005/REC/1) EB115.R4 (EB115/2005/REC/1)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.
Las listas de Denominaciones Comunes Internacionales Propuestas (1–105) y Recomendadas (1–66) se encuentran reunidas en *Cumulative List No. 14, 2011* (disponible sólo en CD-ROM).

Latin, English, French, Spanish: *Recommended INN*	*Chemical name or description; Molecular formula; Graphic formula*
DCI Recommandée	*Nom chimique ou description; Formule brute; Formule développée*
DCI Recomendada	*Nombre químico o descripción; Fórmula molecular; Fórmula desarrollada*

abexinostatum

abexinostat	3-[(dimethylamino)methyl]-*N*-{2-[4-(hydroxycarbamoyl)phenoxy]ethyl}-1-benzofuran-2-carboxamide
abexinostat	3-[(diméthylamino)méthyl]-*N*-{2-[4-(hydroxycarbamoyl)phénoxy]éthyl}-1-benzofurane-2-carboxamide
abexinostat	3-[(dimetilamino)metil]-*N*-{2-[4-(hidroxicarbamoil)fenoxi]etil}-1-benzofuran-2-carboxamida

$C_{21}H_{23}N_3O_5$



amilomotidum #

amilomotide	virus like particle of bacteriophage Q-beta coat protein that is coupled to multiple copies of human beta-amyloid1-6 peptide fragment; reaction products of bacteriophage Q-beta coat protein with human beta-amyloid protein-(1-6)-peptidylglycylglycyl-L-cysteine and 3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrole-1-yl)-*N*-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}propanamide
amilomotide	pseudo-particule virale de la capside du phage Q-bêta couplée à plusieurs copies du fragment 1-6 de la protéine bêta-amyloïde humaine; produit obtenu par réaction de la protéine de capside du phage Q-bêta avec la protéine bêta-amyloïde humaine-(1-6)peptidylglycylglycyl-L-cystéine et le 3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrole-1-yl)-*N*-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}propanamide
amilomotida	pseudo-particula viral de cápsida del fago Q-beta acoplada a múltiples copias del fragmento 1-6 de la proteína beta-amiloide humana; producto obtenido por reacción de la proteína de cápsida del fago Q-beta con la proteína beta-amiloide humana-(1-6)peptidilglicilglicil-L-cisteína y el 3-(2,5-dioxo-2,5-dihidro-1*H*-pirrol-1-il)-*N*-{6-[(2,5-dioxopirrolidin-1-il)oxi]-6-oxohexil}propanamida

Heavy chain / Chaîne lourde / Cadena pesada

```
AKLETVTLGN IGKDGKQTLV LNPRGVNPTN GVASLSQAGA VPALEKRVTV 50
SVSQPSRNRK NYKVQVKIQN PTACTANGSC DPSVTRQAYA DVTFSFTQYS 100
TDEERAFVRT ELAALLASPL LIDAIDQLNP AY                    132
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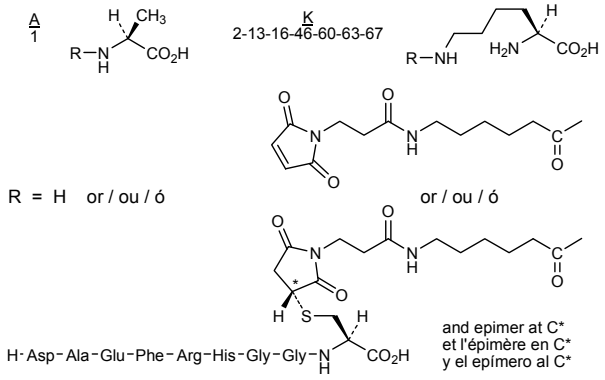
Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
74-80

Modified residues / Résidus modifiés / Residuos modificados



anivamersenum

anivamersen

2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methylcytidine

anivamersen

2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthylcytidine

anivamersén

2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metilctidina

$C_{157}H_{208}N_{56}O_{103}P_{14}$

(3'-5')-mC-mG-mC-mG-mG-mU-mA-mU-mA-mG-mU-mC-mC-mA-mC

asunaprevirum

asunaprevir

tert-butyl {(2*S*)-1-[(2*S*,4*R*)-4-({7-chloro-4-methoxyisoquinolin-1-yl}oxy)-2-({(1*R*,2*S*)-1-[(cyclopropanesulfonyl)carbamoyl]-2-ethenylcyclopropyl}carbamoyl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

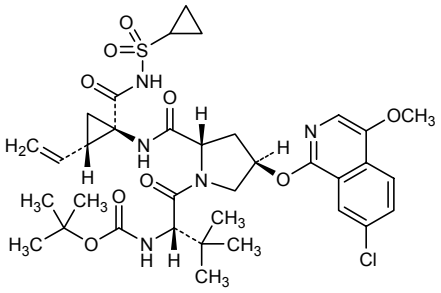
asunaprévir

(2*S*)-1-[(2*S*,4*R*)-4-({7-chloro-4-méthoxyisoquinolin-1-yl}oxy)-2-({(1*R*,2*S*)-1-[(cyclopropanesulfonyl)carbamoyl]-2-éthènylcyclopropyl}carbamoyl)pyrrolidin-1-yl]-3,3-diméthyl-1-oxobutan-2-yl}carbamate de *tert*-butyle

asunaprevir

{(2*S*)-1-[(2*S*,4*R*)-4-({7-cloro-4-metoxiisoquinolin-1-il}oxi)-2-({(1*R*,2*S*)-1-[(ciclopropanosulfonil)carbamoil]-2-etenilciclopropil}carbamoil)pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de *terc*-butilo

$C_{35}H_{46}ClN_5O_9S$



atecegatranum metoxilum

atecegatran metoxil

(2*S*)-1-{(2*R*)-2-[3-chloro-5-(difluoromethoxy)phenyl]-2-hydroxyacetyl}-*N*-({4-[(*Z*)-*N*′-methoxycarbamimidoyl]phenyl}methyl)azetidine-2-carboxamide

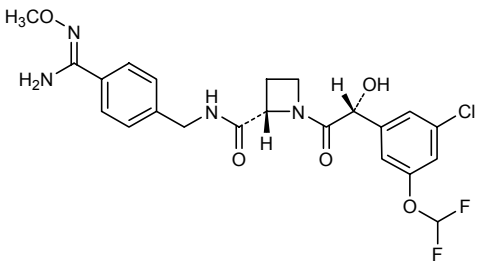
atécégatran métoxil

(2*S*)-1-{(2*R*)-2-[3-chloro-5-(difluorométhoxy)phényl]-2-hydroxyacétyl}-*N*-({4-[(*Z*)-*N*′-méthoxycarbamimidoyl]phényl}méthyl)azétidine-2-carboxamide

atecegatrán metoxilo

(2*S*)-1-{(2*R*)-2-[3-cloro-5-(difluorometoxi)fenil]-2-hidroxiacetil}-*N*-({4-[(*Z*)-*N*′-metoxicarbamimidoil]fenil}metil)azetidina-2-carboxamida

$C_{22}H_{23}ClF_2N_4O_5$



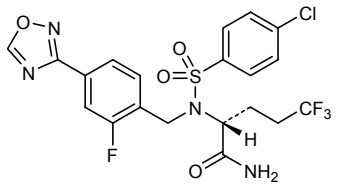
avagacestatum

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

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

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

$C_{20}H_{17}ClF_4N_4O_4S$



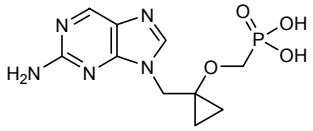
besifovirum

besifovir — [({1-[(2-amino-9*H*-purin-9-yl)methyl]cyclopropyl}oxy)methyl]phosphonic acid

bésifovir — acide [({1-[(2-amino-9*H*-purin-9-yl)méthyl]cyclopropyl}oxy)méthyl]phosphonique

besifovir — ácido [({1-[(2-amino-9*H*-purin-9-il)metil]ciclopropil}oxi)metil]fosfónico

$C_{10}H_{14}N_5O_4P$



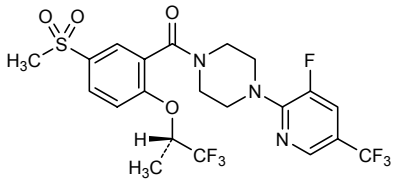
bitopertinum

bitopertin — {4-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}[5-(methanesulfonyl)-2-{[(2*S*)-1,1,1-trifluoropropan-2-yl]oxy}phenyl]methanone

bitopertine — {4-[3-fluoro-5-(trifluorométhyl)pyridin-2-yl]pipérazin-1-yl}[5-(méthanesulfonyl)-2-{[(2*S*)-1,1,1-trifluoropropan-2-yl]oxy}phényl]méthanone

bitopertina — {4-[3-fluoro-5-(trifluorometil)piridin-2-il]piperazin-1-il}[5-(metanosulfonil)-2-{[(2*S*)-1,1,1-trifluoropropan-2-il]oxy}fenil]metanona

$C_{21}H_{20}F_7N_3O_4S$



blosozumabum #

blosozumab — immunoglobulin G4-kappa, anti-[*Homo sapiens* SOST (sclerostin)], humanized monoclonal antibody;
gamma4 heavy chain (1-444) [humanized VH (*Homo sapiens* IGHV1-24*01 (85.70%) -(IGHD)-IGHJ4*01 L123>T (113)) [8.8.11] (1-118) -*Homo sapiens* IGHG4*01 hinge S10>P (226), CH3 K120>del (119-444)], (132-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-13*02 (84.00%) -IGKJ1*01 Q120>G (100)) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (224-224":227-227")-bisdisulfide dimer

blosozumab — immunoglobuline G4-kappa, anti-[*Homo sapiens* SOST (sclérostine)], anticorps monoclonal humanisé;
chaîne lourde gamma4 (1-444) [VH humanisé (*Homo sapiens* IGHV1-24*01 (85.70%) -(IGHD)-IGHJ4*01 L123>T (113)) [8.8.11] (1-118) -*Homo sapiens* IGHG4*01 charnière S10>P (226), CH3 K120>del (119-444)], (132-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-13*02 (84.00%) -IGKJ1*01 Q120>G (100)) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (224-224":227-227")-bisdisulfure

blosozumab — inmunoglobulina G4-kappa, anti-[*Homo sapiens* SOST (esclerostina)], anticuerpo monoclonal humanizado;
cadena pesada gamma4 (1-444) [VH humanizada (*Homo sapiens* IGHV1-24*01 (85.70%) -(IGHD)-IGHJ4*01 L123>T (113)) [8.8.11] (1-118) -*Homo sapiens* IGHG4*01 bisagra S10>P (226), CH3 K120>del (119-444)], (132-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizada (*Homo sapiens* IGKV1-13*02 (84.00%) -IGKJ1*01 Q120>G (100)) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (224-224":227-227")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKVSGFPIK DTFQHWVRQA PGKGLEWMGW  50
SDPEIGDTEY ASKFQGRVTM TEDTSTDTAY MELSSLRSED TAVYYCATGD 100
TTYKFDFWGQ GTTVTVSSAS TKGPSVFPLA PCSRSTSEST AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTKTYT 200
CNVDHKPSNT KVDKRVESKY GPPCPPCPAP EFLGGPSVFL FPPKPKDTLM 250
ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTYRV 300
VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP 350
PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG 400
SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLG       444
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCKASQDVH TAVAWYQQKP GKAPKLLIYW  50
ASTRWTGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSDYPWTFGG 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    145-201    259-319    365-423
         22"-96"  145"-201"  259"-319"  365"-423"
Intra-L  23'-88'   134'-194'
         23'"-88'" 134'"-194'"
Inter-H-L 132-214' 132"-214'"
Inter-H-H 224-224" 227-227"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
295, 295"

brodalumabum #

brodalumab	immunoglobulin G2-kappa, anti-[*Homo sapiens* IL17RA (interleukin 17 receptor A, CD217)], *Homo sapiens* monoclonal antibody; gamma2 heavy chain (1-442) [*Homo sapiens* VH (IGHV1-18*01 (96.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -*Homo sapiens* IGHG2*01 (117-442)], (130-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-15*01 (93.70%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (218-218":219-219":222-222":225-225")-tetrakisdisulfide dimer
brodalumab	immunoglobuline G2-kappa, anti-[*Homo sapiens* IL17RA (récepteur A de l'interleukine 17, CD217)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma2 (1-442) [*Homo sapiens* VH (IGHV1-18*01 (96.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -*Homo sapiens* IGHG2*01 (117-442)], (130-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-15*01 (93.70%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (218-218":219-219":222-222":225-225")-tétrakisdisulfure
brodalumab	inmunoglobulina G2-kappa, anti-[IL17RA (receptor A de la interleukina 17 de *Homo sapiens*, CD217)], anticuerpo monoclonal de *Homo sapiens*; cadena pesada gamma2 (1-442) [*Homo sapiens* VH (IGHV1-18*01 (96.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -*Homo sapiens* IGHG2*01 (117-442)], (130-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-15*01 (93.70%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (218-218":219-219":222-222":225-225")-tetrakisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKASGYTFT RYGISWVRQA PGQGLEWMGW  50
ISTYSGNTNY AQKLQGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARRQ 100
LYFDYWGQGT LVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN 200
VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR 250
TPEVTCVVVD VSHEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV 300
LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR 350
EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PMLDSDGSFF 400
LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK         442
```

Light chain / Chaîne légère / Cadena ligera

```
EIVMTQSPAT LSVSPGERAT LSCRASQSVS SNLAWFQQKP GQAPRPLIYD  50
ASTRATGVPA RFSGSGSGTD FTLTISSLQS EDFAVYYCQQ YDNWPLTFGG 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    143-199   256-316   362-420
         22"-96"  143"-199" 256"-316" 362"-420"
Intra-L  23'-88'   134'-194'
         23'"-88'" 134'"-194'"
Inter-H-L 130-214' 130"-214'"
Inter-H-H 218-218" 219-219" 222-222" 225-225"
```

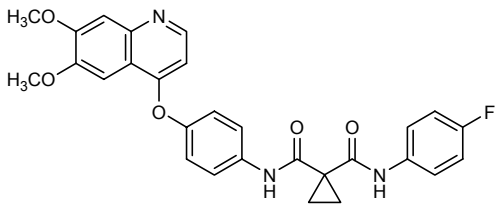
N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

292, 292"

cabozantinibum

cabozantinib	*N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
cabozantinib	*N*-{4-[(6,7-diméthoxyquinoléin-4-yl)oxy]phényl}-*N'*-(4-fluorophényl)cyclopropane-1,1-dicarboxamide
cabozantinib	*N*-{4-[(6,7-dimetoxiquinolin-4-il)oxi]fenil}-*N'*-(4-fluorofenil)ciclopropano-1,1-dicarboxamida

$C_{28}H_{24}FN_3O_5$



calaspargasum pegolum #

calaspargase pegol

pegylated *Escherichia coli* asparaginase;
[27-alanine,64-aspartic acid,252-threonine,263-asparagine]-L-asparaginase 2 (EC 3.5.1.1, L-asparagine amidohydrolase II) *Escherichia coli* (strain K12) tetramer α_4, carbamates with α-carboxy-ω-methoxypoly(oxyethylene)

calaspargase pégol

asparaginase d'*Escherichia coli* pégylée;
carbamates entre le tétramère α_4 de [27-alanine,64-acide aspartique,252-thréonine,263-asparagine]-L-asparaginase 2 (EC 3.5.1.1, L-asparagine amidohydrolase II) d'*Escherichia coli* (souche K12) et le α-carboxy-ω-méthoxypoly(oxyéthylène)

calaspargasa pegol

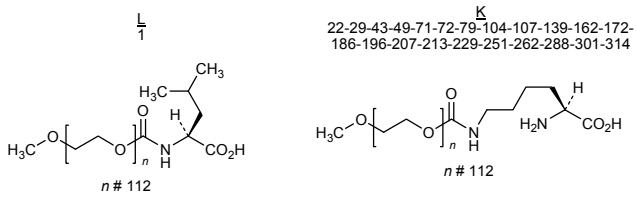
asparaginasa de *Escherichia coli* pegilada;
carbamatos entre el tetrámero α_4 de [27-alanina,64-ácido aspártico,252-treonina,263-asparagina]-L-asparaginasa 2 (EC 3.5.1.1, L-asparagina amidohidrolasa II) de *Escherichia coli* (cepa K12) y el α-carboxi-ω-metoxipoli(oxietileno)

