WHO Drug Information

Contents

International Harmonization

14th International Conference of Drug Regulatory Authorities

The success of the recent 14th International Conference of Drug Regulatory Authorities (ICDRA) held in Singapore from 30 November to 3 December was attested by the presence of 345 participants from over 90 agencies. In addition to the event, participants were invited to celebrate thirty years of ICDRAs. Both developed and developing country officials joined in confirming the value and impact of this forum to national, regional and international medicines regulation by contributing to seven plenaries and nineteen parallel workshops. The quality of the information offered and the lively discussion led to adoption of recommendations which regulators consider important in assuring the quality, safety and efficacy of medicines. These are set out below and on the following pages.

The 14th ICDRA was hosted by the Health Sciences Authority of Singapore in collaboration with the World Health Organization. The Conference continues to be a cornerstone of international harmonization of medicines regulation and is highly appreciated for the platform it provides in highlighting matters of urgency and relevance to an often difficult but vital sector of the health care system.

ICDRA RECOMMENDATIONS

Improving drug regulation as part of health systems strengthening

Major trends relating to regulatory support for medical products present medicines agencies and WHO with numerous challenges. The increasing complexity of regulatory work — whether as a result of new technologies, globalization of commercial activities or internationalization of product development — is particularly onerous.

Increasing autonomy of management and decision-making in governmental regulatory systems, together with greater interaction between regulators and the private sector in the development of standards and regulations has led to the need for greater efforts to improve interaction between regulatory agencies and civil society, scientific institutions, governmentally-managed health insurance systems and reimbursement schemes.

Given the current fast-paced and exacting climate, it is difficult for regulators to draw a fair balance between the potential risks of a new medicine and public expectations of availability and safety. Additionally, the introduction of high performance information systems and instant access together with demand for relevant, quality information puts greater pressure on regulators to react professionally and with transparency in a minimum of time.

In spite of many positive developments in the Global regulatory arena it is worrying that the gaps among regulatory systems

are rather increasing than decreasing. This is partly caused by the human and financial resource gap existing between well-resourced and resource-constrained settings.

A medical products regulatory system, supported by relevant legislation, is an essential component of a *functioning health system*. A medicines regulatory system includes, at the very least, the necessary legislation and regulation, a regulatory authority which subjects all pharmaceutical products to premarketing evaluation, marketing authorization and postmarketing surveillance. The regulatory system should also include an inspectorate, access to a medicines quality control laboratory, enforcement mechanisms and safety monitoring.

Moderators
John Lim, Singapore and Thomas Lönngren, European Union

Presentations
Challenges of biomedical advancement – evolving role of the regulator. John Lim, Singapore

Drug regulation and public health in the EU. Thomas Lönngren, EU

Strengthening regulatory capacity around the Globe: our common and vital interest. Margaret Hamburg, USA

Recommendations

WHO should:

- Continue to assist medicines regulatory authorities (MRAs) in garnering political support at national or regional levels to build regulatory capacity.
- Work with Member States in ongoing promotion of collaboration and coordination to develop MRA capacity in pharmacovigilance, identifying core minimum functions, and mapping of major initiatives that may facilitate cooperation.

Medicines regulatory authorities should:

- Commit to and collaborate in prioritizing, developing and teaching regulatory science to strengthen scientific robustness in advancing regulatory innovation and thought leadership, exploring new regulatory tools and frameworks, and conducting environmental scanning.
- Keep abreast of developments in health technology assessment to minimize duplication of activities and explore ways to better interface with parties involved in health technology assessment.
- Take account of the wider health and non-health environment in which they operate nationally and internationally, proactively strengthen networks, engage stakeholders, and clarify policies and positions in order to enhance their regulatory mission and effectiveness, especially in crisis preparedness and risk management.
- Work with their governments to reiterate to the WHO governing bodies (World Health Assembly and Executive Board) the importance of strengthening regulatory capacity and cooperation as an essential part of overall health systems strengthening.

Collaboration and cooperation among regulatory agencies

The rapid advancement in biomedical sciences and the invention of novel therapeutic products have made it more critical than ever for medicines regulatory agencies to work together to achieve the goal of protecting and advancing public health.

The 14th ICDRA re-affirmed the importance of regional harmonization efforts which are already on-going in different parts of the world in various forms and models. It was also recognized that WHO

could further support these collaborative initiatives by providing technical assistance where capacity building is needed. Furthermore, WHO is in a unique position to facilitate networking and information exchange among regulators.

Moderators
Supriya Sharma, Canada and Christina Lim, Singapore

Presentations
Recent developments in cooperation of regulatory authorities among ASEAN countries. Yuppadee Javrongrit, Thailand

Collaboration among regulatory authorities in the European Union: a micro-agency perspective. Alar Irs, Estonia

First joint product assessment experience from EAC partner states. Hiiti Sillo, Tanzania

Reporting back from the pre-ICDRA meeting. Stewart Jessamine, New Zealand

Recommendations

Regional working groups should:

- Strengthen efforts to build capacity to develop/adopt common technical standards and requirements.

WHO should:

- Provide a mechanism for sharing ongoing regional harmonization activities and provide technical assistance and extend existing training programmes to Member States when needed.
- In view of the positive outcome of the EAC/WHO pilot project on joint evaluation, help to establish a mechanism for collaboration with other regional groupings in similar joint evaluation projects.
- Provide a protected electronic platform for regulators to share information and experience on specific regulatory topics of common interests, similar to that for the Paediatric Medicines Regulators Network (PmRN).
- Facilitate twinning of less developed agencies with well-established agencies for capacity building and training.

Report from the pre-ICDRA meeting: *Effective collaboration: the future for medicines regulation*

Recommendations

Promotion of increased regulatory effectiveness

WHO should:

- Actively promote cooperation and collaboration programmes and use information generated by other MRAs as a tool to improve regulatory capacity and effectiveness.
- Collect best practices of collaboration and cooperation between medicines regulatory authorities including information exchange, joint assessments and inspections and activities aimed at reducing duplication.
- Work with national MRAs to define recommended elements of model product assessment reports, including benefit risk considerations. WHO should facilitate the sharing of model assessment reports and promote the optimal use of public information on marketing authorization assessments and product information.
- Encourage MRAs to implement quality management systems and undertake benchmarking of their regulatory systems and processes to enhance regulatory performance.

Improved Inspection processes

WHO should:

- Encourage Member States to make more information about GMP and GCP inspections public and/or accessible to other regulators.
- Actively promote the use of the WHO collaborative procedure for inspections to regulatory authorities with limited resources.
- Coordinate a review of the current risk management approach to regulation of the API supply chain.

Clinical trial initiatives

WHO should:

- Encourage improved regulation of clinical trials through better cooperation e.g., by expanding the African Vaccine Regulatory Forum (AVAREF) to all medicines and involving additional Member States. Applying AVAREF experience in other WHO regions should be explored.
- Consider establishing an advisory network for clinical trial and GCP related issues.

Well-resourced medicines regulatory authorities should:

- Publish information related to marketing authorizations and their variations in clearly identifiable sections of their web sites in a form that is readily accessible to other regulatory authorities.
- Continue to provide technical assistance concerning clinical trial oversight systems and assist through joint assessment of complex cases (e.g., childhood vaccination, biological products) of clinical trial applications.

Medicines regulatory authorities should:

- Take account of one another's work with a view to improving the efficiency of the global regulatory system.
- Commit resources to form cooperative networks based on uniformity of standards and inspection systems.
- Engage with regional and international initiatives promoting harmonization, information sharing and use of data generated by other regulators as a tool for improving timely access to medicines and medical products.
- Actively support the establishment of robust harmonized clinical trial oversight mechanisms in all Member States.

Inspection initiatives

- Medicines regulatory authorities should actively participate in inspection consortia and other collaborative arrangements aimed to increase efficiencies and reduce duplicative efforts .

Specific regulatory initiatives

WHO should:

- Encourage regulators operating schemes that openly and transparently utilize data from other countries (e.g., Canada, New Zealand, Singapore and Switzerland) to:
  - Document their processes and experiences to provide a resource for use by other countries;
  - Engage with consortia such as APEC to develop a framework for good review practices and a common approach to using other regulators' information;
  - Undertake research to validate the safety of their approach to regulation;

- Work with highly evolved agencies, such as the US FDA and European Medicines Agency (EMA), in devising initiatives to improve regulatory science and the risk management approach required by new approaches to regulation.

Biosimilars

Biosimilars should be regulated as biologicals. Therefore, a generic medicines ("biogeneric") regulatory approach is not appropriate and should not be used. For copy products already licensed as "biogenerics", Member States are encouraged to develop/update risk management strategies.

Member States are encouraged to implement WHO Guidelines on evaluation of similar biotherapeutic products as a whole. This means that only products licensed on the basis of the full comparability study, should be considered and named as similar biotherapeutics.

Clinical and statistical expertise in Member States should be strengthened to improve evaluation of the data submitted by the manufacturers for licensing.

Additional efforts are needed to address specific issues related to pharmacovigilance of biosimilars.

Moderators
Elwyn Griffiths, Canada and Arpah Abas, Malaysia

Presentations
Diversity of regulatory requirements and way forward Arpah Abas, Malaysia

Clinical evaluation of similar biotherapeutic products Sookyung Suh, Republic of Korea

Round table discussion
Yanet Hechavarria Nunez, Cuba, Prapassorn Thanaphollert, Thailand, Kai Tong Tam and Wang Woon Poh, Singapore, Laura Castanheira, Brazil

Recommendations

WHO should:

- Consider developing guidelines on risk management strategies for copy products already licensed as "biogenerics".
- Develop a template for Member States to share information on the scientific basis for licensing biosimilars.
- Supplement its guidance on evaluation of similar biotherapeutic products by providing guidelines for evaluation of biotherapeutic products in general.
- Conduct a review of existing international reference preparations for assay of biotherapeutics, identify gaps and take action to fill those gaps.

Blood and blood products

This session reported on WHO follow-up action in response to Recommendations made at the 13th ICDRA. Building technical capacity of national regulatory systems and national regulatory authorities will be the next fundamental steps for effective control of blood products. The session aimed to identify main priorities and mechanisms to move forward and the type of assistance expected from WHO by Member States.

Moderators
Jay Epstein, USA and Lucky Slamet, Indonesia

Presentations
World Health Assembly Resolution on availability, quality and safety of blood products. Ana Padilla, WHO

Impact of WHO Guidelines on GMP for Blood Establishments. Christian Schaerer, Switzerland

Regulation of advanced blood cell therapies. Klaus Chichutek, Germany

Assessment criteria for national blood regulatory systems. Peter Ganz, Canada

Panel Discussion
Ways forward to strengthening blood products regulation. Joao Batista da Silva, Brazil, Isabelle Sainte-Marie, France, Eric Karikari-Boateng, Ghana, Diana Teo, Singapore

Recommendations

WHO should:

- Focus on capacity building for implementation of quality assurance systems for blood and blood products through development of independent regulatory authorities.
- Primary attention should be placed on strengthening regional regulatory networks.
- Facilitate education and training to make best use of the GMP Guidelines for Blood Establishments and the BRN Assessment Criteria for National Blood Regulatory Systems.

Member States should:

- Give primary attention to establishment of appropriate national legal frameworks for blood product regulation and empowerment and support of an effective regulatory authority in implementing WHA Resolution 63.12.
- Consider adoption of the WHO Guidelines on GMP for Blood Establishments and the BRN Assessment Criteria for National Blood Regulatory Systems as strategies to strengthen blood regulation in their jurisdictions.

WHO and Member States should:

- Take advantage of existing systems such as economical and regulatory regional and sub-regional networks to advance blood products regulations.

Herbal medicines: current regulatory challenges and cooperation

Through continuous effort at country level and collaboration with WHO, regulation of herbal medicines has been strengthened and data on regulatory experiences collected in more than 60% of WHO Member States.

The workshop was organized to present examples of current major regulatory challenges concerning herbal medicines: both national experiences and topics identifying high priorities. It also reported on progress in global regulatory cooperation by the International Regulatory Cooperation for Herbal Medicines (IRCH). Discussion focused on how collaboration among regulatory authorities could address and overcome challenges and identify collaborative initiatives for improving regulation of herbal medicines.

Moderators
Kustantinah Soerjosoebandora, Indonesia and Akua Amartey, Ghana

Presentations
Current regulatory challenges relating to herbal medicines: Adulteration of herbal medicines. Muhammad Lukmani Ibrahim, Malaysia

Current regulatory challenges relating to herbal medicines: Evidence for Health Claim. Jenny Bernett, Australia

Experience of regulatory cooperation - International Regulatory Cooperation for Herbal Medicines (IRCH). Shen Kuan Yee, Singapore

Challenges in regulation of herbal medicines in Ghana. Akua Amartey, Ghana

Challenges and opportunities in regulation of herbal medicines in Indonesia. Kustantinah Soerjosoebandora, Indonesia

Recommendations

Member States should:

- Strengthen national capability in the implementation of regulation on herbal medicines.
- Include traditional medicine/complementary and alternative medicine (TM/CAM) in the national health plan as appropriate.
- Be a member of a regulatory cooperation group, such as the International Regulatory Cooperation for Herbal Medicines (IRCH) and its working groups, for mutual benefit and achieving substantial progress.

WHO should:

- Further support Member States in the integration of TM/CAM into national health systems, where appropriate, and to develop tools supporting Member States to establish relevant policies and regulations in TM/CAM towards integration.
- Continue coordinating the network of IRCH in general and specifically by: providing technical support to the work of IRCH and its working groups, improving the WHO Mednet-based information exchange tool for IRCH and developing other tools to support Member States in sharing technical information on the top priority issues identified by IRCH.

Paediatric medicines

As a follow up to recommendations made at the 13th ICDRA and the pre-ICDRA meeting concerning medicines for children, a workshop was organized to consider two important issues: clinical trials in children and experience of registration/licensing essential medicines for children.

The presentations included an overview of some of the issues to do with clinical trials in children from the European perspective; experience to date of clinical trials in children in Malaysia and experiences from South Africa and Ghana of licensing essential medicines for children.

Moderators
Murray Lumpkin, USA and Vasyl Blikhar, Ukraine

Presentations
Optimizing clinical trial design for paediatric populations. Agnes Saint Raymond, EU

Experience with authorizing paediatric clinical trials. Selvaraja Seerangam, Malaysia

Availability of Essential Medicines for Children in South Africa: situation analysis and what regulators can do to improve it. Khadija Jamaloodien, South Africa

Availability of Essential Medicines for Children: registered medicines in Ghana. Delese Darko, Ghana.

Recommendations

WHO should:

- Enhance and foster collaboration and communication between MRAs (through the Paediatric Medicines Regulators Network (PmRN) and other mechanisms), especially on:
  - common standards for clinical trials in children.
  - capacity to assess clinical trials in children.
  - development of innovative pharmacovigilance methods to enhance reporting of adverse reactions related to use of medicines in children.
- Support countries to evaluate and adopt appropriate incentives and legislative structures to encourage development of optimal medicines for children.

- Work with countries to foster effective interaction between regulators and paediatricians to promote development and licensing of better medicines for children.
- Work with countries and regulators as well as industry to define efficient regulatory pathways for medicines for children.

Vaccines and biologicals

Moderators
Jianhua Ding, China and Karen Midthun, USA

Presentations
The paradigm has changed — meningococcal A conjugate, a vaccine designed for Africa. Mahamadou Compaore, Burkina Faso

Linking regulatory decisions and public health decisions for vaccines. Lucky Slamet, Indonesia

On the problem of finding an adventitious agent in an approved biological. Karen Midthun, USA

Recommendations

Member States should:

- Strengthen interactions between regulatory agencies and immunization programmes.
- Improve capacity to evaluate causality for adverse events following immunization.
- Strengthen crisis communication skills to manage vaccine safety events.

WHO should:

- Assist countries to leverage regulatory evaluations conducted elsewhere to expedite national approval of vaccines of public health importance.
- Enhance the ability of countries to assess and respond to adverse events following immunization.
- Facilitate the interactions between NRAs and national immunization advisory committees, to enable continuous assessment of the benefits and risks of vaccines.
- Assist countries to develop risk management strategies to respond to scientific advances for detection of adventitious agents in biological medicines.
- Enhance communications to countries on regulatory decisions by reference NRAs on prequalified vaccines.

Pandemic H1N1: lessons learned

Moderator
Klaus Cichutek, Germany

Presentations
Regulators response to a Pandemic: lessons learnt. Pia Caduff, Switzerland

Views from a country receiving donated products. Delese Darko, Ghana

The international dimension of the regulatory response to the H1N1 pandemic. Cathy Parker, Canada

Recommendations

Member States should:

- Make regulatory preparedness for pandemic influenza essential in all countries.

National regulatory authorities (NRAs) should:

- Review lessons learned from the H1N1 pandemic to be better prepared in the future.
- Improve crisis communications skills and capacity, especially for product safety in a pandemic scenario.

- Ensure scope for flexibility to adapt to evolving circumstances in an emergency.
- Utilize existing networks, infrastructures and tools for information sharing, wherever possible.

WHO should:

- Strengthen international collaboration on pandemic safety surveillance and communications.
- Provide technical assistance to regulators in recipient countries on the quality, safety and efficacy of products donated to respond to public health emergencies.
- Promote international regulatory research to enable access to pandemic influenza vaccines and drugs in a more timely way.
- Strengthen regulatory capacity to catalyse and support efforts to increase influenza vaccine production worldwide.
- Utilize the model of global networking of regulators used in the H1N1 pandemic in any future public health emergency of international concern.
- Consolidate and share safety information between countries to support national regulatory decisions.

Interchangeability

Moderators
Ian Hudson, United Kingdom and Ashraf Bayoumi, Egypt

Presentations
Implementing new EU bioequivalence guidelines with emphasis on biowaiver option. Ian Hudson, United Kingdom

Assessment of bioequivalence studies: experience from WHO Prequalification Programme. Jan Welink, The Netherlands

Experience of implementing bioequivalence requirement in Ethiopia. Mengistab W. Areagy, Ethiopia

How to prove interchangeability of generic medicines with originators: Korean experience. Sangaeh Park, Republic of Korea

Recommendations

Medicines regulatory authorities should:

- Encourage comparability of products and promote exchange of information and reliance upon evaluation efforts of "reference" regulatory authorities.
- Request manufacturers to provide information proving that the product submitted has the same safety, efficacy and quality profile as the product originally approved by the "reference" regulatory authority. If alternative manufacturing sites, processes or formulation not covered by the original approval by the "reference" authority are used, it is important to link modifications to support the conclusion that the "reference" regulatory authority evaluation will in fact still be informative and can be relied on.

Pharmacovigilance

Although pharmacovigilance (PV) is now firmly established in industrialized countries, it is still a new concept in many others. Current interest from global health initiatives, particularly in public health programmes, are providing opportunities to introduce the basic principles of PV in resource-limited settings. However, these must be appropriately aligned to country needs and capacity if they are to have a long-term impact. The workshop was planned to underscore the place of PV in a regulatory framework, to highlight the importance of PV in informing policies in priority disease programmes, to discuss issues in communication and information

sharing between countries and to delineate the minimum PV capacity that is needed to address these concerns.

Moderators
Cheng Leng Chan, Singapore and Luisa Helena Valdivieso, Venezuela

Presentations
Minimal capacity for vaccine vigilance. Murilo Freitas Dias, Brazil

Working with public health programmes: addressing minimum requirements for Pharmacovigilance. Helen Byomire, Uganda

Recent developments in monitoring of adverse drug reactions in China. Min Yan, China

Pharmacovigilance in the national HIV/AIDS treatment programme. Olena Matveyeva, Ukraine

Recommendations

WHO should:

- Make pharmacovigilance a key topic of the next ICDRA.
- Reinforce recommendations that the pharmacovigilance system be nested within the healthcare system to address multiple growing safety needs.
- Develop robust strategies for sharing safety information.
- Target training on risk communication and crisis handling and develop platforms for sharing good pharmacovigilance cases.
- Integrate the minimum core requirements for vaccine monitoring through the WHO Programme for International Drug Monitoring.

Member States should:

- Integrate PV into proposals to the Global Fund to fight AIDs, Tuberculosis and Malaria and other donors.
- Ensure funds are not diverted to non-PV activities within the healthcare system.
- Implement at least minimum core requirements for pharmacovigilance as integral components of drug regulation and paramount in safeguarding public health.
- Ensure good collaboration between pharmacovigilance centres and public health programmes.

Good regulatory practices: developing business processes

Moderators
Nazarita Tan Tacandong, Philippines and Patrick Deboyser, European Union

Presentations
Innovative Review Practices for better efficiencies. Daniel Tan, Singapore

Establishing quality management systems. Petra Doer, Switzerland

New work procedures and IT systems for licensing. Flavia Morais, Brazil

Recommendations

WHO should:

- Collect best practices in respect of implementation of quality management systems (QMS) by national regulatory authorities and explore the possibility of creating a model QMS for medicines regulatory authorities with guidance for its implementation.
- Establish a scheme for the exchange of complete medicines assessment reports (complementary to public assessment

reports) between medicines regulatory authorities, for the purpose of abridged authorization procedures based on the authorization granted by another medicines regulatory authority.

Stability

This workshop presented experience gathered during implementation of recently published new and revised WHO guidelines regarding stability requirements for both medicines and vaccines.

The discussion on stability-related regulatory requirements for medicines have been on the agenda of previous ICDRAs and have triggered numerous recommendations. This is the first time that vaccines were also discussed in a full session.

Presentations described harmonization efforts undertaken within various national and regional settings and the prequalification programmes operated by WHO. The presentation on vaccine stability described new trends in implementation.

Moderators
Lucky Slamet, Indonesia and Elwyn Griffiths, Canada

Presentations
Implementation of medicines stability testing requirements worldwide and in different regional contexts. Justina Molzon, USA

Experience of assessing stability data provided by applicants to the WHO Prequalification Programme. Gabriel Kaddu, Uganda

Stability evaluation of vaccines: lessons learnt. Teeranart Jivapaisarnpong, Thailand

Recommendations

National regulatory authorities should:

- Communicate requirements for stability studies needed to update the current list annexed to the WHO Stability Guidelines for Medicines.
- Implement WHO Guidelines on Stability Evaluation of Vaccines, as a whole.
- Ensure that vaccine stability evaluation should focus on the assessment of real time-real condition studies and a life cycle of stability evaluation.
- Strengthen statistical expertise to improve evaluation of the data submitted by manufacturers.

Manufacturers, particularly those interested in participating in the WHO Prequalification Programme for Medicines, should consider the new requirements set at 30 ºC 75% RH as of September 2011.

WHO should :

- Update the above-mentioned WHO Stability Guidelines for Medicines list.
- Publicize information on the new requirements.
- Continue organizing workshops on implementation of vaccine stability evaluation.
- Assist NRAs in evaluating stability data by providing additional tools for review of thermal stability studies.

Clinical trials and globalization

Noting that clinical trials have now become a global enterprise with trials being conducted in many countries around the world, the workshop was organized to discuss the impact of globalization on clinical trials — both on the conduct of clinical trials and on the use of data from these trials for national regulatory decision making when data come from clinical trials conducted internationally and often in different ethnic populations and under different medical care conditions.

During the workshop, participants heard from Brazil about the efforts being made there to build capacity to inspect clinical trials with respect to their compliance with GCP. Japan reported on efforts to prospectively design clinical trial development plans such that potential ethnic (intrinsic and extrinsic) differences in study populations can be investigated in parallel rather than sequentially as has most often been the case, so that information on the benefit-to-risk profile of a product can more efficiently be obtained and any "drug lag" minimized. From Tanzania, the presentation covered efforts there to work regionally and nationally to establish procedures to help prevent "ethics committee shopping" and to strengthen clinical trial regulatory oversight by pooling scientific and other resources among neighbouring countries.

Moderators
Margaret Hamburg, USA and Lucia Turcan, Moldova

Presentations
Impact of trial design on GCP inspections Laura Castanheira, Brazil

Experiences and Challenges to promote Multi Regional Clinical Trials Shinobu Uzu, Japan

Establishing a mechanism to avoid "shopping around" for ethical approval Adam Fimbo, Tanzania

Recommendations

WHO should:

- Continue to facilitate cooperation among national drug regulatory authorities in assessing, authorizing and inspecting multicentre clinical trials affecting several countries. Such efforts could include: (i) facilitation of information sharing on regulatory and ethics committee decisions on clinical trials, and (ii) capacity building with respect to GCP.
- Reconfirm its commitment to and support of public registries of clinical trials prior to their start to help assure public knowledge of regulatory and ethics committee decisions regarding these trials.
- Improve public awareness and encourage participation in multiregional and international clinical trials for the improvement of medical care and public health.
- Continue to assist national regulatory authorities in their regulatory decision-making efforts to extrapolate data from Phase I to Phase IV clinical trials conducted outside their nation to the situation, both ethnically and with respect to medical care, within their country.

Education and training for regulatory officials

Moderators
Emer Cooke, European Union and Mandisa Hela, South Africa

Presentations
CDER's education and training programs to promote professional competencies. Justina Molzon, USA

General capacity building for regulators and specific capacity building for the inspectorate: ANMAT's experience. Roberto Lede and Rodolpho Mocchetto, Argentina

Parallel review experience of vaccines by two authorities: benefits for providers and recipients and lessons learned. Prapassorn Thanaphollert, Thailand and Dr Surinder Singh, India

EU experience in training regulatory officials. Emer Cooke, EU

Recommendations

Medicines regulatory authorities should:

- Define training objectives and develop training plans to meet these objectives.

WHO should:

- Identify and promote sharing of training programmes and materials among regulators in order to facilitate common approaches and worksharing. The use of e-learning approaches should be encouraged.

- Maintain a network of training contact points.

Medicines promotion and rational use

Rational use is the final step in achieving the full potential of a medicine. What role do regulators have in ensuring this once it has passed through the regulatory process? The speakers and audience felt that regulators clearly had a role in rational use although this could vary from country to country depending on the many and various stakeholders involved.

In keeping with the overall theme of coordination and collaboration, there were many examples presented of existing legislation concerning promotion of medicines including activities in Member States that could be modified and used in other countries, especially those with an institutionalized basis for promotion. There were schemes where a tax on industry activities meant sustainable financial support for such activities.

Moderators
Alar Irs, Estonia and Sonam Dorji, Bhutan

Presentations
Medicines promotion and rational use according to the Spanish Law. Jos Louis Dopico, Spain

Generic entries of new chemical entities: challenges for controlling promotion and ensuring safety. Rohini Fernandopulle, Sri Lanka

Rational use: up from down under. John Dowden, Australia

Recommendations

Member States should:

- Support initiatives in the rational use of drugs by providing, in a readily available format (e.g., on the Internet), an objective summary of product characteristics upon authorization and ensure it is updated in a timely manner as new information becomes available.

