WHO Drug Information

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International Nonproprietary Names

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Abbreviations and web sites

CHMP Committee for Medicinal Products for Human Use (EMA)
EMA European Medicines Agency (www.ema.europa.eu)
EU European Union
FDA U.S. Food and Drug Administration (www.fda.gov)
Health Canada Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
MHRA Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
PRAC Pharmacovigilance Risk Assessment Committee (EMA)
PMDA Pharmaceutical and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic Swiss Agency for Therapeutic Products (www.swissmedic.ch)
TGA Therapeutic Goods Administration, Australia (www.tga.gov.au)
U.S. United States of America

Note:
The online version of this issue (available at www.who.int/medicines/publications/druginformation) has direct clickable hyperlinks to the documents and web pages referenced.
WHO Prequalification

Building quality-assured manufacturing capacity in Nigeria

As a fast growing economy and large provider of goods and services to countries in the region, Nigeria is poised to expand its pharmaceutical production to achieve self-sufficiency in essential medicines and compete on regional and global markets. To this end, government health authorities and local manufacturers requested WHO support and technical assistance to prequalify several locally produced medicines, as a way to fast-track the building of local capacity to manufacture medicines according to international quality standards. An integral part of the process is the strengthening of national regulatory capacity to enforce these standards on an ongoing basis.

The Nigerian quest
While no medicines manufacturer in West Africa has so far achieved prequalification of a pharmaceutical product by the World Health Organization (WHO), Nigeria is attempting to change the status quo. A number of companies belonging to the Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG-MAN) are working to reach a manufacturing quality standard that will enable them to have some of their products WHO-prequalified and apply for international medicines tenders.

The project has been supported by the Nigerian government and by the National Agency for Food and Drug Administration (NAFDAC). WHO was approached to provide technical assistance to both manufacturers and regulators especially in the areas of good manufacturing practice and dossier submissions in line with WHO and international standards.

Role of WHO
The WHO prequalification programme aims to ensure that medicines for priority diseases meet global standards of quality, safety and efficacy. By evaluating needed pharmaceutical products – including those produced in countries with limited regulatory capacity – the WHO prequalification team (WHO/PQT) provides a basis for national and international procurers to make cost-effective choices among finished products of assured quality.

WHO/PQT has increasingly engaged in activities that go beyond dossier assessment and site inspections. The team is training national regulators, providing guidance to manufacturers, facilitating registration in countries and supporting post-procurement quality control. The experts who advise manufacturers in preparing prequalification submissions work independently of the prequalification dossier assessment and inspection groups. The main objective of these activities is to disseminate sound knowledge and practices and to ensure that all the actors work together according
to the same international quality standards.

From the WHO perspective, the Nigerian project is in line with these aims. Given the importance of Nigeria in its geo-economic region, it is hoped that increased production of quality medicines in the country will also lead to better quality medicines in West Africa as a whole.

**Snapshot of Nigeria’s pharmaceutical landscape**

Nigeria is a natural candidate for the local capacity strengthening offered by WHO/PQT. The country’s pharmaceutical industry is vibrant and expanding, with over 100 pharmaceutical manufacturers and a mostly local ownership organized under the umbrella of the Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG-MAN). Nigeria accounts for approximately 60% of the pharmaceutical production in the Economic Community of West African States (ECOWAS) by volume (1). Production is geared mostly towards essential medicines, including antimalarials and HIV medicines.

On the other hand, drug manufacturers in Nigeria face a number of constraints. These include a weak financial base, high production costs as a result of the high cost of imported pharmaceutical ingredients and machinery, infrastructural problems, outdated technology and weak distribution systems. In addition, as there are no contract research organizations in West Africa proven to work in line with international standards, manufacturers need to rely on expertise from Europe and Asia when they require bioequivalence studies or specific laboratory testing. Due to these factors, the country imports about 70% of its medicines, mainly from Asia, Europe and the Americas.

In terms of the regulatory environment, the National Agency for Food and Drug Administration and Control (NAFDAC) has in recent years enacted numerous enforcement activities to combat substandard and counterfeit medicines. It has also consistently worked with WHO to strengthen its quality control and post-marketing monitoring of pharmaceuticals. But challenges persist, which are largely related to insufficient capacity to ensure full regulatory functions in line with international standards, including speedy registration of medicines.

Despite these challenges, the country’s pharmaceutical sector is one of the strongest in Africa in terms of size, range of products manufactured and potential to meet and sustain international pharmaceutical quality standards.

**The project**

*Selection of manufacturers*

In 2011 NAFDAC and WHO/PQT came to an agreement on the principles of the project and, in collaboration with PMG-MAN, selected eight manufacturers that had expressed commitment to invest in quality improvements and that were deemed technically ready to embark on a programme to align their manufacturing operations with international quality standards. WHO/PQT arranged for external experts to verify the production standards at the manufacturing sites and to assess product data and documentation.

*Capacity-building*

Based on the results of the assessments by the external experts, WHO/PQT initiated an intensive capacity-building programme for Nigerian manufacturers.
and regulators. Since 2012, several training sessions on good manufacturing practices, combined with site visits at participating companies, have been co-organized by WHO/PQT and NAFDAC. In parallel, WHO-appointed experts have advised the companies on specific quality issues related to various medicines.

In response to observations raised during the audits and document reviews, the companies implemented a series of corrective actions. They upgraded their equipment, improved manufacturing processes, and established professional procedures to build documentation for pharmaceutical ingredients and finished products. These corrective actions exceed currently applicable regulatory requirements in Nigeria. Implementation is monitored by NAFDAC professionals, who report on progress to WHO. The process is ongoing, with a current focus on the development of technically sound product dossiers.

WHO/PQT also works with the participating manufacturers to identify all their medicinal products eligible for prequalification. This will facilitate progress towards GMP-compliant production of additional medicines of interest for international organizations. For example, interest may come from UN Commission for Lifesaving Commodities for Women and Children (UNCoLSC), given that a large portion of the medicines needed in the West African region are reproductive health and paediatric products.

**Regulatory and in-country support**

On the regulatory side, NAFDAC has proved to be a strong partner in capacity-building efforts. The authority has upgraded its laboratories, recruited more specialized staff and has established new departments, such as the Clinical Trial/Pharmacovigilance and Post Marketing Surveillance and Drug Evaluation and Research Directorates. NAFDAC professionals also participate actively in trainings organized for local industry.

The close support by the WHO Country Office has also been an asset to the project. The process has opened doors for Nigerian stakeholders and international organizations to work together more closely.

**Pre-submission audits**

The WHO prequalification team normally plans its inspections on a risk-basis once companies have submitted a prequalification dossiers. To enable applicants to work on product dossiers and good manufacturing practice (GMP) in parallel, the new concept of pre-submission GMP audits was piloted in Nigeria. An inspection can be scheduled before a dossier has been submitted, provided that the expert advisors and NAFDAC notify WHO/PQT that the manufacturer has achieved – in principle – compliance with WHO GMP. Prequalification inspectors then verify the status of general GMP compliance while completion of a prequalification dossier is still ongoing.

Successful audits represent a milestone in the progress towards prequalification, and the outcomes are considered by organizations looking for companies that manufacture needed health products in line with international GMP.

A series of pre-audits was organized in 2013 and 2014 at Nigerian manufacturing sites in close co-operation with NAFDAC, whose regulatory inspectors played an active role in verifying the corrective actions adopted after the audit and drafting parts of the inspection reports.
**Funding**
The Nigerian Ministry of Health has invested considerably into the project. In addition, advocacy is on-going for a special intervention fund from the development banks in Nigeria, ECOWAS and the African Development Bank (AfDB).

WHO’s participation in the project has largely depended on financial backing from UNITAID, which was used to support technical assistance, transfer of knowledge, capacity building, audits and inspections and human resources.

From the manufacturers’ side, information from PMG-MAN indicates that the companies participating in the project have invested a cumulative amount exceeding USD 400 million over the last four years.

**Achievements**

**GMP compliance**
The pre-submission audits led to a landmark success being achieved in April 2014, when Swiss Pharma Nigeria Limited (Swipha) was confirmed to be operating at an acceptable level of compliance with WHO GMP guidelines for the manufacture of oral solid dosage forms (2). Swipha was the first pharmaceutical manufacturer in Sub-Saharan West Africa to pass a GMP inspection by WHO/PQT after implementing successful corrective and preventative action (CAPA). Three other companies participating in the project - Evans Medical Plc, May & Baker Nigeria Plc and CHI Pharmaceuticals Ltd – reached this standard in November 2014, after successfully implementing corrective and preventive action (CAPA) identified during WHO pre-submission audits in May 2014 (3).

**Prequalification dossiers**
One Nigerian company has submitted a prequalification dossier to WHO and this has been accepted for screening. Another submission is expected before the end of the year, with more to follow in the near future. The choice of medicines includes antimalarials, antiretrovirals, zinc sulphate and antibiotics.

**Outlook and impact**

**Tenders**
The achievements made by participating manufacturers open up opportunities for international tenders, where compliance with stringent GMP is a minimum requirement for any pharmaceutical product. Additional requirements apply to key categories such as antiretrovirals, anti-TB products and antimalarials. In these categories, compliance with stringent GMP enables manufacturers to apply for review of relevant products by the Expert Review Panel (ERP). Products that have received a positive ERP opinion can then compete in international tenders in situations where no or only one WHO-prequalified or stringently authorized competitor product is available on the market (4).

It is hoped that African ministries of health, regional initiatives and international procurers will consider WHO GMP-compliant African manufacturers in tenders for purchase of medicines in the region. This would support quality-assured local production, and would signal recognition of the cost that quality assurance entails for manufacturers.

**Raising the bar for medicines quality**
Feedback from PMG-MAN suggests that the project is beginning to yield wider benefits. The understanding of world class manufacturing practices in
Nigeria has improved. As a result, the perception of the importance of quality in pharmaceutical manufacturing is gradually shifting. Other Nigerian companies do not want to be left behind and are also becoming interested in upgrading their production, with support from PMG-MAN, to achieve WHO prequalification of their products.

NAFDAC has benefitted through hands-on participation in prequalification inspections, assessments, training workshops and other capacity-building activities, with access to prequalification inspection and assessment reports.

Local regulatory oversight
Medicines regulation is essentially a public function that should be assured by the governments of countries where medicines are produced and used. NAFDAC’s active follow-up of individual manufacturers’ progress and verification of corrective actions has proved extremely valuable in working towards this goal. The process has strengthened communication between industry and regulators, with a common understanding of the quality issues at stake.

The cooperation with NAFDAC under this project marks the start of a new model whereby the local regulatory authority assumes responsibility for ensuring that WHO prequalification requirements continue to be met. This approach is of course dependent on objective evidence that the local regulatory authority can in fact conduct routine monitoring and maintenance to the required standards. The activities will therefore be coordinated with, and reported to, WHO/PQT. In addition, NAFDAC assessors will work closely with the WHO prequalification assessors to review product dossiers submitted by Nigerian companies in line with international standards.

Challenges
Further challenges lie ahead before the Nigerian pharmaceutical sector will be able to reach the level of quality production and autonomy to which it aspires. Most challenges are related to the need for further guidance in manufacturing practices, dossier development, bio-equivalence and supply chain management. To address these needs, the initial timeline for the project was extended.

Important also is the choice of products for prequalification, which must be well considered to ensure that it serves both quality and commercial objectives.

Other challenges are related to financing. Given the fact that WHO prequalification will not occur immediately, financial incentives may well be needed for the companies to continue to progress. And while WHO prequalification of a number of Nigerian-made products in the near future seems feasible and can enable companies to win international procurement tenders, further change is needed to ensure a sustainable supply of quality medicines in the region and to resolve supply management problems.

Conclusion
The close cooperation between Nigerian manufacturers, regulators and WHO starts to produce results. The general understanding of international regulatory standards has improved, and several companies are well on their way towards prequalification of their products.

As corrective measures and upgrades continue, Nigerian authorities and manufacturers will need to find ways to raise sufficient funds to put into place
sustainable structures and processes for production of quality-assured pharmaceuticals.

Spokespersons of NAFDAC and PMG-MAN have expressed satisfaction with progress made to date and remain firmly committed to enhancing the pharmaceutical sector to make it work both for public health and the pharmaceutical industry.

WHO will continue to advocate for greater support of this kind of cross-sectoral capacity-building. Ensuring that affordable, quality-assured medicines are within reach of all those who need them is a pillar of an effective health system and an area requiring greater attention from the international community.

References

2. WHO/PQT. First Nigerian manufacturer considered compliant with WHO GMP. Prequalification Update, 4 April 2014.
Pharmacopoeial standards

Global specifications: the example of capreomycin

Capreomycin is used to treat multi-drug-resistant tuberculosis, an increasing public health problem. The example of the new capreomycin monographs in The International Pharmacopoeia shows how international specifications can provide added value for WHO Member States, including countries with resource limitations.