$C_{1516}H_{2423}N_{415}O_{492}S_8$ (peptide monomer)

Monomer / Monomère / Monómero

```
LPNITILATG GTIAGGGDSA TKSNYTAGKV GVENLVNAVP QLKDIANVKG 50
EQVVNIGSQD MNDDVWLTLA KKINTDCDKT DGFVITHGTD TMEETAYFLD 100
LTVKCDKPVV MVGAMRPSTS MSADGPFNLY NAVVTAADKA SANRGVLVVM 150
NDTVLDGRDV TKTNTTDVAT FKSVNYGPLG YIHNGKIDYQ RTPARKHTSD 200
TPFDVSKLNE LPKVGIVYNY ANASDLPAKA LVDAGYDGIV SAGVGNGNLY 250
KTVFDTLATA AKNGTAVVRS SRVPTGATTQ DAEVDDAKYG FVASGTLNPQ 300
KARVLLQLAL TQTKDPQQIQ QIFNQY                           326
```

approximately 9 residues are pegylated out of 23 (1 L and 22 K)
environ 9 résidus sur 23 (1 L et 22 K) sont pegylés
aproximadamente están pegilados 9 restos de 23 (1L y 22K)



Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
77-105 77'-105' 77'''-105''' 77''''-105''''

cantuzumabum ravtansinum #

cantuzumab ravtansine	immunoglobulin G1-kappa, anti-[*Homo sapiens* MUC1 sialylated carbohydrate, tumour-associated (CA242, cancer antigen 242)], humanized monoclonal antibody conjugated to maytansinoid DM4; gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV7-4-1*02 (76.50%) -(IGHD)-IGHJ2*01 R120>Q (111), L123>T (114)) [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* IGKV2-28*01 (82.00%) -IGKJ3*01 V124>L (109), D125>E (110), I126>L (111)) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (228-228":231-231")-bisdisulfide dimer ; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM4 [$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine] via the reducible SPDB linker [*N*-succinimidyl 4-(2-pyridyldithio)butanoate] For the *ravtansine* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"**
cantuzumab ravtansine	immunoglobuline G1-kappa, anti-[*Homo sapiens* glycane sialylé de MUC1, associé à des tumeurs (CA242, antigène du cancer 242)], anticorps monoclonal humanisé conjugué au maytansinoïde DM4; chaîne lourde gamma1 (1-449) [VH humanisé (*Homo sapiens* IGHV7-4-1*02 (76.50%) -(IGHD)-IGHJ2*01 R120>Q (111), L123>T (114)) [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* IGKV2-28*01 (82.00%) -IGKJ3*01 V124>L (109), D125>E (110), I126>L (111)) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimère (228-228":231-231")-bisdisulfure; conjugué, sur 3 à 4 lysyl en moyenne, au maytansinoïde DM4 [$N^{2'}$-déacétyl-$N^{2'}$-(4-mercapto-4-méthyl-1-oxopentyl)-maytansine] via le linker SPDB réductible [4-(2-pyridyldithio)butanoate de *N*-succinimidyle] Pour la partie *ravtansine*, veuillez vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*
cantuzumab ravtansina	inmunoglobulina G1-kappa, anti-[*Homo sapiens* glicano sialilo de MUC1, asociado al tumor (CA242, antígeno del cancer 242)] anticuerpo monoclonal humanizado conjugado con el maitansinoide DM4; cadena pesada gamma1 (1-449) [VH humanizada (*Homo sapiens* IGHV7-4-1*02 (76.50%) -(IGHD)-IGHJ2*01 R120>Q (111), L123>T (114)) [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* IGKV2-28*01 (82.00%) -IGKJ3*01 V124>L (109), D125>E (110), I126>L (111)) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dímero (228-228":231-231")-bisdisulfuro; conjugado, en 3-4 grupos lisil por término medio, con el maitansinoide DM4 [$N^{2'}$-desacetil-$N^{2'}$-(4-mercapto-4-metil-1-oxopentil)-maitansina] mediante el conector SPDB reducible [*N*-4-(2-piridilditio)butanoato de succinimidilo] Para la fracción *ravtansina*, se ruega referirse al documento *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGETVKI SCKASDYTFT YYGMNWVKQA PGQGLKWMGW  50
IDTTTGEPTY AQKFQGRIAF SLETSASTAY LQIKSLKSED TATYFCARRG 100
PYNWYFDVWG QGTTVTVSSA 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

```
DIVMTQSPLS VPVTPGEPVS ISCRSSKSLL HSNGNTYLYW FLQRPGQSPQ  50
LLIYRMSNLV SGVPDRFSGS GSGTAFTLRI SRVEAEDVGV YYCLQHLEYP 100
FTFGPGTKLE LKRTVAAPSV 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"

ceftolozanum

ceftolozane

(6*R*,7*R*)-3-[(5-amino-4-{[(2-aminoethyl)carbamoyl]amino}-1-methyl-1*H*-pyrazol-2-ium-2-yl)methyl]-7-[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

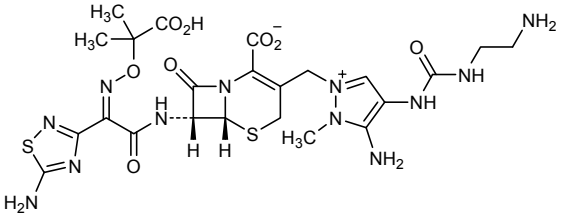
ceftolozane

(6*R*,7*R*)-3-[(5-amino-4-{[(2-aminoéthyl)carbamoyl]amino}-1-méthyl-1*H*-pyrazol-2-ium-2-yl)méthyl]-7-[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acétamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ène-2-carboxylate

ceftolozano

(6*R*,7*R*)-3-[(5-amino-4-{[(2-aminoetil)carbamoil]amino}-1-metil-1*H*-pirazol-2-io-2-il)metil]-7-[(2*Z*)-2-(5-amino-1,2,4-tiadiazol-3-il)-2-{[(2-carboxipropan-2-il)oxo]imino}acetamido]-8-oxo-5-tia-1-azabiciclo[4.2.0]oct-2-eno-2-carboxilato

$C_{23}H_{30}N_{12}O_8S_2$



cenderitidum

cenderitide

natriuretic peptide receptor type B (NPR-B) agonist;
human C-type natriuretic peptide-(32-53)-peptide (CNP-22) fusion protein with eastern green mamba (*Dendroaspis angusticeps*) natriuretic peptide-(24-38)-peptide

cendéritide

agoniste du récepteur du peptide natriurétique de type B;
peptide natriurétique de type-C humain-(32-53)-peptide (CNP-22) protéine de fusion avec le peptide natriurétique de *Dendroaspis angusticeps* (mamba vert)-(24-38)-peptide

cenderitida

agonista del receptor del péptido natriurético de tipo B;
péptido natriurético de tipo-C humano-(32-53)-péptido (CNP-22) proteína de fusión con el péptido natriurético de *Dendroaspis angusticeps* (mamba vert)-(24-38)-péptido

$C_{158}H_{263}N_{49}O_{50}S_3$

```
GLSKGCFGLK  LDRIGSMSGL  GCPSLRDPRP  NAPSTSA 37
```

Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
6-22

cepeginterferonum alfa-2b #
cepeginterferon alfa-2b

pegylated human interferon alpha-2b;
$N^{2.1}$-{4-[ω-methoxypoly(oxyethylene)]butyl}-human interferon alpha-2b

cépeginterféron alfa-2b

interféron alpha-2b humain pégylé;
$N^{2.1}$-{4-[ω-méthoxypoly(oxyéthylène)]butyl}-interféron alpha-2b humain

cepeginterferón alfa-2b

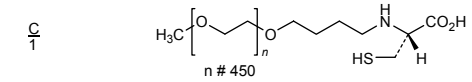
interferón alfa-2b humano pegilado;
$N^{2.1}$-{4-[ω-metoxipoli(oxietileno)]butil}-interferón alfa-2b humano

$C_{865}H_{1359}N_{229}O_{256}S_9\ [C_2H_4O]_n$

```
CDLPQTHSLG SRRTLMLLAQ MRRISLFSCL KDRHDFGFPQ EEFGNQFQKA 50
ETIPVLHEMI QQIFNLFSTK DSSAAWDETL LDKFYTELYQ QLNDLEACVI 100
QGVGVTETPL MKEDSILAVR KYFQRITLYL KEKKYSPCAW EVVRAEIMRS 150
FSLSTNLQES LRSKE                                      165
```

Disulfide bridges location / Positions des ponts disulfure / Posiciones de los puentes disulfuro
1-98 29-138

Modified residue / Résidu modifié / Residuo modificado



conberceptum #
conbercept

fusion protein for immune applications (FPIA) comprising *Homo sapiens* FLT1 (fms-related tyrosine kinase 1, vascular endothelial growth factor receptor 1, VEGFR1, vascular permeability factor receptor, tyrosine-protein kinase FRT) fragment, fused with *Homo sapiens* KDR (kinase insert domain receptor, vascular endothelial growth factor receptor 2, VEGFR2, protein-tyrosine kinase receptor FLK1, CD309) fragment, fused with *Homo sapiens* immunoglobulin G1 Fc fragment;
FLT1, 132-232 precursor fragment (1-101) -KDR, 227-421 precursor fragment (102-296) -glycyl-prolyl-glycyl (297-299) -gamma1 chain H-CH2-CH3 fragment (300-526) [*Homo sapiens* IGHG1*03 hinge 6-15 P13>L (307) (300-309), CH2 (310-419), CH3-CH-S (420-526)]; (305-305':308-308')-bisdisulfide dimer

conbercept

protéine de fusion pour applications immunitaires (FPIA) comprenant un fragment d'*Homo sapiens* FLT1 (tyrosine kinase 1 apparentée au fms, récepteur 1 du facteur de croissance de l'endothélium vasculaire, VEGFR1, récepteur du facteur de perméabilité vasculaire, tyrosine-protéine kinase FRT), fusionné à un fragment *d'Homo sapiens* KDR (récepteur à domaine kinase, récepteur 2 du facteur de croissance de l'endothélium vasculaire, VEGFR2, récepteur tyrosine-protéine kinase FLK1, CD309), fusionné au fragment Fc de l'*Homo sapiens* immunoglobuline G1;
FLT1, fragment 132-232 du précurseur (1-101) -KDR, fragment 227-421 du précurseur (102-296) - glycyl-prolyl-glycyl (297-299) - fragment H-CH2-CH3 de la chaîne gamma1 (300-526) [*Homo sapiens* IGHG1*03 charnière 6-15 P13>L (307) (300-309), CH2 (310-419), CH3-CH-S (420-526)]; dimère (305-305':308-308')-bisdisulfure

conbercept

proteína de fusión para aplicaciones inmunitarias (FPIA) que comprende un fragmento de FLT1 de *Homo sapiens* (tirosina kinasa 1 relacionada con fms, receptor 1 del factor de crecimiento del endotelio vascular, VEGFR1, receptor del factor de permeabilidad vascular, tirosina-protein kinasa FRT), fusionada a un fragmento *de* KDR de *Homo sapiens* (receptor con dominio kinasa, receptor 2 del factor de crecimiento del endotelio vascular, VEGFR2, receptor tirosina-protein kinasa FLK1, CD309), fusionado al fragmento Fc de la inmunoglobulina G1 de *Homo sapiens*;
FLT1, fragmento 132-232 de precursor (1-101) -KDR, fragmento 227-421 del precursor (102-296) - glicil-prolil-glicil (297-299) - fragmento H-CH2-CH3 de la cadena gamma1 (300-526) [*Homo sapiens* IGHG1*03 bisagra 6-15 P13>L (307) (300-309), CH2 (310-419), CH3-CH-S (420-526)]; dímero (305-305':308-308')-bisdisulfuro

Fused chain / chaine fusionnée / cadena fusionada