- Encourage routine analysis of the post approval use of medicines and make these data public.

- Where pharmaceutical advertising and promotion is permitted, clearly define in the legislation the acceptable extent of promotional activities and the mechanisms for effective oversight and mobilize resources for enforcement.

WHO should:

- Publish best practices on rational use of medicines for Member States to adapt and adopt.

- Facilitate information exchange between Member States to encourage effective practices of medicines promotion control (e.g., by compiling and maintaining a list of relevant national contact points) as well as by organizing, on a regional basis, workshops for regulators to address practices in promotion and effective regulation. A possibility to generalize the results of these meetings into a guide of promotion control for the regulatory agencies should be explored.

- Evaluate the need to revise and further promote the 1988 WHO Ethical Criteria

for Medicinal Drug Promotion in view of recent developments in regulatory and industry practice.

- Compile an explanatory guide for the lay press on objective reporting of risks and benefits of medicinal products.

Counterfeit medicines

The topic of counterfeit medicines has been on the agenda from the Ninth ICDRA onwards and numerous recommendations have been issued. During the session, it was decided to re-emphasize selected recommendations.

Moderators
Paul B. Orhii, Nigeria and Susanne Keitel, France

Presentations
Introduction to Medical Products Anti-counterfeiting Situation in China. Lei Sun, China

Experience of working together from a European network of enforcement officer. Naeem Ahmed, UK

Basel Medicrime Conference 2010: further development of Council of Europe Medicrime Convention. Andreas Balsiger, Switzerland

Overview of fighting counterfeit medicines in Russia. Sergey Glagolev, Russia

Recommendations

The 14th ICDRA reiterates and draws attention to the recommendations of the 12th and 13th ICDRAs, congratulating WHO for its continued work in the anti-counterfeiting area.

Medicines regulatory authorities should:

- Develop and adopt multipronged anti-counterfeiting strategies addressing at least:

  Proper regulatory oversight; securing the supply chain; increasing and applying penalties; increasing public and health professional vigilance and awareness; developing and applying effective authentication and detection technologies; and improving coordination with all concerned stakeholders at the national and international level.

WHO should:

- Assist MRAs to strengthen their capacity to detect and combat counterfeit medical products and to exchange information at the international level.

- Promote a harmonized definition of a counterfeit medicinal product that focuses on the protection of public health and takes into account the need to safeguard legitimate generic medicines.

WHO and medicines regulatory authorities should:

- Promote the development of collaborative networks based on the principle of single points of contact.

Snake antivenom immunoglobulins (antisera)

The main purpose for this workshop was to discuss ways forward to support implementation of regulatory systems for snake antivenom immunoglobulins and ways of collaboration among regulators and to discuss proposals to evaluate the quality of snake antivenoms and the need for venom reference preparations.

Snake envenomings are neglected diseases with high morbidity and mortality so that availability of adequate and appropriate antivenoms for medically significant poisonous snakes is a critical unmet need, especially in Africa and parts of Asia. In particular, support is needed at the regional level to address current barriers to the availability of suitable, safe and effective products.

WHO has worked to raise global awareness of this problem and has developed two critical tools:

- A worldwide database on medically important snakes and the available antivenoms.
- Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins.

Essential steps to address the critical shortage of snake antivenoms include:

- Improved reporting of snake bites to define the local needs (epidemiology and pharmacovigilance).
- Regulatory oversight of antivenom production and distribution (GMP, specificity of antivenoms).
- Availability of high quality reference venoms to permit testing of the neutralization potency and species specificity of antivenoms by control laboratories.
- Regional cooperation to address the problem of limited resources in the face of a very large number of poisonous snakes.

Moderators
Jay Epstein, USA and Eric Karikari-Boateng, Ghana

Presentations
Experience of regulating antisera: possibilities for international cooperation to ensure quality and availability. Laura Castanheira, Brazil

Quality of venoms: a critical step in the production of snake antivenoms. Fred Siyoi, Kenya

Impact of the WHO website on the regulatory control of snake antivenoms. Wichuda Jariyapan, Thailand

Discussion Panel:
Capacity building for regulatory systems of snake antivenoms. Graham Dickson, Australia, Mandisa Hela, South Africa, Bhupendra Thapa, Nepal.

Recommendations

Member States should:

- Take advantage of local expertise and existing networks to link promotion and oversight of antivenoms to other public health efforts.
- Establish mandatory reporting of snake bites and their therapies, including use of standardized report forms to define the local epidemiology.
- Establish regulatory systems capable of assuring GMP manufacturing and appropriate specificity of distributed antivenoms, including lot release.
- Cooperate in development of regional control laboratories and regionally relevant reference venoms.

WHO should:

- Continue efforts to raise awareness of snake bites as a neglected public health issue.
- Provide training on use of the worldwide database and the WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins.
- Support regional efforts to establish regulatory systems, including development of regionally significant high quality reference venoms.
- Promote an international scientific dialogue on preclinical and clinical standards for establishing the efficacy of antivenoms.

Current topics

Transparency in medicines regulation
WHO should continue supporting initiatives aimed at increasing medicines regulation transparency and monitoring.

Electronic nicotine delivery devices (ENDS)
National regulatory authorities should regulate ENDS as a combination of drugs and medical devices addressing as a first priority safety concerns.

Regulatory actions to contain artemisinin resistance
National regulatory authorities should take appropriate action to enforce the implementation of WHA Resolution 60.18 concerning the suspension of marketing and use of oral artemisinin-based monotherapies. WHO should continue to provide the required assistance to Member States.

Securing uninterrupted pharmaceutical supply
Member States should make efforts to improve the regulatory environment in order to facilitate securing the uninterrupted supply of medicines. This would involve sharing information, learning from best practices and developing measures to prevent and manage risks related to global medicines shortages.

WHO should explore establishing mechanisms for exchange of information on medicines shortages due to quality failures and lack of incentives for production. The potential for establishing an informal international network to share information and ideas on prevention and risk minimization of medicines shortages should be explored

Combating antimicrobial resistance
WHO should facilitate clarifying the roles and responsibilities of regulators in combating antimicrobial resistance. A model action plan for countries should be created. WHO should continue to emphasize the vital importance of rational use of medicines as a tool to prevent drug resistance.

International Conference of Drug Regulatory Authorities: personal reminiscences

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More than 30 years ago, together with a group of drug regulatory officials, the World Health Organization initiated an interesting pilot project to convene drug regulatory authorities of WHO Member States for consultation with the idea of harmonizing regulatory information and improving collaboration. The very first meeting was given the title of International Conference of Drug Regulatory Authorities (ICDRA) and was convened in Annapolis (USA) in 1980. As a result of its success, it was agreed that another ICDRA should be repeated two years later. This visionary endeavour has now stood the test of time and many govern-

Table 1. International Conferences of Drug Regulatory Authorities: hosting and dates

1st	1980 Annapolis (USA)	8th	1996 Manama (Bahrain)
2nd	1982 Rome (Italy)	9th	1999 Berlin (Germany)
3rd	1984 Saltsjobaden (Sweden)	10th	2002 Hong Kong (S.A.R. China)
4th	1986 Tokyo (Japan)	11th	2004 Madrid (Spain)
5th	1989 Paris (France)	12th	2006 Seoul (Republic of Korea)
6th	1991 Ottawa (Canada)	13th	2008 Bern (Switzerland)
7th	1994 Nordwijkerhout (Netherlands)	14th	2010 Singapore

ments have since enthusiastically volunteered to host the ICDRA. Table 1 below shows details of the ICDRAs held since 1980 up to the latest conference in November 2010.

Over the past thirty years, the main objectives of the ICDRAs have remained almost unaltered:

- to promote collaboration between drug regulatory authorities.
- to reach a consensus on matters of interest.
- to facilitate timely and adequate exchange of information.
- to discuss issues of international relevance.

Conclusions drawn from the ICDRAs are summarized in numerous documents and reports and are available as an objective product of the work achieved [1]. However, the aim of the present article is to recount the evolution of important drug regulatory affairs as witnessed within the scope of certain subjective reminiscences of a frequent ICDRA participant, attending 11 ICDRAs out of the total 14 and covering a 26-year period of time.

I have no personal memory of the first and second ICDRAs. They were attended by my predecessor, Dr Istvan Bayer, at that time Head of the Hungarian Human Medicines Regulatory Agency. When he returned from the first ICDRA, he declared that it was “a most interesting initiative”. Following the second conference, Dr Bayer spoke of the many possibilities of collaboration with WHO. In 1982, as a result of contacts during the ICDRA, negotiations began to appoint our National Institute of Pharmacy as a *WHO Collaborating Centre for Drug Information and Quality Assurance*, reporting to the Regional Office for Europe (EURO). The Institute was also involved in technical projects led by WHO Headquarters.

The third ICDRA was the first one I actually attended, accompanying Dr Bayer. It was held in Saltsjobaden, near Stockholm in Sweden. Although it was 16 years ago, let me pick up two interesting memories.

The first was a round-table discussion where participants were requested to outline their medicine registration systems. After the US, Australian and European representatives had spoken, one surprising statement was delivered by a South American delegate. He stated that his country had no registration system — people were practically free to import medicines and the Ministry of Health had no inventory of medicines used in the country. However, he added, they did not feel any effect from the shortcomings of this system. Today, the same South American country has a very strong medicines regulatory authority and is active with WHO and other international collaborative initiatives. Here, one can witness an example of the progress achieved within only twenty five years.

My second recollection is of a very uneasy dispute between the European Community (EC) on the one hand and the European Free Trade Association (EFTA) and the Nordic Council on Medicines [2–3] country representatives. The essence of the issue was that the Nordic countries exercised a “need clause” in drug registration while it was forbidden by EC rules. (In short, the “need clause” meant selection of the “best” medicine, i.e., active ingredient in the same therapeutic group. This was then registered and the others rejected).

The reason why the discussion exploded was that WHO EURO had begun a project of sharing drug registration experiences by publishing individual country drug assessments. The Nordic countries were active in WHO and, based on harmonized Nordic Evaluation Reports, some “need-clause based” assess-

ments appeared in WHO documents. The bloc of EC countries rejected this in a formal “declaration”.

The essence of the issue was whether drug regulatory authority review should be restricted to quality, safety and efficacy or should also be directed to other questions — in this case therapeutic added value leading to the present healthcare technology assessment. It is interesting to note how this issue will be revisited periodically during later ICDRAs.

The fourth ICDRA in Tokyo in 1986 was the first I attended as Director-General of the Hungarian Agency (accompanied by my predecessor who was invited by WHO). To my knowledge, it became the first ICDRA referred to in WHO documents as the initiating source of WHO activities. Since then, almost all WHO regulatory guidance documents refer to recommendations emanating from the ICDRAs. As an example, “During the fourth ICDRA held in Tokyo in 1986, WHO was requested to compile a list of medicinal plants and to establish specifications for the most widely used medicinal plants and simple preparations.” This activity led to model monographs being published, and is now at the fourth Volume. Herbal regulatory collaboration has been crowned by establishment of the International Regulatory Cooperation for Herbal Medicines, (IRCH) in 2005 [4].

Possible regulatory actions in relation to Reye’s syndrome (a consequence of administrating acetylsalicylic acid to children having viral infections) were thoroughly discussed. At the time, as I remember, there were articles in the press requesting complete withdrawal of acetylsalicylic acid and “regulatory gossip” suspected a competitor of being involved. Although some regulators questioned the safety of acetylsalicylic acid in general, the recommendation was to make the necessary modifications in the information materials.

There was also much discussion on bioequivalence, since the biowaiver concept had just been introduced into the USA. European regulators, however, were of the opinion that bioequivalence should be based on “bio” studies. It is interesting to note the consequences of this conservative attitude: the biowaiver concept, at least in detailed form, did not appear in a European Medicines Agency guideline until 2010.

Regulators had to wait three years for the next ICDRA which was organized in Paris at the Senate building. This time, background discussions were perhaps more important than the conference. It is accepted history today that the idea to create a tripartite USA, European Union and Japan *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) began to materialize after the Paris ICDRA [5]. Recognizing the success of the ICDRA, on the one hand, and the fact that WHO was developing technical drug registration guidelines for global use, tripartite regulators needed a mechanism which would address the challenges of innovative drug registration in a fast moving environment in collaboration with the pharmaceutical industry. This gave an impetus to the creation of ICH. This was the first ICDRA where I took an active role in the session dealing with the impact of regulatory decisions [6].

To attend the next ICDRA, Europeans would cross the Atlantic. In Ottawa, the aforementioned Guidelines for the Assessment of Herbal Medicines were discussed and found suitable for WHO Expert Committee adoption [7]. However, it is interesting to remember that, earlier, WHO brought technical guidelines to ICDRA sessions where they were “found suitable” for adoption by the relevant WHO Expert Committee. This procedure was maintained during the next ICDRA and then ceased to exist.

The WHO Certification Scheme was also a regular topic of discussion. Because of the contradictory news about its use, WHO decided to improve the Scheme. My role was to contribute to the debate on whether the bioequivalence requirements for registration were identical to those underlying the decision on interchangeability or fixed-fee reimbursement [8]. The issue was a delicate one because of the question (as in the Saltsjobaden ICDRA!) of whether a drug regulator should take other factors than those necessary for registration into consideration.

The Seventh ICDRA took place in the Netherlands. This was the first really big ICDRA, with more than 160 participants from 88 Member States attending [9]. It demonstrated the steady progress and importance of the ICDRAs since the earlier events which were organized as round table discussions and sessions.

Counterfeiting emerged as one of the most challenging issues. Participants called on WHO to develop standards to combat counterfeit medicines, thus initiating creation of the first WHO anti-counterfeit project. The recommendation to Member States stated that those countries lacking an efficient drug regulatory system should implement the WHO's Guiding Principles for Small National Drug Regulatory Authorities [10].

Changes in the WHO Certification Scheme were thoroughly debated, including the issues of computer generated certificates, the licensing status in the country of origin and national provisions for use of the Scheme [11]. Discussion also focused on a modified structure for the WHO good manufacturing practices (GMP) which had been issued following several years of working group consultation in which I had also participated. The truth is that the WHO GMP was restructured to differ, not in content but in structure, from all other existing GMP national or regional guides. The accepted changes in the Certification Scheme were recommended to be submitted to the next Expert Committee for formal endorsement.

In 1996, the ICDRA was held in Manama, Bahrain. It was, again, an appropriate forum for unofficial discussion between regulators who were working on creation of a regional collaboration of Central-eastern European Union candidate countries. *The Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries*, CADREAC, was signed the next year.

The final draft of the WHO Guidelines to combat counterfeit drugs were discussed and presented by myself, on behalf of WHO. The idea that the role of the WHO *International Pharmacopoeia* was changing from a model for national pharmacopoeias to a quality standard for drug procurement (as it is today) was, as far as I remember, first openly discussed at that time [11].

There was an uneasy debate in one of the last sessions where the speaker stated that terminal quality control could completely substitute GMP for biologicals. The majority of the floor speakers, however, were of the opinion that this was not an "either – or" issue. To my best remembrance, this was the last time that the importance of GMP was challenged at an ICDRA.

Three years later, during the Berlin ICDRA, some differences between the interests of the ICH region and those of developing countries became evident. As a consequence, the ICH requested WHO, as an observer in the ICH process, to take into account implications of ICH guidelines for non-ICH countries. This led, for example, to the addition of new climatic zones to the ICH stability guidelines and in the corresponding WHO guideline. The importance of quality assurance became evident also in regulatory work and led to drafting of compo-

nents of a WHO Good Regulatory Practice Package [12].

A special feature of this ICDRA was the move to a more technical organization and introduction of computerized sessions with interpretation into three languages. The programme highlighted national and international anti-tobacco efforts. This was a high priority of the WHO Director-General at that time.

I have no personal memories of the 2002 Hong Kong ICDRA, since it was the third one I did not attend. I know from the literature that new topics emerged in the programme: antimicrobial resistance, regulation of biotechnology products, e-commerce and homeopathy.

At the Eleventh ICDRA in Madrid, relatively new topics were: WHO training in pharmacovigilance and assessment and importance of fixed-dose combinations. Moreover, the question of whether drug regulators should focus, in their evaluation, on issues outside the individual quality-safety-efficacy of new medicines (remember the Saltsjobaden ICDRA!) was evolving again in the form of giving priority to medicines of high public health importance.

The first pre-ICDRA meeting was also convened on the counterfeit medicine issue. The reason for this new phenomenon of pre-ICDRA meetings, open not only to regulators but also industry, nongovernmental organizations and academia, was that these institutions were also interested in attending the ICDRAs that were accessible only to regulatory authorities. In former ICDRAs, to answer this need, industry had been invited to give a keynote address. The new pre-ICDRA meetings — maintained until the present time — solved this issue.

The focus of the pre-ICDRA meeting in Madrid was to discuss the idea of an international convention to fight counterfeit medicines. However, in spite of support from some Member States, this approach was not acceptable. The possibility of an international multi stakeholder taskforce was then put forward and led to establishment of the International Medical Products Anticounterfeiting Taskforce (IMPACT).

In 2006, the ICDRA was held in Seoul. Very interesting discussions were held in the session on pandemic flu preparedness (at that time the H5N1 virus was expected) and on the official introduction of the IRCH initiative. A pre-ICDRA meeting “Improving world health through regulation of biological medicines” was also organized.

Among other topics at the Seoul ICDRA, I would like to highlight two in particular: the regulatory role in advertising control and connections between pharmacoeconomics and regulatory activities. Taking these into account, we can now see an evolution of the idea debated more than 20 years before in the Saltsjobaden ICDRA: connections between drug regulation, cost-containment and therapeutic added-value evaluation!

I attended the next ICDRA in Bern as the retired Head of the Hungarian National Agency (but still active in civil service and in charge of the WHO Collaborating Centre). The pre-ICDRA meeting and also some ICDRA sessions were devoted to paediatrics. Other emerging issues were crisis management and biosimilars.

The latest ICDRA in Singapore, although it is early to evaluate, was also a great success. The pre-ICDRA meeting dealt with different forms of international and regional collaboration, and the main sessions invited us to discuss the lessons learnt following the H1N1 flu pandemic, consequences of the globalization of clinical trials as well as recurrent issues such as good regulatory practice and biosimilars.

Summarizing my personal reminiscences I would like to point out that, in the eighties of the last century, doubts soon dissipated as to whether enough common ground existed between regulators operating in diverse settings around the world to sustain a truly global dialogue. Such doubts have been continually proven unfounded. Moreover, the ICDRA is a unique medicines regulatory forum! It is truly global. Since the 1994 ICDRA, from which I possess data, the number of participating countries has increased slightly but the number of regulatory delegates has increased significantly.

My lifetime has covered various collaborative activities, such as the CMEA or COMECON of the former Eastern Bloc countries, the EFTA Pharmaceutical Inspection Convention, OECD working group, CADREAC, and now the European Union, but none has proved so global as the ICDRAs where, as a rule, in each session moderators and speakers are drawn from all regions with developed and developing countries equally represented. Outcomes of the ICDRA recommendations may also be judged by the number of ongoing country activities, by WHO activities and programmes, and regulatory guidelines subsequently issued.

Above all, the ICDRAs bring together an extremely pleasant company of people working to attain similar objectives and sharing the same or similar views. I must admit that witnessing the evolution of drug regulatory issues from a completely global point of view has been an extremely exciting experience!

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WHO Prequalification of Medicines Programme

Inspection of API manufacturing sites

The WHO Prequalification of Medicines Programme (PQP) aims to make quality priority medicines available for the benefit of those in need. This is achieved through evaluation of product dossiers, inspection of manufacturing sites and clinical research organizations (CROs), and by building national capacity for sustainable manufacturing and monitoring of quality medicines.

When the product dossier and all relevant manufacturing and clinical sites have been found acceptable, the product is prequalified and listed on the Prequalification Programme web site together with the applicant's name and corresponding manufacturing site of the finished product. (http://apps.who.int/prequal). PQP embraces the concept that "good quality must be built into the product during its design and manufacturing process; it cannot be tested into the product afterwards" (1).

One of the most important components of a pharmaceutical product is the active pharmaceutical ingredient (API). Ensuring the quality of the API greatly contributes to achieving the objective of building the quality, safety and efficacy into the product. One of the strategies employed by PQP to achieve this is through inspection of API manufacturing sites to assess compliance with good manufacturing practices (GMP) and to verify data submitted in product dossiers.

PQP inspections

API manufacturing site inspections were initiated in 2003 as an element of finished product prequalification. In 2010, a procedure was initiated to prequalify APIs separately since many problems that PQP faces are related to quality. As part of the procedure, a separate application for APIs is available and they are assessed and inspected before being included in the *WHO List of Prequalified Active Pharmaceutical Ingredients* (http://apps.who.int/prequal). The list provides United Nations agencies, medicines regulatory authorities (MRAs) and others with information on APIs that have been found to meet WHO-recommended quality standards. Identification of sources of good-quality APIs will facilitate the manufacture of good-quality finished pharmaceutical products (FPP) that are needed for procurement by UN agencies and disease treatment programmes. A description of the procedure can be found at http://apps.who.int/prequal/info_applicants/API_introduction.htm. APIs eligible for prequalification are available at: http://apps.who.int/prequal/info_applicants/eoi/EOI-API_v1.pdf

The availability of a list of prequalified quality APIs is particularly valuable to manufacturers of finished dosage forms. This can also expedite prequalification of finished products when applicants have used quality prequalified APIs in their formulations. With information on sources of prequalified APIs, production of quality finished dosage forms of priority essential medicines is facilitated, increasing access to good quality medicines. API prequalification also assists MRAs by enabling them to verify the standard of APIs used to manufacture nationally registered medicines.

An inspection team normally consists of a WHO inspector based in Geneva and a

co-inspector appointed by WHO from a Pharmaceutical Inspection Cooperation Scheme (PIC/S) member inspectorate. An inspector(s) from the national medicines regulatory authority of the country, in which the manufacturing site is located is invited to participate as an observer.

Risk management principles are used to select the site to be inspected, the duration of the inspection and the frequency of inspection. In terms of priorities, inspection of sites for finished pharmaceutical products comes first followed by sites for APIs, CROs and quality control laboratories (QCL) in that order.

Table 1 sets out examples of relative risks associated with products.

More specifically, additional risk factors for APIs are considered. These parameters include:

Polymorphism; solubility in water; complexity of the route of synthesis; solvents used; impurities; sterile versus non sterile API; fermentation; toxicity; activity/potency; particle size; other properties identified to be considered; site compliance information, e.g., from previous acceptable inspections, and type and number of FPPs in which the API is used.

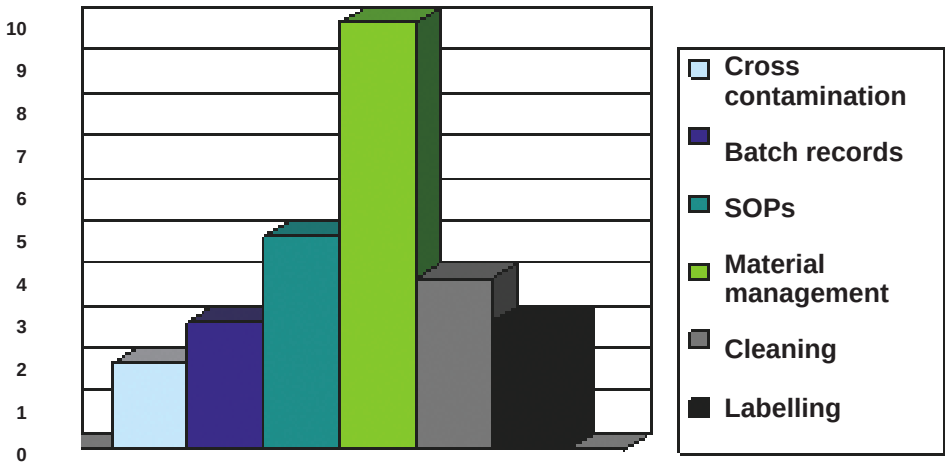
The following order is provided for guidance in determining priorities:

- Sterile APIs.
- Re-inspection when it is more than 12 months past the re-inspection due date.
- A new API manufacturer when the product PQ process may be held up by lack of GMP evidence for the API manufacturer.
- The sole supplier of an API.
- The API is produced by fermentation.
- The API is used in paediatric PQ medicines.
- The API is used in a number of PQ products.

Table 1. Relative risk categories

RELATIVE RISK CATEGORY	PRODUCT TYPE / ACTIVITY			
	Critical	High	Medium	Low
Finished Products:				
Sterile finished products	√			
Non-sterile finished products		√		
APIs:				
Sterile APIs		√		
Non-sterile APIs where there is a special risk (e.g. isomerism, polymorphism, special risk of harmful impurities, etc)			√	
Other non-sterile APIs				√
QC Laboratories			√	
CROs			√	

Figure 1. Inspection of API manufacturers: major deficiencies



All manufacturers of APIs used in prequalified medicinal products should comply with GMP. As a default, all manufacturers of APIs used in prequalified medicinal products should be inspected by the PQP. An inspection by the PQP may be omitted when other acceptable evidence of GMP compliance is provided by the API manufacturer. An inspection by another acceptable organization, such as the EDQM, a PIC/S member country, or the US FDA, may be considered in lieu of an on-site WHO PQP inspection when:

- The inspection was conducted within the last two years with a positive compliance outcome.
- The scope of the inspection covered the specific API in question.
- The API manufacturer submits a copy of the last inspection report for review by the PQP. The review must determine that the inspection was comprehensive and that the inspection report supports the final outcome.
- Irrespective of the above, the PQP reserves the right to inspect any API manufacturer if considered necessary on a risk basis.

Whether inspected by the PQP or when GMP compliance is based on an inspection by another acceptable organization, on-going GMP compliance must be confirmed at least every four years.

Norms and standards used

WHO norms and standards are used in the inspection of API sites. The WHO Expert Committee on Specifications for Pharmaceutical Preparations has revised the WHO GMP for APIs and has recommended a new text that follows closely the principles of ICH Q7 *Good manufacturing practice guide for active pharmaceutical ingredients* published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As a result the *WHO good manufacturing practices for active pharmaceutical ingredients* has been published in 2010 (2).

Statistics

Out of 126 API sites participating in PQ activities, 49 have been accepted based on approval by PIC/S inspectorates and/or ICH countries while 31 were inspected. Six of the inspected sites were found to

be operating at an unacceptable level of compliance with WHO GMP.