Public quality control standards
Pharmacopoeial monographs can be used by manufacturers, regulators and other stakeholders for quality control of active pharmaceutical ingredients (APIs) and finished products against internationally recommended specifications. Pharmacopoeial requirements in countries form part of national legislation, defining the specifications which pharmaceutical products circulating on their market must fulfil.

The International Pharmacopoeia (1) was created to help promote harmonized and suitable quality control testing standards among WHO Member States. It aims to provide analytical tests that can be performed with the recommended equipment for first-stage and medium-sized pharmaceutical quality control laboratories (2) in all regions of the world, including remote areas.

Focus on ‘neglected monographs’
The International Pharmacopoeia focuses on essential medicines that are of public health importance in WHO Member States, and for which monographs are not available in other pharmacopoeias. An example of such a medicine is capreomycin, an aminoglycoside antibiotic discovered in 1960 and first registered in 1971. Today it is part of WHO-recommended regimens to treat multi-drug-resistant tuberculosis, an increasing public health threat in many parts of the world.

Capreomycin was removed from the British Pharmacopoeia in 2003 because of its low use in the UK. Although monographs for capreomycin are included in the United States Pharmacopeia (USP) as well as the Chinese and Indian Pharmacopoeias, WHO decided to develop a further public standard because it was felt that the available methods and specifications were not sufficient to fully characterize and standardize the quality of the substance.

Input from world experts
Experts from universities, WHO Collaborating Centres and national regulatory authorities collaborated to develop the monographs for capreomycin sulfate active substance and capreomycin injection through WHO’s defined step-wise process (3). The initial drafts underwent two public consultations, during which many valuable comments were received.

The new monographs were published in the Third and Fourth Supplement of The International Pharmacopoeia respectively. Their advantages for users are outlined on the next page.
Capreomycin monographs: Added value for WHO Member States

**Comprehensive description**
Produced by fermentation, capreomycin is a mixture of several structurally related components and thus difficult to characterize. *The International Pharmacopoeia* is currently the only pharmacopoeia to give comprehensive information on structures, formulas, relative molecular weights and chemical names for all four major components (capreomycin IA, IB, IIA and IIB). This information facilitates the production and registration of products containing capreomycin.

**Alternative options for identity test**
Two alternative combinations of identity tests are provided, for users to choose the option that can be performed using the equipment that is available in the laboratory (see *Table 1*).

**Table 1. Options for identity test**

<table>
<thead>
<tr>
<th>Test</th>
<th>Option 1</th>
<th>Option 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>IR Spectrophotometry</td>
<td>■</td>
</tr>
<tr>
<td>B</td>
<td>Thin-layer chromatography</td>
<td>■</td>
</tr>
<tr>
<td>C</td>
<td>Absorption spectrum of solution in hydrochloric acid</td>
<td>■</td>
</tr>
<tr>
<td>D</td>
<td>Absorption spectrum of solution in sodium hydroxide</td>
<td>■</td>
</tr>
<tr>
<td>E</td>
<td>General identification test for sulfates</td>
<td>■</td>
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</table>

**First-ever pharmacopoeial test for related substances**
The impurities of capreomycin affect the safety of the finished product. *The International Pharmacopoeia* describes the first-ever pharmacopoeial related substances test for capreomycin and defines acceptable limits for impurities – not an easy task, as toxicity data for old medicines like capreomycin can be challenging to put together. The test uses a high performance liquid chromatography (HPLC) method, a widely used analytical technique (see *Figure 1*).

**Quantification of content**
Other pharmacopoeias propose a microbiological assay, where the content of capreomycin is measured through its inhibitory effect on susceptible microorganisms. The assay in *The International Pharmacopoeia* is based on the same HPLC method as the related substances test (*Figure 1*), enabling a direct calculation of the content in terms of mass. This saves time and resources as the laboratory can perform two tests with the same analytical system.

**Easy-to-use reference standard**
A solution of the reference substance with a defined concentration is needed to quantify capreomycin. Capreomycin absorbs water from the atmosphere. It may therefore be difficult to weigh the substance accurately on an analytical balance.

The European Directorate for the Quality of Medicines and Healthcare (EDQM) is responsible for the establishment and distribution of WHO’s International Chemical Reference Substances. Given the importance of this project and the objective difficulty of weighing capreomycin in a laboratory, the EDQM is currently assessing the feasibility of lyophilizing the reference standard. If this is feasible, the use of the ICRS will become fairly simple i.e. just adding to the vial a predefined volume of solvent.

**Quantification of capreomycin components and related substances by HPLC**
The HPLC method separates the different related compounds in capreomycin sulfate according to their affinity to a lipophilic stationary phase. In the resulting chromatogram the content of each compound is proportionate to the area of the corresponding peak.

**Related substances**: The peak response areas for the impurities are compared with those of the major peaks for capreomycin IA, IB, IIA and IIB; Acceptance limits are:
- All impurities ≤ 2%
- Only one impurity between 1 and 2%
- Sum of all impurities: ≤ 7%

**Assay**: The content is calculated from comparing the four major peak areas of the test substance with those of the reference substance, which has a declared content of capreomycin IA, IB, IIA and IIB.
Supporting market entry of quality-assured products

The International Pharmacopoeia is aligned with the needs of the WHO prequalification programme, which assesses the quality of medicines for procurement by UN agencies and other buyers that have recognized the central importance of medicines quality not only in treating individual patients, but also in reducing the risk of resistance that could make a medicine ineffective for entire populations.

Capreomycin is invited for WHO prequalification. At the end of September 2014 the first API was prequalified, another was under assessment. The first capreomycin injection was prequalified in October 2014, with four other submissions under assessment (4). Appropriate specifications and suitable test methods will support manufacturers in achieving WHO prequalification for their products, resulting in additional quality-assured products on the global market.

Funding

In the past, the work on The International Pharmacopoeia used to be funded from WHO’s regular budget. This funding source has decreased to virtually zero in recent years. The activities are currently funded for the most part by UNITAID, whose financial contribution is gratefully acknowledged. In addition, WHO Member States provide in-kind contributions and support valued at a multiple of the programme’s operational budget. These contributions include activities by national quality control laboratories, national support to WHO collaborating centres, and – very importantly – time given by individual experts.

Conclusion

Quality control testing is a mainstay of pharmaceutical quality assurance in production and regulation. In providing well-designed, globally applicable specifications and test methods for widely used medicines free of charge, WHO fills a need in Member States. The International Pharmacopoeia is useful in development, production, registration and post-market surveillance in countries around the world, and thus helps to ensure that essential medicines used in WHO Member States meet the internationally accepted quality requirements that make them safe and effective.

References


4 WHO. List of all APIs and FPPs invited for prequalification, and number prequalified or currently under assessment per product. (25 September 2014). Available from apps.who.int/prequal - Information for applicants.

Medicines quality assurance

A harmonized self-assessment tool for procurement agencies

In the absence of stringent regulatory systems for medicines in many parts of the world, procurement agencies have an important role in ensuring the quality of pharmaceutical products that they buy for use in treatment programmes. During the recent update of WHO’s quality assurance guidance for procurement agencies, a harmonized tool was developed enabling procurement agencies to assess their compliance with the principles of this guidance.

Background
The WHO Model Quality Assurance System for Procurement Agencies (MQAS) (1) is a WHO guidance document developed at the request of the Global Fund to Fight AIDS, Tuberculosis and Malaria and adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 2006. In the years that followed, international organizations involved in medicines procurement incorporated the MQAS requirements into their quality assurance policies and phased in stringent, harmonized quality criteria for key product categories procured in large quantities and considered crucial for the success of treatment programmes.

In introducing harmonized quality requirements for priority medicines, an important element of the MQAS was its Appendix 6, the interagency product questionnaire. It was adopted as the common format for suppliers to submit data for needed medicines that were not yet available as stringently approved or WHO-prequalified products.

Beyond priority medicines
In August 2011 international organizations came together at a meeting convened by WHO and the Global Fund to discuss ways to assure the quality of all essential medicines being procured, including those not belonging to the key categories.

It was found that for these diverse products often purchased in small quantities, the MQAS did provide valid approaches for quality assurance in procurement. The different agencies had strong quality assurance capacities, and several of them had developed their own systems to implement the MQAS principles. However this resulted in diverging practices and requirements, with duplication of efforts. The need was...
Table 1. Standardized assessment of compliance with the six MQAS modules

<table>
<thead>
<tr>
<th>Module I General requirements (33 items)</th>
<th>Module II Pre-qualification (21 items)</th>
<th>Module III Purchasing (12 items)</th>
<th>Module IV Receipt and storage (35 items)</th>
<th>Module V Distribution (23 items)</th>
<th>Module VI Reassessment (13 items)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organization and management (2 items)</td>
<td>Prequalification procedure (4, including 1 critical)</td>
<td>Purchasing (10)</td>
<td>Receiving – sampling and testing – storage (7, including 1 critical)</td>
<td>Containers and labelling (6, including 1 critical)</td>
<td>Reassessment (1)</td>
</tr>
<tr>
<td>Personnel (3)</td>
<td>Expression of interest (2)</td>
<td>Monitoring of performance of prequalified manufacturers (2)</td>
<td>Quality control (6)</td>
<td>Dispatch (10)</td>
<td>Reassessment of manufacturers (3)</td>
</tr>
<tr>
<td>Quality systems (10, including 2 critical)</td>
<td>Product information, screening and evaluation (5)</td>
<td></td>
<td>Storage (9, including 1 critical)</td>
<td>Transport and transit (7)</td>
<td>Monitoring of contracted-out services (4)</td>
</tr>
<tr>
<td>Documentation (9)</td>
<td>Inspections (7)</td>
<td></td>
<td>Stock control (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counterfeit products (3, including 2 critical)</td>
<td>Prequalification outcome (3)</td>
<td></td>
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<tr>
<td>Self-inspection (2)</td>
<td></td>
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<tr>
<td>Complaints (2)</td>
<td></td>
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<tr>
<td>Recalls (2 critical)</td>
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</tbody>
</table>

*How it works:* A total of 137 items are rated on a scale of 0–100%. Compliance is taken as an overall rating of at least 60% (“Medium level of implementation, e.g. procedures have been developed, but lack scope and depth”) across the 137 items. Depending on the context, a rating of less than 60% for a critical item can lead to the entire module being considered non-compliant.

identified for a harmonized tool to assess compliance with the MQAS.

**Measuring compliance with WHO guidance principles**

An informal, voluntary working group was established at the 2011 meeting and worked together over the next two years to propose a harmonized MQAS compliance self-assessment tool. The tool is based on the six modules of the MQAS, with percentage ratings allocated to a total of 137 items, including ten critical items (*Table 1*). At the same time, the group updated the MQAS guidance itself and complemented it with an aide-memoire for inspection of procurement agencies (2).

The full self-assessment tool developed by the working group, together with instructions and a model report format, is reproduced in *Annex 1*. It supplements the formal WHO guidance texts by providing a consistent yet flexible way to measure the implementation of the principles defined in the guidance.

This tool will enable procurement agencies to assess themselves, to communicate the outcomes in a standardized way, and to take targeted measures for improvement.

**References**


Annex 1:
Self-assessment tool based on the WHO Model Quality Assurance system for procurement agencies (MQAS)

a) Instructions

For whom is this tool intended, and who can use it? The tool can be used by the Quality Manager in a procurement agency for self-assessment of the agency and to identify its level of compliance with the standards as recommended by WHO in the MQAS.

What does the tool contain? The tool contains statements relating to systems and procedures that should be in place in a procurement organization as a means to assess the quality of systems and medicines.

Level of implementation of a system:
- 0% No compliance, or the system/procedure does not exist
- 20% Very low level of compliance or implementation
- 40% Low level of compliance or implementation
- 60% Medium level of implementation (e.g. procedures have been developed, but lack scope and depth)
- 80% A good level of compliance
- 100% Fully implemented and consistently complies with MQAS expectation

Steps in the procedure for assessment:
1. Inspect the individual requirements in each system of each Module.
2. Allocate the percentage to indicate the level of compliance (0–100%). In case the activity is not applicable to the PA, state N/A and do not allocate “0”.
3. Make additional notes on deficiencies in the space provided (if needed) in each section.
4. Calculate the percentage compliance in each Module (I – VI)
5. Reach a conclusion on the level of compliance of the site in each area.
6. For critical issues (marked as !), a score below 60% indicates failure of compliance with standards and may result in an outcome of “non-compliant”.
7. Prepare a report based on the findings and present it in the agreed format.