```
GRPFVEMYSE IPEIIHMTEG RELVIPCRVT SPNITVTLKK FPLDTLIPDG  50
KRIIWDSRKG FIISNATYKE IGLLTCEATV NGHLYKTNYL THRQTNTIID 100
VVLSPSHGIE LSVGEKLVLN CTARTELNVG IDFNWEYPSS KHQHKKLVNR 150
DLKTQSGSEM KKFLSTLTID GVTRSDQGLY TCAASSGLMT KKNSTFVRVH 200
EKPFVAFGSG MESLVEATVG ERVRIPAKYL GYPPPEIKWY KNGIPLESNH 250
TIKAGHVLTI MEVSERDTGN YTVILTNPIS KEKQSHVVSL VVYVPPGPGD 300
KTHTCPLCPA PELLGGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP 350
EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC 400
KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN QVSLTCLVKG 450
FYPSDIAVEW ESNGQPENNY KATPPVLDSD GSFFLYSKLT VDKSRWQQGN 500
VFSCSVMHEA LHNHYTQKSL SLSPGK                           526
```

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

Intra-chain	27-76	121-182	340-400	446-504
	27'-76'	121'-182'	340'-400'	446'-504'
Inter-chains	305-305'	308-308'		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
376, 376'

crenezumabum #

crenezumab

immunoglobulin G4-kappa, anti-[*Homo sapiens* amyloid beta (Abeta) peptides Aβ42 and Aβ40)], humanized monoclonal antibody; gamma4 heavy chain (1-438) [humanized VH (*Homo sapiens* IGHV3-23*04 (89.70%) -(IGHD)-IGHJ4*01 L123>T (107) [8.8.5] (1-112) -*Homo sapiens* IGHG4*01 hinge S10>P (220) (113-438)], (126-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2D-29*02 (86.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (218-218":221-221")-bisdisulfide dimer

crénezumab

immunoglobuline G4-kappa, anti-[*Homo sapiens* peptides *bêta-amyloïdes* (*Abêta)* Aβ42 et Aβ40)], anticorps monoclonal humanisé; chaîne lourde gamma4 (1-438) [VH humanisé (*Homo sapiens* IGHV3-23*04 (89.70%) -(IGHD)-IGHJ4*01 L123>T (107) [8.8.5] (1-112) -*Homo sapiens* IGHG4*01 charnière S10>P (220) (113-438)], (126-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV2D-29*02 (86.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimère (218-218":221-221")-bisdisulfure

crenezumab

inmunoglobulina G4-kappa, anti-[péptidos *beta-amiloides* (*Abeta)* Aβ42 y Aβ40 de *Homo sapiens*)], anticuerpo monoclonal humanizado;
cadena pesada gamma4 (1-438) [VH humanizada (*Homo sapiens* IGHV3-23*04 (89.70%) -(IGHD)-IGHJ4*01 L123>T (107) [8.8.5] (1-112) -*Homo sapiens* IGHG4*01 bisagra S10>P (220) (113-438)], (126-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizada (*Homo sapiens* IGKV2D-29*02 (86.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dímero (218-218":221-221")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYGMSWVRQA PGKGLELVAS  50
INSNGGSTYY PDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCASGD 100
YWGQGTTVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT 150
VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK 200
PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE 250
VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV 300
LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM 350
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS 400
RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLG              438
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPLS LPVTPGEPAS ISCRSSQSLV YSNGDTYLHW YLQKPGQSPQ  50
LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHVP 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     139-195     253-313     359-417
          22"-96"   139"-195"   253"-313"   359"-417"
Intra-L   23'-93'     139'-199'
          23'"-93'"   139'"-199'"
Inter-H-L 126-219'    126"-219'"
Inter-H-H 218-218"    221-221"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
289, 289"

crenolanibum

crenolanib

1-(2-{5-[(3-methyloxetan-3-yl)methoxy]-1*H*-benzimidazol-1-yl}quinolin-8-yl)piperidin-4-amine

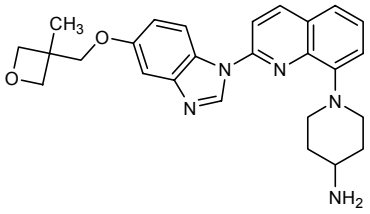
crénolanib

1-(2-{5-[(3-méthyloxétan-3-yl)méthoxy]-1*H*-benzimidazol-1-yl}quinoléin-8-yl)pipéridin-4-amine

crenolanib

1-(2-{5-[(3-metiloxetan-3-il)metoxi]-1*H*-benzoimidazol-1-il}quinolin-8-il)piperidin-4-amina

$C_{26}H_{29}N_5O_2$



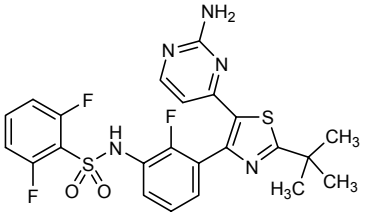
dabrafenibum

dabrafenib — *N*-{3-[5-(2-aminopyrimidin-4-yl)-2-*tert*-butyl-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide

dabrafénib — *N*-{3-[5-(2-aminopyrimidin-4-yl)-2-*tert*-butyl-1,3-thiazol-4-yl]-2-fluorophényl}-2,6-difluorobenzènesulfonamide

dabrafenib — *N*-{3-[5-(2-aminopirimidin-4-il)-2-*terc*-butil-1,3-tiazol-4-il]-2-fluorofenil}-2,6-difluorobencenosulfonamido

$C_{23}H_{20}F_3N_5O_2S_2$



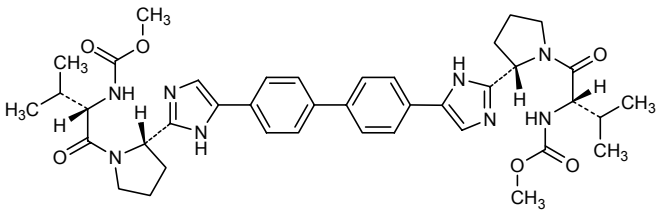
daclatasvirum

daclatasvir — dimethyl *N*,*N*′-([1,1'-biphenyl]-4,4'-diylbis{1*H*-imidazole-5,2-diyl-[(2*S*)-pyrrolidine-2,1-diyl][(1*S*)-3-methyl-1-oxobutane-1,2-diyl]})dicarbamate

daclatasvir — *N*,*N*′-([1,1'-biphényl]-4,4'-diylbis{1*H*-imidazole-5,2-diyl-[(2*S*)-pyrrolidine-2,1-diyl][(1*S*)-3-méthyl-1-oxobutane-1,2-diyl]})dicarbamate de diméthyle

daclatasvir — *N*,*N*′-([1,1'-bifenil]-4,4'-diilbis{1*H*-imidazol-5,2-diil-[(2*S*)-pirrolidina-2,1-diil][(1*S*)-3-metil-1-oxobutano-1,2-diil]})dicarbamato de dimetilo

$C_{40}H_{50}N_8O_6$



dalanterceptum #

dalantercept

fusion protein for immune applications (FPIA) comprising *Homo sapiens* ACVRL1 (activin A receptor type II-like 1, activin receptor-like kinase 1, ALK1, ALK-1, serine/threonine-protein kinase receptor R3, SKR3, transforming growth factor-beta superfamily receptor type I, TGF-B superfamily receptor type I, TSR-I, HHT2, ORW2) fragment, fused with *Homo sapiens* immunoglobulin G1 Fc fragment; ACVR2L1, 22-120 precursor fragment (1-99) -threonyl-triglycyl (100-103) -gamma1 chain H-CH2-CH3 fragment (104-328) [*Homo sapiens* IGHG1*03 hinge 8-15 (104-111), CH2 L1.3>A (115), G1>A (118), A115>V (211) (112-221), CH3 S85.3>P (284) (222-328)]; (107-107':110-110')-bisdisulfide dimer

dalantercept

protéine de fusion pour applications immunitaires (FPIA) comprenant un fragment d'*Homo sapiens* ACVRL1 (récepteur 1 de type II-like de l'activine A, kinase 1 apparentée au récepteur de l'activine, ALK1, ALK-1, récepteur R3 de type sérine/thréonine-protéine kinase, SKR3, récepteur de type I de la superfamille du facteur de croissance transformant bêta, récepteur de type I de la superfamille du TGF-B, TSR-I, HHT2, ORW2), fusionné au fragment Fc de l'*Homo sapiens* immunoglobuline G1;
ACVR2L1, fragment 22-120 du précurseur (1-99) -thréonyl-triglycyl (100-103) -fragment H-CH2-CH3 de la chaîne gamma1 (104-328) [*Homo sapiens* IGHG1*03 charnière 8-15 (104-111), CH2 L1.3>A (115), G1>A (118), A115>V (211) (112-221), CH3 S85.3>P (284) (222-328)]; dimère (107-107':110-110')-bisdisulfure

dalantercept

proteína de fusión para aplicaciones inmunitarias (FPIA) que comprende un fragmento de ACVRL1 de *Homo sapiens* (receptor 1 de tipo II-like de la activina A, kinasa 1 relacionada con el receptor de la activina, ALK1, ALK-1, receptor R3 de tipo serina/treonina-proteinkinasa, SKR3, receptor de tipo I de la superfamilia del factor de crecimiento transformador beta, receptor de tipo I de la superfamilia del TGF-B, TSR-I, HHT2, ORW2), fusionada con el fragmento Fc de la inmunoglobulina G1 de *Homo sapiens*;
ACVR2L1, fragmento 22-120 del precursor (1-99) -treonil-triglicil (100-103) -fragmento H-CH2-CH3 de la cadena gamma1 (104-328) [*Homo sapiens* IGHG1*03 bisagra 8-15 (104-111), CH2 L1.3>A (115), G1>A (118), A115>V (211) (112-221), CH3 S85.3>P (284) (222-328)]; dímero (107-107':110-110')-bisdisulfuro

Fused chain / chaine fusionnée / cadena fusionada