Most of the API sites were located in India and China and this is where most of the inspections have taken place. The sites inspected are those producing many APIs (average 4 APIs per site) mainly for HIV/AIDS, TB and malaria in that order.

According to the WHO PQ quality assurance system and procedure for prequalification, API sites should be re-inspected on a regular basis. Usually the interval between inspections is two to three years.

As noted in Figure 1, key observations of API inspections deficiencies noted during inspections of API sites have been mainly in materials management, documentation, cleaning and cross-contamination.

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Safety and Efficacy Issues

ENCePP launch electronic register of studies

European Union — The European Medicines Agency and the European Network of Centres for Pharmaco-epidemiology and Pharmacovigilance (ENCePP) have launched the ENCePP E-Register of Studies. This electronic register is a publicly accessible resource for the consultation of pharmaco-epidemiological and pharmacovigilance studies conducted by academic centres and other research organisations.

The purpose of the E-Register is to increase the availability of information on the utilisation, safety and effectiveness of medicines used in clinical practice through a readily accessible database resource.

It will also contribute to reducing publication bias by handling both positive and negative study results in the same manner and promote exchange of information, thereby facilitating collaboration within the scientific community and preventing unnecessary duplication of research.

Registration of studies in the register is voluntary, except for those studies wishing to apply for the status of 'ENCePP Studies', a seal awarded to wholly or partially EU-based benefit/risk studies that are carried out in compliance with the ENCePP Code of Conduct for independence and transparency and the ENCePP Checklist of Methodological Research Standards. Studies that potentially qualify for this seal must be entered into the E-Register before they commence.

The E-Register of studies can be accessed through the ENCePP website: at http://www.encepp.eu/encepp/studiesDatabase.jsp

Reference *EMA Press release,* EMA/759118/2010 dated 25 November 2010 at http://www.ema.europa.eu

Methysergide and retroperitoneal fibrosis

Australia — Retroperitoneal fibrosis is a well recognized adverse effect associated with long-term uninterrupted use of methysergide. To reduce the risk of this adverse effect, withdraw methysergide for 3 to 4 weeks at least every 6 months. Reduce the dose gradually during the last 2 to 3 weeks of each course to avoid rebound headache.

Methysergide (Deseril®) is an ergot alkaloid derivative indicated for prophylaxis of migraine, cluster headaches and other vascular headaches. It is considered the most potent of the prophylactic drugs for migraine and may be effective when first- and second-line therapies fail (1).

The most well-known serious adverse effect of methysergide is retroperitoneal fibrosis, which is usually associated with uninterrupted use for longer than six months, although cases have been reported with continuous use for less than six months (2). Pleuro-pulmonary fibrosis and fibrotic changes of the pericardium and cardiac valves have also been associated with methysergide in a small number of patients (3). Intermittent use of methysergide is recommended to reduce the risk of fibrotic complications.

The Therapeutic Goods Administration (TGA) has recently received two reports

of retroperitoneal fibrosis where methysergide was suspected, bringing the total number of reports received to December 2010 to 22. Symptoms and signs such as general malaise, backache, girdle or flank pain, dysuria, oliguria, increased blood nitrogen or vascular insufficiency of the lower limb should raise the suspicion of retroperitoneal fibrosis (2).

Extracted from the Medicines Safety Update, No.1, 2011 at http://www.tga.gov.au

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Clozapine and life–threatening gastrointestinal hypomotility

Canada — Health care professionals are reminded of life-threatening gastrointestinal hypomotility suspected of being associated with the use of clozapine. Gastrointestinal hypomotility may be aggravated by combining clozapine with other potentially constipating medications.

Clozapine is an atypical antipsychotic agent indicated in the management of treatment-resistant schizophrenia (1). It has been marketed in Canada since 1991 under the brand name Clozaril® and is now also available as generic products. Clozapine use is limited to patients who have not responded to, or are intolerant of, conventional antipsychotic medications. Constipation is a common adverse reaction (AR) to the drug. The Canadian product monograph for Clozaril® indicates that constipation occurred in 14% of patients in clinical trials, and higher rates have been reported in case series (1, 2).

The Canadian product monograph also lists paralytic ileus as a contraindication to clozapine use (1). The drug has potent anticholinergic effects that have been associated with varying degrees of impairment of intestinal peristalsis, from constipation to intestinal obstruction, fecal impaction and paralytic ileus (1). On rare occasions, these cases have been fatal.

Clozapine's anticholinergic and antiserotonergic effects may contribute to gastrointestinal hypomotility and colonic distension (2, 3, 4). Intraluminal distension in turn can compromise capillary circulation and lead to colonic mucosal ischemia. In addition, severe fecal retention resulting from hypomotility may promote colonic distension, accumulation of gas and fluids, and bacterial proliferation in the affected bowel segment (3, 4). Bacteria may then invade the underlying ischemic mucosa, resulting in necrosis and systemic sepsis.

The potential for complications and death from severe gastrointestinal hypomotility is considerable (2, 5). For instance, the rate of death from acute colonic pseudo-obstruction (acute colonic dilatation without mechanical obstruction) is 15% in the absence of complications such as ischemia and perforation (5). If spontaneous perforation occurs (3% –15% of cases), mortality rises to 50% or higher (5). Late presentation and diagnosis of bowel obstruction may contribute to fatal outcomes in patients using clozapine (2). This may be related to diminished pain sensitivity in patients with schizophrenia or to difficulty in expressing their pain (2, 6). In addition, concomitant medications may have sedative and analgesic effects, which may mask or attenuate early symptoms and contribute to delayed diagnosis.

As of 15 July 2010, Health Canada received 704 reports of gastrointestinal ARs suspected of being associated with

the use of clozapine. Of these, 28 deaths involving people with ARs related to intestinal obstruction were identified. Reports came from health care professionals and the medical literature (4, 7).

Canadian Adverse Reaction Newsletter, Volume 21, Issue 1, January 2011

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Tamoxifen and antidepressants: drug interaction

Australia — A recent study has suggested a higher death rate amongst women taking tamoxifen for breast cancer who were also using the selective serotonin reuptake inhibitor paroxetine. This is thought to be a result of reduced conversion by cytochrome P450 2D6 of tamoxifen to a major active metabolite. Other studies have not found an association between CYP2D6 inhibitors and poorer outcomes in women taking tamoxifen. Until more conclusive data are available, it may be prudent to avoid, where possible, prescribing antidepressants that inhibit CYP2D6 to women with breast cancer being treated with tamoxifen.

Antidepressant CYP2D6 inhibitors (7,8)*

Potent inhibitors
Bupropion[o]
Fluoxetine
Paroxetine
Moderate inhibitors
Duloxetine
Sertraline (mild inhibitor at doses < 100 mg/day)

** The information provided is a guide only. The precision in categorizing the strength of CYP2D6 inhibition is limited for some antidepressants.*

[o] Not registered in Australia for the treatment of depression.

Antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) are commonly used in women with breast cancer to treat major depressive disorder and, off-label, for hot flushes. It is estimated that up to 25% of women with breast cancer suffer from major depressive disorder during the course of their treatment (1).

Tamoxifen is metabolized to one of its major active metabolites, endoxifen, by CYP2D6. Reduced plasma endoxifen levels have been reported with some SSRIs (2) particularly those that are potent CYP2D6 inhibitors, which could result in reduced efficacy of tamoxifen. A recent observational study found an association between use of tamoxifen

concurrently with paroxetine (an irreversible CYP2D6 inhibitor) and breast cancer mortality (3) but other studies have not found an association between CYP2D6 inhibitors and breast cancer recurrence or death in women taking tamoxifen (4–6).

Although evidence from epidemiological studies is conflicting, the mechanism of the effect is biologically plausible and caution is warranted when prescribing antidepressants that moderately or strongly inhibit CYP2D6 to women taking tamoxifen. Antidepressants with little or no inhibitory effect on CYP2D6 may be suitable alternatives. It should be noted that some other medicines inhibit CYP2D6, with examples of potent inhibitors including quinidine and cinacalcet.

Extracted from Medicines Safety Update, No.1, 2011 at http://www.tga. gov.au

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Dronedarone : severe liver injury

United States of America — The Food and Drug Administration (FDA) is alerting healthcare professionals to cases of rare but severe liver injury, including two cases of acute liver failure leading to liver transplant in patients treated with the heart medication dronedarone (Multaq®).

Dronedarone is approved to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent history of AF/AFL and associated cardiovascular risk factors who are in sinus rhythm or who will be cardioverted.

Dronedarone is contraindicated in patients with NYHA Class IV heart failure or NYHA Class II – III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.

Dronedarone was approved with a Risk Evaluation and Mitigation Strategy (REMS) with a goal of preventing its use in patients with severe heart failure or who have recently been in the hospital for heart failure. In a study of patients with these conditions, patients given dronedarone had a greater than two-fold increase in risk of death.

Patients are advised to contact a healthcare professional immediately if they

experience signs and symptoms of hepatic injury or toxicity while taking dronedarone.

Healthcare professionals should consider obtaining periodic hepatic serum enzymes, especially during the first six months of treatment. If hepatic injury is suspected, dronedarone should be promptly discontinued.

Reference: *FDA Drug Safety Communication*, 14 January 2011 at http://www.fda.gov

Dolasetron mesylate: abnormal heart rhythm

United States of America — The Food and Drug Administration (FDA) has notified healthcare professionals of a contraindication added to the prescribing information for dolasetron mesylate (Anzemet®) advising that the injection form of dolasetron mesylate should no longer be used to prevent nausea and vomiting associated with cancer chemotherapy (CINV) in paediatric and adult patients. New data demonstrate that Anzemet® injection can increase the risk of developing torsade de pointes, an abnormal heart rhythm, which in some cases can be fatal. Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems. Dolasetron mesylate causes a dose-dependant prolongation in the QT, PR, and QRS intervals on an electrocardiogram.

Dolasetron mesylate should not be used in patients with congenital long-QT syndrome. Hypokalaemia and hypomagnesaemia should be corrected before administration. These electrolytes should be monitored after administration as clinically indicated. Use electrocardiogram monitoring in patients with congestive heart failure, patients with bradycardia, patients with underlying heart disease, the elderly and in patients who are renally impaired who are taking dolasetron mesylate. Dolasetron mesylate injection may still be used for the prevention and treatment of postoperative nausea and vomiting because the lower doses used are less likely to affect the electrical activity of the heart and result in abnormal heart rhythms.

Dolasetron mesylate tablets may still be used to prevent CINV because the risk of developing an abnormal heart rhythm with the oral form of this drug is less than that seen with the injection form. However, a stronger warning about this potential risk is being added to the Warnings and Precautions sections of the Anzemet® tablet label.

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

Sitaxentan: update following withdrawal

European Union — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has reviewed the data on liver toxicity, including three cases of fatal liver injury, that have prompted the marketing authorization holder to withdraw sitaxentan (Thelin®) worldwide and discontinue ongoing clinical trials. The Committee has also considered alternative treatment options.

The CHMP reviewed three cases of fatal liver injury. Two of the cases of fatal liver injury were causally related to Thelin®. The new data suggest that serious hepatic toxicity cannot be prevented in all patients. The cases were not associated with identifiable risk factors, could not be detected by frequent monitoring and did not resolve with the discontinuation of sitaxentan.

Thelin® contains the active substance sitaxentan, an endothelin receptor antagonist (ERA) and has been authorized in the European Union (EU) since 2006 for the treatment of pulmonary arterial hypertension.

The CHMP noted that alternative treatment options are available, including two other centrally authorized ERAs, bosentan Tracleer® and ambrisentan (Volibris®). Liver toxicity may be a class-effect, but frequency and intensity could vary. Strict recommendations have to be taken into account in terms of dosing and hepatic monitoring.

Reference: *EMA Press Release,* EMA/CHMP/819948/2010 dated 16 December 2010 at http://www.ema.europa.eu

Bevacizumab use in breast cancer treatment

European Union — The European Medicines Agency has confirmed that the benefits of bevacizumab (Avastin®) in combination with paclitaxel outweigh its risks and that this combination remains a valuable treatment option for patients suffering from metastatic breast cancer.

The Agency's Committee for Medicinal Products for Human Use (CHMP) also concluded that the balance of benefits and risks of bevacizumab in combination with docetaxel is negative and that this combination should no longer be used in the treatment of breast cancer. Patients who are currently being treated with this combination should discuss ongoing treatment with their doctor.

Avastin® is an anticancer medicine which contains the active substance bevacizumab. It is used in combination with other anticancer treatments to treat cancers of the colon, rectum, lung, kidney or breast. The CHMP's review was restricted to the use of Avastin® in breast cancer and does not affect its use in the other indications.

For bevacizumab in combination with paclitaxel, the Committee concluded that the benefits continue to outweigh the risks, because the available data have convincingly shown to prolong progression-free survival of breast cancer patients without a negative effect on the overall survival.

Reference: *EMA Press Release,* EMA/CHMP/815425/2010 dated 16 December 2010 at http://www.ema.europa.eu

Latest developments in pharmacovigilance

The Thirty-third annual meeting of representatives of national centres participating in the WHO Programme for International Drug Monitoring was held in Accra, Ghana from 1 to 3 November 2010. Eight working groups were set up to discuss issues related to the development of pharmacovigilance. Several recommendations were made following these discussions.

The role of pharmacovigilance centres in preventing medication errors

The scope and limits of pharmacovigilance (PV) centres in preventing medication errors and how PV centres can have a proactive role in preventing medication errors were discussed.

Recommendations

- National PV policies should include medication error issues as part of the function of PV centres.
- Standardized definitions/terminologies for medication errors are needed.
- Existing tools should be modified to capture specific information on medication errors.
- National centres should advocate for reporting of medication errors even when they do not lead to adverse events.

• Medication errors should be incorporated into PV training curricula for students and in-service training modules for healthcare professionals.

How to improve the quality of individual case safety reports

This working group looked at problems of the quality of individual case safety reports (ICSRs) and possible solutions. First, a good quality ICSR should be defined. Many reporters are not used to reporting ICSRs and may not include relevant information such as laboratory test results in their reports. This would allow better causality assessments.The working group suggested that possible solutions could be the improved design of reporting forms and analysis and review of national reporting requirements and practice. The Uppsala Monitoring Centre (UMC) has set up a tool for the analysis of completeness and quality of ICSRs submitted to the international PV database which may be helpful in this respect. It may be possible to identify different quality problems in reports from different groups of reporters (i.e., company reports, direct healthcare professional reports and consumer reports) and address these separately.

Establishing pharmacovigilance centres: difficulties and solutions

This working group discussed common problems and challenges when setting up or strengthening a PV centre and how to address these. Some of the problems identified were: under-reporting, low quality of adverse drug reaction (ADR) reports, shortage of qualified staff at national centres, lack of funding of PV centres, lack of interaction with the regulatory authority, the government and other policy makers, and limitation of the legislation base.

Recommendations

• Include PV training in undergraduate and postgraduate curricula of all healthcare professionals, including physicians, pharmacists and nurses.

• Establish active surveillance components, specifically to use public health programmes and the Global Fund PV initiative for the incorporation of PV into the national healthcare system.

• Enhance PV promotional activities, especially by engaging professional organizations of healthcare providers, internet facilities, mass-media, professional conferences etc.

• Motivate and stimulate reporting by providing feedback.

• Make reporting mandatory for healthcare professionals and the industry.

The working group also considered several funding resources to tackle lack of funding of PV centres; government funding (minimal financing), regulatory resources such as fees, the Global Fund, PEPFAR and similar initiatives, and support by non-profit organizations.

AEFIs: causality assessment and signal detection

It is important to ensure the continued safety of vaccines by monitoring adverse events following Immunization (AEFIs). Vaccine-related adverse events that are not rapidly and effectively dealt with can undermine confidence in a vaccination programme and ultimately have dramatic consequences for immunization coverage and disease incidence. It is therefore imperative that methods for reporting ADRs to vaccines, causality assessment and signal detection of AEFIs are in place within PV systems.

Although most countries have AEFI reporting in place, there may be no synergy in communicating reports between national regulatory authorities (NRA), national immunization programmes (NIP) and PV centres.

Recommendations

- Effective communication and collaboration between regulatory authorities, national PV centres and national immunization programmes is key to monitoring vaccine safety.
- Standard operating procedures and guidelines need to be developed to make channels of communication clearer.
- The public and the media should be included in any collaborative efforts to monitor AEFIs.

Optimizing pharmacovigilance activities to fight substandard and poor quality medicines

The problem of poor quality, contaminated and substandard medicines is a particular challenge and systems need to be put in place for the prompt identification and withdrawal of such medicines from the market.

Recommendations

- PV centres could be the first point of call for reporting substandard, poor quality medications.
- Tools need to be redesigned for data collection to make provisions for the reporter to indicate substandard medicines, medication errors, drug abuse, etc.
- Advocacy, education and training and timely information dissemination are key in merging efforts to detect ADRs along with fighting poor quality and substandard medicines.
- Effective collaboration with various parties will be important in achieving and sustaining these initiatives.

Building human resource capacity for pharmacovigilance

In many national centres, PV activities are undertaken by staff involved in other tasks and are therefore unable to focus their efforts on PV. Also, they may not be adequately trained for this role. Many PV centres also face the problem of high staff turnover.

Recommendations

- National Centres should have a minimum qualification/skill profile for PV personnel.
- PV modules should be included in the training curricula of various health professionals to give basic awareness of medicine safety issues.
- Training packages should be developed for specific and continuous development of staff working in PV. Developing these training curricula will require cooperation with WHO collaborating centres for PV, academia and the use of both internal and external PV consultants.
- PV centres should include resources for training within their budgetary requirements for pharmacovigilance.

How to improve awareness of drug safety issues: social marketing of PV

PV in most countries is not well publicized and there is a general lack of understanding of this concept. Social marketing involves selling the needs and benefits of PV to various parties with the aim that they adopt desirable behaviour to enhance drug safety.

Recommendations

- Marketing of PV should be geared towards behavioural changes that will promote ADR reporting. PV marketing should be geared not only to health professionals but also to the general public.
- Marketing can be enhanced using the media and other public initiatives.

- The impact of PV marketing efforts should be measured by analysing prescription data before and after, analysing media coverage and assessing behavioural changes.

Good practice in pharmacovigilance inspections/assessments

Conducting PV inspections is key to ensuring best practices in pharmacovigilance. PV inspections are currently only conducted by a limited number of countries. The power to carry out PV inspections is generally a legal power, so it is enforced by the national regulatory authority (NRA) which may be separate from the PV centre. Also, the targets for inspection are those that are regulated by the NRA, generally pharmaceutical companies rather than individual health professionals. It is important however to note that definitions of PV inspections will vary from country to country.

PV inspections can be conducted on a routine basis (for example, all new companies should be inspected) or when needed (for example, when an anomaly is detected). Based on the experience of countries that have recently commenced PV inspections, it was suggested that a pragmatic approach be that countries start by setting a level of PV inspections which they have the capacity to perform, for example to inspect a certain number of facilities per year.

Recommendations

- NRAs should take responsibility for carrying out PV inspections. Collaboration between the NRA and national PV centres is important where the national PV centre is not part of the regulatory authority.
- Guidelines and procedures need to be developed for carrying out PV inspections and WHO should lead this together with countries that already have established procedures for PV inspections.

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 validated before any regulatory decision can be made.

Regulatory Action and News

Global operation against illegal and counterfeit medicines

New Zealand took part in an international enforcement operation with over 40 countries throughout the world. The operation targeted the on-line sale of counterfeit and illegal medicines, and was designed to raise awareness of the dangers of buying medicines over the internet.

Operation Pangea III, carried out between 5 and 12 October 2010, resulted in multiple arrests across the globe and the seizure of over one million illicit and counterfeit pills. In New Zealand the drug regulator, Medsafe, worked with the Customs Service to intensively screen all mail entering the country during the week of the operation.

From over 400 consignments referred to Medsafe by the Customs Service, 180 were detained because they were found to contain prescription medicines used for the treatment of conditions such as heart disease, diabetes, hair loss and erectile dysfunction. Oral contraceptives and antibiotics were also commonly found. Medsafe noted that these consignments were imported from 35 countries around the world. The operation indicates that consumers continue to self diagnose and self medicate for conditions requiring treatment that should only occur after consultation with a healthcare professional.

Reference: Medsafe at http://www.medsafe.govt.nz/profs/PUArticles/PDF/Prescriber%20Update%20Dec%202010.pdf

Mometasone furoate/formoterol fumarate: withdrawal of marketing authorization application

European Union — The European Medicines Agency has been formally notified by the manufacturer of the decision to withdraw the application for a centralized marketing authorization for the medicine mometasone furoate/formoterol fumarate (Zenhale® pressurised inhalation).

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

The decision to withdraw the application was based on inability to provide additional data within the time-frame allowed in the centralized procedure.

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

Briakinumab: withdrawal of marketing authorization application

European Union — The European Medicines Agency has been formally notified by the manufacturer of the decision to withdraw the application for a centralized marketing authorization for the medicine briakinumab (Ozespa®, 100 mg solution for injection).

This medicine was intended to be used for the treatment of moderate to severe chronic plaque psoriasis in adults who

failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapies including ciclosporin, methotrexate and PUVA.

The decision to withdraw the application was based on the fact that additional new data and analyses could not be generated within the time-frame allowed in the centralized procedure.

Reference: *EMA Press Release*, EMA/40297/2011 dated 17 January 2011 at http://www.ema.europa.eu

Omacetaxine mepesuccinate: withdrawal of marketing authorization application

European Union — The European Medicines Agency has been formally notified by the manufacturer of the decision to withdraw the application for a centralized marketing authorization for the medicine omacetaxine mepesuccinate (Tekinex®, 5 mg powder for solution for injection).

This medicine was intended to be used for the treatment of adults with Philadelphia chromosome-positive chronic myeloid leukaemia (CML) who have the Bcr-Abl T315I kinase domain mutation and who are resistant to prior imatinib therapy.

In its official letter, the company stated that they decided to change the proposed indication of Tekinex® to the treatment of adults with CML who have failed prior treatment with two or more currently approved tyrosine kinase inhibitors (TKIs). The company further stated that they were unable to address the issues identified by the CHMP within the timeframe allowed in the centralized procedure.

Reference: *EMA Press Release*, EMA/9192/2011 dated 12 January 2011 at http://www.ema.europa.eu

Zoledronic acid: withdrawal of application for an extension of indication

European Union — The European Medicines Agency has been formally notified by the manufacturer of the decision to withdraw the application for an extension of indication for the centrally authorized medicine zoledronic acid (Zometa®) 4 mg powder and solvent for solution for infusion and 4 mg/ 5 ml concentrate for solution for infusion.

The application for an extension of indication was to include the adjuvant treatment of hormone receptor-positive early breast cancer (EBC) in premenopausal women for whom hormonal therapy is recommended.

Zometa® was first authorized in the European Union on 20 March 2001. It is currently authorized for the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone, as well as for the treatment of tumour-induced hypercalcaemia.

In its official letter, the company stated that its decision to withdraw the application was based on the CHMP's view that the data provided in support of the application so far would not allow the Committee to recommend approval.

Reference: *EMA Press Release*, EMA/818700/2010 dated 15 December 2010 at http://www.ema.europa.eu

Pandemic influenza vaccine (H5N1): withdrawal of marketing authorization application

European Union — The European Medicines Agency has been formally

notified by the manufacturer of the decision to withdraw the application for a centralized marketing authorization for Emerflu®, a pandemic influenza vaccine (split virion, inactivated, adjuvanted) A/Vietnam/1194/2004 NIBRG-14, 30 μg of haemagglutinin + aluminium hydroxide adjuvant, suspension for injection.

This medicine was intended to be used for prophylaxis of influenza in an officially declared pandemic situation. A core pandemic dossier was submitted in the context of prevention of influenza in an officially declared pandemic situation, according to the mock-up vaccine procedure.

In its official letter, the company stated that its decision to withdraw the application was based on the CHMP's consideration that the data provided do not allow the Committee to conclude on a positive benefit/risk balance.

Reference: *EMA Press Release*, EMA/776824/2010 dated 6 December 2010 at http://www.ema.europa.eu

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 25–26 October 2010. 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 2012 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted through e-mail at: whocc@fhi.no.

ATC level	INN/Common name	ATC code
New ATC level codes (othr than 5th level):		
Drugs used in hereditary angioedema		B06AC
New ATC 5th level codes:		
	linagliptin	A10BH05
	aspoxicillin	J01CA19
	azilsartan medoxomil	C09CA09
	bekanamycin	J01GB13
	cabazitaxel	L01CD04
	carumonam	J01DF02
	cefbuperazone	J01DC13
	cefminox	J01DC12
	cinchocaine	S02DA04
	conestat alfa	B06AC04
	dienogest	G03DB08
	dimeticone	P03AX05
	donepezil and memantine	N06DA52
	doxylamine, combinations	R06AA59
	ecallantide	B06AC03
	emtricitabine, tenofovir disoproxil and rilpivirine	J05AR08
	flomoxef	J01DC14
	fluindione	B01AA12
	iloperidone	N05AX14
	ipilimumab	L01XC11
	meningococcus B, multi-component vaccine	J07AH09

.../...