For each module the calculated level of compliance will fall within one of the three levels below:
- Level I: <60% (Not in compliance – unacceptable)
- Level II: 60% (Acceptable level of compliance)
- Level III: >80% (High level of compliance)
**b) Self-assessment tool**

An *Excel version of this tool is available on request from: druginfo@who.int.*

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MODULE I: Organization and management</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>An authorized organization chart indicates positions, names of responsible persons and reporting lines and is in line with the job descriptions.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>There are written job descriptions defining responsibilities, for all personnel – signed by each employee. The person responsible for prequalification and the person responsible for purchasing is independent of one another.</td>
<td></td>
</tr>
<tr>
<td><strong>Personnel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>There is a sufficient number of qualified, trained staff with the necessary experience and authority to carry out their duties for key activities (including prequalification, purchasing, storage, distribution).</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Relevant personnel have signed and follow an authorized written code of conduct, confidentiality agreements and declaration of interest. These are archived and accessible for verification to ensure that there is no adverse effect on the quality of service provided or on the integrity of pharmaceutical products.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Personnel are trained in accordance with a standard operating procedure (SOP) and training programme, and assessment records are maintained.</td>
<td></td>
</tr>
<tr>
<td><strong>Quality system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>! The PA is authorized/licensed to perform the activities (e.g. distribution of pharmaceutical products) in accordance with national legislation.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>! Authorized procurement and release procedures for all administrative and technical operations performed are in place to ensure that approved pharmaceutical products are sourced only from approved suppliers and distributed by approved entities to persons or entities authorized to acquire such products.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Any delegated and contracted activities are documented in agreements or contracts, and are within the legal framework of the country. There is evidence that the contract accepter complies with the legal requirements and GDP.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>The contracts clearly define responsibilities of the parties. Contracts are signed and dated.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Contract accepters are audited periodically and reports show evidence of findings and corrective actions being taken.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Defined procedures are implemented where the distributor is using electronic systems. These systems and procedures are proven to be reliable and ensure traceability. Transactions are performed only by authorized persons or entities.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Safety procedures are in place and cover personnel, property, environmental protection and product integrity.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>There is a quality manual in place. The quality policy is implemented.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>There is sufficient office space, and other storage space for retention of commodities, documentation, samples, stock, reports, files and other records.</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Computer system applications are appropriate for their intended use. (Including appropriate hardware and software with security systems access; virus protection; firewall; technical support; capacity and memory; maintenance and upgrading plan, and batch traceability). A back-up of electronic records is made and maintained to prevent any accidental data loss.</td>
<td></td>
</tr>
</tbody>
</table>

Continued
Table 1: Quality assurance system

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>A comprehensive documented system exists covering policies, organizational structure(s), procedures, guidelines, norms, standards, manuals, records and related documents.</td>
<td></td>
</tr>
</tbody>
</table>
| 17     | Activities are documented in authorized SOPs (signed and dated). SOPs for all activities are in an appropriate format and cover at least but are not limited to:  
- How to write an SOP:  
- Product dossier evaluation;  
- Inspections;  
- Decision making process for products;  
- Purchasing;  
- Receiving;  
- Issuing and dispatch;  
- Deviations;  
- Change control;  
- Evaluating offers received;  
- Handling of complaints;  
- Handling recalls;  
- Regular reinspection;  
- Quality control  
- Handling counterfeit/substandard products;  
- Handling variations;  
- Evaluating offers received. |        |
| 18     | Documents are designed, completed, reviewed, amended and distributed with care. Documents are reviewed regularly and kept up to date. Superseded documents are removed from use. |        |
| 19     | There is evidence that risk assessment is done to assess potential risks to the quality and integrity of products. |        |
| 20     | An SOP is followed to manage changes such as changes to SOPs and other documents, facilities etc. |        |
| 21     | Procedures cover health and hygiene of personnel. These are implemented and followed. |        |
| 22     | Records (electronic or hard copies, also for manual systems) are maintained for a defined period and ensure product traceability throughout the supply chain which cover products received and distributed. (From the manufacturer/importer to the entity responsible for selling or supplying the product to the patient.) These are readily retrievable with no unauthorized changes, damage, deterioration and/or loss thereof. |        |
| 23     | Records for receiving of products contain at least the date; name of the product; batch numbers and expiry dates, quantity received, or supplied; and name and address of the supplier. |        |
| 24     | A procedure is followed for identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documents and records. |        |
| 25     | There is a procedure to handle counterfeit and suspected counterfeit products. It ensures that regulatory bodies and other relevant competent authorities and the holder of the marketing authorization for the original product are informed immediately in a case of confirmed or suspected counterfeiting of a pharmaceutical product. |        |
| 26     | Counterfeit and suspected counterfeit products are kept secured, separately, clearly labelled and are not sold. |        |

Continued
### Medicines quality assurance

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>A formal decision on the disposal of each counterfeit or suspected counterfeit product, ensuring that it does not reenter the market, is recorded.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Self-inspection</strong></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>An SOP, calendar and reports show evidence of self-inspections being conducted by independent, designated, competent persons.</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>There is evidence of management involvement and effective follow-up of corrective actions taken.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Complaints</strong></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>An SOP is followed for the handling of complaints distinguishing between different types of complaints, e.g. complaints about a product or its packaging, or complaints relating to distribution.</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>All complaints are thoroughly investigated, risk assessment is done and the root cause is identified. Appropriate action is taken. Records are maintained.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Recalls</strong></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>An SOP is in place to effectively and promptly recall products. A progress report and a final report on the recall is issued, which includes reconciliation between delivered and recovered quantities of products. This procedure is checked regularly and updated as required. The effectiveness of the arrangements for recalls is evaluated at regular intervals (e.g. mock recall).</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Recalled pharmaceutical products are segregated during transit and storage and are clearly labelled as such. They are kept under appropriate storage conditions.</td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**

Total calculated for Module I
(e.g. total percentage divided by 33 if all 33 questions were rated):