```
DPVKPSRGPL VTCTCESPHC KGPTCRGAWC TVVLVREEGR HPQEHRGCGN  50
LHRELCRGRP TEFVNHYCCD SHLCNHNVSL VLEATQPPSE QPGTDGQLAT 100
GGGTHTCPPC PAPEALGAPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE 150
DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY 200
KCKVSNKALP VPIEKTISKA KGQPREPQVY TLPPSREEMT KNQVSLTCLV 250
KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGPFFLYSK LTVDKSRWQQ 300
GNVFSCSVMH EALHNHYTQK SLSLSPGK                         328
```

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

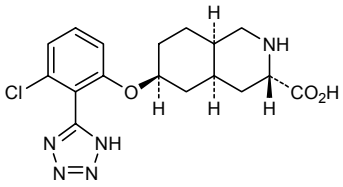
Intra-chain 13-30 15-20 25-48 56-68 69-74 142-202 248-306
13'-30' 15'-20' 25'-48' 56'-68' 69'-74' 142'-202' 248'-306'
Inter-chains 107-107' 110-110'

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
77, 178, 77', 178'

dasolampanelum

dasolampanel	(3*S*,4a*S*,6*S*,8a*R*)-6-[3-chloro-2-(1*H*-tetrazol-5-yl)phenoxy]-decahydroisoquinoline-3-carboxylic acid
dasolampanel	acide (3*S*,4a*S*,6*S*,8a*R*)-6-[3-chloro-2-(1*H*-tétrazol-5-yl)phénoxy]décahydroisoquinoléine-3-carboxylique
dasolampanel	ácido (3*S*,4a*S*,6*S*,8a*R*)-6-[3-cloro-2-(1*H*-tetrazol-5-il)fenoxi]-decahidroisoquinolina-3-carboxilico

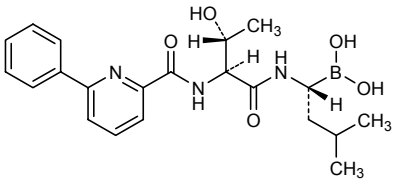
$C_{17}H_{20}ClN_5O_3$



delanzomibum

delanzomib	{(1*R*)-1-[(2*S*,3*R*)-3-hydroxy-2-(6-phenylpyridine-2-carboxamido)butanamido]-3-methylbutyl}boronic acid
délanzomib	acide {(1*R*)-1-[(2*S*,3*R*)-3-hydroxy-2-(6-phénylpyridine-2-carboxamido)butanamido]-3-méthylbutyl}boronique
delanzomib	ácido {(1*R*)-1-[(2*S*,3*R*)-3-hidroxi-2-(6-fenilpiridina-2-carboxamido)butanamido]-3-metilbutil}borónico

$C_{21}H_{28}BN_3O_5$



delcasertibum

delcasertib	human immunodeficiency virus 1 protein Tat-(46-57)-peptide (1→1')-disulfide with L-cysteinyl-[mouse protein kinase C delta type-(8-17)-peptide]
delcasertib	protéine Tat du virus 1 de l'immunodéficience humaine-(46-57)-peptide (1→1')-disulfure avec le L-cystéinyl-(protéine kinase C type delta de souris-(8-17)-peptide
delcasertib	proteína Tat del virus 1 de la inmunodeficiencia humana-(46-57)-péptido (1→1')-disulfuro con la L-cisteinil-[proteína kinasa C tipo delta de ratón-(8-17)-péptido]

$C_{120}H_{199}N_{45}O_{34}S_2$

A chain / Chaîne A / Cadena A
CYGRKKRRQR RR 12

Light chain / Chaîne légère / Cadena ligera
CSFNSYELGS L 11'

Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
1-1'

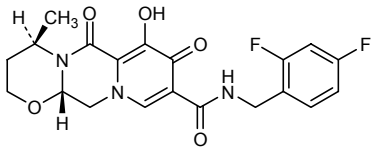
dolutegravirum

dolutegravir — (4*R*,12a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamide

dolutégravir — (4*R*,12a*S*)-*N*-[(2,4-difluorophényl)méthyl]-7-hydroxy-4-méthyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamide

dolutegravir — (4*R*,12a*S*)-*N*-[(2,4-difluorofenil)metil]-7-hidroxi-4-metil-6,8-dioxo-3,4,6,8,12,12a-hexahidro-2*H*-pirido[1',2':4,5]pirazino[2,1-*b*][1,3]oxazina-9-carboxamida

$C_{20}H_{19}F_2N_3O_5$



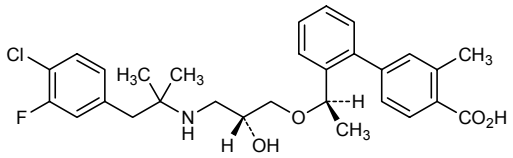
encaleretum

encaleret — 2′-{(1*R*)-1-[(2*R*)-3-{[1-(4-chloro-3-fluorophenyl)-2-methylpropan-2-yl]amino}-2-hydroxypropoxy]ethyl}-3-methyl[1,1′-biphenyl]-4-carboxylic acid

encaléret — acide 2′-{(1*R*)-1-[(2*R*)-3-{[1-(4-chloro-3-fluorophényl)-2-méthylpropan-2-yl]amino}-2-hydroxypropoxy]éthyl}-3-méthyl[1,1′-biphényl]-4-carboxylique

encaleret — ácido 2′-{(1*R*)-1-[(2*R*)-3-{[1-(4-cloro-3-fluorofenil)-2-metilpropan-2-yl]amino}-2-hidroxipropoxi]etil}-3-metil[1,1′-bifenil]-4-carboxílico

$C_{29}H_{33}ClFNO_4$



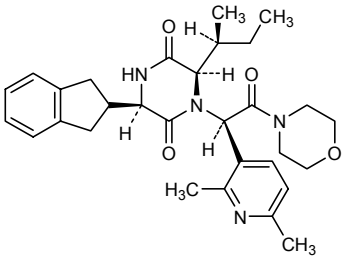
epelsibanum

epelsiban — (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1*R*)-1-(2,6-dimethylpyridin-3-yl)-2-(morpholin-4-yl)-2-oxoethyl]-6-[(2*S*)-butan-2-yl]piperazine-2,5-dione

épelsiban — (3*R*,6*R*)-3-(2,3-dihydro-1*H*-indén-2-yl)-1-[(1*R*)-1-(2,6-diméthylpyridin-3-yl)-2-(morpholin-4-yl)-2-oxoéthyl]-6-[(2*S*)-butan-2-yl]pipérazine-2,5-dione

epelsibán — (3*R*,6*R*)-3-(2,3-dihidro-1*H*-inden-2-il)-1-[(1*R*)-1-(2,6-dimetilpiridin-3-il)-2-(morfolin-4-il)-2-oxoetil]-6-[(2*S*)-butan-2-il]piperazina-2,5-diona

$C_{30}H_{38}N_4O_4$



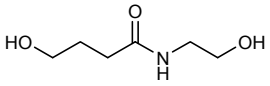
etoxybamidum

etoxybamide — 4-hydroxy-*N*-(2-hydroxyethyl)butanamide

étoxybamide — 4-hydroxy-*N*-(2-hydroxyéthyl)butanamide

etoxibamida — 4-hidroxi-*N*-(2-hidroxietil)butanamida

$C_6H_{13}NO_3$



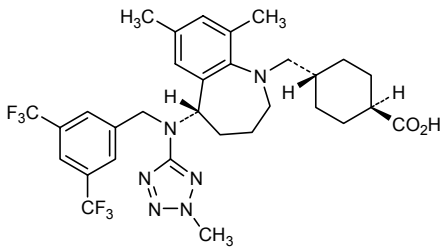
evacetrapibum

evacetrapib — (1*r*,4*r*)-4-({(5*S*)-5-[{[3,5-bis(trifluoromethyl)phenyl]methyl}(2-methyl-2*H*-tetrazol-5-yl)amino]-7,9-dimethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}methyl)cyclohexane-1-carboxylic acid

évacétrapib — acide (1*r*,4*r*)-4-({(5*S*)-5-[{[3,5-bis(trifluorométhyl)phényl]méthyl}(2-méthyl-2*H*-tétrazol-5-yl)amino]-7,9-diméthyl-2,3,4,5-tétrahydro-1*H*-benzazépin-1-yl}méthyl)cyclohexane-1-carboxylique

evacetrapib — ácido (1*r*,4*r*)-4-({(5*S*)-5-[{[3,5-bis(trifluorometil)fenil]metil}(2-metil-2*H*-tetrazol-5-il)amino]-7,9-dimetil-2,3,4,5-tetrahidro-1*H*-1-benzazepin-1-il}metil)ciclohexano-1-carboxílico

$C_{31}H_{36}F_6N_6O_2$



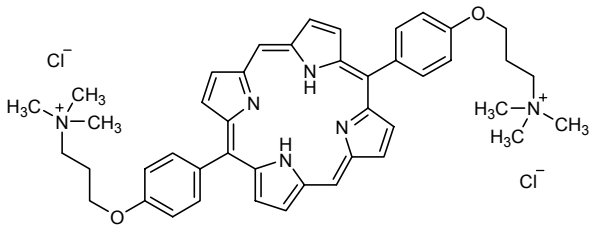
exeporfinii chloridum

exeporfinium chloride — 3,3'-(21*H*,23*H*-porphyrin-5,15-diylbis{[(4,1-phenylene)oxy]-*N,N,N*-trimethylpropan-1-aminium}) dichloride

chlorure d'exéporfinium — dichlorure de 3,3'-[21*H*,23*H*-porphyrin-5,15-diylbis(4,1-phénylèneoxy)]bis[*N,N,N*-triméthylpropan-1-aminium]

cloruro de exeporfinio — dicloruro de 3,3'-(21*H*,23*H*-porfirin-5,15-diilbis{[(4,1-fenileno)oxi]-*N,N,N*-trimetilpropan-1-aminium})

$C_{44}H_{50}Cl_2N_6O_2$



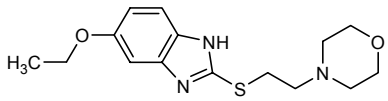
fabomotizolum

fabomotizole — 5-ethoxy-2-{[2-(morpholin-4-yl)ethyl]sulfanyl}-1*H*-benzimidazole

fabomotizole — 5-éthoxy-2-{[2-(morpholin-4-yl)éthyl]sulfanyl}-1*H*-benzimidazole

fabomotizol — 5-etoxi-2-{[2-(morfolin-4-il)etil]sulfanil}-1*H*-benzoimidazol

$C_{15}H_{21}N_3O_2S$



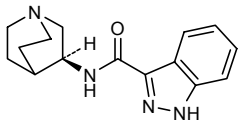
faciniclinum

facinicline — *N*-[(3*S*)-1-azabicyclo[2.2.2]octan-3-yl]-1*H*-indazole-3-carboxamide

facinicline — *N*-[(3*S*)-1-azabicyclo[2.2.2]octan-3-yl]-1*H*-indazole-3-carboxamide

faciniclina — *N*-[(3*S*)-1-azabiciclo[2.2.2]octan-3-il]-1*H*-indazol-3-carboxamida

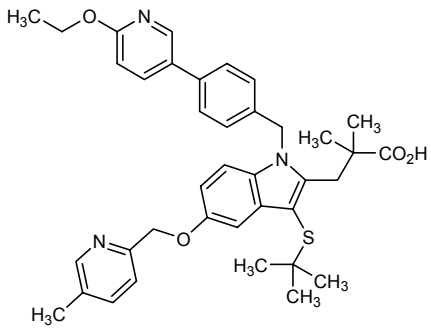
$C_{15}H_{18}N_4O$



fiboflaponum

fiboflapon	3-{3-(*tert*-butylsulfanyl)-1-{[4-(6-ethoxypyridin-3-yl)phenyl]methyl}-5-[(5-methylpyridin-2-yl)methoxy]-1*H*-indol-2-yl}-2,2-dimethylpropanoic acid
fiboflapon	acide 3-{3-(*tert*-butylsulfanyl)-1-{[4-(6-éthoxypyridin-3-yl)phényl]méthyl}-5-[(5-méthylpyridin-2-yl)méthoxy]-1*H*-indol-2-yl}-2,2-diméthylpropanoïque
fiboflapón	ácido 3-{3-(*terc*-butilsulfanil)-1-{[4-(6-etoxipiridin-3-il)fenil]metil}-5-[(5-metilpiridin-2-il)metoxi]-1*H*-indol-2-yl}-2,2-dimetilpropanoico

$C_{38}H_{43}N_3O_4S$



ficlatuzumabum #

ficlatuzumab	immunoglobulin G1-kappa, anti-[*Homo sapiens* HGF (hepatocyte growth factor, scatter factor, SF, hepatopoeitin A)], humanized monoclonal antibody; gamma1 heavy chain (1-448) [humanized VH (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01 V124>L (114)) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03 (119-448)], (221-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV4-1*01 (73.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (227-227":230-230")-bisdisulfide dimer
ficlatuzumab	immunoglobuline G1-kappa, anti-[*Homo sapiens* HGF (facteur de croissance de l'hépatocyte, facteur dispersant, SF, hépatopoïétine A)], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-448) [VH humanisé (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01 V124>L (114)) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03 (119-448)], (221-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV4-1*01 (73.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (227-227":230-230")-bisdisulfure

ficlatuzumab

inmunoglobulina G1-kappa, anti-[HGF de *Homo sapiens* (factor de crecimiento del hepatocito, factor dispersante, SF, hepatopoyetina A)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-448) [VH humanizado (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01 V124>L (114)) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03 (119-448)], (221-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizada (*Homo sapiens* IGKV4-1*01 (73.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (227-227":230-230")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQPGAE VKKPGTSVKL SCKASGYTFT TYWMHWVRQA PGQGLEWIGE  50
INPTNGHTNY NQKFQGRATL TVDKSTSTAY MELSSLRSED TAVYYCARNY 100
VGSIFDYWGQ GTLLTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI 200
CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD 250
TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST 300
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY 350
TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK   448
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPDS LAMSLGERVT LNCKASENVV SYVSWYQQKP GQSPKLLIYG  50
ASNRESGVPD RFSGSGSATD FTLTISSVQA EDVADYHCGQ SYNYPYTFGQ 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    145-201    262-322    368-426
         22"-96"  145"-201"  262"-322"  368"-426"
Intra-L  23'-88'    134'-194'
         23'"-88'"  134'"-194'"
Inter-H-L  221-214'  221"-214'"
Inter-H-H  227-227"  230-230"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
298, 298"

galeteronum

galeterone

17-(1*H*-benzimidazol-1-yl)androsta-5,16-dien-3β-ol

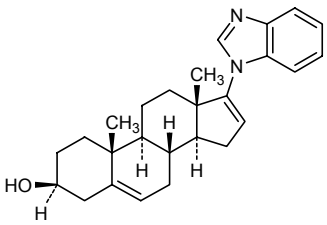
galétérone

17-(1*H*-benzimidazol-1-yl)androsta-5,16-dién-3β-ol

galeterona

17-(1*H*-benzoimidazol-1-il)androsta-5,16-dien-3β-ol

$C_{26}H_{32}N_2O$



ganetespibum

ganetespib

5-[2,4-dihydroxy-5-(propan-2-yl)phenyl]-4-(1-methyl-1*H*-indol-5-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

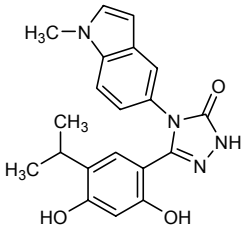
ganétespib

5-[2,4-dihydroxy-5-(propan-2-yl)phényl]-4-(1-méthyl-1*H*-indol-5-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one

ganetespib

5-[2,4-dihidroxi-5-(propan-2-il)fenil]-4-(1-metil-1*H*-indol-5-il)-2,4-dihidro-3*H*-1,2,4-triazol-3-ona

$C_{20}H_{20}N_4O_3$



indatuximabum ravtansinum #

indatuximab ravtansine — immunoglobulin G4-kappa, anti-[*Homo sapiens* SDC1 (syndecan-1, CD138)], chimeric monoclonal antibody conjugated to maytansinoid DM4;
gamma4 heavy chain (1-449) [*Mus musculus* VH (IGHV1-9*01 -(IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG4*01 (123-449)], (136-214')-disulfide with kappa light chain (1'-214') [*Mus musculus* V-KAPPA (IGKV10-94*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (228-228":231-231")-bisdisulfide dimer; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM4 [$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine] via the reducible SPDB linker [*N*-succinimidyl 4-(2-pyridyldithio)butanoate]
For the *ravtansine* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"**

indatuximab ravtansine — immunoglobuline G4-kappa, anti-[*Homo sapiens* SDC1 (syndecan-1, CD138)], anticorps monoclonal chimérique conjugué au maytansinoïde DM4;
chaîne lourde gamma4 (1-449) [*Mus musculus* VH (IGHV1-9*01 -(IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG4*01 (123-449)], (136-214')-disulfure avec la chaîne légère kappa (1'-214') [*Mus musculus* V-KAPPA (IGKV10-94*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (228-228":231-231")-bisdisulfure; conjugué, sur 3 à 4 lysyl en moyenne, au maytansinoïde DM4 [$N^{2'}$-déacétyl-$N^{2'}$-(4-mercapto-4-méthyl-1-oxopentyl)-maytansine] via le linker SPDB réductible [4-(2-pyridyldithio)butanoate de *N*-succinimidyle]
Pour la partie *ravtansine*, veuillez vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

indatuximab ravtansina — inmunoglobulina G4-kappa, anti-[SDC1 de *Homo sapiens* (sindecán-1, CD138)], anticuerpo monoclonal quimérico conjugado con el maitansinoide DM4;
cadena pesada gamma4 (1-449) [*Mus musculus* VH (IGHV1-9*01 -(IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG4*01 (123-449)], (136-214')-disulfuro con la cadena ligera kappa (1'-214') [*Mus musculus* V-KAPPA (IGKV10-94*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (228-228":231-231")-bisdisulfuro; conjugado, en 3-4 grupos lisil por término medio con el maitansinoide DM4 [$N^{2'}$-desacetil-$N^{2'}$-(4-mercapto-4-metil-1-oxopentil)-maitansina] mediante el espaciador SPDB reducible [4-(2-piridilditio)butanoato de *N*-succinimidilo]
Para la fracción *ravtansina*, se ruega referirse al documento *"INN for pharmaceutical substances: Names for radicals, groups and others"**

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQQSGSE LMMPGASVKI SCKATGYTFS NYWIEWVKQR PGHGLEWIGE  50
ILPGTGRTIY NEKFKGKATF TADISSNTVQ MQLSSLTSED SAVYYCARRD 100
YYGNFYYAMD YWGQGTSVTV SSASTKGPSV FPLAPCSRST SESTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
KTYTCNVDHK PSNTKVDKRV ESKYGPPCPS CPAPEFLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV 350
YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSTSS LSASLGDRVT ISCSASQGIN NYLNWYQQKP DGTVELLIYY  50
TSTLQSGVPS RFSGSGSGTD YSLTISNLEP EDIGTYYCQQ YSKLPRTFGG 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 22-96 149-205 263-323 369-437
22''-96'' 149''-205'' 263''-323'' 369''-437''
Intra-L 23'-88' 134'-194'
23'''-88''' 134'''-194'''
Inter-H-L 136-214' 136''-214'''
Inter-H-H 228-228'' 231-231''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

299, 299''

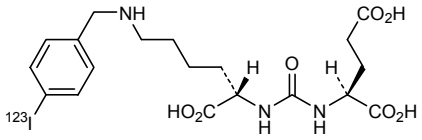
iofolastatum (^{123}I)

iofolastat (^{123}I) — *N*-{[(1*S*)-1-carboxy-5-{[(4-(^{123}I)iodophenyl)methyl]amino}pentyl]carbamoyl}-L-glutamic acid

iofolastat (^{123}I) — acide *N*-{[(1*S*)-1-carboxy-5-{[(4-(^{123}I)iodophényl)méthyl]amino}pentyl]carbamoyl}-L-glutamique

iofolastat (^{123}I) — ácido *N*-{[(1*S*)-1-carboxi-5-{[(4-(^{123}I)iodofenil)metil]amino}pentil]carbamoil}-L-glutámico

$C_{19}H_{26}{}^{123}IN_3O_7$



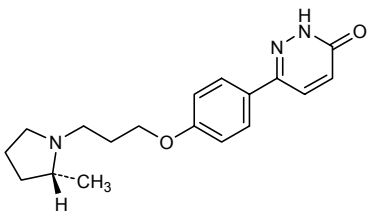
irdabisantum

irdabisant — 6-(4-{3-[(2*R*)-2-methylpyrrolidin-1-yl]propoxy}phenyl)pyridazin-3(2*H*)-one

irdabisant — 6-(4-{3-[(2*R*)-2-méthylpyrrolidin-1-yl]propoxy}phényl)pyridazin-3(2*H*)-one

irdabisant — 6-(4-{3-[(2*R*)-2-metilpirrolidin-1-il]propoxi}fenil)piridazin-3(2*H*)-ona

$C_{18}H_{23}N_3O_2$



ixekizumabum #

ixekizumab

immunoglobulin G4-kappa, anti-[*Homo sapiens* IL17A (interleukin 17A, IL-17A)], humanized monoclonal antibody;
gamma4 heavy chain (1-445) [humanized VH (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG4*01 hinge S10>P (227), CH3 K130>del (120-445)], (133-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2D-29*02 (89.00%) -IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (225-225":228-228")-bisdisulfide dimer

ixékizumab

immunoglobuline G4-kappa, anti-[*Homo sapiens* IL17A (interleukine 17A, IL-17A)], anticorps monoclonal humanisé;
chaîne lourde gamma4 (1-445) [VH humanisé (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG4*01 charnière S10>P (227), CH3 K130>del (120-445)], (133-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV2D-29*02 (89.00%) -IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimère (225-225":228-228")-bisdisulfure

ixekizumab

inmunoglobulina G4-kappa, anti-[*Homo sapiens* IL17A (interleukina 17A, IL-17A)], anticuerpo monoclonal humanizado;
cadena pesada gamma4 (1-445) [VH humanizada (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -*Homo sapiens* IGHG4*01 bisagra S10>P (227), CH3 K130>del (120-445)], (133-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizada (*Homo sapiens* IGKV2D-29*02 (89.00%) -IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dímero (225-225":228-228")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGSSVKV SCKASGYSFT DYHIHWVRQA PGQGLEWMGV  50
INPMYGTTDY NQRFKGRVTI TADESTSTAY MELSSLRSED TAVYYCARYD 100
YFTGTGVYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY 200
TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEFLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL 350
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLG      445
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQTPLS LSVTPGQPAS ISCRSSRSLV HSRGNTYLHW YLQKPGQSPQ  50
LLIYKVSNRF IGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHLP 100
FTFGQGTKLE 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	260-320	366-424
	22"-96"	146"-202"	260"-320"	366"-424"
Intra-L	23'-93'	139'-199'		
	23'"-93'"	139'"-199'"		
Inter-H-L	133-219'	133"-219'"		
Inter-H-H	225-225"	228-228"		

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

ladarixinum

ladarixin

4-[(2*R*)-1-oxo-1-(methanesulfonamido)propan-2-yl]phenyl trifluoromethanesulfonate

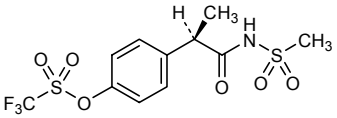
ladarixine

trifluorométhanesulfonate de 4-[(2*R*)-1-oxo-1-(méthanesulfonamido)propan-2-yl]phényle

ladarixina

trifluoromethanesulfonato de 4-[(2*R*)-1-oxo-1-(metanosulfonamido)propan-2-il]fenil

$C_{11}H_{12}F_3NO_6S_2$



lenomorelinum

lenomorelin

$O^{3.26}$-octanoylhuman appetite-regulating hormone (growth hormone-releasing peptide) precursor (protein M46)-(24-51)-peptide (ghrelin-28-C8)

lénomoréline

$O^{3.26}$-octanoylprécurseur de l'hormone humaine de régulation de l'appétit (précurseur du peptide de libération d'hormone de croissance, protéine M46)-(24-51)-peptide (ghréline-28-C8)

lenomorelina

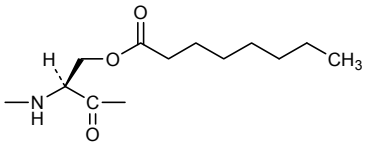
$O^{3.26}$-octanoilprecursor de la hormona humana de regulación del apetito (precursor del péptido de liberación de hormona del crecimiento, proteína M46)-(24-51)-péptido (ghrelina-28-C8)

$C_{149}H_{249}N_{47}O_{42}$

GSSFLSPEHQ RVQQRKESKK PPAKLQPR 28

Modified residue / Résidu modifié / Residuo modificado

S
3
O-octanoyl-L-seryl
O-octanoyl-L-séryl
O-octanoil-L-serilo



lesinuradum

lesinurad

2-{[5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetic acid

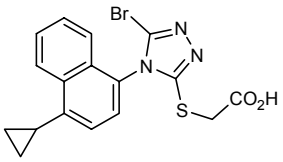
lésinurad

acide 2-{[5-bromo-4-(4-cyclopropylnaphtalén-1-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acétique

lesinurad

ácido 2-{[5-bromo-4-(4-ciclopropilnaftalen-1-il)-4*H*-1,2,4-triazol-3-il]sulfanil}acético

$C_{17}H_{14}BrN_3O_2S$



lexibulinum

lexibulin

1-ethyl-3-[2-methoxy-4-(5-methyl-4-{[(1*S*)-1-(pyridin-3-yl)butyl]amino}pyrimidin-2-yl)phenyl]urea

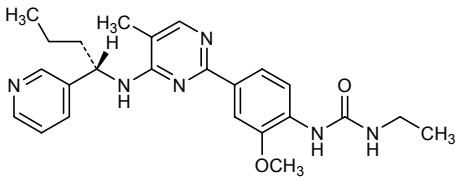
lexibuline

1-éthyl-3-[2-méthoxy-4-(5-méthyl-4-{[(1*S*)-1-(pyridin-3-yl)butyl]amino}pyrimidin-2-yl)phényl]urée

lexibulina

1-etil-3-[2-metoxi-4-(5-metil-4-{[(1*S*)-1-(piridin-3-il)butil]amino}pirimidin-2-il)fenil]urea

$C_{24}H_{30}N_6O_2$



lipegfilgrastimum #

lipegfilgrastim

pegylated granulocyte colony stimulating factor; $O^{3.133}$-[N^5-(*N*-{[ω-methoxypoly(oxyethylene)]carbonyl}glycyl)-α-neuraminyl-(2→6)-α-D-galactopyranosyl]-L-methionyl-des-1-L-alanine-des-37-L-valine-des-38-L-serine-des-39-L-glutamic acid-human granulocyte colony-stimulating factor (G-CSF, pluripoietin)

lipegfilgrastim

facteur de stimulation de colonie de granulocytes humain pégylé; $O^{3.133}$-[N^5-(*N*-{[ω-méthoxypoly(oxyéthylène)]carbonyl}glycyl)-α-neuraminyl-(2→6)-α-D-galactopyranosyl]-L-méthionyl-dès-1-L-alanine-dès-37-L-valine-des-38-L-sérine-dès-39-L-acide glutamique-facteur de stimulation de colonie de granulocytes humain (G-CSF, pluripoïétine)

lipegfilgrastim

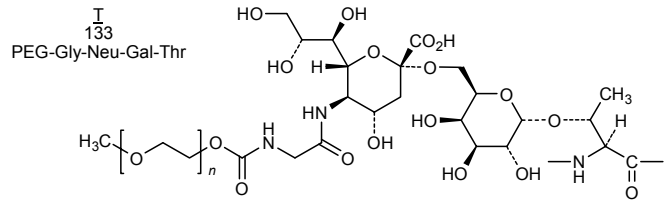
factor de estimulación de colonias de granulocitos humano pegilado; $O^{3.133}$-[N^5-(*N*-{[ω-metoxipoli(oxietileno)]carbonil}glicil)-α-neuraminil-(2→6)-α-D-galactopiranosil]-L-metionil-des-1-L-alanina-des-37-L-valina-des-38-L-serine-des-39-L-ácido glutámico-factor de estimulación de colonias de granulocitos humanos (G-CSF, pluripoyetina)

$C_{864}H_{1369}N_{225}O_{258}S_9$ $[C_2H_4O]_n$