ATC level	INN/Common name	ATC code
	metformin and linagliptin	A10BD11
	metformin and saxagliptin	A10BD10
	motavizumab	J06BB17
	panobinostat	L01XX42
	pentosan polysulfate sodium	G04BX15
	pirfenidone	L04AX05
	ramipril and amlodipine	C09BB07
	rilpivirine	J05AG05
	secukinumab	L04AC10
	sinecatechins	D06BB12
	teduglutide	A16AX08
	telaprevir	J05AE11
	tetrachlorodecaoxide	D03AX11
	vilazodone	N06AX24
	von Willebrand factor	B02BD10

ATC code changes:

INN/common name	Previous ATC	New ATC
alitretinoin	D11AX19	D11AH04
C1-inhibitor, plasma derived	B02AB03	B06AC01
icatibant	C01EB19	B06AC02

ATC name changes

Previous	New	ATC code
Agents for atopic dermatitis, excluding corticosteroids	Agents for dermatitis, excluding corticosteroids	D11AH
Other cold combination preparations	Other cold preparations	R05X

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
asenapine	20	mg	O	N05AH05
corifollitropin alfa	0.15	mg	P	G03GA09
dienogest	2	mg	O	G03DB08
eltrombopag	50	mg	O	B02BX05
fampridine	20	mg	O	N07XX07
flupirtine	0.4	g	O	N02BG07
indacaterol	0.15	mg	Inhal. powder	R03AC18
indometacin, combinations	0.1	g[1]	O	RM01AB51

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INN/common name	DDD	Unit	Adm.R	ATC code
mifamurtide	0.7	mg	P	L03AX15
prucalopride	2	mg	O	A03AE04
roflumilast	0.5	mg	O	R03DX07
velaglucerase alfa	300	U	P	A16AB10

[1.] *Refers to indometacin*

Herbal medicinal products*

New ATC 5th level codes::

Name	ATC code
Horse chestnut, seeds	C05CX03

**Assessed and approved by regulatory authorities based on dossiers including efficacy,*

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 2010. They are included in the January 2011 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
Artemisinin and derivatives, combinations		P01BF
Emergency contraceptives		G03AD
New ATC 5th level codes:		
	acetylsalicylic acid and esomeprazole	B01AC56
	afatinib	L01XE13
	albinterferon alfa-2b	L03AB12
	alendronic acid, calcium and colecalciferol, sequential	M05BB05
	amezinium metilsulfate	C01CA25
	besifloxacin	S01AX23
	briakinumab	L04AC09
	ceftaroline fosamil	J01DI02
	chondrocytes, autologous[1]	M09AX02
	dronedarone	C01BD07
	enalapril and nitrendipine	C09BB06
	eribulin	L01XX41
	fampridine	N07XX07
	idrocilamide	M02AX05
	linagliptin	A10BH05
	mannitol	R05CB16
	naftazone	C05CX02
	naproxcinod	M01AE18
	nebivolol and thiazides	C07BB12
	nimesulide	M02AA26
	olmesartan medoxomil, amlodipine and hydrochlorothiazide	C09DX03
	polyplatillen	L01XA05
	retigabine	N03AX21

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ATC level	INN/Common name	ATC code
	sitafloxacin	J01MA21
	taliglucerase alfa	A16AB11
	technetium (^{99m}Tc) hynic-octreotide	V09IA07
	ticagrelor	B01AC24
	triamcinolone	C05AA12
	voclosporin	L04AD03

[1] *Chondrocytes previously classified in V03AX should be moved to the new code in M09AX02*

ATC code changes:

INN/common name	Previous ATC	New ATC
ephedrine	R03CA02	C01CA26[1]

[1] *Only parenteral formulations*

ATC name changes

Previous	New	ATC code
dextriferronferric oxide	polymaltose complexes	B03AB05
dextriferronferric oxide	polymaltose complexes	B03AC0
dextriferronferric oxide	polymaltose complexes	B03AD04
ferric oxide dextran complex	ferric oxide dextran complexes	B03AC06

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
aldesleukin	0.2	mg	P	L03AC01
amezinium metilsulfate	30	mg	O	C01CA25
antithymocyte immunoglobulin (rabbit)	0.1	g	P	L04AA04
C1-inhibitor	1.4	TU	P	B02AB03
canakinumab	2.7	mg	P	L04AC08
denosumab	0.33	mg	P	M05BX04
dronedarone	0.8	g	O	C01BD07
fentanyl	0.6	mg	N	N02AB03
lasofoxifene	0.5	mg	O	G03XC03
paliperidone	2.5	mg[2]	P depot	N05AX13
polystyrene sulfonate	45	g	O	V03AE01
sitafloxacin	0.1	g	O	J01MA21
tocofersolan	0.2	g[3]	O	A11HA08
tolvaptan	30	mg	O	C03XA01
ulipristal	30	mg	O	G03AD02

[2] *expressed as paliperidone*
[3] *expressed as tocopherol*

Herbal medicinal products*

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
Serenoa repens	0.32	g	O	G04CX02

**Assessed and approved by regulatory authorities based on dossiers including efficacy,*

Recent Publications, Information and Events

Assessment of 26 African regulatory authorities

World Health Organization — Medicines regulation is needed to ensure that all pharmaceutical products on the market are safe, effective and consistently meet approved quality standards. *Assessment of Medicines Regulatory Systems in Sub-Saharan African Countries. An Overview of Findings from 26 Assessment Reports* synthesizes the findings of rapid assessments performed at medicines regulatory authorities (MRAs) in 26 African countries over the last eight years.

Although the emphasis of the assessments was on capacity-building rather than a standardized comparison of indicators, the findings give a reasonable overview of the regulatory situation in Africa. Structures for medicines regulation existed in all countries assessed, and the main regulatory functions were addressed, although in practice the measures were often inadequate and did not form a coherent regulatory system.

Common weaknesses included fragmented legal basis in need of consolidation, weak management structures and processes, and a severe lack of staff and resources. On the whole, countries did not have the capacity to control the quality, safety and efficacy of the medicines circulating on their markets or passing through their territories. Regulatory capacity should be implemented urgently in African countries, using the following approaches:

- Encourage and assist countries to assess their own regulatory systems in a systematic way in order to identify and address gaps.
- Work towards consistent implementation of all essential regulatory functions in African countries, based on the key provisions in the existing legal frameworks.
- Strengthen management structures, specific technical regulatory expertise and physical resources (both human and financial) available to MRAs in Africa.
- Consider mechanisms for sharing the outcomes of regulatory assessments.

Reference: *Assessment of Medicines Regulatory Systems in Sub-Saharan African Countries. An Overview of Findings from 26 Assessment Reports.* (2010) at http://apps.who.int/medicinedocs/en/m/abstract/Js17577en/

Quality of antimalarials in sub–Saharan Africa

World Health Organization — The report of a survey to evaluate the quality of selected antimalarials in six countries of sub-Saharan Africa (Cameroon, Ethiopia, Ghana, Kenya, Nigeria and the United Republic of Tanzania) has now been published. These countries are being supported by WHO to strengthen regulatory control over antimalarial products. The survey was organized independently of manufacturers of antimalarial medicines.

The information obtained through the survey has led to a better understanding of the quality profile of antimalarials available in sub-Saharan Africa. It has

contributed to evidence-based regulatory actions, the development of regulatory systems and their enforcement capacity, the advancement of post-marketing surveillance, and increased cooperation between national drug regulatory authorities.

Reference: World Health Organization. Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. WHO/EMP/QSM/2011.1 available at http://www.who.int/medicines

Good governance for medicines

World Health Organization — Two new documents have recently been published by the Good Governance for Medicines (GGM) Programme:

- The 2010 Progress Report for the Good Governance for Medicines Programme.
- A Compilation of best practices from GGM countries, published as a background document to the WHO World Health Report 2010.

The progress report focuses on achievements in countries. Interest in the GGM programme has been higher than anticipated and momentum for change is building in the implementing countries. A number of new country publications are also now available on the GGM web site.

The 2010 GGM Progress Report is available in English, French and Spanish at http://www.who.int/medicines/areas/policy/goodgovernance/2010progress_report/en/index.html (the Arabic version is on the way).

WHO's World Health Report for 2010, focusing on health systems financing, refers several times to corruption as a source of inefficiency. It also describes the work of the GGM programme.

A background paper to the Report, *A Compilation of best practices from GGM countries*, gives a brief description of activities in a number of GGM countries and focuses mainly on interventions that led to changes and improvements in the pharmaceutical sector. Background Paper No. 25 is available at http://www.who.int/healthsystems/topics/financing/healthreport/25GGM.pdf

Reference: World Health Organization, Good Governance for Medicines (GGM) Programme at http://www.who.int/medicines/ggm

EC/ACP/WHO Partnership on Pharmaceutical Policies

World Health Organization — The EC/ACP/WHO Partnership on Pharmaceutical Policies operating for March 2004 to September 2010, aimed to provide strategic and technical support to 77 African, Caribbean and Pacific Island (ACP) countries for development and implementation of essential medicines policies and good practices. The goal of the programme was to improve the health of the population of ACP countries by increasing the availability and affordability of essential medicines and ensuring acceptable standards of medicines quality, safety and use.

The key principles of the Partnership were to:

- Promote country ownership for planning, implementing and monitoring of the pharmaceutical sector.
- Strengthen the capacity of individual countries and promote a subregional and regional approach.

Key achievements of the Partnership were:

- Forty countries have developed a National Medicines Policy.

- A comprehensive set of pharmaceutical sector data has been collected in 68 countries. Another 20 countries have gone through a comprehensive pharmaceutical assessment using WHO survey tools on access, quality and rational use of medicines.
- Medicines prices have been evaluated and monitored in over 25 countries and the results were used to advocate for lower taxes on pharmaceuticals and higher public expenditure.
- Thirty countries have assessed their regulatory system. Over 45 countries received support to strengthen regulation through training, development of legislation (15 countries), setting up of pharmacovigilance systems (23 countries), and expanded efforts to combat counterfeit medicines (33 countries).
- Forty countries have updated their EMLs and STGs. Studies on medicine use were carried out in more than ten countries.
- Seven sub-regional groups have harmonized policies and regulations and/or set up schemes for pooled procurement of medicines.

Reference: WHO Medicines Programme Coordination. EC/ACP/WHO Partnership on Pharmaceutical Policies at http://www.who.int/medicines/areas/coordination/ecacpwho_partnership/en/index.html

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 65

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 (1–101) and Recommended (1–62) International Nonproprietary Names can be found in *Cumulative List No. 13, 2009* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 65

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 (1–101) et recommandées (1–62) dans la *Liste récapitulative No. 13, 2009* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 65

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 (1–101) y Recomendadas (1–62) se encuentran reunidas en *Cumulative List No. 13, 2009* (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*

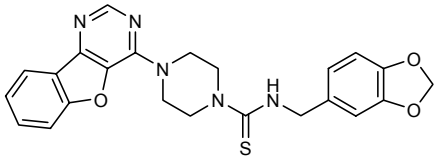
amuvatinibum

amuvatinib — *N*-[(1,3-benzodioxol-5-yl)methyl]-4-([1]benzofuro[3,2-*d*]pyrimidin-4-yl)piperazine-1-carbothioamide

amuvatinib — *N*-[(1,3-benzodioxol-5-yl)méthyl]-4-([1]benzofuro[3,2-*d*]pyrimidin-4-yl)pipérazine-1-carbothioamide

amuvatinib — *N*-[(1,3-benzodioxol-5-il)metil]-4-([1]benzofuro[3,2-*d*]pirimidin-4-il)piperazina-1-carbotioamida

$C_{23}H_{21}N_5O_3S$



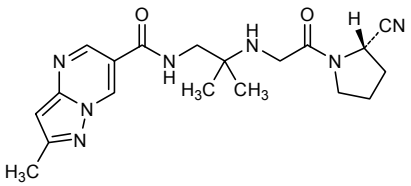
anagliptinum

anagliptin — *N*-[2-({2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoethyl}amino)-2-methylpropyl]-2-methylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide

anagliptine — *N*-[2-({2-[(2*S*)-2-cyanopyrrolidin-1-yl]-2-oxoéthyl}amino)-2-méthylpropyl]-2-méthylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide

anagliptina — *N*-[2-({2-[(2*S*)-2-cianopirrolidin-1-il]-2-oxoetil}amino)-2-metilpropil]-2-metilpirazolo[1,5-*a*]pirimidina-6-carboxamida

$C_{19}H_{25}N_7O_2$



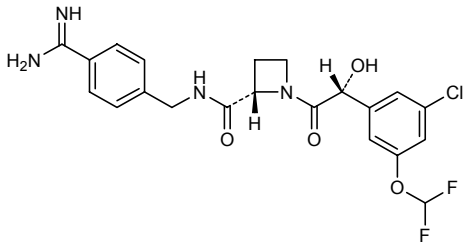
atecegatranum

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

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

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

$C_{21}H_{21}ClF_2N_4O_4$



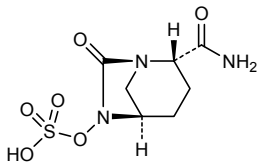
avibactamum

avibactam (1*R*,2*S*,5*R*)-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

avibactam (1*R*,2*S*,5*R*)-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

avibactam (1*R*,2*S*,5*R*)-7-oxo-6-sulfooxi-1,6-diazabiciclo[3.2.1]octano-2-carboxamida

$C_7H_{11}N_3O_6S$



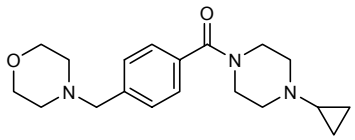
bavisantum

bavisant (4-cyclopropylpiperazin-1-yl}){4-[(morpholin-4-yl)methyl]phenyl}methanone

bavisant (4-cyclopropylpipérazin-1-yl){4-[(morpholin-4-yl)méthyl]phényl}méthanone

bavisant (4-ciclopropilpiperazin-1-il){4-[(morfolin-4-il)metil]fenil}metanona

$C_{19}H_{27}N_3O_2$



bedaquilinum

bedaquiline

(1*R*,2*S*)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol

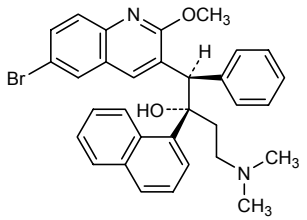
bédaquiline

(1*R*,2*S*)-1-(6-bromo-2-méthoxyquinoléin-3-yl)-4-(diméthylamino)-2-(naphtalén-1-yl)-1-phénylbutan-2-ol

bedaquilina

(1*R*,2*S*)-1-(6-bromo-2-metoxiquinolein-3-il)-4-(dimetilamino)-2-(naftalen-1-il)-1-fenilbutan-2-ol

$C_{32}H_{31}BrN_2O_2$



brentuximabum vedotinum #

brentuximab vedotin

immunoglobulin G1-kappa auristatin E conjugate, anti-[*Homo sapiens* TNFRSF8 (tumor necrosis factor receptor superfamily member 8, KI-1, CD30)], chimeric monoclonal antibody conjugated to auristatin E; gamma1 heavy chain (1-446) [*Mus musculus* VH (IGHV1-84*02 -(IGHD)-IGHJ3*01) [8.8.10] (1-117) -*Homo sapiens* IGHG1*01 CH3 K130>del (118-446)], (220-218')-disulfide (if not conjugated) with kappa light chain (1'-218') [*Mus musculus* V-KAPPA (IGKV3-4*01 -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; (226-226'')-disulfide dimer; conjugated, on an average of 3 to 5 cysteinyl, to monomethylauristatin E (MMAE), via a maleimidecaproyl-valyl-citrullinyl-*p*-aminobenzylcarbamate (mc-val-cit-PABC) linker
For the *vedotin* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

brentuximab védotine

immunoglobuline G1-kappa conjuguée à l'auristatine E, anti-[*Homo sapiens* TNFRSF8 (membre 8 de la superfamille des récepteurs du facteur de nécrose tumorale, KI-1, CD30)], anticorps monoclonal chimérique conjugué à l'auristatine E;
chaîne lourde gamma1 (1-446) [*Mus musculus* VH (IGHV1-84*02 -(IGHD)-IGHJ3*01) [8.8.10] (1-117) -*Homo sapiens* IGHG1*01 CH3 K130>del (118-446)], (220-218')-disulfure (si non conjugué) avec la chaîne légère kappa (1'-218') [*Mus musculus* V-KAPPA (IGKV3-4*01 -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; dimère (226-226'')-disulfure; conjugué, sur 3 à 5 cystéinyl en moyenne, au monométhylauristatine E (MMAE), via un linker maléimidécaproyl-valyl-citrullinyl-*p*-aminobenzylcarbamate (mc-val-cit-PABC)
Pour la partie *védotine*, veuillez vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

brentuximab vedotina

inmunoglobulina G1-kappa conjugada con auristatina E, anti-[*Homo sapiens* TNFRSF8 (miembro 8 de la superfamilia de los receptores del factor de necrosis tumoral, KI-1, CD30)], anticuerpo monoclonal quimérico conjugado con auristatina E;
cadena pesada gamma1 (1-446) [*Mus musculus* VH (IGHV1-84*02 -(IGHD)-IGHJ3*01) [8.8.10] (1-117) -*Homo sapiens* IGHG1*01 CH3 K130>del (118-446)], (220-218')-disulfuro (si non está conjugado) con la cadena ligera kappa (1'-218') [*Mus musculus* V-KAPPA (IGKV3-4*01 -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; dimero (226-226'')-disulfuro; conjugado, en 3 a 5 residuos cisteinil en término medio, con monometilauristatina E (MMAE), mediante un conector maleimidecaproil-valil-citrulinil-*p*-aminobenzilcarbamato (mc-val-cit-PABC)
Por la parte *vedotina*, por favor, vaya al documento *"INN for pharmaceutical substances: Names for radicals, groups and others"**.

Heavy chain / Chaîne lourde / Cadena pesada

```
QIQLQQSGPE VVKPGASVKI SCKASGYTFT DYYITWVKQK PGQGLEWIGW  50
IYPGSGNTKY NEKFKGKATL TVDTSSSTAF MQLSSLTSED TAVYFCANYG 100
NYWFAYWGQG TQVTVSAAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG     446
```

Light chain / Chaîne légère / Cadena ligera

```
DIVLTQSPAS LAVSLGQRAT ISCKASQSVD FDGDSYMNWY QQKPGQPPKV  50
LIYAASNLES GIPARFSGSG SGTDFTLNIH PVEEEDAATY YCQQSNEDPW 100
TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV 150
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV 200
THQGLSSPVT KSFNRGEC                                    218
```

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

```
Intra-H  22-96    144-200    261-321    367-425
         22''-96''  144''-200''  261''-321''  367''-425''
Intra-L  23'-92'    138'-198'
         23'''-92'''  138'''-198'''
Inter-H-L *  220-218'   220''-218'''
Inter-H-H *  226-226''  229-229''
```

*Two or three of the inter-chain disulfide bridges are not present, the antibody being conjugated to an average of 3 to 5 drug linkers each via a thioether bond.
* Deux ou trois des ponts disulfure ne sont pas présents, l'anticorps étant conjugué à une moyenne de 3 à 5 linker-principe actif chacun via une liaison thioéther.
* Faltan dos o tres puentes disulfuro inter-catenarios por estar el anticuerpo conjugado, con sendos enlaces tioéter, a una media de 3 a 5 conectores de principio activo

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

cenicrivirocum

cenicriviroc

8-{4-[2-(butoxy)ethoxy]phenyl}-1-(2-methylpropyl)-*N*-(4-{(*S*)-[(1-propyl-1*H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide

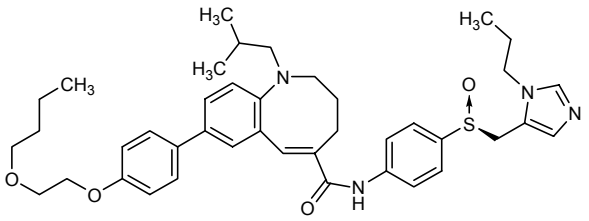
cénicriviroc

8-{4-[2-(butoxy)éthoxy]phényl}-1-(2-méthylpropyl)-*N*-(4-{(*S*)-[(1-propyl-1*H*-imidazol-5-yl)méthyl]sulfinyl}phényl)-1,2,3,4-tétrahydro-1-benzazocine-5-carboxamide

cenicriviroc

8-{4-[2-(butoxi)etoxi]fenil}-1-(2-metilpropil)-*N*-(4-{(*S*)-[(1-propil-1*H*-imidazol-5-il)metil]sulfinil}fenil)-1,2,3,4-tetrahidro-1-benzazocina-5-carboxamida

$C_{41}H_{52}N_4O_4S$



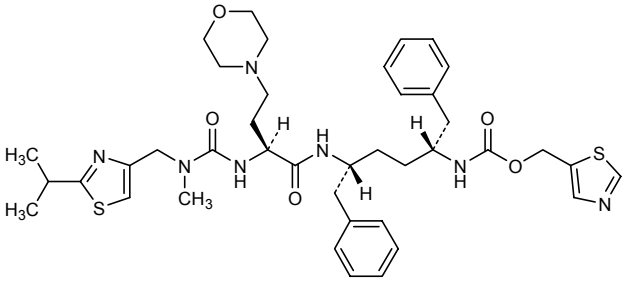
cobicistatum

cobicistat — (1,3-thiazol-5-yl)methyl (5*S*,8*R*,11*R*)-8,11-dibenzyl-2-methyl-5-[2-(morpholin-4-yl)ethyl]-1-[2-(propan-2-yl)-1,3-thiazol-4-yl]-3,6-dioxo-2,4,7,12-tetraazatridecan-13-oate

cobicistat — (5*S*,8*R*,11*R*)-8,11-dibenzyl-2-méthyl-5-[2-(morpholin-4-yl)éthyl]-1-[2-(propan-2-yl)-1,3-thiazol-4-yl]-3,6-dioxo-2,4,7,12-tétraazatridécan-13-oate de (1,3-thiazol-5-yl)méthyle

cobicistat — (5*S*,8*R*,11*R*)-8,11-dibencil-2-metil-5-[2-(morfolin-4-il)etil]-1-[2-(propan-2-il)-1,3-tiazol-4-il]-3,6-dioxo-2,4,7,12-tetraazatridecan-13-oato de (1,3-tiazol-5-il)metilo

$C_{40}H_{53}N_7O_5S_2$



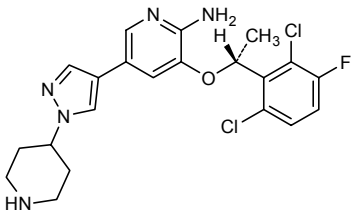
crizotinibum

crizotinib — 3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine

crizotinib — 3-[(1*R*)-1-(2,6-dichloro-3-fluorophényl)éthoxy]-5-[1-(pipéridin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine

crizotinib — 3-[(1*R*)-1-(2,6-dicloro-3-fluorofenil)etoxi]-5-[1-(piperidin-4-il)-1*H*-pirazol-4-il]piridin-2-amina

$C_{21}H_{22}Cl_2FN_5O$



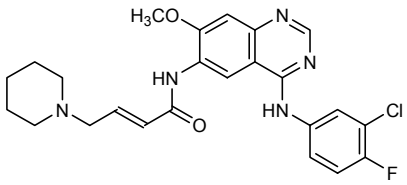
dacomitinibum

dacomitinib — (2*E*)-*N*-{4-[(3-chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}-4-(piperidin-1-yl)but-2-enamide

dacomitinib — (2*E*)-*N*-{4-[(3-chloro-4-fluorophényl)amino]-7-méthoxyquinazolin-6-yl}-4-(pipéridin-1-yl)but-2-énamide

dacomitinib — (2*E*)-*N*-{4-[(3-cloro-4-fluorofenil)amino]-7-metoxiquinazolin-6-il}-4-(piperidin-1-il)but-2-enamida

$C_{24}H_{25}ClFN_5O_2$



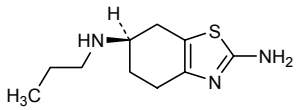
dexpramipexolum

dexpramipexole — (6*R*)-N^6-propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine

dexpramipexole — (6*R*)-N^6-propyl-4,5,6,7-tétrahydro-1,3-benzothiazole-2,6-diamine

dexpramipexol — (6*R*)-N^6-propil-4,5,6,7-tetrahidro-1,3-benzotiazol-2,6-diamina

$C_{10}H_{17}N_3S$



drozitumabum #

drozitumab — immunoglobulin G1-lambda, anti-[*Homo sapiens* TNFRSF10B (tumor necrosis factor receptor superfamily member 10B, DR5, death receptor 5, TRAIL-R2, TNF-related apoptosis-inducing ligand receptor 2, TR-2, CD262)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-451) [*Homo sapiens* VH (IGHV3-20*01 (91.80%) -(IGHD)-IGHJ2*01 R120>K, L123>T) [8.8.14] (1-121) -IGHG1*03 CH1 R120>K (122-451)], (224-212')-disulfide with lambda light chain (1'-213') [*Homo sapiens* V-LAMBDA (IGLV3-19*01 (96.80%) -IGLJ3*01) [6.3.11] (1'-107') -IGLC3*03 (108'-213')]; (230-230'':233-233'')-bisdisulfide dimer

drozitumab — immunoglobuline G1-lambda, anti-[*Homo sapiens* TNFRSF10B (membre 10B de la superfamille des récepteurs du facteur de nécrose tumorale, DR5, death receptor 5, TRAIL-R2, récepteur 2 du ligand inducteur d'une apoptose liée au TNF, TR-2, CD262)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-451) [*Homo sapiens* VH (IGHV3-20*01 (91.80%) -(IGHD)-IGHJ2*01 R120>K, L123>T) [8.8.14] (1-121) -IGHG1*03 CH1 R120>K (122-451)], (224-212')-disulfure avec la chaîne légère lambda (1'-213') [*Homo sapiens* V-LAMBDA (IGLV3-19*01 (96.80%) -IGLJ3*01) [6.3.11] (1'-107') -IGLC3*03 (108'-213')]; dimère (230-230'':233-233'')-bisdisulfure

drozitumab

inmunoglobulina G1-lambda, anti-[*Homo sapiens* TNFRSF10B (miembro 10B de la superfamilia de receptores del factor de necrosis tumoral, DR5, receptor de muerte 5, TRAIL-R2, receptor 2 del ligando inductor de la apoptosis de la familiaTNF, TR-2, CD262)], anticuerpo monoclonal de *Homo sapiens* ;
cadena pesada gamma1 (1-451) [*Homo sapiens* VH (IGHV3-20*01 (91.80%) -(IGHD)-IGHJ2*01 R120>K, L123>T) [8.8.14] (1-121) -IGHG1*03 CH1 R120>K (122-451)], (224-212')-disulfuro con la cadena ligera lambda (1'-213') [*Homo sapiens* V-LAMBDA (IGLV3-19*01 (96.80%) -IGLJ3*01) [6.3.11] (1'-107') -IGLC3*03 (108'-213')]; dímero (230-230":233-233")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVQSGGG VERPGGSLRL SCAASGFTFD DYAMSWVRQA PGKGLEWVSG  50
INWQGGSTGY ADSVKGRVTI SRDNAKNSLY LQMNSLRAED TAVYYCAKIL 100
GAGRGWYFDY WGKGTTVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV 150
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ 200
TYICNVNHKP SNTKVDKKVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK 250
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY 300
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP 350
QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP 400
VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG 450
K                                                       451
```

Light chain / Chaîne légère / Cadena ligera

```
SELTQDPAVS VALGQTVRIT CSGDSLRSYY ASWYQQKPGQ APVLVIYGAN  50
NRPSGIPDRF SGSSSGNTAS LTITGAQAED EADYYCNSAD SSGNHVVFGG 100
GTKLTVLGQP KAAPSVTLFP PSSEELQANK ATLVCLISDF YPGAVTVAWK 150
ADSSPVKAGV ETTTPSKQSN NKYAASSYLS LTPEQWKSHK SYSCQVTHEG 200
STVEKTVAPT ECS                                          213
```

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