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MODULE II: Prequalification procedure
```

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>The prequalification procedure and standards used are based on the WHO-recommended procedures and guidelines. Key steps in prequalification have been defined and are followed meeting the recommendations in the MQAS.</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>The PA has a quality policy to ensure that prequalified products will be sourced – either through its own prequalification procedure, WHO prequalification, or products approved by stringent regulatory authorities (SRA). (Special note: Verify policy regarding products approved by SRAs for export only, as this may not always be appropriately controlled by the SRA).</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Procedures and records show that manufacturing sites comply with WHO good manufacturing practices (GMP) (or other internationally recognized GMP).</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>The persons responsible for prequalification and those responsible for purchasing are independent from another.</td>
<td></td>
</tr>
</tbody>
</table>

**Expression of interest (EOI) – public sector/non-commercial**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>Procedures and clear policies are followed for inviting, receiving and reviewing EOI. Records are maintained.</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Detailed guidelines for the compilation and submission of information on products and manufacturing sites are publicly available.</td>
<td></td>
</tr>
</tbody>
</table>

**Product information, screening and evaluation**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>Product information is received in a suitable format with necessary contents such as a product dossier (detail as described by WHO, e.g. see Appendix 6 of the Model quality assurance system for procurement agencies).</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (“1” = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>Normally, a WHO-type certificate of a pharmaceutical product (CPP) is received with the product information. (If the formulation, strength or other specifications are different from the product for which the WHO-type product certificate (CPP) was issued, arguments and/or data to support the applicability of the certificate despite the differences are requested).</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>There is an appropriate system and infrastructure for the receiving and processing of product information. The screening of product information submitted is done according to an SOP and records are maintained. Written procedures are followed for evaluation. Evaluation reports are prepared for each product which includes a recommendation for acceptance or rejection. The evaluation and the report are done within appropriate time frames.</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Evaluators with suitable qualifications (e.g. in the pharmaceutical field) and experience (e.g. regulatory affairs) evaluate product data.</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Where appropriate (based on risk assessment) samples submitted together with product information packages are tested at laboratories meeting defined standards recommended by WHO.</td>
<td></td>
</tr>
</tbody>
</table>

**Inspections**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (“1” = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>There is appropriate evidence that active pharmaceutical ingredients (API) manufacturers are assessed for compliance with GMP (e.g. by finished pharmaceutical product (FPP) manufacturers).</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Inspections are planned and performed according to an SOP and plan, for FPP manufacturers.</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Audits are performed by suitably qualified, experienced auditors with relevant qualifications, training and experience.</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Waiving of audits is only done under appropriate, defined conditions. In case outcomes of inspections done by other authorities are recognized, such procedure is written and appropriate to ensure that GMP outcomes are reliable.</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Audits cover all aspects of GMP as well as verification of data and information provided (e.g. in product data and site master file).</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>An audit report is prepared after each audit, containing detailed information and lists of deficiencies where relevant. Audit reports are communicated to manufacturers and a copy is kept as a record for a defined period of time.</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Corrective actions to audit findings, and time lines for completing them are received, reviewed, and verified on site when necessary.</td>
<td></td>
</tr>
</tbody>
</table>

**Prequalification outcome**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (“1” = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>A written procedure is followed to finalize outcomes of the product evaluation and inspection (resulting in prequalification). Records are maintained on the process and decision taken. Manufacturers are informed of the outcome.</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>A list of prequalified products and manufacturers, based on the outcome of the evaluation of product data and information and manufacturing site inspections, is maintained. The list is product- and manufacturing site-specific and is reviewed regularly.</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>In case costs are recovered for prequalification, then these are defined in transparent procedures and are based on a fee-for-services structure. Manufacturers are notified of these in advance.</td>
<td></td>
</tr>
</tbody>
</table>

Comments:

Total calculated for Module II (e.g. total percentage divided by 21 if all 21 questions were rated):
Number System/procedure (“1” = critical) Rating

### MODULE III: Purchasing

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (“1” = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>Imported products enter through designated ports of entry as stipulated by national legislation.</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Transparent SOPs are followed for procurement and purchasing, awarding contracts.</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>Suppliers are selected and monitored through a process that takes into account product quality, service reliability, delivery time and financial viability.</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>A written procedure is followed to handle donated products – and it ensures that products of known, appropriate quality are accepted and donated.</td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>A documented procurement quality system is in place covering purchase and procurement. Procedures are in place for: - the establishment of technical specifications; - quantification of requirements; - issuing of a tender (as appropriate); - selection of product(s) and manufacturer(s)</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>Responses to tenders as appropriate are examined by the relevant responsible persons to evaluate compliance with tender terms and conditions. There is evidence that awards are made to the maker of the lowest acceptable bid that meets these conditions.</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>Key activities in purchasing procedures are defined and include product selection and specification, product quantification, selection of suppliers and adjudication of tenders.</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>An SOP is followed for the selection of products, and is based, where possible, on a national formulary or on the essential medicines list.</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>Procurement and tender documents list pharmaceutical products by their INN or national generic names.</td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>Requests for products include quantities and required delivery dates.</td>
<td></td>
</tr>
</tbody>
</table>

### Monitoring of performance of prequalified manufacturers

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (“1” = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>Procedures and records show that there is tracking and monitoring of: - the value of contracts awarded; - purchase and supply of prequalified products; - supplier performance; - product compliance.</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>Monitoring includes at least: - compliance with all of the contract terms and conditions; - sampling and testing; - supplied batches meet agreed specifications; - pharmacovigilance as required in the country; - complaints; - reinspection of manufacturing sites and reassessment of product information; - delivery schedules.</td>
<td></td>
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</tbody>
</table>

Comments: Total calculated for Module III (e.g. total percentage divided by 12 if all 12 questions were rated).
### MODULE IV: Receiving – sampling and testing – storage

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>There is evidence that the products are stored at ports of entry under appropriate conditions; and as short as possible before being taken into stock.</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>! SOPs are followed and records are kept for receiving, sampling, storage and handling of products (including quarantined, rejected, expired, recalled, returned products and suspected counterfeits expired stock).</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>There is sufficient space for the receiving and dispatch of products. Receiving and dispatch bays are separated and protect products from the weather.</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>Product containers are cleaned, if necessary, before taken into storage areas.</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>All incoming materials and products are received and checked in accordance with their SOP and quarantined until released (e.g. meeting specifications as per prequalified dossier, purchase order, certificate of analysis (CoA)).</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>Records for each delivery show description of the goods, quality, quantity, supplier, supplier’s batch number, the date of receipt, assigned batch number and the expiry date.</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>Other procedures implemented include cleaning, pest control, containment and cleaning of spillages, prevention of contamination and cross-contamination; and waste removal. Programs and records are in place where appropriate.</td>
<td></td>
</tr>
</tbody>
</table>

#### Quality control

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>There is a system in place for quality control of finished products procured (e.g. preshipment sampling, testing, and release or sampling, checks on shelf-life and labelling, testing when consignments are received).</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>Sampling plans which ensure that representative samples are taken for testing (used during receiving of consignments) are detailed in SOPs and are based on risk assessment. Qualified and experienced personnel review CoAs accompanying batches received.</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>Adequate laboratory services are used to test products independently according to approved specifications and standards. The laboratory meets general requirements for good practices covering, e.g. facilities, policies and procedures, personnel, equipment, etc.</td>
<td></td>
</tr>
<tr>
<td>77</td>
<td>An SOP clearly describes the process and ensures that materials or products are not released for use until their quality has been judged satisfactory.</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>Out-of-specification results are handled in accordance with an SOP for OOS investigation.</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>Products failing to meet their specifications are rejected in accordance with an SOP and documented evidence exists for the disposition of such products.</td>
<td></td>
</tr>
</tbody>
</table>

#### Storage

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>Access to storage areas is controlled to ensure that no unauthorized person has access (24 hours a day, 7 days a week).</td>
<td></td>
</tr>
<tr>
<td>81</td>
<td>Separated areas are used for the storage of quarantined, rejected, expired, recalled, returned products and suspected counterfeits.</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>Storage areas have sufficient space and ventilation and fire control measures.</td>
<td></td>
</tr>
<tr>
<td>83</td>
<td>Temperature mapping of the storage areas was done in an appropriate manner.</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>Systems are in place to provide, control, monitor and record temperature (and relative humidity where required). Records of monitoring are kept for suitable periods of time. Appropriately calibrated devices (i.e. range, traceable to national standard) are used to monitor the temperature and relative humidity.</td>
<td></td>
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</tbody>
</table>
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<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>85</td>
<td>All products are stored in suitably protective, labelled containers; under appropriate storage conditions as specified on the labels.</td>
<td></td>
</tr>
<tr>
<td>86</td>
<td>Products that should be stored under specified cold conditions (requiring cold-chain) are handled appropriately during transport, delivery, receiving and storage. Temperature mapping studies were done for cold rooms; and power generators are available in case of power failure. Procedures are followed to ensure that ice packs are used in the correct manner in cold-chain boxes. Containers used for the transport are validated to ensure that cool products remain at the required temperature during transport.</td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>Narcotic and psychotropic substances/products are handled in accordance with national legislation and written procedures. These products are stored separately, where access is controlled and reconciliation is done monthly as well as each time stock is issued.</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>Miscellaneous and hazardous materials are handled in accordance with written procedures.</td>
<td></td>
</tr>
</tbody>
</table>

**Stock control**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td>Stock rotation and control is maintained ensuring batch number control and expiry dating.</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>Periodic stock reconciliation is done (actual stock vs recorded stock). Significant stock discrepancies are investigated and results are documented in accordance with written instructions</td>
<td></td>
</tr>
<tr>
<td>91</td>
<td>Damaged containers are handled in accordance with written procedures. Any action taken is documented.</td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>Regular checks are performed according to an SOP – to identify obsolete and outdated products. These are not issued/distributed.</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>Recalled materials are handled in accordance with a written procedure.</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>Returned goods are handled in accordance with a written procedure ensuring physical segregation and appropriate storage conditions. There is no possibility of entry of counterfeit products, or that the product quality is compromised.</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>Product returns and exchanges are done in accordance with terms and conditions of an agreement between the distributor and the recipient.</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>Returned products are transported in accordance with the relevant storage and other requirements.</td>
<td></td>
</tr>
<tr>
<td>97</td>
<td>An authorized person is identified to decide on the disposition of returned goods. The decision is based on, e.g. the nature of the product returned, special storage conditions required, its condition and history; and the time elapsed since it was issued.</td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>There is a procedure for the appropriate destruction of products (complying with international, national and local requirements).</td>
<td></td>
</tr>
<tr>
<td>99</td>
<td>Records are maintained of all returned, rejected and/or destroyed products</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>Rejected goods are handled in accordance with an SOP, are stored separately (locked) and are marked accordingly. Access is controlled.</td>
<td></td>
</tr>
<tr>
<td>101</td>
<td>Waste materials are handled in accordance with a written procedure and are not allowed to accumulate. These are collected in suitable receptacles and disposed of safely and in a sanitary manner.</td>
<td></td>
</tr>
</tbody>
</table>

Comments:

**Total calculated for Module IV**

(e.g. total percentage divided by 35 if all 35 questions were rated):
Continued

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (<em>1</em> = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MODULE V: Distribution of purchased products (Packaging – transport)</strong></td>
<td>Containers and labelling</td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>No repackaging or relabelling is done, unless licensed to do so, and the activities are found to meet international standards such as WHO GMP. (In such a case, repackaging and relabelling of products do not result in loss of identification and authentication of the products; and procedures are in place for the secure disposal of original packaging.)</td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>Products are issued on a first-expiry-first-out (FEFO) basis.</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>Suitable packaging materials and containers are used that give protection and prevent damage of products. Damage is recorded, reported and investigated.</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>Containers bear labels (indicating handling, storage conditions, precautions, identification of contents and source). Where special transport and/or storage conditions are required, these are stated including any special legal requirements, safety symbols, etc.</td>