```
                                                        M 0
TPLGPASSLP QSFLLKCLEQ VRKIQGDGAA LQEKLCATYK LCHPEELVLL 50
GHSLGIPWAP LSSCPSQALQ LAGCLSQLHS GLFLYQGLLQ ALEGISPELG 100
PTLDTLQLDV ADFATTIWQQ MEELGMAPAL QPTQGAMPAF ASAFQRRAGG 150
VLVASHLQSF LEVSYRVLRH LAQP                              174
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
36-42 64-74

Modified residue / Résidu modifié / Residuo modificado



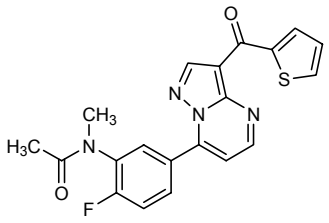
loredіplonum

loredіplon — *N*-{2-fluoro-5-[3-(thiophene-2-carbonyl)pyrazolo[1,5-*a*]pyrimidin-7-yl]phenyl}-*N*-methylacetamide

lorédіplon — *N*-{2-fluoro-5-[3-(thiophéne-2-carbonyl)pryrazolo[1,5-*a*]pyrimidin-7-yl]phényl}-*N*-méthylacétamide

lorediplón — *N*-{2-fluoro-5-[3-(tiofeno-2-carbonil)pirazolo[1,5-*a*]pirimidin-7-il]fenil}-*N*-metilacetamida

$C_{20}H_{15}FN_4O_2S$



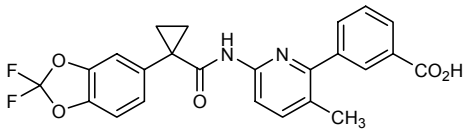
lumacaftorum

lumacaftor — 3-{6-[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropane-1-carboxamido]-3-methylpyridin-2-yl}benzoic acid

lumacaftor — acide 3-{6-[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropane-1-carboxamido]-3-methylpyridin-2-yl}benzoïque

lumacaftor — ácido 3-{6-[1-(2,2-difluoro-1,3-benzodioxol-5-il)ciclopropano-1-carboxamido]-3-metilpiridin-2-il}benzoico

$C_{24}H_{18}F_2N_2O_5$



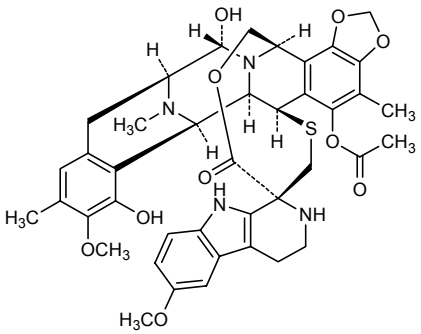
lurbinectedinum

lurbinectedin — (1'*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-8,14-dihydroxy-6',9-dimethoxy-4,10,23-trimethyl-19-oxo-2',3',4',6,7,9',12,13,14,16-decahydro-6a*H*-spiro[7,13-azano-6,16-(epithiopropanooxymethano)[1,3]dioxolo[7,8]isoquinolino[3,2-b][3]benzazocine-20,1'-pyrido[3,4-b]indol]-5-yl acetate

lurbinectédine — acétate de (1'*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-8,14-dihydroxy-6',9-diméthoxy-4,10,23-triméthyl-19-oxo-2',3',4',6,7,9',12,13,14,16-décahydro-6a*H*-spiro[7,13-azano-6,16-(épithiopropanooxyméthano)[1,3]dioxolo[7,8]isoquinolino[3,2-b][3]benzazocine-20,1'-pyrido[3,4-b]indol]-5-yl

lurbinectedina — acetato de (1'*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-8,14-dihidroxi-6',9-dimetoxi-4,10,23-trimetil-19-oxo-2',3',4',6,7,9',12,13,14,16-decahidro-16*H*-spiro[7,13-azano-6,16-(epitiopropanooximetano)[1,3]dioxolo[7,8]isoquinolino[3,2-*b*][3]benzazocina-20,1'-pirido[3,4-*b*]indol]-5-ilo

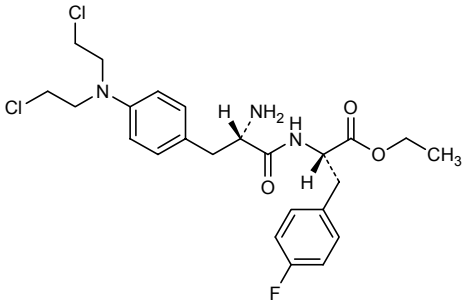
$C_{41}H_{44}N_4O_{10}S$



melphalanum flufenamidum

melphalan flufenamide	ethyl (2*S*)-2-[(2*S*)-2-amino-3-{4-[bis(2-chloroethyl)amino]phenyl}propanamido]-3-(4-fluorophenyl)propanoate
melphalan flufénamide	(2*S*)-2-[(2*S*)-2-amino-3-{4-[bis(2-chloroéthyl)amino]phényl}propanamido]-3-(4-fluorophényl)propanoate d'éthyle
melfalán flufenamida	(2*S*)-2-[(2*S*)-2-amino-3-{4-[bis(2-cloroetil)amino]fenil}propanamido]-3-(4-fluorofenil)propanoato de etilo

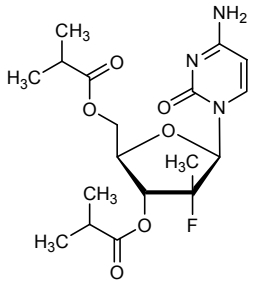
$C_{24}H_{30}Cl_2FN_3O_3$



mericitabinum

mericitabine	(2'*R*)-2'-deoxy-2'-fluoro-2'-methyl-2',3'-bis-*O*-(2-methylpropanoyl)cytidine
méricitabine	3',5'-bis(2-méthylpropanoate) de (2'*R*)-2'-déoxy-2'-fluoro-2'-méthylcytidine
mericitabina	(2'*R*)-2'-desoxi-2'-fluoro-2'-metil-2',3'-bis-*O*-(2-metilpropanoil)citidina

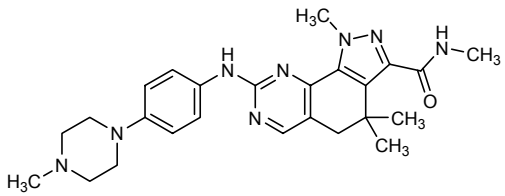
$C_{18}H_{26}FN_3O_6$



milciclibum

milciclib	*N*,1,4,4-tetramethyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline-3-carboxamide
milciclib	*N*,1,4,4-tétraméthyl-8-{[4-(4-méthylpipérazin-1-yl)phényl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline-3-carboxamide
milciclib	*N*,1,4,4-tetrametil-8-{[4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-1*H*-pirazolo[4,3-*h*]quinazolina-3-carboxamida

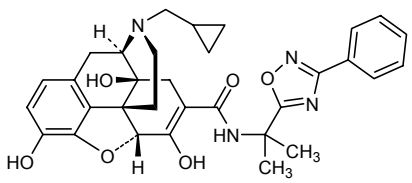
$C_{25}H_{32}N_8O$



naldemedinum

naldemedine	17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14-trihydroxy-*N*-[2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide
naldémédine	17-(cyclopropylméthyl)-6,7-didéhydro-4,5α-époxy-3,6,14-trihydroxy-*N*-[2-(3-phényl-1,2,4-oxadiazol-5-yl)propan-2-yl]morphinan-7-carboxamide
naldemedina	17-(ciclopropilmetil)-6,7-didehidro-4,5α-epoxi-3,6,14-trihidroxi-*N*-[2-(3-fenil-1,2,4-oxadiazol-5-il)propan-2-il]morfinan-7-carboxamida

$C_{32}H_{34}N_4O_6$



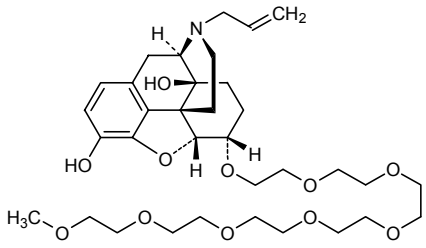
naloxegolum

naloxegol — 4,5α-epoxy-6α-[(3,6,9,12,15,18,21-heptaoxadocosan-1-yl)oxy]-17-(prop-2-en-1-yl)morphinan-3,14-diol

naloxégol — 4,5α-époxy-6α-[(3,6,9,12,15,18,21-heptaoxadocosan-1-yl)oxy]-17-(prop-2-én-1-yl)morphinane-3,14-diol

naloxegol — 4,5α-epoxi-6α-[(3,6,9,12,15,18,21-heptaoxadocosan-1-il)oxi]-17-(prop-2-en-1-il)morfinan-3,14-diol

$C_{34}H_{53}NO_{11}$



narnatumabum #

narnatumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* MST1R (macrophage stimulating 1 receptor, macrophage stimulating protein receptor, MSP receptor, c-met-related tyrosine kinase, protein-tyrosine kinase 8, PTK8, RON, p185-Ron, CD136)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-452) [*Homo sapiens* VH (IGHV3-7*01 (95.90%) -(IGHD)-IGHJ6*01 T127>I (119)) [8.8.15] (1-122) - IGHG1*03 (123-452)], (225-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (98.90%) - IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; (231-231":234-234")-bisdisulfide dimer

narnatumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* MST1R (récepteur 1 stimulant le macrophage, récepteur de la protéine stimulant le macrophage, récepteur de la MSP, tyrosine kinase apparentée à c-met, protéine-tyrosine kinase 8, PTK8, RON, p185-Ron, CD136)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-452) [*Homo sapiens* VH (IGHV3-7*01 (95.90%) -(IGHD)-IGHJ6*01 T127>I (119)) [8.8.15] (1-122) - IGHG1*03 (123-452)], (225-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (98.90%) - IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (231-231":234-234")-bisdisulfure