```
Intra-H   22-96     148-204     265-325     371-429
          22"-96"   148"-204"   265"-325"   371"-429"
Intra-L   21'-86'     135'-194'
          21'"-86'"   135'"-194'"
Inter-H-L   224-212'    224"-212'"
Inter-H-H   230-230"    233-233"
```

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

301, 301"

dulaglutidum #

dulaglutide

glucagon-like peptide-1-immunoglobulin G4 fusion protein, [2-glycyl,16-L-glutamyl,30-glycyl][human glucagon-like peptide 1-(7-37)-peptide] {(8-A>G,22-G>E,36-R>G)-GLP-1(7-37)} fusion protein with tris(tetraglycyl-L-seryl)-L-alanine (linker) fusion protein with des-276-lysine-[57-L-proline,63-L-alanine,64-L-alanine]human immunoglobulin G4 Fc region {(10-S>P)-H-(4-F>A,5-L>A)-CH2-(107-K>-)-CH3 of IGHG4*01}, dimer (55-55':58-58')-bisdisulfide

dulaglutide

protéine de fusion entre le peptide 1 semblable au glucagon et l'immunoglobuline G4, [2-glycyl,16-L-glutamyl,30-glycyl][peptide 1 semblable au glucagon humain-(7-37)-peptide] {(8-A>G,22-G>E,36-R>G)GLP-1(7-37)} protéine de fusion avec le tris(tétraglycyl-L-séryl)-L-alanine (lien) protéine de fusion avec la dès-276-lysine-[57-L-proline,63-L-alanine,64-L-alanine]région Fc de l'immunoglobuline G4 humaine {(10-S>P)H-(4-F>A,5-L>A)CH2-(107-K>-)CH3 du IGHG4*01}, (55-55':58-58')-bisdisulfure du dimère

dulaglutida

proteína de fusión entre el péptido similar al glucagón 1 y la inmunoglobulina G4, [2-glicil,16-L-glutamil,30-glicil][péptido similar al glucagón humano 1-(7-37)-péptido] {(8-A>G,22-G>E,36-R>G)GLP-1(7-37)} proteína de fusión con el tris(tetraglicil-L-seril)-L-alanina (vínculo) proteína de fusión con la des-276-lisina-[57-L-prolina, 63-L-alanina,64-L-alanina]región Fc de la inmunoglobulina G4 humana {(10-S>P)H-(4-F>A,5-L>A)CH2-(107-K>-)CH3 del IGHG4*01}, (55-55':58-58')-bisdisulfuro del dímero

$C_{2646}H_{4044}N_{704}O_{836}S_{18}$

Monomer / Monomère / Monomero

```
HGEGTFTSDV  SSYLEEQAAK  EFIAWLVKGG  GGGGGSGGGG  SGGGGSAESK  50
YGPPCPPCPA  PEAAGGPSVF  LFPPKPKDTL  MISRTPEVTC  VVVDVSQEDP  100
EVQFNWYVDG  VEVHNAKTKP  REEQFNSTYR  VVSVLTVLHQ  DWLNGKEYKC  150
KVSNKGLPSS  IEKTISKAKG  QPREPQVYTL  PPSQEEMTKN  QVSLTCLVKG  200
FYPSDIAVEW  ESNGQPENNY  KTTPPVLDSD  GSFFLYSRLT  VDKSRWQEGN  250
VFSCSVMHEA  LHNHYTQKSL  SLSLG                            275
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
55-55' 58-58' 90-150 90'-150' 196-254 196'-254'

eliglustatum

eliglustat

N-{(1*R*,2*R*)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl}octanamide

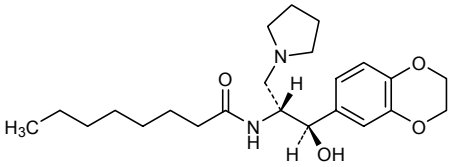
éliglustat

N-{(1*R*,2*R*)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl}octanamide

eliglustat

N-{(1*R*,2*R*)-1-(2,3-dihidro-1,4-benzodioxin-6-il)-1-hidroxi-3-(pirrolidin-1-il)propan-2-il}octanamida

$C_{23}H_{36}N_2O_4$



elpamotidum

elpamotide

L-arginyl-L-phenylalanyl-L-valyl-L-prolyl-L-α-aspartylglycyl-L-asparaginyl-L-arginyl-L-isoleucine
human soluble (Vascular Endothelial Growth Factor Receptor) VEGFR2-(169-177)-peptide

elpamotide

L-arginyl-L-phénylalanyl-L-valyl-L-prolyl-L-α-aspartylglycyl-L-asparaginyl-L-arginyl-L-isoleucine
(Récepteur du Facteur de Croissance de l'Endothélium Vasculaire) RFCEV2 soluble humain-(169-177)-peptide

elpamotida

L-arginil-L-fenilalanil-L-valil-L-prolil-L-α-aspartilglicil-L-asparaginil-L-arginil-L-isoleucina
(receptor del factor de crecimiento endotelial vascular) RFCEV2 soluble humano-(169-177)-péptido

$C_{47}H_{76}N_{16}O_{13}$

H–Arg—Phe—Val—Pro—Asp—Gly—Asn—Arg—Ile–OH
9

ensituximabum #

ensituximab — immunoglobulin G1-kappa, anti-[*Homo sapiens* MUC5AC (mucin 5AC, mucin 5 subtypes A and C tracheobronchial/gastric)], chimeric monoclonal antibody;
gamma1 heavy chain (1-443) [*Mus musculus* VH (IGHV2-3*01 - (IGHD)-IGHJ4*01) [8.7.7] (1-113) -*Homo sapiens* IGHG1*01 CH1 L85.3>P, CH3 T81>M (114-443)], (216-213')-disulfide with kappa light chain (1'-213') [*Mus musculus* V-KAPPA (IGKV4-70*01 - IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; (222-222":225-225")-bisdisulfide dimer

ensituximab — immunoglobuline G1-kappa, anti-[*Homo sapiens* MUC5AC (mucine 5AC, mucine 5 de sous-types A et C trachéo-bronchique/gastrique)], anticorps monoclonal chimérique;
chaîne lourde gamma1 (1-443) [*Mus musculus* VH (IGHV2-3*01 - (IGHD)-IGHJ4*01) [8.7.7] (1-113) -*Homo sapiens* IGHG1*01 CH1 L85.3>P, CH3 T81>M (114-443)], (216-213')-disulfure avec la chaîne légère kappa (1'-213') [*Mus musculus* V-KAPPA (IGKV4-70*01 -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dimère (222-222":225-225")-bisdisulfure

ensituximab — inmunoglobulina G1-kappa, anti-[*Homo sapiens* MUC5AC (mucina 5AC, mucina 5 de subtipos A y C traqueo-bronquial/gástrico], anticuerpo monoclonal quimérico;
cadena pesada gamma1 (1-443) [*Mus musculus* VH (IGHV2-3*01 - (IGHD)-IGHJ4*01) [8.7.7] (1-113) -*Homo sapiens* IGHG1*01 CH1 L85.3>P, CH3 T81>M (114-443)], (216-213')-disulfuro con la cadena ligera kappa (1'-213') [*Mus musculus* V-KAPPA (IGKV4-70*01 - IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dímero (222-222":225-225")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLKESGPD LVAPSQSLSI TCTVSGFSLS KFGVNWVRQP PGKGLEWLGV  50
IWGDGSTSYN SGLISRLSIS KENSKSQVFL KLNSLQADDT ATYYCVKPGG 100
DYWGHGTSVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV 150
TVSWNSGALT SGVHTFPAVL QSSGPYSLSS VVTVPSSSLG TQTYICNVNH 200
KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS 250
RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS 300
VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS 350
RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTM PPVLDSDGSF 400
FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK        443
```

Light chain / Chaîne légère / Cadena ligera

```
QVVLTQSPVI MSASPGEKVT MTCSASSSIS YMYWYQQKPG TSPKRWIYDT  50
SKLASGVPAR FSGSGSGTSY SLTISNMEAG DAATYYCHQR DSYPWTFGGG 100
TNLEIKRTVA 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 22-95 140-196 257-317 363-421
22"-95" 140"-196" 257"-317" 363"-421"
Intra-L 23'-87' 133'-193'
23'"-87'" 133'"-193'"
Inter-H-L 216-213' 216"-213'"
Inter-H-H 222-222" 225-225"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
293, 293"

eteplirsenum
eteplirsen

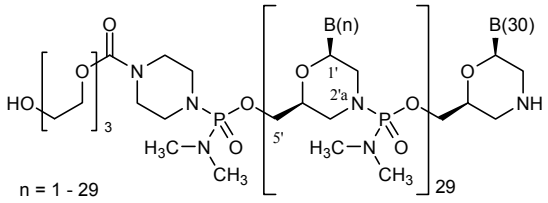
all-P-ambo-5'-{*P*-[4-({2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}carbonyl)piperazin-1-yl]-*N,N*-dimethylphosphonamidate}-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,3'-dideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,3'-dideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,3'-dideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,3'-dideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,3'-dideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,3'-dideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,3'-dideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-dimethylamino-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-2',3'-dideoxy-2',3'-imino-2',3'-secoguanosine

étéplirsen	*tout-P-ambo*-5'-{*P*-[4-({2-[2-(2-hydroxyéthoxy)éthoxy]éthoxy}carbonyl)pipérazin-1-yl]-*N,N*-diméthylphosphonamidate}-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécocytidylyl-(2'a→5')-*P*,3'-didésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécothymidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécocytidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécocytidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadénylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadénylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécocytidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadénylyl-(2'a→5')-*P*,3'-didésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécothymidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécocytidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadénylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadénylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoguanylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoguanylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadénylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadénylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoguanylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadénylyl-(2'a→5')-*P*,3'-didésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécothymidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoguanylyl-(2'a→5')-*P*,2',3'-tridéoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoguanylyl-(2'a→5')-*P*,2',3'-tridéoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécocytidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadénylyl-(2'a→5')-*P*,3'-didésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécothymidylyl-(2'a→5')-*P*,3'-didésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécothymidylyl-(2'a→5')-*P*,3'-didésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécothymidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécocytidylyl-(2'a→5')-*P*,3'-didésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécothymidylyl-(2'a→5')-*P*,2',3'-tridésoxy-*P*-diméthylamino-2',3'-imino-2',3'-sécoadenylyl-(2'a→5')-2',3'-didésoxy-2',3'-imino-2',3'-sécoguanosine

eteplirsén

todo-P-ambo-5'-{*P*-[4-({2-[2-(2-hidroxietoxi)etoxi]etoxi}carbonl)piperazin-1-il]-*N,N*-dimetilfosfonamidato}-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secocitidilil-(2'a→5')-*P*,3'-didesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secotimidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secocitidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secocitidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secocitidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenilil-(2'a→5')-*P*,3'-didesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secotimidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secocitidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoguanilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoguanilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoguanilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenilil-(2'a→5')-*P*,3'-didesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secotimidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secocitidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenill-(2'a→5')-*P*,3'-didesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secotimidilil-(2'a→5')-*P*,3'-didesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secotimidilil-(2'a→5')-*P*,3'-didesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secotimidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secocitidilil-(2'a→5')-*P*,3'-didesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secotimidilil-(2'a→5')-*P*,2',3'-tridesoxi-*P*-dimetilamino-2',3'-imino-2',3'-secoadenilil-(2'a→5')-2',3'-didesoxi-2',3'-imino-2',3'-secoguanosina

$C_{364}H_{569}N_{177}O_{122}P_{30}$



B(1-30):
C-T-C-C-A-A-C-A-T-C-A-A-G-G-A-A-G-A-T-G-G-C-A-T-T-T-C-T-A-G

fasitibanti chloridum

fasitibant chloride

(4*S*)-4-amino-5-{4-[4-(2,4-dichloro-3-{[(2,4-dimethylquinolin-8-yl)oxy]methyl}benzenesulfonamido)oxane-4-carbonyl]piperazin-1-yl}-*N,N,N*-trimethyl-5-oxopentan-1-aminium chloride

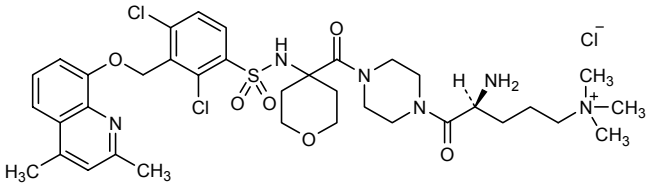
chlorure de fasitibant

chlorure de (4*S*)-4-amino-5-{4-[4-(2,4-dichloro-3-{[(2,4-diméthylquinoléin-8-yl)oxy]méthyl}benzènesulfonamido)oxane-4-carbonyl]pipérazin-1-yl}-*N,N,N*-triméthyl-5-oxopentan-1-aminium

cloruro de fasitibant

cloruro de (4*S*)-4-amino-5-{4-[4-(2,4-dicloro-3-{[(2,4-dimetilquinolein-8-il)oxi]metil}bencenosulfonamido)oxano-4-carbonil]piperazin-1-il}-*N,N,N*-trimetil-5-oxopentan-1-aminio

$C_{36}H_{49}Cl_3N_6O_6S$



fedovapagonum

fedovapagon

(2*S*)-N^2,N^2-dimethyl-N^1-{[2-methyl-4-(2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carbonyl)phenyl]methyl}pyrrolidine-1,2-dicarboxamide

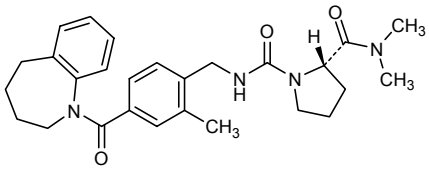
fédovapagon

(2*S*)-N^2,N^2-diméthyl-N^1-{[2-méthyl-4-(2,3,4,5-tétrahydro-1*H*-1-benzazépine-1-carbonyl)phényl]méthyl}pyrrolidine-1,2-dicarboxamide

fedovapagón

(2*S*)-N^2,N^2-dimetil-N^1-{[2-metil-4-(2,3,4,5-tetrahidro-1*H*-1-benzazepina-1-carbonil)fenil]metil}pirrolidina-1,2-dicarboxamida

$C_{27}H_{34}N_4O_3$



florbetapirum (^{18}F)

florbetapir (^{18}F)

4-[(1*E*)-2-(6-{2-[2-(2-[^{18}F]fluoroethoxy)ethoxy]ethoxy}pyridine-3-yl)ethen-1-yl]-*N*-methylaniline

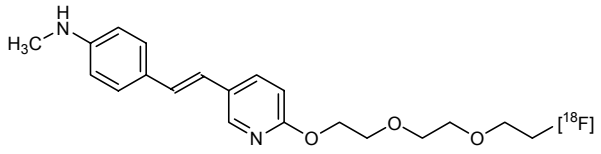
florbétapir (^{18}F)

4-[(1*E*)-2-(6-{2-[2-(2-[^{18}F]fluoroéthoxy)éthoxy]éthoxy}pyridin-3-yl)éthén-1-yl]-*N*-méthylaniline

florbetapir (^{18}F)

4-[(1*E*)-2-(6-{2-[2-(2-[^{18}F]fluoroetoxi)etoxi]etoxi}piridin-3-il)eten-1-il]-*N*-metilanilina

$C_{20}H_{25}{}^{18}FN_2O_3$



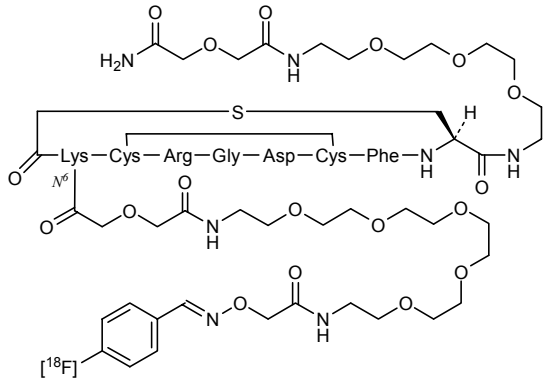
fluciclatidum (^{18}F)

fluciclatide (^{18}F) — *N*^{6}-[(28*E*)-29-(4-[^{18}F]fluorophenyl)-5,25-dioxo-3,9,12,15,18,21,27-heptaoxa-6,24,28-triazanonacos-28-enoyl]-*N*^{2}-(sulfanylacetyl)-L-lysyl-L-cysteinyl-L-arginylglycyl-L-α-aspartyl-L-cysteinyl-L-phenylalanyl-*N*-(17-amino-13,17-dioxo-3,6,9,15-tetraoxa-12-azaheptadecyl)-L-cysteinamide cyclic (2→6)-disulfide cyclic (1→8)-thioether

fluciclatide (^{18}F) — (2→6)-disulfure cyclique et (1→8)-thioéther cyclique du *N*^{6}-[(28*E*)-29-(4-[^{18}F]fluorophényl)-5,25-dioxo-3,9,12,15,18,21,27-heptaoxa-6,24,28-triazanonacos-28-énoyl]-*N*^{2}-(2-sulfanylacétyl)-L-lysyl-L-cystéinyl-L-arginylglycyl-L-α-aspartyl-L-cystéinyl-L-phénylalanyl-1-*N*-(17-amino-13,17-dioxo-3,6,9,15-tétraoxa-12-azaheptadécyl)-L-cystéinamide

fluciclatida (^{18}F) — (2→6)-disulfuro cíclico y (1→8)-tioéter cíclico del *N*^{6}-[(28*E*)-29-(4-[^{18}F]fluorofenil)-5,25-dioxo-3,9,12,15,18,21,27-heptaoxa-6,24,28-triazanonacos-28-enoil]-*N*^{2}-(2-sulfanilacetil)-L-lisil-L-cisteinil-L-arginilglicil-L-α-aspartil-L-cisteinil-L-fenilalanil-1-*N*-(17-amino-13,17-dioxo-3,6,9,15-tetraoxa-12-azaheptadecil)-L-cisteinamida

$C_{75}H_{115}{}^{18}FN_{18}O_{27}S_3$



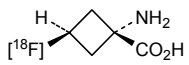
fluciclovinum (^{18}F)

fluciclovine (^{18}F) — (1*r*,3*r*)-1-amino-3[^{18}F]fluorocyclobutane-1-carboxylic acid

fluciclovine (^{18}F) — acide *trans*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylique

fluciclovina (^{18}F) — ácido (1*r*,3*r*)-1-amino-3-[^{18}F]fluorociclobutano-1-carboxílico

$C_5H_8{}^{18}FNO_2$



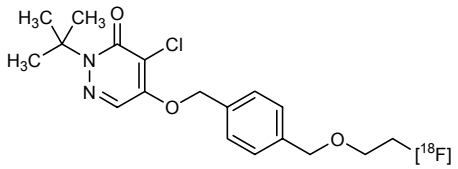
flurpiridazum (^{18}F)

flurpiridaz (^{18}F) — 2-*tert*-butyl-4-chloro-5-({4-[(2-[^{18}F]fluoroethoxy)methyl]phenyl}methoxy)pyridazin-3(2*H*)-one

flurpiridaz (^{18}F) — 2-*tert*-butyl-4-chloro-5-({4-[(2-[^{18}F]fluoroéthoxy)méthyl]phényl}méthoxy)pyridazin-3(2*H*)-one

flurpiridaz (^{18}F) — 2-*terc*-butil-4-cloro-5-({4-[(2-[^{18}F]fluoroetoxi)metil]fenil}metoxi)piridazin-3(2*H*)-ona

$C_{18}H_{22}Cl^{18}FN_2O_3$



foralumabum #

foralumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* CD3E (CD3 epsilon)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-448) [*Homo sapiens* VH (IGHV3-33*01 (95.90%) -(IGHD)-IGHJ2*01) [8.8.11] (1-118) -IGHG1*03 CH2 L1.3(235)>A, L1.2(236)>E (119-448)], (221-215')-disulfide with kappa light chain (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ4*01) [6.3.10] (1'-108') -IGKC*01 (109'-215')]; (227-227'':230-230'')-bisdisulfide dimer

foralumab — immunoglobuline G1 -kappa, anti-[*Homo sapiens* CD3E (CD3 epsilon)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-448) [*Homo sapiens* (IGHV3-33*01 (95.90%) -(IGHD)-IGHJ2*01) [8.8.11] (1-118) -IGHG1*03 CH2 L1.3(235)>A, L1.2(236)>E (119-448)], (221-215')-disulfure avec la chaîne légère kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ4*01) [6.3.10] (1'-108') -IGKC*01 (109'-215')]; dimère (227-227'':230-230'')-bisdisulfure

foralumab — inmunoglobulina G1-kappa, anti-[*Homo sapiens* CD3E (CD3 epsilon)], anticuerpo monoclonal de *Homo sapiens;* cadena pesada gamma1 (1-448) [*Homo sapiens* (IGHV3-33*01 (95.90%) -(IGHD)-IGHJ2*01) [8.8.11] (1-118) -IGHG1*03 CH2 L1.3(235)>A, L1.2(236)>E (119-448)], (221-215')-disulfuro con la cadena ligera kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ4*01) [6.3.10] (1'-108') -IGKC*01 (109'-215')]; dímero (227-227'':230-230'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVESGGG VVQPGRSLRL SCAASGFKFS GYGMHWVRQA PGKGLEWVAV  50
IWYDGSKKYY VDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARQM 100
GYWHFDLWGR GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI 200
CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPEAEGGPS 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
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Light chain / Chaîne légère / Cadena ligera

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EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD  50
ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPLTFG 100
GGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK 150
VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ 200
GLSSPVTKSF NRGEC                                       215
```

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

Intra-H 22-96 145-201 262-322 368-426
22''-96'' 145''-201'' 262''-322'' 368''-426''
Intra-L 23'-88' 135'-195'
23'''-88''' 135'''-195'''
Inter-H-L 221-215' 221''-215'''
Inter-H-H 227-227'' 230-230''

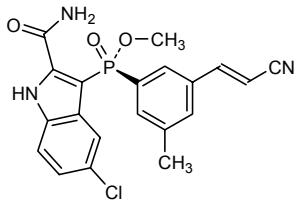
N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
298, 298''

fosdevirinum
fosdevirine — methyl (*R*)-(2-carbamoyl-5-chloro-1*H*-indol-3-yl){3-[(1*E*)-2-cyanoethen-1-yl]-5-methylphenyl}phosphinate

fosdévirine — (*R*)-(2-carbamoyl-5-chloro-1*H*-indol-3-yl){3-[(1*E*)-2-cyanoéthén-1-yl]-5-méthylphényl}phosphinate de méthyle

fosdevirina — (*R*)-(2-carbamoil-5-cloro-1*H*-indol-3-il){3-[(1*E*)-2-cianoeten-1-il]-5-metilfenil}fosfinato de metilo

$C_{20}H_{17}ClN_3O_3P$



ganitumabum #
ganitumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* IGF1R (insulin-like growth factor 1 receptor, IGF1-R, IGF-1R, CD221)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-449) [*Homo sapiens* VH (IGHV4-4*02 (100.00%) -(IGHD)-IGHJ3*02) [9.7.12] (1-119) -IGHG1*01 (120-449)], (222-219')-disulfide with kappa light chain (1'-219') [*Homo sapiens* V-KAPPA (IGKV2-28*01 (95.00%) -IGKJ1*01) [11.3.9] (1'-112') -IGKC*01 (113'-219')]; (228-228'':231-231'')-bisdisulfide dimer

ganitumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* IGF1R (récepteur du facteur de croissance 1 analogue à l'insuline, IGF1-R, IGF-1R, CD221)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-449) [*Homo sapiens* VH (IGHV4-4*02 (100.00%) -(IGHD)-IGHJ3*02) [9.7.12] (1-119) -IGHG1*01 (120-449)], (222-219')-disulfure avec la chaîne légère kappa (1'-219') [*Homo sapiens* V-KAPPA (IGKV2-28*01 (95.00%) -IGKJ1*01) [11.3.9] (1'-112') -IGKC*01 (113'-219')]; dimère (228-228":231-231")-bisdisulfure

ganitumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* IGF1R (receptor del factor de crecimiento 1 análogo a la insulina, IGF1-R, IGF-1R, CD221)], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma1 (1-449) [*Homo sapiens* VH (IGHV4-4*02 (100.00%) -(IGHD)-IGHJ3*02) [9.7.12] (1-119) -IGHG1*01 (120-449)], (222-219')-disulfuro con la cadena ligera kappa (1'-219') [*Homo sapiens* V-KAPPA (IGKV2-28*01 (95.00%) -IGKJ1*01) [11.3.9] (1'-112') -IGKC*01 (113'-219')]; dímero (228-228":231-231")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQESGPG LVKPSGTLSL TCAVSGGSIS SSNWWSWVRQ PPGKGLEWIG  50
EIYHSGSTNY NPSLKSRVTI SVDKSKNQFS LKLSSVTAAD TAVYYCARWT 100
GRTDAFDIWG QGTMVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DVVMTQSPLS LPVTPGEPAS ISCRSSQSLL HSNGYNYLDW YLQKPGQSPQ  50
LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCMQGTHWP 100
LTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200
VTHQGLSSPV TKSFNRGEC                                   219
```

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

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

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

gataparsenum

gataparsen

all-P-ambo-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thioucytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyluridine

gataparsen

tout-*P*-*ambo*-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioguanylyl-(3'→5')-2'-déoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioadénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioadénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyluridine

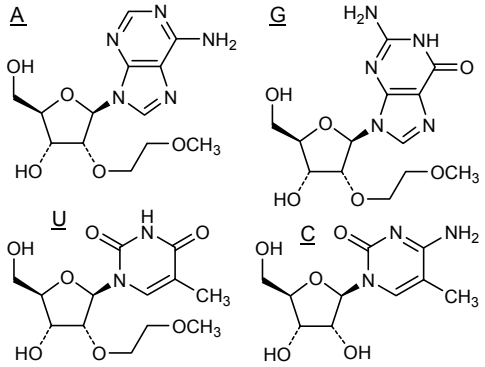
gataparsén

todo-*P*-*ambo*-2'-*O*-(2-metoxietil)-5-metil-*P*-tiouridilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioguanilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metil-*P*-tiouridilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioguanilil-(3'→5')-2'-desoxi-5-metil-*P*-tiocitidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-*P*-tiotimidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-5-metil-*P*-tiocitidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioadenilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioadenilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metil-*P*-tiouridilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metiluridina