<td></td>
</tr>
<tr>
<td>106</td>
<td>Special care is taken when using dry ice in shipment containers.</td>
<td></td>
</tr>
<tr>
<td>107</td>
<td>Damaged and/or broken containers are handled according to procedures, also considering those that contained potentially toxic and hazardous products.</td>
<td></td>
</tr>
<tr>
<td><strong>Dispatch</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>108</td>
<td>Dispatch and transportation is done after the receipt of a written, valid delivery order.</td>
<td></td>
</tr>
<tr>
<td>109</td>
<td>Written procedures for the dispatch are implemented, and cover, e.g. the nature of the product and special precautions.</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>Detailed records for dispatch are maintained which provide for traceability and facilitate recalls and investigation of counterfeits.</td>
<td></td>
</tr>
<tr>
<td>111</td>
<td>Written agreements with third-party carriers are in place if these are used.</td>
<td></td>
</tr>
<tr>
<td>112</td>
<td>Delivery schedules are prepared and suitable vehicles are selected.</td>
<td></td>
</tr>
<tr>
<td>113</td>
<td>Vehicles and equipment used to distribute, store or handle pharmaceutical products are suitable for their purpose and appropriately equipped.</td>
<td></td>
</tr>
<tr>
<td>114</td>
<td>Non-dedicated vehicles and equipment used are subjected to procedures which ensure that the quality of the pharmaceutical product is not compromised.</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>Vehicles and containers are loaded carefully and systematically. Where necessary, storage conditions are monitored, recorded and checked during transport. Devices/equipment used are appropriately calibrated.</td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>Products with different status are kept separately during transport, e.g. rejected, recalled and returned products and are securely packaged, clearly labelled.</td>
<td></td>
</tr>
<tr>
<td>117</td>
<td>Procedures ensure that no unauthorized persons can enter/tamper with vehicles and/or equipment.</td>
<td></td>
</tr>
<tr>
<td><strong>Transport and transit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>118</td>
<td>Products and containers are secured to prevent unauthorized access, theft and other misappropriation of products during transportation.</td>
<td></td>
</tr>
<tr>
<td>119</td>
<td>Appropriate documentation accompanies products in transit.</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>Procedures are in place to ensure that during transport: - the identity of the product is maintained; - the correct storage conditions are maintained; - there is no contamination of products; - precautions are taken against spillage, breakage, misappropriation and theft.</td>
<td></td>
</tr>
</tbody>
</table>
### Medicines quality assurance

#### Continued

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>121</td>
<td>Deviations in storage conditions during transport are addressed, investigated and reported in accordance with an SOP.</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>Hazardous substances and other dangerous products are transported in safe, dedicated and secure containers and vehicles, and according to agreements and legislation.</td>
<td></td>
</tr>
<tr>
<td>123</td>
<td>Narcotics and other dependence-producing substances are transported in safe and secure containers and vehicles and in compliance with agreements and legislation.</td>
<td></td>
</tr>
<tr>
<td>124</td>
<td>Procedures are followed for cleaning spillages.</td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**

Total calculated for Module V
(e.g. total percentage divided by 23 if all 23 questions were rated):

---

#### MODULE VI: Reassessment

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>Procedures and records show that requalification is done at regular intervals. This includes reinspection of manufacturers and reevaluation of product information or data.</td>
<td></td>
</tr>
</tbody>
</table>

**Reassessment of manufacturers**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>126</td>
<td>There is a procedure, programme (plan) and records that show reassessment of manufacturers taking place at least every three to five years. (This covers routine and non-routine assessment.)</td>
<td></td>
</tr>
<tr>
<td>127</td>
<td>A system is in place (e.g. agreement or SOP) ensuring that manufacturers inform the PA immediately of any changes to the manufacturing site or equipment that may have an impact on its prequalification.</td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>A procedure is followed providing for suspension and withdrawal of a prequalified facility.</td>
<td></td>
</tr>
</tbody>
</table>

**Reevaluation of products**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>129</td>
<td>Product information is reviewed routinely every three years or sooner if major changes occur.</td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>There is a system in place (agreement/procedure) that ensures that manufacturers inform the procurement agency of any contemplated changes to the product that may affect its safety, performance, efficacy or quality.</td>
<td></td>
</tr>
<tr>
<td>131</td>
<td>A system is in place to review the requested changes (see above) and communicating approved changes to the procurement agency.</td>
<td></td>
</tr>
<tr>
<td>132</td>
<td>Non-routine reevaluation of products is done according to a procedure.</td>
<td></td>
</tr>
<tr>
<td>133</td>
<td>An SOP is used to manage variations to product information.</td>
<td></td>
</tr>
</tbody>
</table>

**Monitoring of contracted-out services**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>134</td>
<td>Agreements are in place for activities contracted out such as storage, distribution, quality control, and are reviewed periodically.</td>
<td></td>
</tr>
<tr>
<td>135</td>
<td>There is evidence of compliance with a procedure for the monitoring of the performance of contractors and follow-up of non-compliance.</td>
<td></td>
</tr>
<tr>
<td>136</td>
<td>Management information shows continuous monitoring of performance of contractors which include tracking of cost, order and delivery status, lead-time and compliance with contract terms and conditions. Problems are reported and investigated with action taken.</td>
<td></td>
</tr>
<tr>
<td>137</td>
<td>On-site audits are done at intervals to verify compliance with standards, agreements and to verify source data where appropriate.</td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**

Total calculated for Module VI
(e.g. total percentage divided by 13 if all 13 questions were rated):

---
**c) Model report format**

**Section 1: General information**

<table>
<thead>
<tr>
<th>Name of organization:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Website reference:</td>
<td></td>
</tr>
<tr>
<td>Physical address:</td>
<td></td>
</tr>
<tr>
<td>Postal address:</td>
<td></td>
</tr>
<tr>
<td>Tel.:</td>
<td></td>
</tr>
<tr>
<td>Fax:</td>
<td></td>
</tr>
<tr>
<td>Contact person:</td>
<td></td>
</tr>
<tr>
<td>Email address:</td>
<td></td>
</tr>
</tbody>
</table>

**Activities (tick all that apply):**
- Prequalification
- Purchasing
- Receiving and storage
- Distribution

| Date of inspection: |  |
| Products and/or services: |  |
| Inspector: |  |

**Section 2: Summary**

**General information about the procurement agent and site**

**History of inspections**

**Focus of the inspection and inspected areas**

**Summary of findings**

**General requirements for procurement agencies:**

**Prequalification:**

**Purchasing:**

**Receiving and storage:**

**Distribution (including the ability to supply the needed products in quantities required):**

**Reassessment:**

*Continued*
**Model report format, continued**

<table>
<thead>
<tr>
<th>Outcome and conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Module I: General requirements</strong></td>
</tr>
<tr>
<td><strong>Module II: Prequalification</strong></td>
</tr>
<tr>
<td><strong>Module III: Purchasing</strong></td>
</tr>
<tr>
<td><strong>Module IV: Receiving and Storage</strong></td>
</tr>
<tr>
<td><strong>Module V: Distribution</strong></td>
</tr>
<tr>
<td><strong>Module VI: Reassessment</strong></td>
</tr>
<tr>
<td>Level I: &lt;60% (Not in compliance – unacceptable)</td>
</tr>
<tr>
<td>Level II: 60% (Acceptable level of compliance)</td>
</tr>
<tr>
<td>Level III: &gt;80% (High level of compliance)</td>
</tr>
</tbody>
</table>

**Comments:**

**Conclusion (Select and complete as appropriate):**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the self-assessment, including the observations listed above – the agency was considered to be operating at a high level of compliance with the MQAS for the following modules:……………...

And/or

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the self-assessment, including the observations listed above – the agency was considered to be operating at an acceptable level of compliance with the MQAS for the following modules:……………...

And/or

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the self-assessment, including the observations listed above – the agency was considered to be operating at an unacceptable level of compliance with the MQAS for the following modules:……………...

**Signature:** __________________________  **Date:** __________________________

**Name:** __________________________
Safety news

Unchanged recommendations

Testosterone: cardiac risk not confirmed

European Union – The European Medicines Agency (EMA) has reviewed available data from studies on testosterone-containing medicines, following concerns over serious side effects on the heart and blood vessels. Testosterone is used to treat hypogonadism (lack of testosterone produced by the body) in men. Available data do not provide consistent evidence that the use of testosterone increases the risk of heart problems in these patients, and hypogonadism itself may increase this risk.

The EMA recommended that testosterone-containing medicines should only be used where lack of testosterone has been confirmed by signs and symptoms as well as laboratory tests. The product information for these medicines will be updated to include this recommendation, together with warnings against use in men with severe heart, liver or kidney problems, and information that data on safety and effectiveness in patients over 65 years of age are limited and that age-specific testosterone reference values do not exist.

Clinical studies on the safety of testosterone are still ongoing, and their results will be considered in future regular benefit-risk assessments for these medicines. (1)

New Zealand – Medsafe’s Medicines Adverse Reactions Committee (MARC) has reviewed the available information about cardiovascular risks associated with testosterone therapy, and has found that the evidence of increased cardiovascular risk was not conclusive. The Committee recommended that marketing authorization holders should be requested to update the warnings and precautions section in the product information, and that general articles should be published to raise awareness of this risk. (2)

► (1) EMA Press release, 21 November 2014.
(2) Medsafe. Minutes of the 159th Medicines Adverse Reactions Committee Meeting - 11 September 2014.

Agomelatine: strengthened advice to monitor liver function

European Union – The EMA has concluded its regular benefit-risk assessment of agomelatine (Valdoxan®, Thymanax®), used to treat major depression in adults, and has recommended measures to reiterate the importance of liver monitoring, the cornerstone for the safe use of agomelatine.

Agomelatine has a risk of severe side effects on the liver, especially in vulnerable patients. Nevertheless it remains a valuable treatment option in certain situations. Strengthened advice on liver function monitoring will be included in the product information, and a patient booklet will be distributed.

The current product information includes a warning that the medicine should not be used in patients aged 75 years or more. The EMA considered that available data
does not justify upgrading of this warning to a contraindication.

► EMA News, 26 September 2014.

**Restricted use**

**Intravenous nicardipine: only to control high blood pressure in specialist settings**

United Kingdom – In agreement with the Medicines and Healthcare Products Regulatory Agency (MHRA), the marketing authorization holder of an intravenous nicardipine medicine has informed health professionals of the outcomes of a European regulatory review of intravenous nicardipine, initiated in 2012 at the request of the MHRA. The EMA had advised that these medicines should only be used to treat acute life-threatening hypertension and post-operative hypertension. Treatment should be administered by a specialist and in a well-controlled environment. Other uses are not recommended.

In adults, continuous infusion should be started at a rate of 3–5 mg/h. The rate can then be increased but should not exceed 15 mg/h, it should gradually be reduced when the target blood pressure is reached. Blood pressure should be monitored continuously during infusion and for at least 12 hours thereafter.

► MHRA Safety Communication, 12 September 2014.


**Bromocriptine: not for pre-menstrual syndrome or benign breast disease**

New Zealand – Medsafe has reviewed data on the efficacy and safety of bromocriptine when used to treat premenstrual symptoms and mastalgia. Available data provide insufficient evidence to recommend bromocriptine use for these indications, and information from its use of similar doses for other indications suggest that bromocriptine may cause fibrosis and impulse control disorders. Medsafe will therefore request the marketing authorization holder of bromocriptine to remove the above indications from the data sheet. (1)

Earlier, Medsafe had made recommendations on the safety and efficacy of bromocriptine for lactation suppression (2) in response to an EMA review started on the subject, and – as mentioned in the previous issue of WHO Drug Information – the EMA had recommended against the routine use of bromocriptine to stop lactation or to relieve pain or swelling of the breasts after childbirth (3).

► (1) Medsafe. Minutes of the 159th Medicines Adverse Reactions Committee Meeting - 11 September 2014.

► (2) Minutes of the 156th Medicines Adverse Reactions Committee Meeting - 5 December 2013.

(3) EMA Press release, 21 August 2014.

**Colistimethate sodium: reserve for serious infections resistant to standard antibiotics**

European Union – Colistinin and colistimethate sodium (known as polymyxins) have been available since the 1960s, but have been in little use until they were brought back in recent years as an option to treat infections resistant to standard antibiotics. The EMA has reviewed the safety and effectiveness of injectable and liquid inhaled products containing colistimethate sodium.
The review concluded that injection or infusion of colistimethate sodium should be reserved for the treatment of serious infections caused by susceptible (i.e. aerobic Gram-negative) bacteria in patients whose other treatment options are limited. The medicine should be given with another suitable antibiotic where possible. Great caution is advised when using intravenous colistimethate sodium together with other medications that are potentially nephrotoxic or neurotoxic.

The Committee recommended that doses should always be expressed in international units (IU) to avoid medication errors, and proposed a conversion table for inclusion in the product information. Despite limited data the Committee recommended doses for use in patients with kidney problems and in children, and provided guidance on dosage for intraventricular or intrathecal or injection in adults, i.e. when the medicine is given directly into fluid surrounding the brain or spinal cord.

Valproate: not to be used in pregnancy

European Union – The EMA has recommended strengthening the restrictions on the use of valproate medicines due to the risk of malformations and developmental problems in children exposed to valproate in the womb.

Valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. Where valproate is the only option, women should use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

In some countries valproate is authorized for the prevention of migraine. Pregnancy should be excluded before starting valproate treatment for migraine, and women should use effective contraception.

The EMA further recommended that educational materials should be provided to all healthcare professionals in the EU and to women who are prescribed valproate to inform them of these risks.

These strengthened restrictions are based on a review of available data as well as consultations with patients, affected families and experts.

Sulfur hexafluoride: not to be used with dobutamine in certain patients

United Kingdom – The marketing authorization holder, in agreement with the EMA and the MHRA, have informed health professionals that rare but severe and sometimes fatal arrhythmias have been reported in patients with cardiovascular instability undergoing stress echocardiography with sulfur hexafluoride (SonoVue®) in combination with dobutamine.

Sulfur hexafluoride is therefore contraindicated in combination with dobutamine in patients with conditions suggesting cardiovascular instability, e.g. recent acute coronary syndrome or clinically unstable ischaemia.

When administered alone, sulfur hexafluoride should be used in such at-risk patients only with extreme caution and after a careful risk/benefit assessment. Vital signs should be closely monitored during and after administration, because in these patients allergy-like and/