narnatumab — inmunoglobulina G1-kappa, anti-[*Homo sapiens* MST1R (receptor 1 estimulante el macrófago, receptor de la proteína estimulante el macrófago, receptor de la MSP, tirosina kinasa relacionada con c-met, proteína-tirosina kinase 8, PTK8, RON, p185-Ron, CD136)], *Homo sapiens* anticuerpo monoclonal;
cadena pesada gamma1 (1-452) [*Homo sapiens* VH (IGHV3-7*01 (95.90%) -(IGHD)-IGHJ6*01 T127>I (119)) [8.8.15] (1-122) - IGHG1*03 (123-452)], (225-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (98.90%) - IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (231-231":234-234")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYLMTWVRQA PGKGLEWVAN  50
IKQDGSEKYY VDSVKGRFTI SRDNAKNSLN LQMNSLRAED TAVYYCTRDG 100
YSSGRHYGMD VWGQGTTVIV 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

```
EIVLTQSPAT LSLSPGERAT LSCRASQSVS RYLAWYQQKP GQAPRLLIYD  50
ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPRTFGQ 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 22-96 149-2105 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''

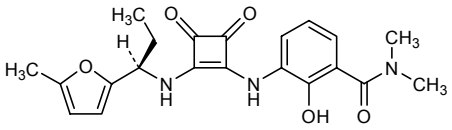
navarixinum

navarixin — 2-hydroxy-*N,N*-dimethyl-3-[(2-{[(1*R*)-1-(5-methylfuran-2-yl)propyl]amino}-3,4-dioxocyclobut-1-en-1-yl)amino]benzamide

navarixine — 2-hydroxy-*N,N*-diméthyl-3-[(2-{[(1*R*)-1-(5-méthylfuran-2-yl)propyl]amino}-3,4-dioxocyclobut-1-én-1-yl)amino]benzamide

navarixina — 2-hidroxi-*N,N*-dimetil-3-[(2-{[(1*R*)-1-(5-metilfuran-2-il)propil]amino}-3,4-dioxociclobut-1-en-1-il)amino]benzamida

$C_{21}H_{23}N_3O_5$



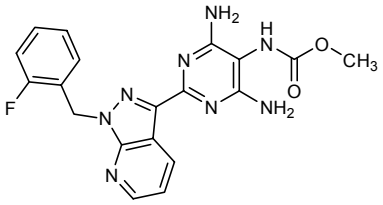
nelociguatum

nelociguat — methyl (4,6-diamino-2-{1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}pyrimidin-5-yl)carbamate

nélociguat — (4,6-diamino-2-{1-[(2-fluorophényl)méthyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}pyrimidin-5-yl)carbamate de méthyle

nelociguat — (4,6-diamino-2-{1-[(2-fluorofenil)metil]-1*H*-pirazolo[3,4-*b*]piridin-3-il}pirimidin-5-il)carbamato de metilo

$C_{19}H_{17}FN_8O_2$



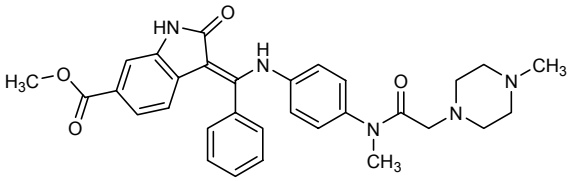
nintedanibum

nintedanib — methyl (3*Z*)-3-[({4-[*N*-methyl-2-(4-methylpiperazin-1-yl)acetamido]phenyl}amino)(phenyl)methylidene]-2-oxo-2,3-dihydro-1*H*-indole-6-carboxylate

nintédanib — (3*Z*)-3-[({4-[*N*-méthyl-2-(4-méthylpipérazin-1-yl)acétamido]phényl}amino)(phényl)méthylidène]-2-oxo-2,3-dihydro-1*H*-indole-6-carboxylate de méthyle

nintedanib — (3*Z*)-3-[({4-[*N*-metil-2-(4-metilpiperazin-1-il)acetamido]fenil}amino)(fenil)metiliden]-2-oxo-2,3-dihidro-1*H*-indol-6-carboxilato de metilo

$C_{31}H_{33}N_5O_4$



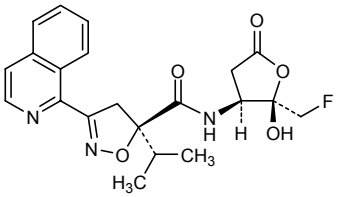
nivocasanum

nivocasan — (5*R*)-*N*-[(2*S*,3*S*)-2-(fluoromethyl)-2-hydroxy-5-oxooxolan-3-yl]-3-(isoquinolin-1-yl)-5-(propan-2-yl)-4,5-dihydro-1,2-oxazole-5-carboxamide

nivocasan — (5*R*)-*N*-[(2*S*,3*S*)-2-(fluorométhyl)-2-hydroxy-5-oxooxolan-3-yl]-3-(isoquinoléin-1-yl)-5-(propan-2-yl)-4,5-dihydro-1,2-oxazole-5-carboxamide

nivocasán — (5*R*)-*N*-[(2*S*,3*S*)-2-(fluorometil)-2-hidroxi-5-oxooxolan-3-il]-3-(isoquinolin-1-il)-5-(propan-2-il)-4,5-dihidro-1,2-oxazol-5-carboxamida

$C_{21}H_{22}FN_3O_5$



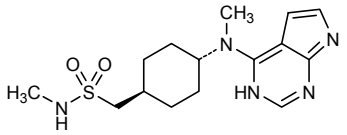
oclacitinibum

oclacitinib — *N*-methyl{*trans*-4-[methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]cyclohexyl}methanesulfonamide

oclacitinib — *N*-méthyl[*trans*-4-(méthyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamino)cyclohexyl]méthanesulfonamide

oclacitinib — *N*-metil{*trans*-4-[metil(7*H*-pirrolo[2,3-*d*]pirimidin-4-il)amino]ciclohexil}metanosulfonamida

$C_{15}H_{23}N_5O_2S$



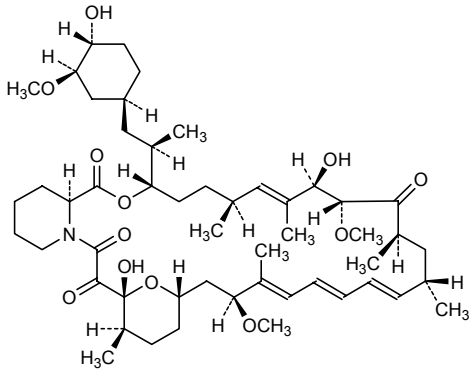
olcorolimusum

olcorolimus — (3*S*,6*S*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihydroxy-3-{(1*R*)-1-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl)propan-2-yl}-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-3,4,5,6,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34[a]-icosahydro-11*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,11,28,29(31*H*)-tetrone

olcorolimus — (3*S*,6*S*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihydroxy-3-{(1*R*)-1-[(1*S*,3*R*,4*R*)-4-hydroxy-3-méthoxycyclohexyl)propan-2-yl}-10,21-diméthoxy-6,8,12,14,20,26-hexaméthyl-3,4,5,6,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34[a]-icosahydro-11*H*-23,27-époxypyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,11,28,29(31*H*)-tétrone

olcorolimús — (3*S*,6*S*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihidroxi-3-{(1*R*)-1-[(1*S*,3*R*,4*R*)-4-hidroxi-3-metoxiciclohexil)propan-2-il}-10,21-dimetoxi-6,8,12,14,20,26-hexametil-3,4,5,6,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34[a]-icosahidro-11*H*-23,27-epoxipirido[2,1-*c*][1,4]oxaazaciclohentriacontina-1,11,28,29(31*H*)-tetrona

$C_{51}H_{81}NO_{12}$



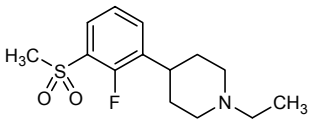
ordopidinum

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

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

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

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



ozoralizumabum #

ozoralizumab immunoglobulin single chain VH-VH'-VH, trivalent bispecific anti-[*Homo sapiens* TNF (tumor necrosis factor, TNF superfamily member 2, TNFSF2, TNFA, TNF-alpha)] VH and anti-[*Homo sapiens* ALB (albumin, human serum albumin, HAS)] VH', humanized *Lama glama* monoclonal antibody;
scVH-VH'-VH (1-363) [humanized VH (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (105)) [8.8.8] (1-115) - 9-mer linker (tetraglycyl-seryl-triglycyl-seryl) (116-124) -humanized VH' (*Homo sapiens* IGHV3-23*04 (89.60%) -(IGHD)-IGHJ1*01 W118>S (229), G119>S (230) [8.8.8] (125-239) -9-mer linker (tetraglycyl-seryl-triglycyl-seryl) (240-248) -humanized VH (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (353)(249-363)

ozoralizumab immunoglobuline single chain VH-VH'-VH, trivalente bispécifique anti-[*Homo sapiens* TNF (facteur de nécrose tumorale, membre 2 de la superfamille du TNF, TNFSF2, TNFA, TNF-alpha)] VH et anti-[*Homo sapiens* ALB (albumine, sérum albumine humaine, SAH)] VH', anticorps monoclonal de *Lama glama* humanisé;
scVH-VH'-VH (1-363) [VH humanisé (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (105)) [8.8.8] (1-115) -9-mer linker (tétraglycyl-séryl-triglycyl-séryl) (116-124) -VH' humanisé (*Homo sapiens* IGHV3-23*04 (89.60%) -(IGHD)-IGHJ1*01 W118>S (229), G119>S (230) [8.8.8] (125-239) -9-mer linker (tétraglycyl-séryl-triglycyl-séryl) (240-248) -VH humanisé (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (353)(249-363)

ozoralizumab inmunoglobulina de cadena sencilla VH-VH'-VH, trivalente biespecífica anti-[TNF de *Homo sapiens* (factor de necrosis tumoral, miembro 2 de la superfamilia del TNF, TNFSF2, TNFA, TNF-alpha)] VH y anti-[*Homo sapiens* ALB (albumina, albumina sérica humana SAH)] VH', anticuerpo monoclonal de *Lama glama* humanizado;
scVH-VH'-VH (1-363) [VH humanizado (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (105)) [8.8.8] (1-115) - conector nonámero (tetraglicil-seril-triglicil-seril) (116-124) -VH' humanizado (*Homo sapiens* IGHV3-23*04 (89.60%) -(IGHD)-IGHJ1*01 W118>S (229), G119>S (230) [8.8.8] (125-239) - espaciador nonámero (tetraglicil-seril-triglicil-seril) (240-248) -VH humanizado (*Homo sapiens* IGHV3-74*01 (88.80%) -(IGHD)-IGHJ1*01 W118>R (353)(249-363)

scVH-VH'-VH chain / Chaîne scVH-VH'-VH / Cadena scVH-VH'-VH

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS DYWMYWVRQA PGKGLEWVSE  50
INTNGLITKY PDSVKGRFTI SRDNAKNTLY LQMNSLRPED TAVYYCARSP 100
SGFNRGQGTL VTVSSGGGGS GGGSEVQLVE SGGGLVQPGN SLRLSCAASG 150
FTFSSFGMSW VRQAPGKGLE WVSSISGSGS DTLYADSVKG RFTISRDNAK 200
TTLYLQMNSL RPEDTAVYYC TIGGSLSRSS QGTLVTVSSG GGGSGGGSEV 250
QLVESGGGLV QPGGSLRLSC AASGFTFSDY WMYWVRQAPG KGLEWVSEIN 300
TNGLITKYPD SVKGRFTISR DNAKNTLYLQ MNSLRPEDTA VYYCARSPSG 350
FNRGQGTLVT VSS                                         363
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-chain 22-96 146-220 270-34

pateclizumabum #

pateclizumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* LTA (lymphotoxin alpha, TNFSF1, tumor necrosis factor superfamily member 1, LT)], humanized monoclonal antibody;
gamma1 heavy chain (1-447) [humanized VH (*Homo sapiens* IGHV3-74*01 (76.50%) -(IGHD)-IGHJ5*01) [8.9.11] (1-118) -*Homo sapiens* IGHG1*03 CH1 R120>K (215), CH3 K130>del (119-447)], (221-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (88.40%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (227-227":230-230")-bisdisulfide dimer

patéclizumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* LTA (lymphotoxine alpha, TNFSF1, membre 1 de la superfamille du facteur de nécrose tumorale, LT)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-447) [VH humanisé (*Homo sapiens* IGHV3-74*01 (76.50%) -(IGHD)-IGHJ5*01) [8.9.11] (1-118) -*Homo sapiens* IGHG1*03 CH1 R120>K (215), CH3 K130>del (119-447)], (221-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (88.40%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (227-227":230-230")-bisdisulfure

pateclizumab

inmunoglobulina G1-kappa, anti-[LTA *de Homo sapiens* (linfotoxina alfa, TNFSF1, miembro 1 de la superfamilia del factor de necrosis tumoral, LT)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-447) [VH humanizada (*Homo sapiens* IGHV3-74*01 (76.50%) -(IGHD)-IGHJ5*01) [8.9.11] (1-118) -*Homo sapiens* IGHG1*03 CH1 R120>K (215), CH3 K130>del (119-447)], (221-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizada (*Homo sapiens* IGKV1-39*01 (88.40%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (227-227":230-230")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGYTFT SYVIHWVRQA PGKGLEWVGY  50
NNPYNAGTNY NEKFKGRFTI SSDKSKNTAY LQMNSLRAED TAVYYCSRPT 100
MLPWFAYWGQ GTLVTVSSAS 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
TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPG    447
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASQAVS SAVAWYQQKP GKAPKLLIYS  50
ASHRYTGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQE SYSTPWTFGQ 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 22-96 145-201 262-322 368-426
22"-96" 145"-201" 262"-322" 368"-426"
Intra-L 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L 221-214' 221"-214'"
Inter-H-H 227-227" 230-230"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

298, 298"

pegadricasum #

pegadricase

pegylated Urate Oxidase from *Candida utilis*, [198-threonine(S>T)]uricase (EC 1.7.3.3, urate oxidase) *Pichia jadinii* (Yeast) (*Candida utilis*) tetramer, 6-amino group of an average of 3 lysine residues, mostly in position 16, 19, and 85 of each monomer, are amidified with α-(3-carboxypropanoyl)-ω-methoxypoly(oxyethylene)

pégadricase

urate oxidase de *Candida utilis* pégylée, [198-thréonine(S>T)]uricase (EC 1.7.3.3, urate oxydase) *Pichia jadinii* (levure) (*Candida utilis*), tétramère, la fonction amine en 6 de certaines lysines, en moyenne 3, principalement en positions 16, 19, et 85 de chaque monomère, sont amidifiées par le α-(3-carboxypropanoyl)-ω-méthoxypoly(oxyéthylène)

pegadricasa

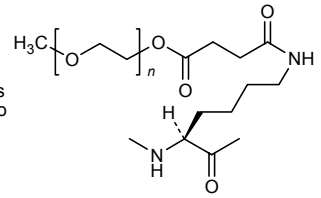
urato oxidasa de *Candida utilis* pegilada, [198-treonina(S>T)]uricasa (EC 1.7.3.3, urato oxidasa) *Pichia jadinii* (levadura) (*Candida utilis*), tetrámero, la función amina en 6 de ciertas lisinas, 3 por término medio, principalmente en las posiciones 16, 19, y 85 de cada monómero, está amidificada con α-(3-carboxipropanoil)-ω-metoxipoli(oxietileno)

Monomer / Monomère / Monómero

```
MSTTLSSSTY GKDNVKFLKV KKDPQNPKKQ EVMEATVTCL LEGGFDTSYT  50
EADNSSIVPT DTVKNTILVL AKTTEIWPIE RFAAKLATHF VEKYSHVSGV 100
SVKIVQDRWV KYAVDGKPHD HSFIHEGGEK RITDLYYKRS GDYKLSSAIK 150
DLTVLKSTGS MFYGYNKCDF TTLQPTTDRI LSTDVDATWV WDNKKIGTVY 200
DIAKAADKGI FDNVYNQARE ITLTTFALEN SPSVQATMFN MATQILEKAC 250
SVYSVSYALP NKHYFLIDLK WKGLENDNEL FYPSPHPNGL IKCTVVRKEK 300
TKL                                                    303
```

Modified residues / Résidus modifiés / Residuos modificados

K
16, 19, 85
main pegylation sites
principaux sites pégylés
principios sitios pegilado



peginterferonum lambda-1a #

peginterferon lambda-1a

pegylated interferon lambda-1; pegylated interleukin 29; *N*-{3-[α-methylpoly(oxyethylene)oxy]propyl}-L-methionyl{[171-serine]human interleukin-29 (IFN-λ-1)-(7-181)-peptide}

péginterféron lambda-1a

interféron lambda-1 pégylé; interleukine-29 pégylée; *N*-{3-[α-méthylpoly(oxyéthylène)oxy]propyl}-L-méthionyl{[171-sérine] interleukine-29 humaine (IFN-λ-1)-(7-181)-peptide}

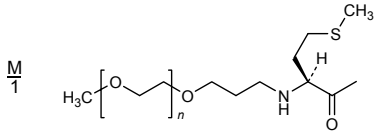
peginterferón lambda-1a

interferón lambda-1 pegilado; interleukina-29 pegilada; *N*-{3-[α-metilpoli(oxietileno)oxi]propil}-L-metionil{[171-serina] interleukina-29 humana (IFN-λ-1)-(7-181)-péptido}

$C_{875}H_{1408}N_{254}O_{251}S_5\ (C_2H_4O)_n$