$C_{204}H_{278}N_{59}O_{111}P_{17}S_{17}$

(3'→5')d(*P*-thio)(r<u>U</u>-r<u>G</u>-r<u>U</u>-r<u>G</u>-<u>C</u>-T-A-T-T-<u>C</u>-T-G-T-G-r<u>A</u>-r<u>A</u>-r<u>U</u>-r<u>U</u>)

Modified nucleosides / Nucléosides modifiés / Nucleosidos modificados:



gemigliptinum

gemigliptin

1-{(2*S*)-2-amino-4-[2,4-bis(trifluoromethyl)-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-4-oxobutyl}-5,5-difluoropiperidin-2-one

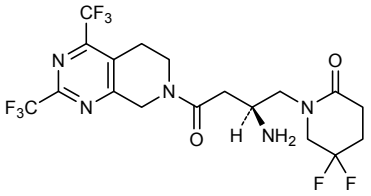
gémigliptine

1-{(2*S*)-2-amino-4-[2,4-bis(trifluorométhyl)-5,8-dihydropyrido[3,4-*d*]pyrimidin-7(6*H*)-yl]-4-oxobutyl}-5,5-difluoropipéridin-2-one

gemigliptina

1-{(2*S*)-2-amino-4-[2,4-bis(trifluorometil)-5,8-dihidropirido[3,4-*d*]pirimidin-7(6*H*)-il]-4-oxobutil}-5,5-difluoropiperidin-2-ona

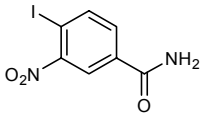
$C_{18}H_{19}F_8N_5O_2$



iniparibum

iniparib	4-iodo-3-nitrobenzamide
iniparib	4-iodo-3-nitrobenzamide
iniparib	4-iodo-3-nitrobenzamida

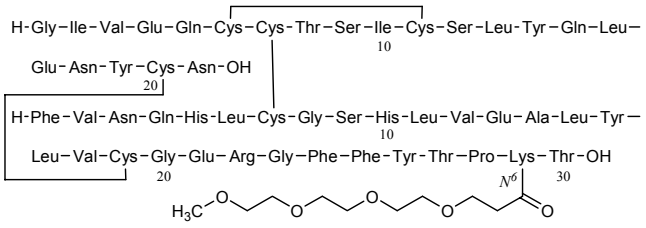
$C_7H_5IN_2O_3$



insulinum tregopilum

insulin tregopil	$N^{6,29B}$-(4,7,10,13-tetraoxatetradecanoyl)human insulin
insuline trégopil	$N^{6,29B}$-(4,7,10,13-tétraoxatétradécanoyl)insuline humaine
insulina tregopilo	$N^{6,29B}$-(4,7,10,13-tetraoxatetradecanoil)insulina humana

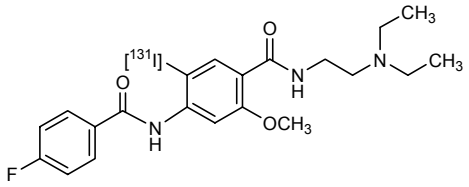
$C_{267}H_{401}N_{65}O_{82}S_6$



ioflubenzamidum (^{131}I)

ioflubenzamide (^{131}I)	*N*-[2-(diethylamino)ethyl]-4-(4-fluorobenzamido)-5-[^{131}I]iodo-2-methoxybenzamide
ioflubenzamide (^{131}I)	*N*-[2-(diéthylamino)éthyl]-4-(4-fluorobenzamido)-5-[^{131}I]iodo-2-méthoxybenzamide
ioflubenzamida (^{131}I)	*N*-[2-(dietilamino)etil]-4-(4-fluorobenzamido)-5-[^{131}I]iodo-2-metoxibenzamida

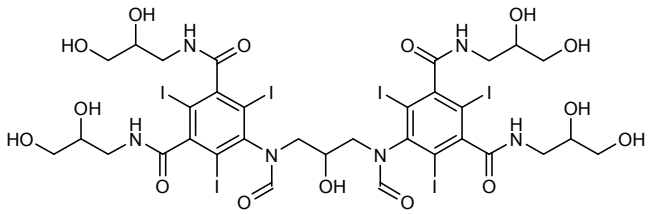
$C_{21}H_{25}F^{131}IN_3O_3$



ioforminolum

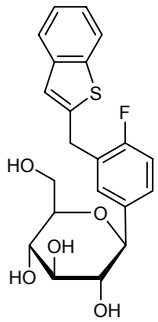
ioforminol	*all-ambo*-5,5'-[2-hydroxypropane-1,3-diylbis(formylazanediyl)]bis[*N,N'*-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide]
ioforminol	*tout-ambo*-5,5'-[2-hydroxypropane-1,3-diylbis(formylazanediyl)]bis[*N,N'*-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzène-1,3-dicarboxamide]
ioforminol	*todo-ambo*-5,5'-[2-hidroxipropano-1,3-diilbis(formilazanodiil)]bis[*N,N'*-bis(2,3-dihidroxipropil)-2,4,6-triiodobenceno-1,3-dicarboxamida]

$C_{33}H_{40}I_6N_6O_{15}$



ipragliflozinum

ipragliflozin	(1*S*)-1,5-anhydro-1-*C*-{3-[(1-benzothiophen-2-yl)methyl]-4-fluorophenyl}-D-glucitol
ipragliflozine	(1*S*)-1,5-anhydro-1-*C*-{3-[(1-benzothiophén-2-yl)méthyl]-4-fluorophényl}-D-glucitol
ipragliflozina	(1*S*)-1,5-anhidro-1-*C*-{3-[(1-benzotiofen-2-il)metil]-4-fluorofenil}-D-glucitol $C_{21}H_{21}FO_5S$



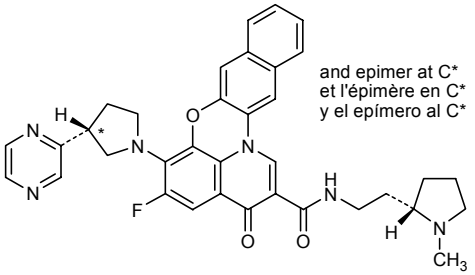
itarnafloxinum

itarnafloxin — 5-fluoro-*N*-{2-[(2*S*)-1-methylpyrrolidin-2-yl]ethyl}-3-oxo-6-[(3*RS*)-3-(pyrazin-2-yl)pyrrolidin-1-yl]-3*H*-benzo[*b*]pyrido[3,2,1-*kl*]phenoxazine-2-carboxamide

itarnafloxine — 5-fluoro-*N*-{2-[(2*S*)-1-méthylpyrrolidin-2-yl]éthyl}]-3-oxo-6-[3-(pyrazin-2-yl)pyrrolidin-1-yl]-3*H*-benzo[*b*]pyrido[3,2,1-*kl*]phénoxazine-2-carboxamide

itarnafloxina — 5-fluoro-*N*-{2-[(2*S*)-1-metilpirrolidin-2-il]etil}-3-oxo-6-[(3*RS*)-3-(pirazin-2-il)pirrolidin-1-il]-3*H*-benzo[*b*]pirido[3,2,1-*kl*]fenoxazina-2-carboxamida

$C_{35}H_{33}FN_6O_3$



itolizumabum #

itolizumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* CD6 (Tp120, T12)], humanized monoclonal antibody;
gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV3-21*08 (83.70%) -(IGHD)-IGHJ5*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-17*01 (76.80%) -IGKJ2*01 F118>L, Q120>S) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (228-228":231-231")-bisdisulfide dimer

itolizumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* CD6 (Tp120, T12)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-449) [VH humanisé (*Homo sapiens* IGHV3-21*08 (83.70%) -(IGHD)-IGHJ5*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-17*01 (76.80%) -IGKJ2*01 F118>L, Q120>S) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (228-228":231-231")-bisdisulfure

itolizumab — inmunoglobulina G1-kappa, anti-[*Homo sapiens* CD6 (Tp120, T12)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-449) [VH humanizado (*Homo sapiens* IGHV3-21*08 (83.70%) -(IGHD)-IGHJ5*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-17*01 (76.80%) -IGKJ2*01 F118>L, Q120>S) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (228-228":231-231")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVKPGGSLKL SCAASGFKFS RYAMSWVRQA PGKRLEWVAT  50
ISSGGSYIYY PDSVKGRFTI SRDNVKNTLY LQMSSLRSED TAMYYCARRD 100
YDLDYFDSWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCKASRDIR SYLTWYQQKP GKAPKTLIYY  50
ATSLADGVPS RFSGSGSGQD YSLTISSLES DDTATYYCLQ HGESPFTLGS 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

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

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

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

lorvotuzumabum mertansinum #

lorvotuzumab mertansine	immunoglobulin G1-kappa, anti-[*Homo sapiens* NCAM1 (neural cell adhesion molecule 1, CD56, NCAM-1)], humanized monoclonal antibody conjugated to maytansinoid DM1; gamma1 heavy chain (1-448) [humanized VH (*Homo sapiens* IGHV3-30*03 (91.80%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*01 (119-448)], (221-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2-30*02 (92.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (227-227":230-230")-bisdisulfide dimer; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM1 via a thiopentanoate linker For the *mertansine* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"**
lorvotuzumab mertansine	immunoglobuline G1-kappa, anti-[*Homo sapiens* NCAM1 (molécule d'adhésion 1 de cellule neurale, CD56, NCAM-1)], anticorps monoclonal humanisé conjugué au maytansinoïde DM1; chaîne lourde gamma1 (1-448) [VH humanisé (*Homo sapiens* IGHV3-30*03 (91.80%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*01 (119-448)], (221-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV2-30*02 (92.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimère (227-227":230-230")-bisdisulfure; conjugué, sur 3 à 4 lysyl en moyenne, au maytansinoïde DM1 via un linker thiopentanoate Pour la partie *mertansine*, veuillez vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

lorvotuzumab mertansina

inmunoglobulina G1-kappa, anti-[*Homo sapiens* NCAM1 (molécula de adhesión 1 de celula neural, CD56, NCAM-1)], anticuerpo monoclonal humanizado conjugado con maitansinoide DM1; cadena pesada gamma1 (1-448) [VH humanizado (*Homo sapiens* IGHV3-30*03 (91.80%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*01 (119-448)], (221-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizado (*Homo sapiens* IGKV2-30*02 (92.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimero (227-227":230-230")-bisdisulfuro; conjugado, en 3 a 4 residuos lisil por término medio, con maitansinoide DM1 con un conector tiopentanoato
Por la parte *mertansina*, por favor, vaya al documento *"INN for pharmaceutical substances: Names for radicals, groups & others"*.*

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SFGMHWVRQA PGKGLEWVAY  50
ISSGSFTIYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARMR 100
KGYAMDYWGQ 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
TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK   448
```

Light chain / Chaîne légère / Cadena ligera

```
DVVMTQSPLS LPVTLGQPAS ISCRSSQIII HSDGNTYLEW FQQRPGQSPR  50
RLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCFQGSHVP 100
HTFGQGTKVE 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    145-201    262-322    368-426
         22"-96"  145"-201"  262"-322"  368"-426"
Intra-L  23'-93'   139'-199'
         23'"-93'" 139'"-199'"
Inter-H-L  221-219'  221"-219'"
Inter-H-H  227-227"  230-230"
```

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

maraciclatidum

maraciclatide

N^6-(5-{[5-{[3-(hydroxyimino)-2-methylbutan-2-yl]amino}-3-(2-{[3-(hydroxyimino)-2-methylbutan-2-yl]amino}ethyl)pentyl]amino}-5-oxopentanoyl)-N^2-(2-sulfanylacetyl)-L-lysyl-L-cysteinyl-L-arginylglycyl-L-α-aspartyl-L-cysteinyl-L-phenylalanyl-*N*-(17-amino-13,17-dioxo-3,6,9,15-tetraoxa-12-azaheptadecyl)-L-cysteinamide cyclic (2→6)-disulfide cyclic (1→8)-thioether

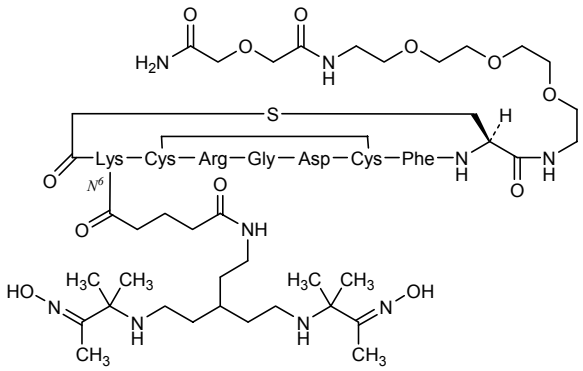
maraciclatide

(2→6)-disulfure cyclique et (1→8)-thioéther cyclique du N^6-(5-{[5-{[3-(hydroxyimino)-2-méthylbutan-2-yl]amino}-3-(2-{[3-(hydroxyimino)-2-méthylbutan-2-yl]amino}éthyl)pentyl]amino}-5-oxopentanoyl)-N^2-(2-sulfanylacétyl)-L-lysyl-L-cystéinyl-L-arginylglycyl-L-α-aspartyl-L-cystéinyl-L-phénylalanyl-1-*N*-(17-amino-13,17-dioxo-3,6,9,15-tétraoxa-12-azaheptadécyl)-L-cystéinamide

maraciclatida

(2→6)-disulfuro cíclico y (1→8)-tioéter cíclico del N^6-(5-{[5-{[3-(hidroxiimino)-2-metilbutan-2-il]amino}-3-(2-{[2-(hidroxiimino)-2-metilbutan-2-il]amino}etil)pentil]amino}-5-oxopentanoil)-N^2-(2-sulfanilacetil)-L-lisil-L-cisteinil-L-ar3inilglicil-L-α-aspartil-L-cisteinil-L-fenilalanil-1-*N*-(17-amino-13,17-dioxo-3,6,9,15-tetraoxa-12-azaheptadecil)-L-cisteinamida

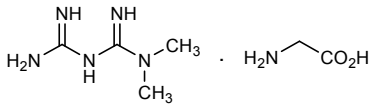
$C_{72}H_{120}N_{20}O_{21}S_3$



metformini glycinas

metformin glycinate	*N*,*N*-dimethyl-1,2,3-triimidodicarbonic diamide glycinate (1:1)
glycinate de metformine	glycinate du diamide *N*,*N*-diméthyl-1,2,3-triimidodicarbonique (1:1)
glicinato de metformina	glicinato de la diamida *N*,*N*-dimetil-1,2,3-triimidodicarbóníco (1:1)

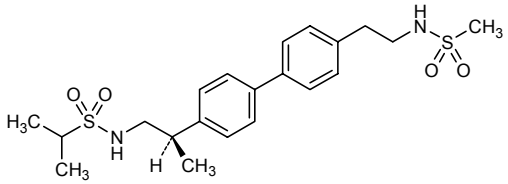
$C_4H_{11}N_5 \cdot C_2H_5NO_2$



mibampatorum

mibampator	*N*-[(2*R*)-2-{4'-[2-(methanesulfonamido)ethyl][1,1'-biphenyl]-4-yl}propyl]propane-2-sulfonamide
mibampator	*N*-[(2*R*)-2-{4'-[2-(méthanesulfonamido)éthyl][1,1'-biphényl]-4-yl}propyl]propane-2-sulfonamide
mibampator	*N*-[(2*R*)-2-{4'-[2-(metanosulfonamido)etil][1,1'-bifenil]-4-il}propil]propano-2-sulfonamida

$C_{21}H_{30}N_2O_4S_2$



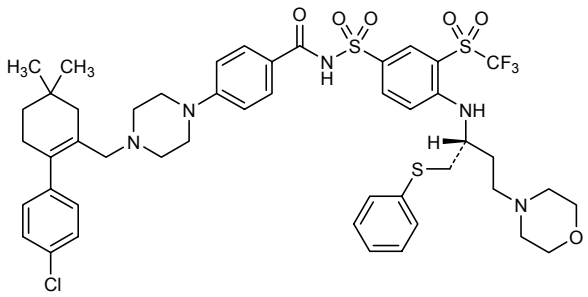
navitoclaxum

navitoclax — 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-(4-{[(2*R*)-4-(morpholin-4-yl)-1-(phenylsulfanyl)butan-2-yl]amino}-3-(trifluoromethanesulfonyl)benzenesulfonyl]benzamide

navitoclax — 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-(4-{[(2*R*)-4-(morpholin-4-yl)-1-(phenylsulfanyl)butan-2-yl]amino}-3-(trifluoromethanesulfonyl)benzenesulfonyl]benzamide

navitoclax — 4-(4-{[2-(4- clorofenil)-5,5- dimetilciclohex -1-en-1-il]metil}piperazin-1-il)-*N*-(4-{[(2*R*)-1-(fenilsulfanil)-4-(morfolin-4-il)-butan-2-il]amino}-3-(trifluorometanosulfonil)bencenosulfonil]benzamida

$C_{47}H_{55}ClF_3N_5O_6S_3$



nonacogum beta pegolum #

nonacog beta pegol — pegylated human blood coagulation factor IX; human coagulation factor IX (EC 3.4.21.22, Christmas factor, plasma thromboplastin component), en average of one sialyl unit of the N-linked carbohydrates are 5-*N*-[*N*-({2,3-bis[ω-methoxypoly(oxyethane-1,2-diyl)]propoxy}carbonyl)glycyl]-5-*N*-deacetyl

nonacog bêta pégol — facteur IX humain de coagulation sanguine, pégylé; facteur IX humain de coagulation (EC 3.4.21.22, facteur Christmas, facteur antihémophile B) dont quelques unités sialyl, en moyenne une par molécule d'enzyme, de la partie N-glycosyl sont 5-*N*-[*N*-({2,3-bis[ω-méthoxypoly(oxyéthylène)]propoxy}carbonyl)glycyl]-5-*N*-désacétyl

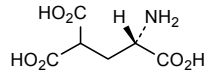
nonacog beta pegol — factor IX humano de coagulación sanguínea, pegilado; factor IX humano de coagulación (EC 3.4.21.22, factor Christmas, factor antihemofilico B) algunas de cuyas unidades sialil, una por molécula de enzima, por término medio, de la fracción N-glicosil son 5-*N*-[*N*-({2,3-bis[ω-metoxipoli(oxietilen)]propoxi}carbonil)glicil]-5-*N*-desacetil

```
YNSGKLEEFV QGNLERECME EKCSFEEARE VFENTERTTE FWKQYVDGDQ 50
CESNPCLNGG SCKDDINSYE CWCPFGFEGK NCELDVTCNI KNGRCEQFCK 100
NSADNKVVCS CTEGYRLAEN QKSCEPAVPF PCGRVSVSQT SKLTRAEAVF 150
PDVDYVNSTE AETILDNITQ STQSFNDFTR VVGGEDAKPG QFPWQVVLNG 200
KVDAFCGGSI VNEKWIVTAA HCVETGVKIT VVAGEHNIEE TEHTEQKRNV 250
IRIIPHHNYN AAINKYNHDI ALLELDEPLV LNSYVTPICI ADKEYTNIFL 300
KFGSGYVSGW GRVFHKGRSA LVLQYLRVPL VDRATCLRST KFTIYNNMFC 350
AGFHEGGRDS CQGDSGGPHV TEVEGTSFLT GIISWGEECA MKGKYGIYTK 400
VSRYVNWIKE KTKLT                                    415
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
18-23 51-62 56-71 73-82 88-99 95-109
111-124 132-289 206-222 336-350 361-389

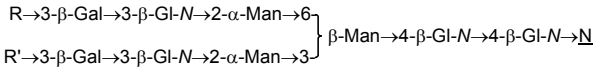
Modified residues / Résidus modifiés / Residuos modificados

E
7-8-15-17-20-21-26-27-30-33-36-40
4-carboxyGlu



Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)

Asn-157 Asn-167



R = α-Sia, R' = α-Sia or PEG-α-Sia or R' = α-Sia, R = α-Sia or PEG-α-Sia

Gal = D-galactopyranosyl
Gl-*N* = 2-(acetylamino)-2-deoxy-D-glucopyranosyl
Man = D-mannopyranosyl
PEG- = *O*-[α-methylpoly(oxyethylene) hydrogen phosphate]
Sia = 5-*N*-acetyl-α-neuramin-2-yl

Other positions of post-translational modifications:
partial-hydroxylation of Asp64; O-linked glycosylation on positions Ser53 and Ser61, partially O-linked glycosylation on positions Thr159 and Thr169

Autres positions de modifications post-traductionelles:
hydroxylation partielle de Asp64; glycosylation O-liée sur les positions Sér53 et Sér61, glycosylation partielle O-liée sur les positions Thr159 et Thr169

Otras posiciones de modificaciones post-traducción
hidroxilación parcial de Asp64; glicosilación O-ligada en las posiciones Ser53 y Ser61, glicosilación parcial O-ligada en las posiciones Thr159 y Thr169

obinutuzumabum #

obinutuzumab

immunoglobulin G1, anti-[*Homo sapiens* CD20 (membrane-spanning 4-domains subfamily A member 1, MS4A1, B lymphocyte surface antigen B1, Leu-16, Bp35)], humanized monoclonal antibody, GA101;
gamma1 heavy chain (1-448) [humanized VH (*Homo sapiens* FR/*Mus musculus* CDR, *Homo sapiens* IGHJ4*01) [8.8.12] (1-119) - *Homo sapiens* IGHG1*01 (120-448)], (222-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* FR/*Mus musculus* CDR, *Homo sapiens* IGKJ4*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (228-228":231-231")-bisdisulfide dimer
immunomodulator

obinutuzumab

immunoglobuline G1, anti-[*Homo sapiens* CD20 (membre 1 de la sous-famille A à 4 domaines transmembranaires, MS4A1, antigène de surface B1 des lymphocytes B, Leu-16, Bp35)], anticorps monoclonal humanisé, GA101;
chaîne lourde gamma1 (1-448) [VH humanisé (*Homo sapiens* FR/*Mus musculus* CDR, *Homo sapiens* IGHJ4*01) [8.8.12] (1-119) - *Homo sapiens* IGHG1*01 (120-448)], (222-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* FR/*Mus musculus* CDR, *Homo sapiens* IGKJ4*01) [11.3.9] (1'-112') - *Homo sapiens* IGKC*01 (113'-219')]; dimère (228-228":231-231")-bisdisulfure
immunomodulateur

obinutuzumab

inmunoglobulina G1, anti-[*Homo sapiens* CD20 (miembro 1 de la sub-familia A de 4 dominios transmembranarios, MS4A1, antígeno de superficie B1 de los linfocitos B, Leu-16, Bp35)], anticuerpo monoclonal humanizado, GA101;
cadena pesada gamma1 (1-448) [VH humanizada (*Homo sapiens* FR/*Mus musculus* CDR, *Homo sapiens* IGHJ4*01) [8.8.12] (1-119) - *Homo sapiens* IGHG1*01 (120-448)], (222-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizada (*Homo sapiens* FR/*Mus musculus* CDR, *Homo sapiens* IGKJ4*01) [11.3.9] (1'-112') - *Homo sapiens* IGKC*01 (113'-219')]; dímero (228-228'':231-231'')-bisdisulfuro
inmunomodulador

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGSSVKV SCKASGYAFS YSWINWVRQA PGQGLEWMGR  50
IFPGDGDTDY NGKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARNV 100
FDGYWLVYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQTPLS LPVTPGEPAS ISCRSSKSLL HSNGITYLYW YLQKPGQSPQ  50'
LLIYQMSNLV SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCAQNLELP 100'
YTFGGGTKVE 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

```
22-96    22''-96''    23'-93'    23'''-93'''  139'-199'  139'''-199'''  146-202  146''-202''
219'-222 219'''-222'' 228-228''  231-231''    263-323    263''-323''    369-427  369''-427''
```

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación

```
Ser-53  Ser-61  Asn-157  Thr-159  Asn-167  Thr-169
```

olaratumabum #

olaratumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* PDGFRA (platelet-derived growth factor receptor alpha subunit, CD140a, PDGFR2)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-457) [*Homo sapiens* VH (IGHV4-39*01 (90.90%) -(IGHD)-IGHJ5*01 G119>D) [10.7.19] (1-127) -IGHG1*03 (128-457)], (230-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; (236-236'':239-239'')-bisdisulfide dimer

olaratumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* PDGFRA (sous-unité alpha du récepteur du facteur de croissance dérivé des plaquettes, CD140a, PDGFR2)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-457) [*Homo sapiens* VH (IGHV4-39*01 (90.90%) -(IGHD)-IGHJ5*01 G119>D) [10.7.19] (1-127) -IGHG1*03 (128-457)], (230-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (236-236'':239-239'')-bisdisulfure

olaratumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* PDGFRA (subunidad alfa del receptor del factor de crecimiento derivado de las plaquetas, CD140a, PDGFR2)], *Homo sapiens* anticuerpo monoclonal;
cadena pesada gamma1 (1-457) [*Homo sapiens* VH (IGHV4-39*01 (90.90%) -(IGHD)-IGHJ5*01 G119>D) [10.7.19] (1-127) -IGHG1*03 (128-457)], (230-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-11*01 (100.00%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimero (236-236":239-239")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QLQLQESGPG LVKPSETLSL TCTVSGGSIN SSSYYWGWLR QSPGKGLEWI  50
GSFFYTGSTY YNPSLRSRLT ISVDTSKNQF SLMLSSVTAA DTAVYYCARQ 100
STYYYGSGNY YGWFDRWDQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA 150
ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS 200
SSLGTQTYIC NVNHKPSNTK VDKRVEPKSC DKTHTCPPCP APELLGGPSV 250
FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK 300
PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK 350
GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN 400
YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS 450
LSLSPGK                                               457
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD  50
ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPAFGQ 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  22-97     154-210    271-331    377-435
         22"-97"   154"-210"  271"-331"  377"-435"
Intra-L  23'-88'   134'-194'
         23"'-88"' 134"'-194"'
Inter-H-L  230-214'  230"-214"'
Inter-H-H  236-236"  239-239"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
30, 30", 307, 307"

olokizumabum #

olokizumab

immunoglobulin G4-kappa, anti-[*Homo sapiens* IL6 (interleukin 6; IL-6)], humanized monoclonal antibody;
gamma4 heavy chain (1-447) [humanized VH (*Homo sapiens* IGHV3-72*01 (84.00%) -(IGHD)-IGHJ4*01) [8.10.11] (1-120) -*Homo sapiens* IGHG4*01 hinge S10(228)>P (121-447)], (134-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-33*01 (84.20%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (226-226":229-229")-bisdisulfide dimer

olokizumab

immunoglobuline G4-kappa, anti-[*Homo sapiens Homo sapiens* IL6 (interleukine 6; IL-6)], anticorps monoclonal humanisé;
chaîne lourde gamma4 (1-447) [VH humanisé (*Homo sapiens* IGHV3-72*01 (84.00%) -(IGHD)-IGHJ4*01) [8.10.11] (1-120) -*Homo sapiens* IGHG4*01 charnière S10(228)>P (121-447)], (134-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-33*01 (84.20%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (226-226":229-229")-bisdisulfure

olokizumab

inmunoglobulina G4-kappa, anti-[*Homo sapiens Homo sapiens* IL6 (interleukina 6; IL-6)], anticuerpo monoclonal humanizado; cadena pesada gamma4 (1-447) [VH humanizado (*Homo sapiens* IGHV3-72*01 (84.00%) -(IGHD)-IGHJ4*01) [8.10.11] (1-120) -*Homo sapiens* IGHG4*01 bisagra S10(228)>P (121-447)], (134-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-33*01 (84.20%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (226-226":229-229")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFNFN DYFMNWVRQA PGKGLEWVAQ  50
MRNKNYQYGT YYAESLEGRF TISRDDSKNS LYLQMNSLKT EDTAVYYCAR 100
ESYYGFTSYW GQGTLVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK 150
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT 200
YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT 350
LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK    447
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCQASQDIG ISLSWYQQKP GKAPKLLIYN  50
ANNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCLQ HNSAPYTFGQ 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 22-98 147-203 261-321 367-425
22"-98" 147"-203" 261"-321" 367"-425"
Intra-L 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L 134-214' 134"-214'"
Inter-H-H 226-226" 229-229"