Safety news

or vasodilatory reactions may lead to life-threatening conditions.
Sulfur hexafluoride is a contrast agent used in diagnostic procedures involving echocardiography and Doppler sonography.
► MHRA Safety Information, 1 October 2014.

Safety warnings

Ivabradine: heart problems
European Union – The EMA has completed its review of ivabradine – used to treat heart failure and symptoms of angina – and has made recommendations aimed at reducing the risk of heart attack and bradycardia.
When used for angina, ivabradine should only be started if the patient’s resting heart rate is at least 70 beats per minute. Doctors should consider stopping treatment if there is no or only limited improvement in angina symptoms after three months.
Ivabradine should not be prescribed together with verapamil or diltiazem that reduce the heart rate, and patients should be monitored for atrial fibrillation. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.

Voriconazole: phototoxicity and squamous skin cancer
United Kingdom – The marketing authorization holder, in consultation with the MHRA, has reminded health professionals that voriconazole (Vfend®) is associated with a risk of phototoxicity and skin squamous cell carcinoma.
Voriconazole is used for the treatment of worsening, possibly life-threatening fungal infections and prophylaxis of invasive fungal infections in certain transplant recipients.
Health professionals are reminded to adhere to the advice given in the product information. If phototoxic reactions occur, they should refer the patient to a dermatologist and should consider stopping voriconazole treatment. If treatment is continued, the skin should be checked frequently and thoroughly, and voriconazole treatment should be stopped if precancerous skin lesions or squamous cell carcinoma are identified.
Voriconazole is also associated with a risk of liver toxicity. The UK product information (available at www.medicines.org.uk) has been updated with revised advice on monitoring liver function.
► MHRA Drug safety message, 10 October 2014.

Carvedilol: Rare severe skin reactions
New Zealand – The marketing authorization holder of carvedilol (Dilatrend®) has informed health professionals that very rare cases of severe cutaneous adverse reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported during treatment with the product, and that treatment should be permanently discontinued in patients who experience severe cutaneous adverse reactions possibly attributable to this medicine. The product information has been updated accordingly.
► Medsafe Safety information, sent 26 November 2014.
Immunoglobulins: rare but serious risk of blood clots

Canada – Health Canada, in collaboration with marketing authorization holders, has informed health professionals of the risk of thromboembolic events in patients using non-hyperimmune immunoglobulins. Such events can occur regardless of dose or route of administration and in the absence of known risk factors. Canadian product monographs for all non-hyperimmune immunoglobulins (GamaSTAN® S/D, Gammagard Liquid, Gammagard S/D, Gamunex®, Hizentra®, IGIVnex®, Immune Serum Globulin (Human), Octagam® 5%, Octagam® 10%, and Privigen®) were updated to include thromboembolic events in the Serious Warnings and Precautions section.

► Health Canada Advisory, 9 October 2014.

Simeprevir: increased bilirubin may cause serious outcomes

Japan – The Pharmaceutical and Medical Devices Agency (PMDA) has informed health care professionals that eight cases, including three fatal ones, of remarkably increased blood bilirubin in patients treated with simeprevir have been reported in Japan within 10 months following market authorization. Simeprevir is a recently approved medicine used in combination with other medicinal products for the treatment of chronic hepatitis C.

While the risk of increased blood bilirubin levels with simeprevir is known, the three deaths occurred after hepatic dysfunction and renal impairment to which the PMDA considers that hyperbilirubinaemia may have contributed. The PMDA has requested that the product information should be updated to advise health professionals to test blood bilirubin regularly during simeprevir treatment and to monitor patients carefully even after simeprevir is stopped. Prompt action is important, as measures to avoid serious outcomes may be less effective once jaundice, general malaise and/or other symptoms occur.

► PMDA Investigation results, 24 October 2014.

Basiliximab: cardiac adverse events when used off-label in heart transplants

United Kingdom – In agreement with the EMA and the MHRA, the marketing authorization holder has reminded health professionals that basiliximab (Simulect®) is indicated only for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation. Its efficacy and safety in other transplant indications have not been demonstrated.

In several small clinical trials in heart transplant recipients, serious adverse events such as cardiac arrest, atrial flutter and palpitations have been reported more frequently with basiliximab than with other induction agents. The warnings section of the Summary of Product Characteristics will be updated accordingly.

The communication follows a review by European drug regulatory agencies regarding the off-label use of basiliximab in heart transplants.

► MHRA Drug safety message, 10 October 2014.

Ustekinumab: serious skin conditions

Canada – The marketing authorization holder, in consultation with Health Canada, has informed health professionals about rare reports of exfoliative dermatitis and erythrodermic
psoriasis in psoriasis patients receiving ustekinumab (Stelara®). These skin conditions can occur within a few days of starting treatment, can be severe and can lead to hospitalization. Treatment with ustekinumab should be discontinued if a drug reaction is suspected, and the symptoms should be treated.

Exfoliative dermatitis can appear as redness and shedding of the skin over almost the entire area of the body, which may be itchy or painful. Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis as part of the natural course of their disease.

The product monograph will be updated to reflect this information. (1)

European Union – At its October meeting, the EMA’s Committee for Medicinal Products for Human Use (CHMP) adopted a safety variation to add the risk of serious skin conditions with ustekinumab to the Summary of Product Characteristics. Health professionals in the EU will be informed and the product information will be updated. (2)

(2) EMA/CHMP. Opinions on safety variations/PSURs adopted at the CHMP meeting of 20-23 October 2014.

Ponatinib: blood vessel blockage

European Union – The EMA has reviewed the benefits and risks of ponatinib (Iclusig®) and has recommended to include strengthened warnings about the risk of blood clots or blood vessel blockage in the product information. The risk is likely to be dose-related, although available data are not sufficient to make a formal recommendation on dose reduction.

Ponatinib is authorized for use in patients with chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia who cannot take or tolerate several other medicines of the same class.

The recommended starting dose should remain 45 mg of ponatinib once a day. The cardiovascular status of the patient should be assessed before starting therapy and regularly monitored during treatment.

Healthcare professionals should consider a dose reduction in patients with ‘chronic phase’ CML who are responding well to treatment, and who might be at particular risk of blood vessel blockage. Dose modifications or treatment interruption should be considered to manage treatment toxicity; if a reduced dose is used, patients should be monitored for maintenance of therapeutic response. Ponatinib should be stopped if there has been no response after three months of treatment. Patients should be monitored for high blood pressure or signs of heart problems.

Educational material will be provided to healthcare professionals, and a new study on the safety and benefits at lower doses of the medicine is planned.

► EMA Press release, 24 October 2014.

Diclofenac and other NSAIDs: cardiovascular risks and liver damage

Australia – The Therapeutic Goods Administration (TGA) has reviewed a range of non-steroidal anti-inflammatory drugs (NSAIDs) and has found that the known risks at prescription-only dosages – high blood pressure, heart failure, heart attack and stroke, as well as liver damage in the case of diclofenac – also
apply to over-the-counter (OTC) forms of diclofenac, naproxen and ibuprofen.

While the OTC products are safe at the recommended doses and for short durations, inappropriate use or overuse can pose a significant health risk. The TGA has reminded health professionals of prescribing recommendations for NSAIDs, and has encouraged them to educate patients on the signs and symptoms of serious cardiovascular toxicity and the need to seek medical attention immediately if they occur.

The recommendations are based on a review of cardiovascular risks associated with diclofenac, naproxen, ibuprofen, celecoxib, etoricoxib, indomethacin, meloxicam and piroxicam, as well as a full safety review of diclofenac. The TGA is exploring options to reduce the risks. (1)

Canada – The marketing authorization holders of systemic diclofenac products (Voltaren®, Arthrotec®), in consultation with Health Canada, have informed health professionals that at doses from 150 mg per day these products have a risk of heart problems and stroke that is comparable to that of COX-2 inhibitors (coxibs). The risk may increase with the dose and duration of use.

The maximum recommended daily dose for all indications has been reduced to 100 mg in product information and labelling of diclofenac-containing tablets and suppositories, except for Voltaren Rapide® which allows for a 200 mg dose only on the first day of treatment for dysmenorrhea. The lowest effective dose should be used for the shortest possible duration. COX-2 inhibitors and diclofenac are not recommended in patients with pre-existing cardiovascular disease (CVD) or cerebrovascular disease, or presenting risk factors for CVD. Treatment options other than NSAIDs, particularly COX-2 inhibitors and diclofenac, should be considered first in these patients. (2)

► (1) TGA Safety advisory, 7 October 2014. (2) Health Canada Advisory, October 6, 2014.

Denosumab: osteonecrosis of the jaw and hypocalcaemia

United Kingdom – The manufacturer, in consultation with regulatory authorities, has warned that denosumab (Prolia®, Xgeva®) is associated with a risk of osteonecrosis of the jaw and hypocalcaemia. Denosumab is used to prevent bone complications in osteoporosis and certain types of cancer.

Treatment should not be started in patients due to undergo, or recovering from, oral surgery. Appropriate preventive dentistry is recommended before patients with risk factors for osteonecrosis of the jaw are given denosumab. During treatment, good oral hygiene and dental check-ups are encouraged.

The risk of hypocalcaemia increases with the degree of renal impairment. Before treatment existing hypocalcaemia must be corrected. Adequate calcium and vitamin D intake is important especially in patients with renal impairment.

Patients should immediately report any pain or swelling in the mouth, loose teeth, as well as any symptoms of hypocalcaemia.

► MHRA. Information sent to healthcare professionals in August about the safety of medicines. 2014.

Pregabalin: liver damage

Japan – The PMDA has informed health professionals that cases of fulminant hepatitis and hepatic dysfunction have
been reported in patients treated with pregabalin in Japan, including cases where causality could not be ruled out. Pregabalin is used for the treatment of neuropathic pain and fibromyalgia. The Agency recommended to revise the package insert to include these adverse events in the section on clinically significant adverse reactions.

While hepatic effects in patients taking pregabalin have also been reported to EU and WHO pharmacovigilance databases, the data do not support the conclusion that these adverse effects are associated with the use of pregabalin specifically.

► PMDA. Summary of investigation results. Pregabalin. 16 September 2014.

Zopiclone: next-day impairment

Canada – The manufacturer, in consultation with Health Canada, has informed health professionals of new dosage recommendations for the sleeping medication zopiclone (Imovane®) to minimize the risk of next-day impairment. This follows recommendations provided by the EMA for zolpidem and by the FDA for eszopiclone (see WHO Drug Information Vol. 28, No. 2, 2014).

The recommended starting dose of zopiclone has been reduced to 3.75 mg (one-half of the 7.5 mg tablet) at bedtime; the lowest effective dose for each patient should be used. The prescribed dose should not exceed 5 mg in elderly patients, in those with hepatic or renal impairment or in those being treated with potent CYP3A4 inhibitors. Dose adjustment may be needed if other CNS-depressant drugs are used at the same time. Patients should be informed of the risks and should wait at least 12 hours before driving or engaging in other activities requiring full mental alertness.


Bupropion: serious cardiovascular events

Australia – The TGA is adding strengthened warnings to product information for bupropion (Zyban® and other brand names) as serious cardiovascular adverse events have been reported with this medicine in Australia. The events included myocardial infarction, cerebrovascular accidents, and severe hypertension requiring acute treatment. A higher rate of hypertension was observed when bupropion was combined with nicotine transdermal patches. Bupropion is registered for use in Australia as a short-term adjunctive therapy, in conjunction with counselling and abstinence, to assist in smoking cessation.

The TGA advises that care should be taken when using bupropion, especially in patients with a recent history of myocardial infarction or unstable heart disease as there is limited information about the safety of bupropion in these patients. Blood pressure should be monitored during treatment, especially in patients with pre-existing hypertension, and consideration be given to stopping treatment if a clinically significant increase is observed.

► Medicines Safety Update. Volume 5, Number 5, October 2014.

Galantamine hydrobromide: serious skin reactions

Canada – The manufacturer, in consultation with Health Canada, has provided new safety information
about the risk of serious skin reactions associated with the use of galantamine hydrobromide (Reminyl ER®), used for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer’s type. Very rare cases of serious skin reactions including cases of Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and erythema multiforme have been reported with this medicine. Health care professionals should inform patients and caregivers about the signs of these serious skin reactions, and discontinue the medicine at the first appearance of skin rash. (1) Japan – The PMDA has requested a revision of the package insert for galantamine hydrobromide (Reminyl®), to include acute generalized exanthematous pustulosis in the section on clinically significant adverse reactions of the package insert. The change was based on expert opinions and available evidence from reports of this adverse event in other countries. (2) Australia – the marketing authorization holder has updated the product information for Reminyl® and other galantamine-containing products to reflect the risk of serious skin reactions. (3)

► (1) Health Canada Advisory, 18 November 2014.
(2) PMDA Summary of investigation results: galantamine hydrobromide, 20 November 2014.
(3) TGA Safety advisory, 8 December 2014.

Dimethyl fumarate: rare brain infection
United States – The U.S. Food and Drug Administration (FDA) has alerted health professionals and the public that a patient with multiple sclerosis who was being treated with dimethyl fumarate (Tecfidera®) developed progressive multifocal leukoencephalopathy (PML), a rare and serious brain infection, and later died. The patient had taken dimethyl fumarate for more than four years before the adverse event occurred.

The FDA decided to add information describing this case on the drug label and has advised that patients taking dimethyl fumarate should contact their health care professionals right away if they experience symptoms such as new or worsening weakness; trouble using their arms or legs; or changes to their thinking, eyesight, strength or balance. Health care professionals should stop dimethyl fumarate if PML is suspected.


Omalizumab: slightly increased risk of heart and brain adverse events
United States of America – An FDA review of safety studies suggests a slightly higher risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the injectable asthma drug omalizumab (Xolair®) than in those who were not treated with the medicine. Information about these potential risks have been added to the drug label. Also, information about uncertain findings regarding a potential risk of cancer was added to the drug label.

Omalizumab is used to treat patients 12 years and older with moderate to severe persistent asthma and elevated immunoglobulin E levels, and those with chronic hives without a known cause, if these conditions cannot be controlled by other treatments. Health care professionals should periodically reassess
the need for continued therapy with omalizumab.

► FDA Drug safety communication, 26 September 2014.

Risk minimization measures

Methylphenidate: web-based prescribing guide
European Union – Following an EMA review of Ritalin® and other methylphenidate-containing medicines which called for the risk minimization measures (1), six MPH Marketing Authorisation Holders (MAHs) in the EU have collaborated in order to produce a web-based physician’s guide to methylphenidate prescribing (2).

Methylphenidate is part of a multi-modal treatment approach for attention deficit hyperactivity disorder (ADHD).