```
     MKPTT TGKGCHIGRF KSLSPQELAS FKKARDALEE SLKLKNWSCS 50
SPVFPGNWDL RLLQVRERPV ALEAELALTL KVLEAAAGPA LEDVLDQPLH 100
TLHHILSQLQ ACIQPQPTAG PRPRGRLHHW LHRLQEAPKK ESAGCLEASV 150
TFNLFRLLTR DLKYVADGNL SLRTSTHPES T                    181
```

Modified residue / Résidu modifié / Residuo modificado



Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
15-112 49-145

pegnivacoginum

pegnivacogin

a ribonucleic acid aptamer which binds Factor XIa; ester of 2'-*O*-methyl-5'-*O*-phosphonoguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3' →5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→3')-thimidine with 6-[(2,6-bis{*N*-[ω-methoxypoly(oxyethylene)carbonyl]}-DL-lysyl)amino]hexan-1-ol

pégnivacogin

acide ribonucleique aptamère se liant au Factor XIa;
ester de 2'-*O*-méthyl-5'-*O*-phosphonoguanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-déoxy-2'-fluorocytidylyl-(3'→5')-2'-déoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→3')-thimidine avec 6-[(2,6-bis{*N*-[ω-méthoxypoly(oxyéthylène)carbonyl]}-DL-lysyl)amino]hexan-1-ol

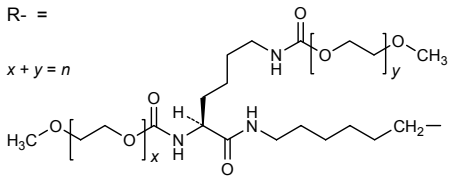
pegnivacogina

aptámero de ácido ribomucléico que se une a Factor XIa;
éster of 2'-*O*-metil-5'-*O*-fosfonoguanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-guanilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-2'-*O*-metilcitidilil-(3'→3')-timidina con 6-[(2,6-bis{*N*-[ω-metoxipoli(oxietileno)carbonil]}-DL-lisil)amino]hexan-1-ol

$C_{327}H_{422}F_{11}N_{114}O_{213}P_{31}\ (C_2H_4O)_n$

(3'-5')-R-pmG-mU-mG-mG-mA-dflC-dflU-mA-dflU-mA-dflC-dflC-mG-dflC-mG-dflU-mA-mA-dflU-mG-dflC-mU-G-mC-dflC-dflU-mC-mC-mA-mC3'-3'dT
Legend:
dfl = 2'-deoxy-2'-fluoro ; m = 2'-O-methyl ; p (as prefix) = 5'-phosphate

R- =



pimasertibum

pimasertib

N-[(2*S*)-2,3-dihydroxypropyl]-3-[(2-fluoro-4-iodophenyl)amino]pyridine-4-carboxamide

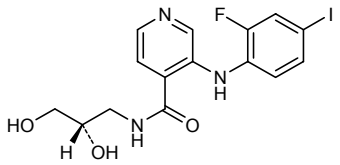
pimasertib

N-[(2*S*)-2,3-dihydroxypropyl]-3-[(2-fluoro-4-iodophényl)amino]pyridine-4-carboxamide

pimasertib

N-[(2*S*)-2,3-dihidroxipropil]-3-[(2-fluoro-4-iodofenil)amino]piridina-4-carboxamida

$C_{15}H_{15}FIN_3O_3$



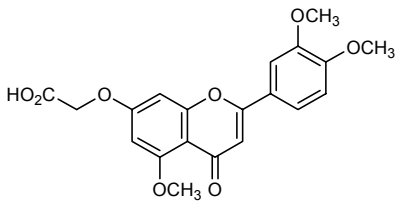
recoflavonum

recoflavone {[2-(3,4-dimethoxyphenyl)-5-methoxy-4-oxo-4*H*-chromen-7-yl]oxy}acetic acid

récoflavone acide {[2-(3,4-diméthoxyphényl)-5-méthoxy-4-oxo-4*H*-chromen-7-yl]oxy}acétique

recoflavona ácido {[2-(3,4-dimetoxifenil)-5-metoxi-4-oxo-4*H*-cromen-7-il]oxi}acético

$C_{20}H_{18}O_8$



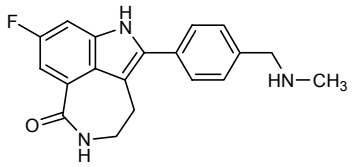
rucaparibum

rucaparib 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6*H*-pyrrolo[4,3,2-*ef*][2]benzazepin-6-one

rucaparib 8-fluoro-2-{4-[(méthylamino)méthyl]phényl}-1,3,4,5-tétrahydro-6*H*-pyrrolo[4,3,2-*ef*][2]benzazépin-6-one

rucaparib 8-fluoro-2-{4-[(metilamino)metil]fenil}-1,3,4,5-tetrahidro-6*H*-pirrolo[4,3,2-*ef*][2]benzazepin-6-ona

$C_{19}H_{18}FN_3O$



safotibantum

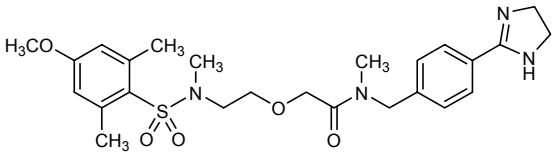
safotibant *N*-{[4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl]methyl}-2-{2-[(4-methoxy-2,6-dimethylbenzenesulfonyl)(methyl)amino]ethoxy}-*N*-methylacetamide

safotibant *N*-{[4-(4,5-dihydro-1*H*-imidazol-2-yl)phényl]méthyl}-2-{2-[(4-méthoxy-2,6-diméthylbenzènesulfonyl)(méthyl)amino]éthoxy}-*N*-méthylacétamide

safotibant

N-{[4-(4,5-dihidro-1*H*-imidazol-2-il)fenil]metil}-2-{2-[(4-metoxi-2,6-dimetilbencenosulfonil)(metil)amino]etoxi}-*N*-metilacetamido

$C_{25}H_{34}N_4O_5S$



selepressinum

selepressin

vasopressin type 1a (V1a) receptor agonist; [2-L-phenylalanine,3-L-isoleucine,4-(6-oxo-L-lysine),8-[5-*N*-(propan-2-yl)-L-ornithine]]human vasopressin

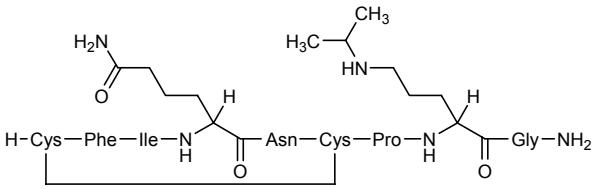
sélépressine

agoniste du récepteur de la vasopressine type 1a (V1a); [2-L-phénylalanine,3-L-isoleucine,4-(6-oxo-L-lysine),8-[5-*N*-(propan-2-yl)-L-ornithine]]vasopressine humaine

selepresina

agonista del receptor de la vasopresina tipo 1ª (V1a); [2-L-fenillalanina,3-L-isoleucina,4-(6-oxo-L-lisina),8-[5-*N*-(propan-2-yl)-L-ornitina]]vasopresina humana

$C_{46}H_{73}N_{13}O_{11}S_2$



sepantronii bromidum

sepantronium bromide

1-(2-methoxyethyl)-2-methyl-4,9-dioxo-3-[(pyrazin-2-yl)methyl]-4,9-dihydro-1*H*-naphtho[2,3-*d*]imidazolium bromide

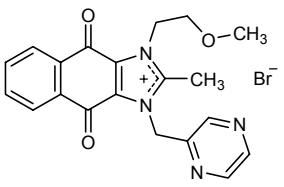
bromure de sépantronium

bromure de 1-(2-méthoxyéthyl)-2-méthyl-4,9-dioxo-3-[(pyrazin-2-yl)méthyl]-4,9-dihydro-1*H*-naphto[2,3-*d*]imidazolium

bromuro de sepantronio

bromuro de 2-metil-1-(2-metoxietil)-4,9-dioxo-3-[(pirazin-2-il)metil]-4,9-dihidro-1*H*-nafto[2,3-*d*]imidazolio

$C_{20}H_{19}BrN_4O_3$



serelaxinum

serelaxin — human relaxin 2 (relaxin H2)

sérélaxine — rélaxine 2 humaine (rélaxine H2)

serelaxina — relaxina 2 humana (relaxina H2)

$C_{256}H_{408}N_{74}O_{74}S_8$

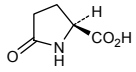
B chain / Chaîne B / Cadena B
DSWMEEVIKL CGRELVRAQI AICGMSTWS 29

A chain / Chaîne A / Cadena A
QLYSALANKC CHVGCTKRSL ARFC 24'

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
10'-15' 11-11' 23-24'

Modified residue / Résidu modifié / Residuo modificado

Q
1'
L-pyroglutamic acid



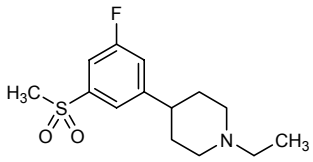
seridopidinum

seridopidine — 1-ethyl-4-[3-fluoro-5-(methanesulfonyl)phenyl]piperidine

séridopidine — 1-éthyl-4-[3-fluoro-5-(méthylsulfonyl)phényl]pipéridine

seridopidina — 1-etil-4-[3-fluoro-5-(metanosulfonil)fenil]piperidina

$C_{14}H_{20}FNO_2S$



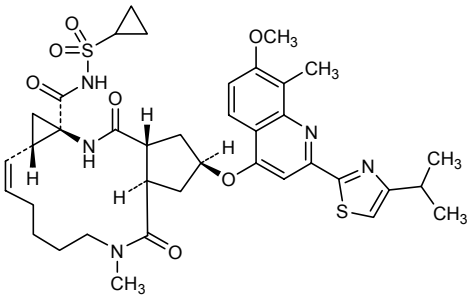
simeprevirum

simeprevir — (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(cyclopropanesulfonyl)-2-({7-methoxy-8-methyl-2-[4-(propan-2-yl)-1,3-thiazol-2-yl]quinolin-4-yl}oxy)-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotetradecine-12a(1*H*)-carboxamide

siméprévir — (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(cyclopropanesulfonyl)-2-({7-méthoxy-8-méthyl-2-[4-(propan-2-yl)-1,3-thiazol-2-yl]quinoléin-4-yl}oxy)-5-méthyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tétradécahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotétradécine-12a(1*H*)-carboxamide

simeprevir — (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(ciclopropanosulfonil)-2-({7-metoxi-8-metil-2-[4-(propan-2-il)-1,3-tiazol-2-il]quinolin-4-il}oxi)-5-metil-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahidrociclopenta[*c*]ciclopropa[*g*][1,6]diazaciclotetradecina-12a(1*H*)-carboxamida

$C_{38}H_{47}N_5O_7S_2$



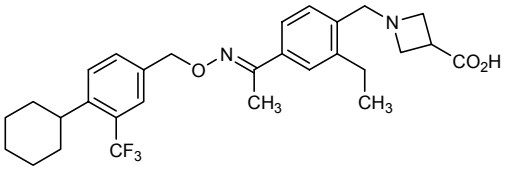
siponimodum

siponimod — 1-({4-[(1*E*)-1-({[4-cyclohexyl-3-(trifluoromethyl)phenyl]methoxy}imino)ethyl]-2-ethylphenyl}methyl)azetidine-3-carboxylic acid

siponimod — acide 1-({4-[(1*E*)-1-({[4-cyclohexyl-3-(trifluorométhyl)phényl]méthoxy}imino)éthyl]-2-éthylphényl}méthyl)azétidine-3-carboxylique

siponimod — ácido 1-({4-[(1*E*)-1-({[4-ciclohexil-3-(trifluorometil)fenil]metoxi}imino)etil]-2-etilfenil}metil)azetidina-3-carboxílico

$C_{29}H_{35}F_3N_2O_3$



sirukumabum #

sirukumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* IL6 (interleukin 6, IL-6)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-449) [*Homo sapiens* VH (IGHV3-7*01 (87.80%) -(IGHD)-IGHJ6*01) [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-213')-disulfide with kappa light chain (1'-213') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (87.40%) -IGKJ4*01) [5.3.9] (1'-107') -IGKC*01 (107'-213')]; (228-231":228-231")-bisdisulfide dimer

sirukumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* IL6 (interleukine 6, IL-6)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-449) [*Homo sapiens* VH (IGHV3-7*01 (87.80%) -(IGHD)-IGHJ6*01) [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-213')-disulfure avec la chaîne légère kappa (1'-213') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (87.40%) -IGKJ4*01) [5.3.9] (1'-107') -IGKC*01 (107'-213')]; dimère (228-228":231-231")-bisdisulfure

sirukumab

inmunoglobulina G1-kappa, anti-[IL6 de *Homo sapiens* (interleukina 6, IL-6)], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma1 (1-449) [*Homo sapiens* VH (IGHV3-7*01 (87.80%) -(IGHD)-IGHJ6*01) [8.8.12] (1-119) -IGHG1*01 (120-449)], (222-213')-disulfuro con la cadena ligera kappa (1'-213') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (87.40%) -IGKJ4*01) [5.3.9] (1'-107') -IGKC*01 (107'-213')]; dímero (228-228":231-231")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS PFAMSWVRQA PGKGLEWVAK  50
ISPGGSWTYY SDTVTGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARQL 100
WGYYALDIWG QGTTVTVSSA 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 LSCSASISVS YMYWYQQKPG QAPRLLIYDM  50
SNLASGIPAR FSGSGSGTDF TLTISSLEPE DFAVYYCMQW SGYPYTFGGG 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"

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-3^a,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

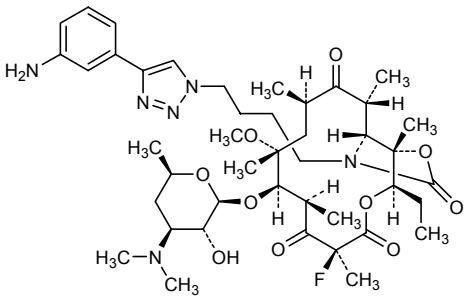
solithromycine

(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

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-3^a,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

$C_{43}H_{65}FN_6O_{10}$ 760981-83-7



spriferminum #

sprifermin — L-methionyl[human fibroblast growth factor 18 (FGF-18, zFGF5)-(1-169)-peptide

sprifermine — L-méthionyl[facteur 18 de croissance du fibroblaste humain (FGF-18, zFGF5)-(1-169)-peptide]

esprifermina — L-metionil[factor 18 de crecimiento de fibroblastos humanos (FGF-18, zFGF5)-(1-169)-péptido]

$C_{876}H_{1396}N_{258}O_{256}S_6$

```
                                                                M
EENVDFRIHV  ENQTRARDDV  SRKQLRLYQL  YSRTSGKHIQ  VLGRRISARG  50
EDGDKYAQLL  VETDTFGSQV  RIKGKETEFY  LCMNRKGKLV  GKPDGTSKEC  100
VFIEKVLENN  YTALMSAKYS  GWYVGFTKKG  RPRKGPKTRE  NQQDVHFMKR  150
YPKGQPELQK  PFKYTTVTK                                      169
```

Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
82-100

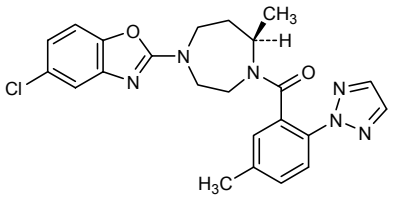
suvorexantum

suvorexant — [(7*R*)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl]methanone

suvorexant — [(7*R*)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-méthyl-1,4-diazépan-1-yl][5-méthyl-2-(2*H*-1,2,3-triazol-2-yl)phényl]méthanone

suvorexant — [(7*R*)-4-(5-cloro-1,3-benzoxazol-2-il)-7-metil-1,4-diazepan-1-il][5-metil-2-(2*H*-1,2,3-triazol-2-il)fenil]metanona

$C_{23}H_{23}ClN_6O_2$



tabalumabum #

tabalumab — immunoglobulin G4-kappa, anti-[*Homo sapiens* TNFSF13B (tumor necrosis factor superfamily member 13B, BAFF, THANK, TALL-1, TALL1, BLYS, BLyS, B cell activating factor, B lymphocyte stimulator, CD257)], *Homo sapiens* monoclonal antibody; gamma4 heavy chain (1-450) [*Homo sapiens* VH (IGHV4-34*01 (100.00%) -(IGHD)-IGHJ4*01) [8.7.17] (1-123) -IGHG4*01 hinge S10>P (231) (124-450)], (137-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (97.90%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*05 (108'-214')]; (229-229":232-232")-bisdisulfide dimer

tabalumab — immunoglobuline G4-kappa, anti-[*Homo sapiens* TNFSF13B (membre 13B de la superfamille du facteur de nécrose tumorale, BAFF, THANK, TALL-1, TALL1, BLYS, BLyS, facteur d'activation des cellules B, stimulateur des lymphocytes B, CD257)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma4 (1-450) [*Homo sapiens* VH (IGHV4-34*01 (100.00%) -(IGHD)-IGHJ4*01) [8.7.17] (1-123) -IGHG4*01 charnière S10>P (231) (124-450)], (137-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (97.90%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*05 (108'-214')]; dimère (229-229":232-232")-bisdisulfure

tabalumab — inmunoglobulina G4-kappa, anti-[TNFSF13B *de Homo sapiens* (miembro 13B de la superfamilia del factor de necrosis tumoral, BAFF, THANK, TALL-1, TALL1, BLYS, BLyS, factor de activación de células B, estimulante de linfocitos B, CD257)], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma4 (1-450) [VH de *Homo sapiens* (IGHV4-34*01 (100.00%) -(IGHD)-IGHJ4*01) [8.7.17] (1-123) -IGHG4*01 bisagra S10>P (231) (124-450)], (137-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (97.90%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*05 (108'-214')]; dímero (229-229":232-232")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQQWGAG LLKPSETLSL TCAVYGGSFS GYYWSWIRQP PGKGLEWIGE  50
INHSGSTNYN PSLKSRVTIS VDTSKNQFSL KLSSVTAADT AVYYCARGYY 100
DILTGYYYYF DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC 150
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG 200
TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP 250
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN 300
STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ 350
VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 400
LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK 450
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSLSPGERAT LSCRASQSVS RYLAWYQQKP GQAPRLLIYD  50
ASNRATGIPA RFSGSGSGTD STLTISSLEP EDFAVYYCQQ RSNWPRTFGQ 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSNTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

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