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

opicaponum

opicapone

2,5-dichloro-3-[5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl]-4,6-dimethylpyridine *N*-oxide

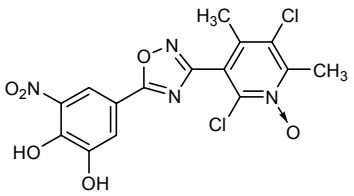
opicapone

N-oxyde de 2,5-dichloro-3-[5-(3,4-dihydroxy-5-nitrophényl)-1,2,4-oxadiazol-3-yl]-4,6-diméthylpyridine

opicapona

N-óxido de 2,5-dicloro-3-[5-(3,4-dihidroxi-5-nitrofenil)-1,2,4-oxadiazol-3-il]-4,6-dimetilpiridina

$C_{15}H_{10}Cl_2N_4O_6$



orantinibum

orantinib

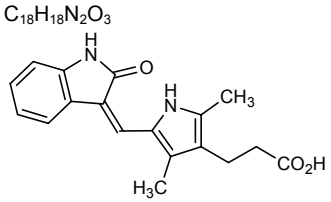
3-(2,4-dimethyl-5-{[(3*Z*)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]methyl}-1*H*-pyrrol-3-yl)propanoic acid

orantinib

acide 3-(2,4-diméthyl-5-{[(3*Z*)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidène]méhyl}-1*H*-pyrrol-3-yl)propanoïque

orantinib

ácido 3-(2,4-dimetil-5-{[(3*Z*)-2-oxo-1,2-dihidro-3*H*-indol-3-ilideno]metil}-1*H*-pirrol-3-il)propanoico



oxelumabum #

oxelumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* TNFSF4 (Tumor necrosis factor ligand superfamily member 4, OX40 ligand, OX-40L, TAX transcriptionally-activated glycoprotein 1, TXGP1, gp34, CD252], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-449) [*Homo sapiens* VH (IGHV3-23*01 (94.90%) -(IGHD)-IGHJ4*01 T122>A) [8.8.13] (1-120) -IGHG1*01 K130>del (121-449)], (223-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1D-16*01 (100.00%) -IGKJ2*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; (229-229":232-232")-bisdisulfide dimer

oxélumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* TNFSF4 (membre 4 de la superfamille des ligands du facteur de nécrose tumorale, ligand de OX40, OX40L, glycoprotéine 1 activée transcriptionellement par TAX, TXGP1, CD252], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-449) [*Homo sapiens* VH (IGHV3-23*01 (94.90%) -(IGHD)-IGHJ4*01 T122>A) [8.8.13] (1-120) -IGHG1*01 K130>del (121-449)], (223-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1D-16*01 (100.00%) -IGKJ2*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (229-229":232-232")-bisdisulfure

oxelumab — inmunoglobulina G1-kappa, anti-[*Homo sapiens* TNFSF4 (miembro 4 de la superfamilia de ligandos del factor de necrosis tumoral, ligando de OX40, OX40L, glicoproteína 1 activada por transcripción por TAX, TXGP1, CD252], anticuerpo monoclonal de *Homo sapiens*; cadena pesada gamma1 (1-449) [*Homo sapiens* VH (IGHV3-23*01 (94.90%) -(IGHD)-IGHJ4*01 T122>A) [8.8.13] (1-120) -IGHG1*01 K130>del (121-449)], (223-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1D-16*01 (100.00%) -IGKJ2*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimero (229-229":232-232")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada
```
EVQLLESGGG LVQPGGSLRL SCAASGFTFN SYAMSWVRQA PGKGLEWVSI  50
ISGSGGFTYY ADSVKGRFTI SRDNSRTTLY LQMNSLRAED TAVYYCAKDR 100
LVAPGTFDYW GQGALVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK 150
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT 200
YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP 250
KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN 300
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ 350
VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 400
LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPG  449
```

Light chain / Chaîne légère / Cadena ligera
```
DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA  50
ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNSYPYTFGQ 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 22-96 147-203 264-324 370-428
22"-96" 147"-203" 264"-324" 370"-428"
Intra-L 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L 223-214' 223"-214'"
Inter-H-H 229-229" 232-232"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
300, 300"

pegdinetanibum #

pegdinetanib

94 residues protein derived from human fibronectin 10th type III domain, pegylated:
glycyl[1438-L-arginine(D>R),1439-L-histidine(A>H),1441-L-histidine(A>H),1442-L-phenylalanine(V>F),1443-L-proline(T>P),1444-L-threonine(V>T),1467-L-leucine(G>L),1468-L-glutamine(S>Q),1469-L-proline(K>P),1470-L-proline(S>P),1492-L-aspartic acid(G>D),1493-glycine(R>G),1494-L-arginine(G>R),1495-L-asparagine(D>N),1496-glycine(S>G),1497-L-arginine(P>R),1498-L-leucine(A>L),1499-L-leucine(S>L),1501-L-isoleucine(K>I),1515-*S*-[(3*RS*)-1-(1-{[α-methylpoly(oxyethylene)]carbamoyl}-3-[({[α-methylpoly(oxyethylene)]carbamoyl}oxy)methyl]-8,13-dioxo-1,4-dioxa-9,12-diazapentadecan-15-yl)-2,5-dioxopyrrolidin-3-yl]-L-cysteine(S>C)]human fibronectin-(1424-1516)-peptide

pegdinétanib

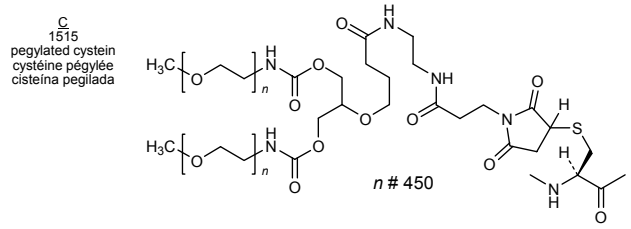
protéine de 94 résidus derivée du 10ème domaine de type III de la fibronectine humaine pégylée :
glycyl[1438-L-arginine(D>R),1439-L-histidine(A>H),1441-L-histidine(A>H),1442-L-phénylalanine(V>F),1443-L-proline(T>P),1444-L-thréonine(V>T),1467-L-leucine(G>L),1468-L-glutamine(S>Q),1469-L-proline(K>P),1470-L-proline(S>P),1492-acide L-aspartique(G>D),1493-glycine(R>G),1494-L-arginine(G>R),1495-L-asparagine(D>N),1496-glycine(S>G),1497-L-arginine(P>R),1498-L-leucine(A>L),1499-L-leucine(S>L),1501-L-isoleucine(K>I),1515-*S*-[(3*RS*)-1-(1-{[α-méthylpoly(oxyéthylène)]carbamoyl}-3-[({[α-méthylpoly(oxyéthylène)]carbamoyl}oxy)méthyl]-8,13-dioxo-1,4-dioxa-9,12-diazapentadécan-15-yl)-2,5-dioxopyrrolidin-3-yl]-L-cystéine(S>C)]fibronectine humaine-(1424-1516)-peptide

pegdinetanib

proteína de 94 residuos derivada del décimo dominio de tipo III de la fibronectina humana pegilada :
glicil[1438-L-arginina(D>R),1439-L-histidina(A>H),1441-L-histidina(A>H),1442-L-fenilalanina(V>F),1443-L-prolina(T>P),1444-L-treonina(V>T),1467-L-leucina(G>L),1468-L-glutamina(S>Q),1469-L-prolina(K>P),1470-L-prolina(S>P),1492-ácido L-aspártico(G>D),1493-glicina(R>G),1494-L-arginina(G>R),1495-L-asparagina(D>N),1496-glicina(S>G),1497-L-arginina(P>R),1498-L-leucina(A>L),1499-L-leucina(S>L),1501-L-isoleucina(K>I),1515-*S*-[(3*RS*)-1-(1-{[α-metilpoli(oxietileno)]carbamoil}-3-[({[α-metilpoli(oxietileno)]carbamoil}oxi)metil]-8,13-dioxo-1,4-dioxa-9,12-diazapentadecan-15-il)-2,5-dioxopirrolidin-3-il]-L-cisteína(S>C)]fibronectina humana-(1424-1516)-péptido

```
                                    GEVVAATP TSLLISWRHP HFPTRYYRIT 1450
YGETGGNSPV QEFTVPLQPP TATISGLKPG VDYTITVYAV TDGRNGRLLS 1500
IPISINYRTE IDKPCQ                                       1516
```

Modified residue / Résidu modifié / Residuo modificado



peginesatidum #

peginesatide

pegylated erythropoietin receptor agonist, $N^{6.21}$,$N^{6.21'}$-{[(N^2,N^6-bis{[ω-methoxypoly(oxyethylene)]carbonyl}-L-lysyl-β-alanyl)imino]bis(methylenecarbonyl)}bis[*N*-acetylglycylglycyl-L-leucyl-L-tyrosyl-L-alanyl-L-cysteinyl-L-histidyl-L-methionylglycyl-L-prolyl-L-isoleucyl-L-threonyl-3-(naphthalen-1-yl)-L-alanyl-L-valyl-L-cysteinyl-L-glutaminyl-L-prolyl-L-leucyl-L-arginyl-*N*-methylglycyl-L-lysinamide] (6→15:6'→15')-bisdisulfure cyclic

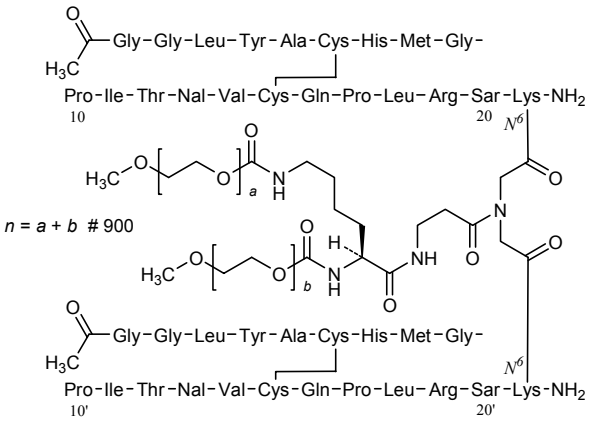
péginésatide

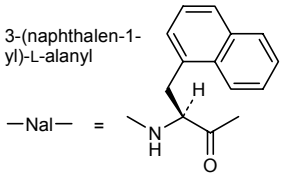
agoniste du récepteur de l'érythropoïétine, pégylé (6→15:6'→15')-bisdisulfure cyclique du $N^{6.21}$,$N^{6.21'}$-{[(N^2,N^6-bis{[ω-méthoxypoly(oxyéthylène)]carbonyl}-L-lysyl-β-alanyl)imino]bis(méthylènecarbonyl)}bis[acétylglycylglycyl-L-leucyl-L-tyrosyl-L-alanyl-L-cystéinyl-L-histidyl-L-méthionylglycyl-L-prolyl-L-isoleucyl-L-thréonyl-3-(naphtalén-1-yl)-L-alanyl-L-valyl-L-cystéinyl-L-glutaminyl-L-prolyl-L-leucyl-L-arginyl-*N*-méthylglycyl-L-lysinamide]

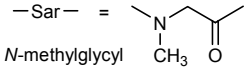
peginesatida

agonista del receptor de la eritropoyetina, pegilado (6→15:6'→15')-bisdisulfuro cíclico del $N^{6.21}$,$N^{6.21'}$-{[(N^2,N^6-bis{[ω-metoxipoli(oxietileno)]carbonil}-L-lisil-β-alanil)imino]bis(metilenocarbonil)}bis{S^6,S^{15}-ciclo[*N*-acetilglicilglicil-L-leucil-L-tirosil-L-alanil-L-cisteinil-L-histidil-L-metionilglicil-L-prolil-L-isoleucil-L-treonil-3-(naftalen-1-il)-L-alanil-L-valil-L-cisteinil-L-glutaminil-L-prolil-L-leucil-L-arginil-*N*-metilglicil-L-lisinamida]

$C_{231}H_{350}N_{62}O_{58}S_6[C_2H_4O]_n$







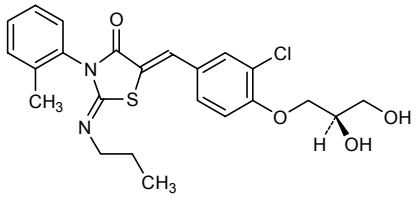
ponesimodum

ponesimod — (2*Z*,5*Z*)-5-{3-chloro-4-[(2*R*)-2,3-dihydroxypropoxy]phenylmethylidene}-3-(2-methylphenyl)-2-(propylimino)-1,3-thiazolidin-4-one

ponésimod — (2*Z*,5*Z*)-5-{3-chloro-4-[(2*R*)-2,3-dihydroxypropoxy]phénylméthylidène}-3-(2-méthylphényl)-2-(propylimino)-1,3-thiazolidin-4-one

ponesimod — (2*Z*,5*Z*)-5-{3-cloro-4-[(2*R*)-2,3-dihidroxipropoxi]fenilmetilideno}-3-(2-metilfenil)-2-(propilimino)-1,3-tiazolidin-4-ona

$C_{23}H_{25}ClN_2O_4S$



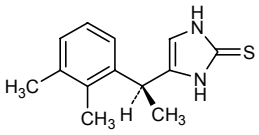
rezatomidinum

rezatomidine — 4-[(1*S*)-1-(2,3-dimethylphenyl)ethyl]-1,3-dihydro-2*H*-imidazol-2-thione

rézatomidine — 4-[(1*S*)-1-(2,3-diméthylphényl)éthyl]-1,3-dihydro-2*H*-imidazole-2-thione

rezatomidina — 4-[(1*S*)-1-(2,3-dimetilfenil)etil]-1,3-dihidro-2*H*-imidazol-2-tiona

$C_{13}H_{16}N_2S$



roledumabum #

roledumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* RHD (Rhesus blood group D antigen, RhD, CD240D)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-456) [*Homo sapiens* VH (IGHV3-30*01 (86.70%) -(IGHD)-IGHJ3*02) [8.8.19] (1-126) -IGHG1*01 (127-456)], (229-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-8*01 (89.50%) -IGKJ1*01 K123>R, K127>T) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; (235-235'':238-238'')-bisdisulfide dimer

rolédumab	immunoglobuline G1-kappa, anti-[*Homo sapiens* RHD (antigène groupe sanguin Rhésus D, RhD, CD240D)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-456) [*Homo sapiens* VH (IGHV3-30*01 (86.70%) -(IGHD)-IGHJ3*02) [8.8.19] (1-126) -IGHG1*01 (127-456)], (229-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-8*01 (89.50%) -IGKJ1*01 K123>R, K127>T) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (235-235":238-238")-bisdisulfure
roledumab	inmunoglobulina G1-kappa, anti-[*Homo sapiens* RHD (antígeno sanguíneo D Rhesus, RhD, CD240D)], anticuerpo monoclonal de *Homo sapiens* ; cadena pesada gamma1 (1-456) [*Homo sapiens* VH (IGHV3-30*01 (86.70%) -(IGHD)-IGHJ3*02) [8.8.19] (1-126) -IGHG1*01 (127-456)], (229-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-8*01 (89.50%) -IGKJ1*01 K123>R, K127>T) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (235-235":238-238")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVESGGG VVQPGRSLRL SCTASGFTFK NYAMHWVRQA PAKGLEWVAT  50
ISYDGRNIQY ADSVKGRFTF SRDNSQDTLY LQLNSLRPED TAVYYCARPV 100
RSRWLQLGLE DAFHIWGQGT MVTVSSASTK GPSVFPLAPS SKSTSGGTAA 150
LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS 200
SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF 250
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP 300
REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG 350
QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY 400
KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL 450
SLSPGK                                                 456
```

Light chain / Chaîne légère / Cadena ligera

```
AIRMTQSPSS FSASTGDRVT ITCRASQDIR NYVAWYQQKS GKAPKFLIYA  50
ASTLQSGVPS RFSGSGSGTD FTLTINSLQS EDFATYYCQQ YYNSPPTFGQ 100
GTRVEITRTV 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

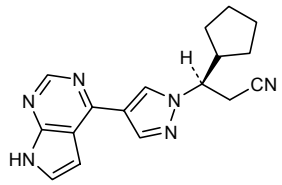
```
Intra-H  22-96    153-209   270-330   376-434
         22"-96"  153"-209" 270"-330" 376"-434"
Intra-L  23'-88'   134'-194'
         23'"-88'" 134'"-194'"
Inter-H-L  229-214'  229"-214'"
Inter-H-H  235-235"  238-238"
```

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

ruxolitinibum

ruxolitinib	(3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]propanenitrile
ruxolitinib	(3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]propanenitrile
ruxolitinib	(3*R*)-3-ciclopentil-3-[4-(7*H*-pirrolo[2,3-*d*]pirimidin-4-il)-1*H*-pirazol-1-il]propanonitrilo

$C_{17}H_{18}N_6$



samalizumabum #

samalizumab	immunoglobulin G2-kappa, anti-[*Homo sapiens* CD200 (OX-2)], humanized monoclonal antibody; gamma2 heavy chain (1-442) [humanized VH (*Homo sapiens* IGHV1-69*01 (73.50%) -(IGHD)-IGHJ4*01 L123>T, V124>L) [8.8.10] (1-117) -*Homo sapiens* IGHG2*01 CH1-hinge-CH2 1.6-1.1 (118-232)- IGHG4*01 CH2 1-125, CH3 1-129 K130>del (233-442)], (131-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-33*01 (81.10%) -IGKJ2*01 Q120>G) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (219-219":220-220":223-223":226-226")-tetrakisdisulfide dimer
samalizumab	immunoglobuline G2-kappa, anti-[*Homo sapiens* CD200 (OX-2)], anticorps monoclonal humanisé; chaîne lourde gamma2 (1-442) [VH humanisé (*Homo sapiens* IGHV1-69*01 (73.50%) -(IGHD)-IGHJ4*01 L123>T, V124>L) [8.8.10] (1-117) -*Homo sapiens* IGHG2*01 CH1-charnière-CH2 1.6-1.1 (118-232)- IGHG4*01 CH2 1-125, CH3 1-129 K130>del (233-442)], (131-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-33*01 (81.10%) -IGKJ2*01 Q120>G) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (219-219":220-220":223-223":226-226")-tétrakisdisulfure
samalizumab	inmunoglobulina G2-kappa, anti-[*Homo sapiens* CD200 (OX-2)], anticuerpo monoclonal humanizado; cadena pesado gamma2 (1-442) [humanizado VH (*Homo sapiens* IGHV1-69*01 (73.50%) -(IGHD)-IGHJ4*01 L123>T, V124>L) [8.8.10] (1-117) -*Homo sapiens* IGHG2*01 CH1-bisagra-CH2 1.6-1.1 (118-232)- IGHG4*01 CH2 1-125, CH3 1-129 K130>del (233-442)], (131-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizada(*Homo sapiens* IGKV1-33*01 (81.10%) -IGKJ2*01 Q120>G) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (219-219":220-220":223-223":226-226")-tetrakisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQQSGSE LKKPGASVKI SCKASGYSFT DYIILWVRQN PGKGLEWIGH  50
IDPYYGSSNY NLKFKGRVTI TADQSTTTAY MELSSLRSED TAVYYCGRSK 100
RDYFDYWGQG TTLTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SNFGTQTYTC 200
NVDHKPSNTK VDKTVERKCC VECPPCPAPP VAGPSVFLFP PKPKDTLMIS 250
RTPEVTCVVV DVSQEDPEVQ FNWYVDGVEV HNAKTKPREE QFNSTYRVVS 300
VLTVLHQDWL NGKEYKCKVS NKGLPSSIEK TISKAKGQPR EPQVYTLPPS 350
QEEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF 400
FLYSRLTVDK SRWQEGNVFS CSVMHEALHN HYTQKSLSLS LG         442
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASIGDRVT ITCKASQDIN SYLSWFQQKP GKAPKLLIYR  50
ANRLVDGVPS RFSGSGSGTD YTLTISSLQP EDFAVYYCLQ YDEFPYTFGG 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 22-96 144-200 257-317 363-421
22"-96" 144"-200" 257"-317" 363"-421"
Intra-L 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L 131-214' 131"-214'"
Inter-H-H 219-219" 220-220" 223-223" 226-226"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
293, 293"

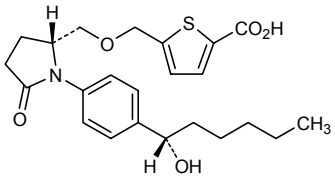
simenepagum

simenepag — 5-({[(2*R*)-1-{4-[(1*S*)-1-hydroxyhexyl]phenyl}-5-oxopyrrolidin-2-yl]methoxy}methyl)thiophene-2-carboxylic acid

siménépag — acide 5-({[(2*R*)-1-{4-[(1*S*)-1-hydroxyhexyl]phényl}-5-oxopyrrolidin-2-yl]méthoxy}méthyl)thiophène-2-carboxylique

simenepag — ácido 5-({[(2*R*)-1-{4-[(1*S*)-1-hidroxihexil]fenil}-5-oxopirrolidin-2-il]metoxi}metil)tiofeno-2- carboxílico

$C_{23}H_{29}NO_5S$



somatropinum pegolum #

somatropin pegol — $N^{5.141}$-[(2*E*)-({2-[({2,3-bis[ω-methoxypoly(oxyethylene)]propoxy}= carbonyl)amino]ethoxy}imino)ethyl]human somatotropin (growth hormone)

somatropine pégol — $N^{5.141}$-[(2*E*)-({2-[({2,3-bis[ω-méthoxypoly(oxyéthylène)]propoxy}= carbonyl)amino]éthoxy}imino)éthyl]somatotropine humaine (hormone de croissance)

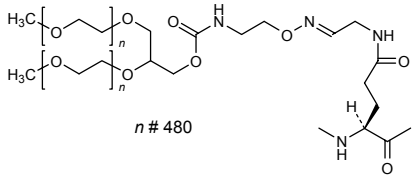
somatropina pegol — $N^{5.141}$-[(2*E*)-({2-[({2,3-bis[ω-metoxipoli(oxietileno)]propoxi}carbonil)= amino]etoxi}imino)etil]somatotropina humana (hormona de crecimiento)

```
FPTIPLSRLF DNAMLRAHRL HQLAFDTYQE FEEAYIPKEQ KYSFLQNPQT  50
SLCFSESIPT PSNREETQQK SNLELLRISL LLIQSWLEPV QFLRSVFANS 100
LVYGASDSNV YDLLKDLEEG IQTLMGRLED GSPRTGQIFK QTYSKFDTNS 150
HNDDALLKNY GLLYCFRKDM DKVETFLRIV QCRSVEGSCG F         191
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
53-165 182-189

Modified residue / Résidu modifié / Residuo modificado

Q
Gln(141)



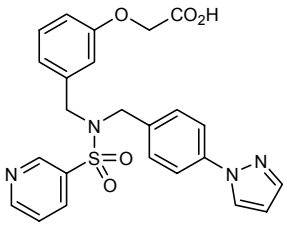
taprenepagum

taprenepag — 2-{3-[(*N*-{[4-(1*H*-pyrazol-1-yl)phenyl]methyl}pyridine-3-sulfonamido)methyl]phenoxy}acetic acid

taprénépag — acide 2-{3-[(*N*-{[4-(1*H*-pyrazol-1-yl)phényl]méthyl}pyridine-3-sulfonamido)méthyl]phénoxy}acétique

taprenepag — ácido 2-{3-[(*N*-{[4-(1*H*-pirazol-1-il)fenil]metil}piridina-3-sulfonamido)metil]fenoxi}acético

$C_{24}H_{22}N_4O_5S$



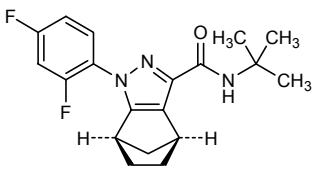
tedalinabum

tedalinab — (4*S*,7*R*)-*N*-*tert*-butyl-1-(2,4-difluorophenyl)-4,5,6,7-tetrahydro-1*H*-4,7-methanoindazole-3-carboxamide

tédalinab — (4*S*,7*R*)-*N*-*tert*-butyl-1-(2,4-difluorophényl)-4,5,6,7-tétrahydro-1*H*-4,7-méthanoindazole-3-carboxamide

tedalinab — (4*S*,7*R*)-*N*-*terc*-butil-1-(2,4-difluorofenil)-4,5,6,7-tetrahidro-1*H*-4,7-metanoindazol-3-carboxamida

$C_{19}H_{21}F_2N_3O$



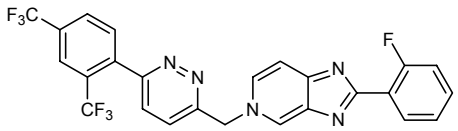
tegobuvirum

tegobuvir — 5-({6-[2,4-bis(trifluoromethyl)phenyl]pyridazin-3-yl}methyl)-2-(2-fluorophenyl)-5*H*-imidazo[4,5-*c*]pyridine

tégobuvir — 5-({6-[2,4-bis(trifluorométhyl)phényl]pyridazin-3-yl}méthyl)-2-(2-fluorophényl)-5*H*-imidazo[4,5-*c*]pyridine

tegobuvir — 5-({6-[2,4-bis(trifluorometil)fenil]piridazin-3-il}metil)-2-(2-fluorofenil)-5*H*-imidazo[4,5-*c*]piridina