The website proposes checklists aiming to minimize the risk of cardiovascular, cerebrovascular, neuropsychiatric and growth disorders. Health professionals should review or complete these checklists before treatment starts and during therapy. The materials provided on the website should be used together with the full prescribing information for each individual product.


(2) Methylphenidate (MPH): physician’s guide to prescribing [web site]. Available at: http://www.methylphenidate-guide.eu/

Medicines review started

<table>
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<tr>
<th>Medicine</th>
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| Dual anti-platelet therapy | Prevention of stent thrombosis and heart attacks                                                                 | Preliminary clinical trial data have shown a higher overall risk of death with dual anti-platelet therapy for 30 months compared to 12 months. This risk was not observed in previous large trials. | ► FDA, 16 November 2014.  
► Health Canada Advisory, 18 November 2014. |

Manufacturing quality issues

Health Canada restricts imports from various Indian sites

Canada – Health Canada has taken action to restrict imports of finished pharmaceutical products from Apotex Research Private Limited, active pharmaceutical ingredients (APIs) from Apotex Pharmachem India Pvt Ltd and from IPCA Laboratories, as well as products made with APIs from these sites (1).

Health Canada has also restricted the import of health products from three Micro Labs facilities in India: Bangalore, Goa and Hosur (2). Only products that are on authority’s “medically necessary” list will be allowed on the market, subject to prior testing by an independent third party.

In both cases, the regulatory action was triggered by data integrity concerns identified in inspections by international partners. The import ban is a precautionary measure. No specific safety issues have been identified with products already on the market, and neither Health Canada nor its regulatory partners have requested a recall of these products. Health Canada continues to work with regulatory partners to monitor compliance with good manufacturing practices at the sites.

World Health Organization – In June 2014 the WHO Prequalification Team had published on its website a notice of concern addressed to Micro Labs Ltd (3). To date the notice of concern has not been lifted. In August 2014 the prequalification team published information about WHO action taken regarding the deficiencies noted at the IPCA site (4).

(1) Health Canada Advisory, 30 September 2014.
(2) Health Canada Advisory, 27 October 2014.
(3) WHO Prequalification update, 6 June 2014.
(4) WHO Prequalification update, 14 August 2014.

Site review started

<table>
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<td>GVK Biosciences,</td>
<td>Contract research organization</td>
<td>Findings of non-compliance with good clinical practice. An inspection by the French medicines agency ANSM had raised concerns about study data used to support the marketing authorization applications of generic medicines. Some EU Member States have decided to suspend medicines marketing authorizations issued on the basis of studies conducted at the GVK Biosciences site.</td>
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<td>Hyderabad, India</td>
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<td>WHO Prequalification update, 7 August 2014</td>
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<td>EMA Press release, 5 December 2014</td>
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Regulatory news

Ebola

Update on treatments and vaccines

The Ebola crisis has prompted an unprecedented cooperation between regulators to support WHO and to advise on possible pathways for the development, evaluation and approval of medicines to fight Ebola. Progress towards provision of treatments and vaccines is summarized below.

In August 2014, a WHO-convened panel had agreed unanimously that it is ethically acceptable to use of experimental medicines and vaccines under the exceptional circumstances of the Ebola epidemic (1). In early September, WHO convened a consultation on potential Ebola therapies and vaccines (2). The importance of supportive care and community response was stressed in this and subsequent discussions.

Treatments

In September, more than 200 experts from around the world met at WHO and agreed to prioritize convalescent blood and plasma therapies for further investigation. Many questions remain to be answered about the safety and efficacy of convalescent therapies, the feasibility of implementation in countries with shattered health systems, and the prospects of scaling up therapy to curb the fatality rate (2). To support implementation, WHO has issued new interim guidance on the use of convalescent therapies for national health authorities and blood transfusion services (3). The first clinical trials of – possibly curative – transfusions of whole blood or blood plasma from recovered patients have been scheduled to be conducted in Liberia, in line with WHO technical guidelines (4).

In September the European Medicines Agency (EMA) established an expert group to review available information on Ebola experimental treatments – excluding convalescent therapies – and invited developers to submit their data (5).

Vaccines

On 29–30 September, 70 experts attended a WHO-convened consultation on Ebola vaccines. They took stock of the many ongoing efforts to rapidly evaluate the safety and efficacy of Ebola vaccines for deployment as soon as possible to critical frontline workers and ultimately to populations at risk in mass vaccination campaigns. Two candidate vaccines have clinical-grade vials available for safety trials. (6)

In October, WHO convened industry leaders and key partners to discuss trials and production of Ebola vaccine (7). Consensus was achieved to make results available in December 2014, to begin efficacy trials at the same time, and to scale up production in 2015.

Also in October the EMA gave its first scientific advice on a development plan for an Ebola vaccine, using a new ‘rolling review’ procedure for data assessment and sharing of outcomes with healthcare decision-makers in affected countries (8).

At the time of writing, safety trials of vaccines were underway in the U.S., U.K., Mali and Switzerland, and about to begin
in Gabon, Germany and Kenya. The two Swiss trials are coordinated by WHO, with testing done on healthy volunteers, some of whom will be deployed in the fight against Ebola in West Africa (9).

At the meeting of the African Vaccine Regulatory Forum (AVAREF) in early November, delegates discussed collaborative mechanisms to fast-track clinical trial approvals and registration of Ebola treatments and vaccines in affected countries, and – importantly – reaffirmed the need to build stronger health systems (10).

Supportive care

Industry leaders and key partners have emphasized that community engagement remains key to fight Ebola and have called on local communities, national governments, NGOs and international organizations to scale up concerted activities urgently. (7). Meanwhile, a WHO-coordinated retrospective study has shown that supportive care, especially rehydration and correction of metabolic abnormalities, may contribute to patient survival (11).

Diagnostics

Quick and accurate diagnosis is key in fighting Ebola. WHO has launched two urgent initiatives to accelerate the delivery of rapid, sensitive, safe and simple Ebola diagnostic tests to West African countries. The first is a close collaboration of manufacturers, researchers, Médecins sans Frontières (MSF) staff, and the non-profit organization Foundation for Innovative New Diagnostics (FIND), and aims to support the development of suitable tests. The second is the establishment of an emergency rapid review mechanism for assessing a diagnostic’s quality, safety and performance. (12)

► (1) WHO Statement, 12 August 2014.
(2) WHO. Ebola situation assessment - 26 September 2014.
(3) WHO. Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks. Version 1.0, September 2014.
(4) WHO. Ebola situation assessment, 6 November 2014.
(5) EMA Press release, 26 September 2014.
(6) WHO. Experimental Ebola vaccines. 1 October 2014.
(7) WHO News release, 24 October 2014.
(8) EMA Press release, 29 October 2014.
(9) WHO News release, 6 November 2014.
(10) WHO Essential Medicines and Health Products. African regulators’ meeting looking to expedite approval of vaccines and therapies for Ebola [web page].

Clinical trials transparency

EMA adopts policy on publication of clinical reports

European Union – The EMA’s Management Board has unanimously adopted a new policy to publish the clinical trial reports that underpin the decision-making on medicines. The policy will enter into force on 1 January 2015 and will apply to clinical reports supporting all applications for centralized marketing authorizations submitted after that date.

According to the policy’s terms of use, the reports cannot be used for commercial purposes. In the limited instances
where they may contain commercially confidential information, this will be redacted in accordance with the principles outlined in the policy’s annexes.

The new policy will serve as a complementary tool ahead of the implementation of the new EU Clinical Trials Regulation that will come into force not before May 2016. Public access to clinical reports will enable academics and researchers to re-assess data sets, and will help to avoid duplication of clinical trial ► EMA Press release, 2 October 2014.

Pre-market assessment

EMA revises guidance on biosimilars

European Union – The EMA has published its revised guideline on biosimilars. The main change is that developers can now use a comparator product authorized outside the European Economic Area (EEA) in certain clinical studies and in non-clinical studies conducted in vivo. This new concept aims to avoid unnecessary repetition of clinical trials. The comparator must be authorized by a regulatory authority with similar rigorous scientific and regulatory standards to those of EMA, and the applicant must establish that the comparator is representative of the reference medicine authorized in the EEA.

A biosimilar is a biological medicine that is similar to an already authorized reference product (comparator). To obtain a marketing authorization the developer must demonstrate in studies that the biosimilar is as safe and effective as the reference medicine, and meets the EMA’s quality requirements.

While the revised guideline will come into force as of 30 April 2015, applicants can apply some or all of its provisions with immediate effect. Two related guidelines and procedural guidance are also being updated.

► EMA Press release, 29 October 2014.

EMA proposes harmonized clinical trials plan for vaccine in children

European Union – The EMA has proposed a single development plan for new tetanus-diphtheria-acellular pertussis vaccines that all pharmaceutical companies across the EU should follow. The proposal aims to avoid the duplication of similar clinical trials and the unnecessary exposure of children to clinical testing.

As the schedules of child vaccinations vary slightly between EU countries, a large number of fairly similar clinical trials are currently conducted in children when a new vaccine is being developed. The EMA collaborated with the European Centre for Disease Prevention and Control (ECDC) to define a single schedule for clinical trials. A panel of public health vaccinology experts have endorsed the proposal.

The proposed plan has been released for a three-month public consultation.

► EMA News, 23 September 2014.

EMA pilot to seek patient views on medicines risks and benefits

European Union – The European Medicines Agency (EMA) has launched a pilot project to involve patients in the assessment of the benefits and risks of medicines in its Committee for Medicinal Products for Human Use (CHMP). Patients will be invited to present their views on medicines for which there is an unmet medical need and where the Committee has doubts on its regulatory
decisions at any stage of the product life cycle. EMA has published a document outlining the principles of this approach.

The first active substance included in this pilot project has been afamelanotide, leading to the approval of a treatment for erythropoietic protoporphyria (EPP), a rare genetic blood disorder which causes an absolute intolerance to light (see also page 466).

The pilot project stems from a wider EMA strategy to involve patients in the Agency’s activities. It will run for at least one year, leading up to a proposal for full implementation.

► EMA Press release, 26 September 2014.

Australia to recognize EU conformity assessment for medical devices

Australia – New regulations will allow Australian manufacturers to obtain market approval for most medical devices based on conformity assessment certification from European notified bodies, the accredited organizations that carry out product assessments in the EU.

The highest risk devices such as those containing medicines or tissues of animal, biological or microbial origin, or Class 4 in vitro diagnostics (IVDs) including HIV tests, will still need TGA conformity assessment. The respective regulatory amendments are expected to be in place later this year.

► Australian Assistant Minister for Health, Media release, 15 October 2014.

Editor’s note: As the above media release mentions, regulators commonly adapt the level of control for IVDs to the level of risk that product deficiencies would pose for public health. IVDs (including products like tuberculosis or malaria IVDs, which are considered ‘low-risk’ in industrialized countries) are crucial in guiding treatment decisions for priority diseases. On the other hand, regulation of IVDs is still very limited or absent in many countries. Read more in WHO Drug Information Vol. 28, No. 3, 2014 on what WHO is doing to bring quality-assured IVDs to its Member States.

Pharmacovigilance

Canada passes Vanessa’s Law

Canada – The Government of Canada has passed modernized laws for drugs and medical devices. The Protecting Canadians from Unsafe Drugs Act, known as “Vanessa’s Law”, will enable the Government to recall unsafe medicines, impose tough penalties, compel pharmaceutical companies to make changes to products or do further testing, require mandatory adverse events reporting by health care institutions, and require transparency on regulatory decisions.

The Act introduces the most profound and important changes to the Food and Drugs Act in its fifty years of existence. It is named after an Australian Member of Parliament’s daughter who died of a heart attack while on a prescription drug that was later deemed unsafe and removed from the market.


EU project on using smartphones for drug safety information

European Union – The MHRA is leading a consortium of regulators, academics and the pharmaceutical industry in a three-year project, known as WEB-RADR, to develop new ways of gathering information on suspected adverse drug reactions (ADRs) using smartphones and social media. WEB-RADR will help to
develop recommendations on how these new tools should be used ethically and scientifically alongside existing drug safety monitoring systems.

The project is funded through the Innovative Medicines Initiative, a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA).


EMA expands public web access to reports on suspected side effects

European Union – The EMA has added to its website information on suspected adverse drug reactions for an additional 1,700 active substances contained in medicines approved in the European Union (EU) by national authorities. The information comes directly from the EudraVigilance database. The web site was launched in 2012 and initially only contained adverse events information for centrally authorized medicines. Over the next few years it will be expanded to cover all medicines available in the EU.

Since July 2012 European pharmacovigilance legislation provides the possibility for patients to report side effects directly to the authorities in all EU Member States. Increasing numbers of patient reports are being received in the EudraVigilance database.

► EMA Press release, 6 October 2014.

Australia, Switzerland create web portals to report adverse reactions

Australia - The TGA has launched a new web-based service for consumers to report adverse events associated with medicines and vaccines.

In 2013 only about 3% of adverse events reports received by the TGA came from consumers. The new web site is part of TGA’s activities taken in line with an international trend for regulators to encourage reporting by consumers. The TGA has also published a brochure outlining what and how to report, and is undertaking awareness activities and consumer research. (1)

Switzerland – With immediate effect, healthcare professionals and pharmaceutical companies can report suspected adverse drug reactions directly on the Internet through Swissmedic’s “EIViS” (Electronic Vigilance System) online reporting portal. Use of the portal is subject to registration on the EIViS website, and companies are also required to attend a Swissmedic training course. Data protection and security satisfy the most stringent requirements.

Swissmedic hopes that EIViS will result in more and better reports being received nearer to the event, helping to improve drug and patient safety in Switzerland. (2)

► (1) TGA News, 24 September 2014.
(2) Swissmedic Announcement, 6 October 2014.

New MHRA guidance on reporting adverse drug reactions in children

United Kingdom – The MHRA has announced new simplified guidance on how healthcare professionals should report suspected adverse drug reactions (ADRs) in children to its Yellow Card Scheme (mhra.gov.uk/yellowcard).

Recognizing that it is impractical to report all suspected ADRs in children, the new guidance asks that healthcare professionals report those reactions that are serious, medically significant or result
in harm, and those that are associated with newer drugs and vaccines, identified by a black triangle symbol in the Yellow Card Scheme. The guidance also places greater importance on the reporting of medication errors in children resulting in suspected ADRs, and explains the many reasons why monitoring of ADRs in children is particularly important.