```
Intra-H  22-95    150-206    264-324    370-428
         22"-95"  150"-206"  264"-324"  370"-428"
Intra-L  23'-88'   134'-194'
         23'"-88'" 134'"-194'"
Inter-H-L  137-214'  137"-214'"
Inter-H-H  229-229"  232-232"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

300, 300"

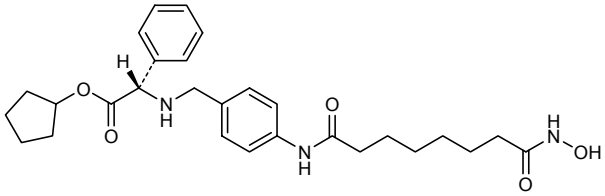
tefinostatum

tefinostat — cyclopentyl (2*S*)-2-[({4-[8-(hydroxyamino)-8-oxooctanamido]phenyl}methyl)amino]-2-phenylacetate

téfinostat — (2*S*)-2-[({4-[8-(hydroxyamino)-8-oxooctanamido]phényl}methyl)amino]-2-phénylacétate de cyclopentyle

tefinostat — (2*S*)-2-[({4-[8-(hidroxiamino)-8-oxooctanamido]fenil}metil)amino]-2-fenilacetato de ciclopentilo

$C_{28}H_{37}N_3O_5$



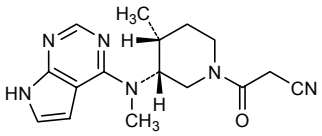
tofacitinibum

tofacitinib — 3-{(3*R*,4*R*)-4-methyl-3-[methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl}-3-oxopropanenitrile

tofacitinib — 3-{(3*R*,4*R*)-4-méthyl-3-[méthyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]pipéridin-1-yl}-3-oxopropanenitrile

tofacitinib — 3-{(3*R*,4*R*)-4-metil-3-[metil(7*H*-pirrolo[2,3-*d*]pirimidin-4-il)amino]piperidin-1-il}-3-oxopropanonitrilo

$C_{16}H_{20}N_6O$



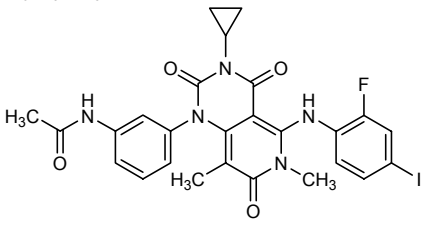
trametinibum

trametinib — *N*-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phenyl)acetamide

tramétinib — *N*-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophényl)amino]-6,8-diméthyl-2,4,7-trioxo-3,4,6,7-tétrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phényl)acétamide

trametinib — *N*-(3-{3-ciclopropil-5-[(2-fluoro-4-iodofenil)amino]-6,8-dimetil-2,4,7-trioxo-3,4,6,7-tetrahidropirido[4,3-*d*]pirimidin-1(2*H*)-il}fenil)acetamida

$C_{26}H_{23}FIN_5O_4$



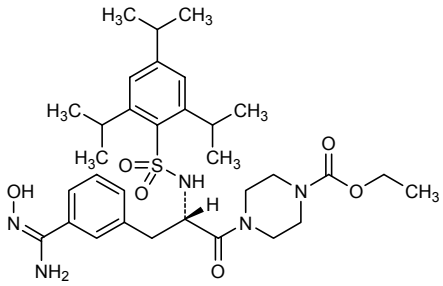
upamostatum

upamostat — ethyl 4-{(2*S*)-3-{3-[(*E*)- *N*'-hydroxycarbamimidoyl]phenyl}-2-[2,3,5-tri(propan-2-yl)benzenesulfonamido]propanoyl}piperazine-1-carboxylate

upamostat — 4-{(2*S*)-3-{3-[(*E*)- *N*'-hydroxycarbamimidoyl]phényl}-2-[2,3,5-tri(propan-2-yl)benzènesulfonamido]propanoyl}pipérazine-1-carboxylate d'éthyle

upamostat — 4-{(2*S*)-3-{3-[(*E*)- *N*'-hidroxicarbamimidoil]fenil}-2-[2,3,5-tri(propan-2-il)bencenosulfonamido]propanoil}piperazina-1-carboxilato de etilo

$C_{32}H_{47}N_5O_6S$



vatelizumabum #

vatelizumab — immunoglobulin G4-kappa, anti-[*Homo sapiens* ITGA2 (integrin alpha 2, CD49b, GPIa, subunit of the alpha2beta1 integrin (VLA-2, collagen receptor))], humanized monoclonal antibody; gamma4 heavy chain (1-446) [humanized VH (*Homo sapiens* IGHV4-59*01 (79.40%) -(IGHD)-IGHJ6*01) [8.7.13] (1-119) -*Homo sapiens* IGHG4*01 (120-446)], (133-213')-disulfide with kappa light chain (1'-213') [humanized V-KAPPA (*Homo sapiens* IGKV6D-41*01 (77.90%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; (225-225":228-228")-bisdisulfide dimer

vatélizumab — immunoglobuline G4-kappa, anti-[*Homo sapiens* ITGA2 (intégrine alpha 2, CD49b, GPIa, sous-unité de l'intégrine alpha2bêta1 (VLA-2, récepteur du collagène))], anticorps monoclonal humanisé; chaîne lourde gamma4 (1-446) [VH humanisé (*Homo sapiens* IGHV4-59*01 (79.40%) -(IGHD)-IGHJ6*01) [8.7.13] (1-119) -*Homo sapiens* IGHG4*01 (120-446)], (133-213')-disulfure avec la chaîne légère kappa (1'-213') [V-KAPPA humanisé (*Homo sapiens* IGKV6D-41*01 (77.90%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dimère (225-225":228-228")-bisdisulfure

vatelizumab — inmunoglobulina G4-kappa, anti-[*Homo sapiens* ITGA2 (integrina alfa 2, CD49b, GPIa, subunidad de la integrina alfa2beta1 (VLA-2, receptor del colageno))], anticuerpo monoclonal humanizado; cadena pesada gamma4 (1-446) [VH humanizada (*Homo sapiens* IGHV4-59*01 (79.40%) -(IGHD)-IGHJ6*01) [8.7.13] (1-119) -*Homo sapiens* IGHG4*01 (120-446)], (133-213')-disulfuro con la cadena ligera kappa (1'-213') [V-KAPPA humanizada (*Homo sapiens* IGKV6D-41*01 (77.90%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dímero (225-225":228-228")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQESGPG LVKPSETLSL TCTVSGFSLT NYGIHWIRQP PGKGLEWLGV  50
IWARGFTNYN SALMSRLTIS KDNSKNQVSL KLSSVTAADT AVYYCARAND 100
GVYYAMDYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY 200
TCNVDHKPSN TKVDKRVESK YGPPCPSCPA PEFLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL 350
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLGK     446
```

Light chain / Chaîne légère / Cadena ligera

```
DFVMTQSPAF LSVTPGEKVT ITCSAQSSVN YIHWYQQKPD QAPKKLIYDT  50
SKLASGVPSR FSGSGSGTDY TFTISSLEAE DAATYYCQQW TTNPLTFGQG 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	22-95	146-202	260-320	366-424
	22"-95"	146"-202"	260"-320"	366"-424"
Intra-L	23'-87'	133'-193'		
	23'"-87'"	133'"-193'"		
Inter-H-L	133-213'	133"-213'"		
Inter-H-H	225-225"	228-228"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

296, 296"

* *"INN for pharmaceutical substances: Names for radicals, groups & others"* document available at / document disponible à / documento disponible en :
http://www.who.int/medicines/services/inn/publication/en/index.html

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

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

Recommended International Non Proprietary Names (Rec. INN): List 6
(Chronicle of the WHO, December 1959, Vol. 13, No. 12)

p. 468 **mecamylaminum**
mecamylamine *replace the chemical name by the following*

(1*RS*,2*SR*,4*SR*)-*N*,2,3,3-tetramethylbicyclo[2.2.1]heptan-2-amine

Denominations communes internationales recommandées (DCI Rec.): Liste 6
(Chronique de l'OMS, Vol. 13, No. 12, décembre 1959)

p. 488 **mecamylaminum**
mécamylamine *remplacer le nom chimique par le suivant*

(1*RS*,2*SR*,4*SR*)-*N*,2,3,3-tétraméthylbicyclo[2.2.1]heptan-2-amine

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 6
(Crónica de la OMS, Vol. 13, No. 12, diciembre de 1959)

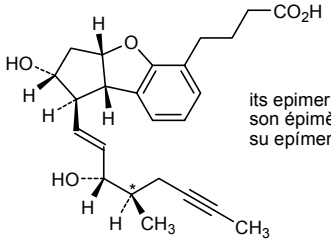
p. 501 **mecamylaminum**
mecamilamina *sustitúyase el nombre químico por el siguiente*

(1*RS*,2*SR*,4*SR*)-*N*,2,3,3-tetrametilbiciclo[2.2.1]heptan-2-amina

Recommended International Non Proprietary Names (Rec. INN): List 31
(WHO Drug Information, Vol. 5, No. 3, 1991)

p. 17 **beraprostum**
beraprost *replace the chemical name and the structure by the following ones*

rac-4-{(1*R*,2*R*,3a*S*,8b*S*)-2-hydroxy-1-[(1*E*,3*S*,4*RS*)-3-hydroxy-4-methyloct-1-en-6-ynyl]-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*][1]benzofuran-5-yl}butanoic acid



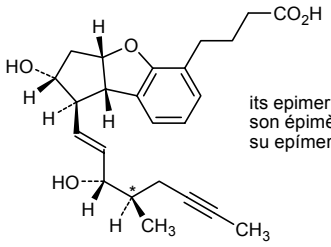
its epimer at C* and their enantiomers
son épimère en C* et leurs énantiomères
su epímero al C* y sus enantiómeros

Denominations communes internationales recommandées (DCI Rec.): Liste 31
(Informations pharmaceutiques OMS, Vol. 5, No. 3, 1991)

p. 18 **beraprostum**
béraprost

remplacer le nom chimique et la structure par les suivants

acide *rac*-4-{(1*R*,2*R*,3a*S*,8b*S*)-2-hydroxy-1-[(1*E*,3*S*,4*RS*)-3-hydroxy-4-méthyloct-1-én-6-ynyl]-2,3,3a,8b-tétrahydro-1*H*-cyclopenta[*b*][1]benzofuran-5-yl}butanoïque



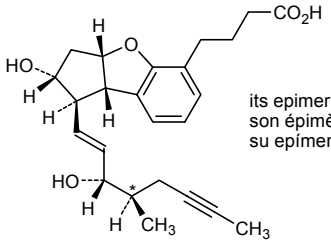
its epimer at C* and their enantiomers
son épimère en C* et leurs énantiomères
su epímero al C* y sus enantiómeros

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 31
(Información farmacéutica OMS, Vol. 5, No. 3, 1991)

p. 18 **beraprostum**
beraprost

sustitúyase el nombre químico y la estructura por los siguientes

ácido *rac*-4-{(1*R*,2*R*,3a*S*,8b*S*)-2-hidroxi-1-[(1*E*,3*S*,4*RS*)-3-hidroxi-4-metiloct-1-en-6-inil]-2,3,3a,8b-tetrahidro-1*H*-ciclopenta[*b*][1]benzofuran-5-il}butanoico



its epimer at C* and their enantiomers
son épimère en C* et leurs énantiomères
su epímero al C* y sus enantiómeros

Recommended International Non Proprietary Names (Rec. INN): List 62
Denominations communes internationales recommandées (DCI Rec.): Liste 62
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 62
(WHO Drug Information, Vol. 23, No. 3, 2009)

p. 250	*delete/supprimer/suprimáse*	*insert/insérer/insertese*
	ingenoli mebutatum	**ingenoli mebutas**

Recommended International Non Proprietary Names (Rec. INN): List 63
Denominations communes internationales recommandées (DCI Rec.): Liste 63
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 63
(WHO Drug Information, Vol. 24, No. 1, 2010)

p. 69 **olodaterolum**

olodaterol *replace the chemical name by the following*
olodatérol *remplacer le nom chimique par le suivant*
olodaterol *sustitúyase el nombre químico por el siguiente*

6-hydroxy-8-[(1*R*)-1-hydroxy-2-{[1-(4-methoxyphenyl)-2-methylpropan-2-yl]amino}ethyl]-2*H*-1,4-benzoxazin-3(4*H*)-one

6-hydroxy-8-[(1*R*)-1-hydroxy-2-{[1-(4-méthoxyphényl)-2-méthylpropan-2-yl]amino}éthyl]-2*H*-1,4-benzoxazin-3(4*H*)-one

6-hidroxi-8-[(1*R*)-1-hidroxi-2-{[1-(4-metoxifenil)-2-metilpropan-2-il]amino}etil]-2*H*-1,4-benzoxazin-3(4*H*)-ona

Recommended International Non Proprietary Names (Rec. INN): List 64
Denominations communes internationales recommandées (DCI Rec.): Liste 64
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 64
(WHO Drug Information, Vol. 24, No. 3, 2010)

p. 264 **condoliasum #**

condoliase *replace the structure by the following*
condoliase *remplacer la structure par la suivante*
condoliasa *sustitúyase la estructura por la siguiente*

```
ATSNPAFDPK NLMQSEIYHF AQNNPLADFS SDKNSILTLS DKRSIMGNQS 50
LLWKWKGGSS FTLHKKLIVP TDKEASKAWG RSSTPVFSFW LYNEKPIDGY 100
LTIDFGEKLI STSEAQAGFK VKLDFTGWRA VGVSLNNDLE NREMTLNATN 150
TSSDGTQDSI GRSLGAKVDS IRFKAPSNVS QGEIYIDRIM FSVDDARYQW 200
SDYQVKTRLS EPEIQFHNVK PQLPVTPENL AAIDLIRQRL INEFVGGEKE 250
TNLALEENIS KLKSDFDALN IHTLANGGTQ GRHLITDKQI IIYQPENLNS 300
QDKQLFDNYV ILGNYTTLMF NISRAYVLEK DPTQKAQLKQ MYLLMTKHLL 350
DQGFVKGSAL VTTHHWGYSS RWWYISTLLM SDALKEANLQ TQVYDSLLWY 400
SREFKSSFDM KVSADSSDLD YFNTLSRQHL ALLLLEPDDQ KRINLVNTFS 450
HYITGALTQV PPGGKDGLRP DGTAWRHEGN YPGYSFPAFK NASQLIYLLR 500
DTPFSVGESG WNNLKKAMVS AWIYSNPEVG LPLAGRHPFN SPSLKSVAQG 550
YYWLAMSAKS SPDKTLASIY LAISDKTQNE STAIFGETIT PASLPQGFYA 600
FNGGAFGIHR WQDKMVTLKA YNTNVWSSEI YNKDNRYGRY QSHGVAQIVS 650
NGSQLSQGYQ QEGWDWNRMQ GATTIHLPLK DLDSPKPHTL MQRGERGFSG 700
TSSLEGQYGM MAFDLIYPAN LERFDPNFTA KKSVLAADNH LIFIGSNINS 750
SDKNKNVETT LFQHAITPTL NTLWINGQKI ENMPYQTTLQ QGDWLIDSNG 800
NGYLITQAEK VNVSRQHQVS AENKNRQPTE GNFSSAWIDH STRPKDASYE 850
YMVFLDATPE KMGEMAQKFR ENNGLYQVLR KDKDVHIILD KLSNVTGYAF 900
YQPASIEDKW IKKVNKPAIV MTHRQKDTLI VSAVTPDLNM TRQKAATPVT 950
INVTINGKWQ SADKNSEVKY QVSGDNTELT FTSYFGIPQE IKLSPLP    997
```

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

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

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

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