$C_{25}H_{14}F_7N_5$



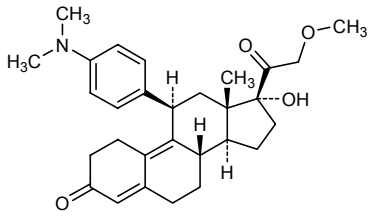
telapristonum

telapristone — 11β-[4-(dimethylamino)phenyl]-17-hydroxy-21-methoxy-19-norpregna-4,9-diene-3,20-dione

télapristone — 11β-[4-(diméthylamino)phényl]-17-hydroxy-21-méthoxy-19-norprégna-4,9-diène-3,20-dione

telapristona — 11β-[4-(dimetilamino)fenil]-17-hidroxi-21-metoxi-19-norpregna-4,9-dieno-3,20-diona

$C_{29}H_{37}NO_4$



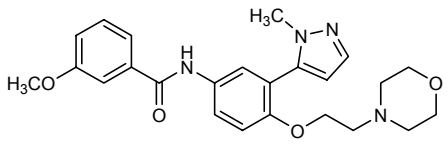
temanogrelum

temanogrel — 3-methoxy-*N*-{3-(1-methyl-1*H*-pyrazol-5-yl)-4-[2-(morpholin-4-yl)ethoxy]phenyl}benzamide

témanogrel — 3-méthoxy-*N*-{3-(1-méthyl-1*H*-pyrazol-5-yl)-4-[2-(morpholin-4-yl)éthoxy]phényl}benzamide

temanogrel — *N*-{3-(1-metil-1*H*-pirazol-5-il)-4-[2-(morfolin-4-il)etoxi]fenil}-3-metoxibenzamida

$C_{24}H_{28}N_4O_4$



tiprelestatum

tiprelestat — human elafin (elastase-specific inhibitor, skin-derived antileukoproteinase, peptidase inhibitor 3)

tiprélestat — élafine humaine (inhibiteur spécifique de l'élastase, antileukoprotéinase dérivé de la peau, inhibiteur 3 de peptidase)

tiprelestat — elafina humana (inhibidor específico de la elastasa, antileukoproteinasa derivada de la piel, inhibidor 3 de peptidasa)

$C_{254}H_{416}N_{72}O_{75}S_{10}$

```
AQEPVKGPVS  TKPGSCPIIL  IRCAMLNPPN  RCLKDTDCPG  IKKCCEGSCG  50
MACFVPQ                                                     57
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
16-45 23-49 32-44 38-53

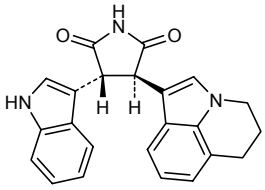
tivantinibum

tivantinib — (3*R*,4*R*)-3-(5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione

tivantinib — (3*R*,4*R*)-3-(5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoléin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione

tivantinib — (3*R*,4*R*)-3-(5,6-dihidro-4*H*-pirrolo[3,2,1-*ij*]quinolein-1-il)-4-(1*H*-indol-3-il)pirrolidina-2,5-diona

$C_{23}H_{19}N_3O_2$



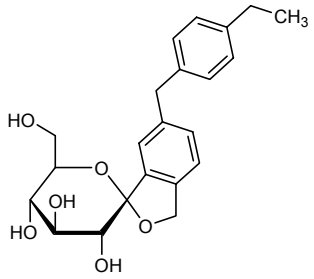
tofogliflozinum

tofogliflozin — (1*S*,3'*R*,4'*S*,5'*S*,6'*R*)-6-[(4-ethylphenyl)methyl]-6'-(hydroxymethyl)-3',4',5',6'-tetrahydro-3*H*-spiro[2-benzofuran-1,2'-pyran]-3',4',5'-triol

tofogliflozine — (1*S*,3'*R*,4'*S*,5'*S*,6'*R*)-6-[(4-éthylphényl)méthyl]-6'-(hydroxyméthyl)-3',4',5',6'-tétrahydro-3*H*-spiro[2-benzofuran-1,2'-pyran]-3',4',5'-triol

tofogliflozina — (1*S*,3'*R*,4'*S*,5'*S*,6'*R*)-6-[(4-etilfenil)metil]-6'-(hidroximetil)-3',4',5',6'-tetrahidro-3*H*-espiro[2-benzofurano-1,2'-pirano]-3',4',5'-triol

$C_{22}H_{26}O_6$



trastuzumabum emtansinum #

trastuzumab emtansine

immunoglobulin G1-kappa, anti-[*Homo sapiens* ERBB2 (epidermal growth factor receptor 2, HER-2, p185c-erbB2, NEU, EGFR2)], humanized monoclonal antibody conjugated to maytansinoid DM1; gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV3-66*01 (81.60%) -(IGHD)-IGHJ6*01 T123>L) [8.8.13] (1-120) - *Homo sapiens* IGHG1*03 (121-449) CH1 R120>K], (223-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') - *Homo sapiens* IGKC*01 (108'-214')]; (229-229":232-232")-bisdisulfide dimer; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM1 via a succinimidyl-4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) linker
For the *emtansine* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

trastuzumab emtansine

immunoglobuline G1-kappa, anti-[*Homo sapiens* ERBB2 (récepteur 2 du facteur de croissance épidermique, HER-2, p185c-erbB2, NEU, EGFR2)]], anticorps monoclonal humanisé conjugué au maytansinoïde DM1;
chaîne lourde gamma1 (1-449) [VH humanisé (*Homo sapiens* IGHV3-66*01 (81.60%) -(IGHD)-IGHJ6*01 T123>L) [8.8.13] (1-120) - *Homo sapiens* IGHG1*03 (121-449) CH1 R120>K], (223-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') - *Homo sapiens* IGKC*01 (108'-214')]; dimère (229-229":232-232")-bisdisulfure; conjugué, sur 3 à 4 lysyl en moyenne, au maytansinoïde DM1 via un linker succinimidyl-4-(*N*-maléimidométhyl) cyclohexane-1-carboxylate (SMCC)
Pour la partie *emtasine*, veuillez vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

trastuzumab emtansina

inmunoglobulina G1-kappa, anti-[*Homo sapiens* ERBB2 (receptor 2 del factor de crecimiento epidérmico, HER-2, p185c-erbB2, NEU, EGFR2)]], anticuerpo monoclonal humanizado conjugado con maitansinoide DM1;
cadena pesada gamma1 (1-449) [VH humanizado (*Homo sapiens* IGHV3-66*01 (81.60%) -(IGHD)-IGHJ6*01 T123>L) [8.8.13] (1-120) - *Homo sapiens* IGHG1*03 (121-449) CH1 R120>K], (223-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') - *Homo sapiens* IGKC*01 (108'-214')]; dimero (229-229":232-232")-bisdisulfuro; conjugado, en 3 a 4 residuos lisil por término medio, con el maitansinoide DM1 mediante un conector succinimidil-4-(*N*-maleimidometil) ciclohexano-1-carboxilato (SMCC)
Por la parte *emtansina*, por favor, vaya al documento *"INN for pharmaceutical substances: Names for radicals, groups & others"*.*

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR  50
IYPTNGYTRY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCSRWG 100
GDGFYAMDYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK 150
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT 200
YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP 250
KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN 300
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ 350
VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 400
LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPG  449
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS  50
ASFLYSGVPS RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ 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    147-203    264-324    370-428
         22"-96"  147"-203"  264"-324"  370"-428"
Intra-L  23'-88'   134'-194'
         23'"-88'" 134'"-194'"
Inter-H-L  223-214'  223"-214'"
Inter-H-H  229-229"  232-232"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
300, 300"

ulimorelinum

ulimorelin

(2*R*,5*S*,8*R*,11*R*)-5-cyclopropyl-11-[(4-fluorophenyl)methyl]-2,7,8-trimethyl-2,3,4,5,7,8,10,11,13,14,15,16-dodecahydro-6*H*-1,4,7,10,13-benzoxatetraazacyclooctadecine-6,9,12-trione

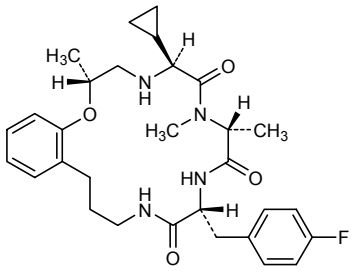
ulimoréline

(2*R*,5*S*,8*R*,11*R*)-5-cyclopropyl-11-[(4-fluorophényl)méthyl]-2,7,8-triméthyl-2,3,4,5,7,8,10,11,13,14,15,16-dodécahydro-6*H*-1,4,7,10,13-benzoxatétraazacyclooctadécine-6,9,12-trione

ulimorelina

(2*R*,5*S*,8*R*,11*R*)-5-ciclopropil-11-[(4-fluorofenil)metil]-2,7,8-trimetil-2,3,4,5,7,8,10,11,13,14,15,16-dodecahidro-6*H*-1,4,7,10,13-benzoxatetraazaciclooctadecino-6,9,12(5*H*)-triona

$C_{30}H_{39}FN_4O_4$



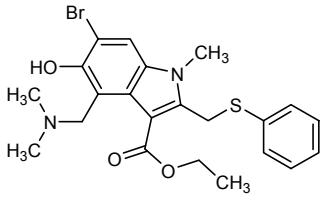
umifenovirum

umifenovir — ethyl 6-bromo-4-[(dimethylamino)methyl]-5-hydroxy-1-methyl-2-[(phenylsulfanyl)methyl]-1*H*-indole-3-carboxylate

umifénovir — 6-bromo-4-[(diméthylamino)méthyl]-5-hydroxy-1-méthyl-2-[(phénylsulfanyl)méthyl]-1*H*-indole-3-carboxylate d'éthyle

umifenovir — 6-bromo-4-[(dimetilamino)metil]-5-hidroxi-1-metil-2-[(fenilsulfanil)metil]-1*H*-indol-3-carboxilato de etilo

$C_{22}H_{25}BrN_2O_3S$



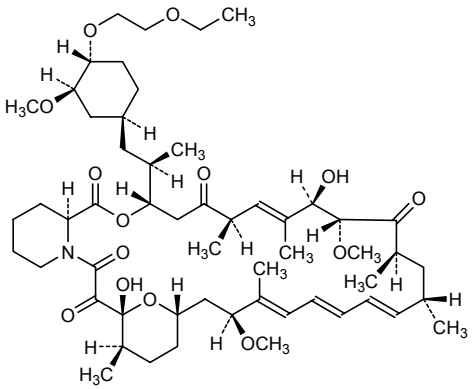
umirolimusum

umirolimus — (3*S*,6*R*,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*)-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-ethoxyethoxy)-3-méthoxycyclohexyl]-1-methylehyl}-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-3,4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34ª-octadecahydro-23,27-epoxy-5*H*-pyrido[2,1-*c*][1,4]oxazacyclohentriacontine-1,5,11,28,29(6*H*,31*H*)-pentone

umirolimus — (3*S*,6*R*,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*)-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-ethoxyethoxy)-3-méthoxycyclohexyl]-1-methylehyl}-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-3,4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34ª-octadecahydro-23,27-epoxy-5*H*-pyrido[2,1-*c*][1,4]oxazacyclohentriacontine-1,5,11,28,29(6*H*,31*H*)-pentone

umirolimús — (3*S*,6*R*,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*)-3-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-etoxietoxi)-3-metoxiciclohexil]-1-metiletil}-9,27-dihidroxi-10,21-dimetoxi-6,8,12,14,20,26-hexametil-3,4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34ª-octadecahidro-23,27-epoxi-5*H*-pirido[2,1-*c*][1,4]oxazaciclohentriacontina-1,5,11,28,29(6*H*,31*H*)-pentona

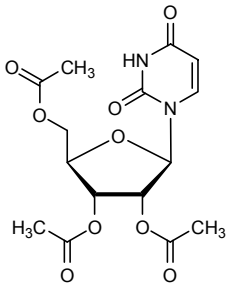
$C_{55}H_{87}NO_{14}$



uridini triacetas

uridine triacetate	2',3',5'-tri-*O*-acetyluridine
triacétate d'uridine	2',3',5'-tri-*O*-acétyluridine
triacetato de uridina	2',3',5'-tri-*O*-acetiluridina

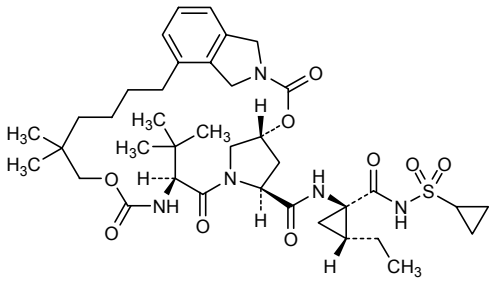
$C_{15}H_{18}N_2O_9$



vaniprevirum

vaniprevir	(5*R*,7*S*,10*S*)-10-*tert*-butyl-*N*-{(1*R*,2*R*)-1-[*N*-(cyclopropanesulfonyl)carbamoyl]-2-ethylcyclopropyl}-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1*H*,3*H*,5*H*-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide
vaniprévir	(5*R*,7*S*,10*S*)-10-*tert*-butyl-*N*-{(1*R*,2*R*)-1-[*N*-(cyclopropanesulfonyl)carbamoyl]-2-éthylcyclopropyl}-15,15-diméthyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodécahydro-1*H*,3*H*,5*H*-2,23:5,8-diméthano-4,13,2,8,11-benzodioxatriazacyclohénicosine-7-carboxamide
vaniprevir	(5*R*,7*S*,10*S*)-10-*terc*-butil-*N*-{(1*R*,2*R*)-1-[*N*-(ciclopropanosulfonil)carbamoil]-2-etilciclopropil} -15,15-dimetil-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahidro-1*H*,3*H*,5*H*-2,23:5,8-dimetano-4,13,2,8,11-benzodioxatriazaciclohenicosina-7-carboxamida

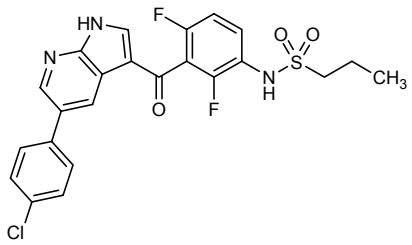
$C_{38}H_{55}N_5O_9S$



vemurafenibum

vemurafenib	*N*-{3-[5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-b]pyridin-3-carbonyl]-2,4-difluorophenyl}propane-1-sulfonamide
vémurafénib	*N*-{3-[5-(4-chlorophényl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-carbonyl]-2,4-difluorophényl}propane-1-sulfonamide
vemurafenib	*N*-{3-[5-(4-clorofenil)-1*H*-pirrolo[2,3-*b*]piridin-3-carbonil]-2,4-difluorofenil}propano-1-sulfonamida

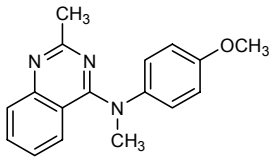
$C_{23}H_{18}ClF_2N_3O_3S$



verubulinum

verubulin	*N*-(4-methoxyphenyl)-*N*,2-dimethylquinazolin-4-amine
vérubuline	*N*-(4-méthoxyphényl)-*N*,2-diméthylquinazolin-4-amine
verubulina	*N*,2-dimetil-*N*-(4-metoxifenil)quinazolin-4-amina

$C_{17}H_{17}N_3O$



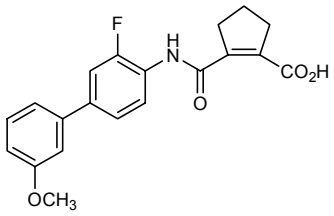
vidofludimusum

vidofludimus — 2-[*N*-(3-fluoro-3'-methoxy[1,1'-biphenyl]-4-yl)carbamoyl]cyclopent-1-ene-1-carboxylic acid

vidofludimus — acide 2-[*N*-(3-fluoro-3'-méthoxy[1,1'-biphényl]-4-yl)carbamoyl]cyclopent-1-ène-1-carboxylique

vidofludimús — ácido 2-[*N*-(3-fluoro-3'-metoxi[1,1'-bifenil]-4-il)carbamoil]ciclopent-1-eno-1-carboxílico

$C_{20}H_{18}FNO_4$



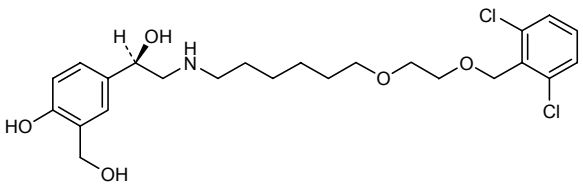
vilanterolum

vilanterol — 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorophenyl)methoxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol

vilantérol — 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorophényl)méthoxy]éthoxy}hexyl)amino]-1-hydroxyéthyl}-2-(hydroxyméthyl)phénol

vilanterol — 4-{(1*R*)-2-[(6-{2-[(2,6-diclorofenil)metoxi]etoxi}hexil)amino]-1-hidroxietil}-2-(hidroximetil)fenol

$C_{24}H_{33}Cl_2NO_5$



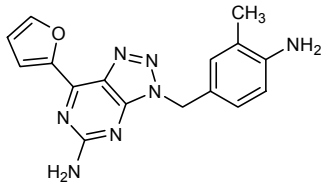
vipadenantum

vipadenant — 3-[(4-amino-3-methylphenyl)methyl]-7-(furan-2-yl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5-amine

vipadénant — 3-[(4-amino-3-méthylphényl)méthyl]-7-(furan-2-yl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-5-amine

vipadenant — 3-[(4-amino-3-metilfenil)metil]-7-(furan-2-il)-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-5-amina

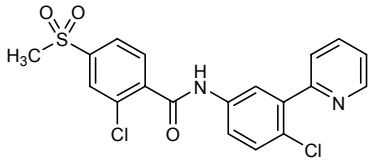
$C_{16}H_{15}N_7O$



vismodegibum

vismodegib	2-chloro-*N*-[4-chloro-3-(pyridin-2-yl)phenyl]-4-(methanesulfonyl)benzamide
vismodégib	2-chloro-*N*-[4-chloro-3-(pyridin-2-yl)phényl]-4-(méthylsulfonyl)benzamide
vismodegib	2-cloro-*N*-[4-cloro-3-(piridin-2-il)fenil]-4-(metanosulfonil)benzamida

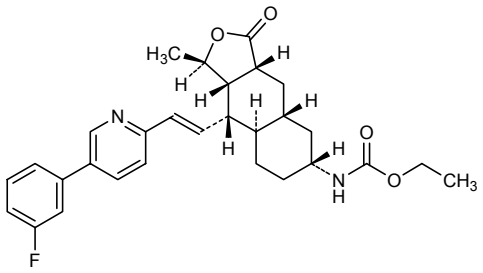
$C_{19}H_{14}Cl_2N_2O_3S$



vorapaxarum

vorapaxar	ethyl [(1*R*,3a*R*,4a*R*,6*R*,8a*R*,9*S*,9a*S*)-9-{(1*E*)-2-[5-(3-fluorophenyl)pyridine-2-yl]ethen-1-yl}-1-methyl-3-oxododecahydronaphtho[2,3-*c*]furan-6-yl]carbamate
vorapaxar	[(1*R*,3a*R*,4a*R*,6*R*,8a*R*,9*S*,9a*S*)-9-{(1*E*)-2-[5-(3-fluorophényl)pyridin-2-yl]éthén-1-yl}-1-méthyl-3-oxododécahydronaphto[2,3-*c*]furan-6-yl]carbamate d'éthyle
vorapaxar	[(1*R*,3a*R*,4a*R*,6*R*,8a*R*,9*S*,9a*S*)-9-{(1*E*)-2-[5-(3-fluorofenil)piridin-2-il]eten-1-il}-1-metil-3-oxododecahidronafto[2,3-*c*]furan-6-il]carbamato de etilo

$C_{29}H_{33}FN_2O_4$



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

Recommended International Non Proprietary Names (Rec. INN): List 6
(WHO Chronicle, Vol. 20, No. 11, 1966)

	dalanatum insulinum	
p. 424	dalanated insulin	*replace the description by the following*
		an insulin derivative prepared by the removal of the *C*-terminal alanine from the B chain of insulin

Recommended International Non Proprietary Names (Rec. INN): List 31
Denominations communes internationales recommandées (DCI Rec.): Liste 31
Denominaciones Comunes Internacionales Recomandadas (DCI Rec.): Lista 31
(WHO Drug Information, Vol. 5, No. 3, 1991)

p. 13	*delete/supprimer/suprimáse*	*insert/insérer/insertese*
	suplatastum tosilas	**suplatasti tosilas**

Recommended International Non Proprietary Names (Rec. INN): List 51
Denominations communes internationales recommandées (DCI Rec.): Liste 51
Denominaciones Comunes Internacionales Recomandadas (DCI Rec.): Lista 51
(WHO Drug Information, Vol. 18, No. 1, 2004)

p. 102	*delete/supprimer/suprimáse*	*insert/insérer/insertese*
	ralfinamidum	**priralfinamidum**
	ralfinamide	priralfinamide
	ralfinamide	priralfinamide
	ralfinamida	priralfinamida

Recommended International Non Proprietary Names (Rec. INN): List 59
Denominations communes internationales recommandées (DCI Rec.): Liste 59
Denominaciones Comunes Internacionales Recomandadas (DCI Rec.): Lista 59
(WHO Drug Information, Vol. 22, No. 1, 2008)

p. 66	*delete/supprimer/suprimáse*	*insert/insérer/insertese*
	sergliflozinum etabonas	**sergliflozini etabonas**

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

p. 56	**fonturacetamum**	
	fonturacetam	*replace the chemical name by the following*
	fonturacétam	*remplacer le nom chimique par le suivant*
	fonturacetam	*sustitúyase el nombre químico por el siguiente*
		rac-2-(2-oxo-4-phenylpyrolidin-1-yl)acetamide
		rac-2-(2-oxo-4-phénylpyrolidin-1-yl)acétamide
		rac-2-(4-fenil-2-oxopirolidin-1-il)acetamida

p. 74 **sifalimumabum**

sifalimumab	*replace the description by the following*
sifalimumab	*remplacer la description par la suivante*
sifalimumab	*sustitúyase la descripción por la siguiente*

immunoglobulin G1-kappa, anti-[*Homo sapiens* interferon alpha (IFN-alpha)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-446) [*Homo sapiens* VH (IGHV1-18*01 (95.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) –IGHG1*03 CH1 R120>K (213) (117-446)], (219-213')-disulfide with kappa light chain (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (99.00%) –IGKJ1*01) [7.3.9] (1'-108') -IGKC*01 (109'-215')]; (225-225'':228-228'')-bisdisulfide dimer

immunoglobuline G1-kappa, anti-[*Homo sapiens* interféron alpha (IFN-alpha)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-446) [*Homo sapiens* VH (IGHV1-18*01 (95.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) –IGHG1*03 CH1 R120>K (213) (117-446)], (219-215')-disulfure avec la chaîne légère kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (99.00%) –IGKJ1*01) [7.3.9] (1'-108') -IGKC*01 (109'-215')]; dimère (225-225'':228-228'')-bisdisulfure

inmunoglobulina G1-kappa, anti-[interferón alfa (IFN-alfa) de *Homo sapiens*], anticuerpo monoclonal de *Homo sapiens*;
cadena pesada gamma1 (1-446) [*Homo sapiens* VH (IGHV1-18*01 (95.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) –IGHG1*03 CH1 R120>K (213) (117-446)], (219-215')-disulfuro con la cadena ligera kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (99.00%) –IGKJ1*01) [7.3.9] (1'-108') -IGKC*01 (109'-215')]; dímero (225-225'':228-228'')-bisdisulfuro

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

p. 260 **afatinibum**

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

(2*E*)-*N*-[4-(3-chloro-4-fluoroanilino)-7-{[(3*S*)-oxolan-3-yl]oxy}quinazolin-6-yl]-4-(dimethylamino)but-2-enamide

(2*E*)-*N*-[4-(3-chloro-4-fluoroanilino]-7-{[(3*S*)-oxolan-3-yl]oxy}quinazolin-6-y]-4-(diméthylamino)but-2-énamide

(2*E*)-*N*-[4-(3-cloro-4-fluoroanilino)-7-{[(3*S*)-oxolan-3-il]oxi}quinazolin-6-il]-4-(dimetilamino)but-2-enamida

p. 279 **sotaterceptum**

sotatercept	*replace the description by the following*
sotatercept	*remplacer la descriptions par la suivante*
sotatercept	*sustitúyase la descripción por la siguiente*

fusion protein for immune applications (FPIA) comprising *Homo sapiens* ACVR2A (activin receptor type 2A, activin receptor type IIA) fragment fused with *Homo sapiens* immunoglobulin G1 Fc fragment;
Homo sapiens ACVR2A, 21-135 precursor fragment (1-115) -threonyl-triglycyl linker (116-119) -gamma1 chain H-CH2-CH3 fragment (120-344) [*Homo sapiens* IGHG1*03 hinge (120-127), CH2, A115>V (227) (128-237), CH3 (238-344)]; (123-123':126-126')-bisdisulfide dimer

protéine de fusion pour applications immunitaires (FPIA) comprenant un fragment d'*Homo sapiens* ACVR2A (récepteur type 2A de l'activine, récepteur type IIA de l'activine) fusionné au fragment Fc de l'*Homo sapiens* immunoglobuline G1;
fragment précurseur 21-135 de *Homo sapiens* ACVR2A (1-115) -linker thréonyl-triglycyl (116-119) -fragment H-CH2-CH3 de chaîne gamma1 (120-344) [*Homo sapiens* IGHG1*03 charnière (120-127), CH2, A115>V (227) (128-237), CH3 (238-344)]; dimère (123-123':126-126')-bisdisulfure

proteína de fusión para aplicaciones inmunitarias (FPIA) que comprende un fragmento de ACVR2A (receptor tipo 2A de la activina, receptor tipo IIA de la activina) de *Homo sapiens* fusionado al fragmento Fc de la inmunoglobulina G1 de *Homo sapiens*;
fragmento precursor 21-135 de ACVR2A de *Homo sapiens* (1-115)-conector treonil-triglicil (116-119) -fragmento H-CH2-CH3 de cadena gamma1 (120-344) [*Homo sapiens* IGHG1*03 bisagra(120-127), CH2, A115>V (128-237), CH3 (238-344)]; dímero (123-123':126-126')-bisdisulfuro

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

* *"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

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.