Organizations

Australia and New Zealand to keep separate regulatory authorities
The Australian and New Zealand Governments have agreed to cease efforts to establish a joint therapeutic products regulator, the Australia New Zealand Therapeutic Products Agency (ANZTPA). The decision was taken after a review of progress and an assessment of the costs and benefits involved. The two countries will continue to co-operate on the regulation of therapeutic products. (1)

The New Zealand authority has announced that work will now be undertaken to strengthen the national regulatory scheme for therapeutic products. (2)

(2) Medsafe Media release, 20 November 2014.

Veterinary medicines

EU proposes veterinary medicines legislation revisions
European Union – The EMA has welcomed a major revision of the legal framework for veterinary medicines in the EU proposed by the European Commission. The revision includes measures to fight the development of antimicrobial resistance, notably by restricting the veterinary use of certain antimicrobials that are reserved for the treatment of infections in people. It also proposes streamlined marketing authorization procedures, simpler pharmacovigilance rules, better incentives for innovation, and clearer rules for internet retailing of veterinary medicines.

Other EU institutions will now consider the Commission’s proposals and will adopt their positions.

► EMA News, 10 September 2014.

Sales of veterinary antibiotics in Europe decrease
European Union – Sales of veterinary antibiotics have decreased by 15% according to the Fourth European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report. Increased awareness of the threat of antimicrobial resistance as well as national programmes, campaigns and restrictions have been cited among the reasons for the decrease.

The ESVAC report is issued every year to inform antimicrobial policy and the responsible use of antimicrobials in EU Member States.

► EMA Press release, 15 October 2014.
Netupitant and palonosetron for chemotherapy-induced nausea

Product name: Akynzeo®
Class: Netupitant and palonosetron fixed-dose combination; ATC code: A04AA55
Approval: FDA
Use: Treatment of nausea and vomiting in patients undergoing cancer chemotherapy.
Benefits: Added effectiveness in preventing vomiting episodes in the acute, delayed and overall phases after the start of cancer chemotherapy, compared with oral palonosetron alone.

FDA News release, 10 October 2014.

Naloxegol for opioid-induced constipation

Product name: Movantik®
Class: Peripherally acting opioid receptor antagonist; ATC code: A06AH03
Approval: FDA, EMA
Use: Oral treatment for opioid-induced constipation in adults with chronic non-cancer pain.
Benefits: Additional supportive care option to decrease the constipating side effects of opioids.
Safety information: The FDA is requiring a postmarketing study to further evaluate the potential risk of cardiovascular adverse events.

FDA News, 16 September 2014.
EMA /CHMP Summary of opinion, 25 September 2014.

Dulaglutide for type 2 diabetes

Product name: Trulicity®
Class: Glucagon-like peptide-1 (GLP-1) receptor agonist
Approval: FDA; EMA
Use: Once-weekly subcutaneous injection to improve glycaemic control in adults with type 2 diabetes.

Benefits: New treatment option for patients with type 2 diabetes who cannot be managed with first-line regimens. Can be used alone or added to existing treatment regimens.

Safety information: Dulaglutide should not be used in patients with diabetic ketoacidosis or those with severe stomach or intestinal problems. As thyroid C-cell tumours have been observed in rodent studies, dulaglutide should not be used in patients with a personal or family history of medullary thyroid carcinoma (MTC), or in patients with multiple endocrine neoplasia syndrome type 2 (which predisposes them to MTC).

FDA News release, 18 September 2014.
EMA /CHMP Summary of opinion, 25 September 2014.

Antihaemophilic factor (recombinant), porcine sequence in acquired haemophilia A

Product name: Obizur®
Class: Porcine coagulation factor VIII
Approval: FDA (orphan drug designation)
Use: Treatment of bleeding episodes in adults with acquired hemophilia A (acquired factor VIII deficiency).

Benefits: Porcine Factor VIII is similar enough to human Factor VIII to be effective in blood clotting, but is less likely to be affected by the antibodies against human Factor VIII that are present in people with acquired haemophilia A.

FDA News release, 24 October 2014.

Nonacog gamma in haemophilia B

Product name: Rixubis®
Class: Antihaemorrhagic, blood coagulation factor IX; ATC code: B02BD04
Approval: EMA
Use: Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) in patients of all age groups.
Benefits: Ability to prevent and treat bleeds in patients with haemophilia B including during surgery.

► EMA/CHMP Summary of opinion, 23 October 2014.

Afamelanotide for erythropoietic protoporphyria
Product name: Scenessé®
Class: Protective against UV radiation for systemic use; ATC code: D02BB02
Approval: EMA (orphan designation)
Use: Prevention of phototoxicity in adults with erythropoietic protoporphyria (EPP), a rare genetic disease causing intolerance to light.
Benefits: Afamelanotide stimulates the production of eumelanin, which naturally protects the skin against phototoxic reactions caused by sunlight, thereby significantly improving patients’ quality of life.
Safety information: The company will implement a risk management plan and establish a registry of patients to collect safety and efficacy data.
Note: The approval was granted under exceptional circumstances, despite a lack of robust efficacy data due to the difficulties to recruit patients for placebo-controlled trials. Assessment was supported by data from the use of the medicine in compassionate use programmes globally. In addition, the EMA Committee heard feedback from patients and healthcare professionals involved in an expert group. This was the first time that patients were involved in EMA discussions on the benefits and risks of a medicine (see also page 461).
► EMA Press release, 24 October 2014.

Darunavir & cobicistat for HIV infection
Product name: Rezolsta®
Approval: EMA

Class: Antiretroviral fixed-dose combination; ATC code: J05AR14
Use: Treatment of human immunodeficiency virus (HIV) in antiretroviral therapy (ART)-naive adults and ART-experienced adults with no darunavir (DRV) resistance associated mutations.
Benefits: Ability to provide sustainable virological suppression if given in combination with other antiretroviral medicinal products for treatment of HIV-1 infection.
► EMA/CHMP Summary of opinion, 25 September 2014.

Ledipasvir & sofosbuvir for hepatitis C infection
Product name: Harvoni®
Class: Fixed-dose combination of two direct-acting antivirals. Sofosbuvir is an NS5B inhibitor; ledipasvir – a new drug – is an NS5A inhibitor. ATC Code (temporary classification): J05AX65
Approval: EMA (accelerated assessment), FDA (priority review, breakthrough therapy designation)
Use: Treatment of chronic hepatitis C virus infection in adults.
Benefits: High cure rates in patients with chronic HCV infection without the need for treatments involving interferons. The latter are associated with poor tolerability and potentially serious side effects that rule out such treatment in a considerable proportion of HCV patients.
► EMA News, 26 September 2014.
FDA News release, 10 October 2014.

Dasabuvir for hepatitis C infection
Product name: Exviera®
Class: Antiviral agent, NS5B inhibitor. ATC code (temporary classification): J05AX16
Approval: EMA (accelerated assessment)
Use: Treatment of chronic hepatitis C in adults, in combination with other medicinal products.
Approved

**Benefits:** Ability to inhibit viral replication in infected host cells which can lead to the eradication of the virus, correlating to a cure of chronic hepatitis C virus (HCV) infection, in both non-cirrhotic and compensated cirrhotic patients with genotype 1a/1b HCV infection.

▶ EMA/CHMP opinion, 20 November 2014.

**Ombitasvir & paritaprevir & ritonavir for hepatitis C infection**

**Product name:** Viekirax®

**Class:** Fixed-dose combination of two antiviral agents, inhibitors of NS5A (ombitasvir) and NS3/4A (paritaprevir), with ritonavir as a pharmacokinetic enhancer. ATC code (temporary classification): J05AX67

**Approval:** EMA (accelerated assessment)

**Use:** Treatment of chronic hepatitis C in adults, in combination with other medicinal products.

**Benefits:** Ability to inhibit viral replication in infected host cells which can lead to the eradication of the virus, correlating to a cure of chronic hepatitis C virus (HCV) infection, in both non-cirrhotic and compensated cirrhotic patients with genotype 1a/1b and 4 HCV infection.

▶ EMA/CHMP opinion, 20 November 2014.

**Meningococcus B vaccine**

**Product name:** Trumenba®

**Class:** Meningococcal Group B vaccine; ATC code: J07AH09

**Approval:** FDA (accelerated approval, breakthrough therapy)

**Use:** Prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10–25 years of age.

**Benefits:** First licenced meningococcal group B vaccine in the U.S.; in addition to licenced vaccines for serogroups A, C, Y and W.

▶ FDA News release, 29 October 2014.

**Pembrolizumab for advanced melanoma**

**Product name:** Keytruda®

**Class:** Antineoplastic; PD-1 pathway blocker (first in class). ATC code (temporary classification): L01XC18

**Approval:** FDA (accelerated approval; breakthrough therapy, orphan product, priority review)

**Use:** Treatment of advanced or unresectable melanoma no longer responding to other drugs (ipilimumab, or ipilimumab and a BRAF inhibitor in patients whose tumors express a BRAF V600 mutation)

**Benefits:** Substantial improvement over existing therapies; shrinking tumours in approximately 24 percent of patients. Improvement on survival remains to be established.

**Safety information:** Potential for severe immune-mediated side effects that can involve healthy organs, including the lung, colon, hormone-producing glands and liver. In safety studies, such effects occurred uncommonly.

▶ FDA News release, 4 September 2014.

**Ramucirumab for gastric cancer**

**Product name:** Cyramza®

**Class:** Human receptor-targeted antibody that specifically binds VEGF Receptor 2 and blocks angiogenesis by binding of VEGF-A, VEGF-C, and VEGF-D.

**Approval:** EMA (orphan designation)

**Use:** Treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. Ramucirumab can be used in combination with paclitaxel, or as monotherapy in patients for whom treatment in combination with paclitaxel is not appropriate.

**Benefits:** Ability to improve the survival in patients compared to chemotherapy alone (when used in combination with
chemotherapy) and compared to placebo (when used alone).

**Secukinumab for plaque psoriasis**

**Product name**: Cosentyx®
**Class**: Immunosuppressant; ATC code: L04AC10
**Approval**: EMA
**Use**: Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy
**Benefits**: More efficacious than placebo with respect to two co-primary endpoints in clinical studies.

**Pirfenidone for idiopathic pulmonary fibrosis**

**Product name**: Esbriet®
**Class**: Immunosuppressant; ATC code: L04AX05
**Approval**: FDA (fast track, priority review, orphan product, and breakthrough designations).
**Use**: Treatment of idiopathic pulmonary fibrosis
**Benefits**: Additional treatment option for patients with idiopathic pulmonary fibrosis, a serious, chronic condition. Current treatments include oxygen therapy, pulmonary rehabilitation, and lung transplant.
**Notes**: The FDA also approved nintedanib for the same use, see below. Pirfenidone was approved by EMA in 2011 under orphan designation.
**Safety information**: Not recommended for patients with moderate to severe liver problems. Can cause birth defects or death to an unborn baby; women who are able to get pregnant should use adequate contraception during and for at least three months after the last dose of treatment.

**Nintedanib for non-small cell lung cancer / idiopathic pulmonary fibrosis**

**Product name**: EU: Vargatef®, Ofev®; U.S.: Ofev®
**Class**: Tyrosine kinase inhibitor antineoplastic agent, angiogenesis inhibitor. ATC code (temporary classification): L01XE31
**Approval**: EMA (orphan designation for Ofev®), FDA (fast track, priority review, orphan product, and breakthrough designations)
**Use**: Vargatef®: In combination with docetaxel, treatment of locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology after first-line chemotherapy. Ofev®: Treatment of idiopathic pulmonary fibrosis.
**Benefits**: Vargatef®: Improvement in progression-free survival and overall survival compared to docetaxel plus placebo. Ofev®: Additional treatment option for patients with idiopathic pulmonary fibrosis.
**Safety information**: Not recommended for patients with moderate to severe liver problems. Can cause birth defects or death to an unborn baby; women who are able to get pregnant should use adequate contraception during and for at least three months after the last dose of treatment.

**Olaparib for a subtype of ovarian cancer**

**Product name**: Lynparza®
**Class**: Poly ADP ribose polymerase (PARP) inhibitor (first-in-class)
**Approval**: EMA (orphan designation)
**Use**: Monotherapy for the maintenance treatment of adult patients with relapsed, platinum-sensitive epithelial ovarian,
fallopian tube or primary peritoneal cancer carrying a BRCA gene mutation, and who have responded to platinum-based chemotherapy.

**Benefits:** Targeted treatment of a subtype of ovarian cancer for which limited treatment options are available.

► EMA Press release, 24 October 2014.

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**Blinatumomab for a rare form of acute lymphoblastic leukaemia**

**Product name:** Blincyto®

**Class:** Immunotherapeutic monoclonal antibody, T-cell engager

**Approval:** FDA (breakthrough therapy designation, priority review and orphan product designation)

**Use:** Treatment of relapsed or refractory Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukaemia.

**Benefits:** Potential for substantial improvement over available therapies. The manufacturer is required to conduct a study to verify that the drug improves survival.

**Safety information:** Boxed warning about the risks of low blood pressure and difficulty breathing (cytokine release syndrome) at the start of the first treatment, difficulty with thinking (encephalopathy) and other nervous system side effects. The medicine was approved with a Risk Evaluation and Mitigation Strategy, which consists of a communication plan to inform health care providers about the serious risks and the potential for preparation and administration errors.

► FDA News release, 3 December 2014.

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**Abuse-deterrent hydrocodone single-entity, extended release product**

**Product name:** Hysingla ER®

**Class:** Opioid analgesic

**Approval:** FDA (in line with guidance on abuse-deterrent properties)

**Use:** To treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

**Benefits:** The formulation is expected to reduce abuse by ingestion, snorting or injection.

**Safety information:** The product can still be abused or misused, and can then cause an overdose that may result in death. Additional postmarketing studies will be conducted to assess the effects of the abuse-deterrent features on the risk for abuse, and the consequences of that abuse in the community.

**Note:** This is the fourth extended-release opioid analgesic to be approved by the FDA with labelling consistent with the FDA's 2013 draft guidance on evaluation and labelling of abuse-deterrent opioids (after OxyContin®, Targiniq® and Embeda®).


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**Ketoconazole for Cushing’s syndrome**

**Product name:** Ketoconazole HRA®

**Class:** Antimycotic for systemic use; ATC code: J02AB02

**Approval:** EMA (orphan designation; accelerated approval of new indication)

**Use:** Treatment of Cushing’s syndrome

**Benefits:** Additional treatment option when surgery or other medicines fail or cannot be administered.

**Note:** Ketoconazole has been used “off-label” for more than 30 years to treat this rare and potentially life-threatening condition, although it has never been authorized for this indication in the EU.

**Safety information:** In July 2013, EMA recommended to suspend the marketing
authorizations of oral ketoconazole medicines to treat fungal infections due to the risk of liver injury. In the treatment of Cushing’s syndrome however, the benefits are greater than the risks, which can be managed by close monitoring of the patients’ liver function. The product is to be prescribed only by specialists as the posology needs to be individualized for each patient. Relevant information will be sent to healthcare professionals in the EU.

► EMA Press release, 26 September 2014.

Ulipristal emergency contraceptive without prescription

Product name: ellaOne®
Class: Emergency contraceptive; ATC code: G03AD02
Approval: EMA/CHMP recommendation, to be sent to the European Commission for a legally binding decision.
Use: To prevent unintended pregnancy. Must be taken within 120 hours (five days) of unprotected intercourse or contraceptive failure; works best if taken within 24 hours.

Benefits: Making the medicine available without prescription in the EU should speed up women’s access to the medicine and therefore increase its effectiveness.

Safety information: The safety profile of ulipristal is comparable to that of levonorgestrel-containing emergency contraceptives, which are already available without prescription in most EU countries and are registered for use up to 72 hours after unprotected intercourse or contraceptive failure.

Notes: If granted by the European Commission, the re-classification to non-prescription status would in principle need to be implemented by all EU Member States. Any exception regarding the non-prescription status of this medicine would fall within the responsibilities of the Member States.

Publications and events

Access to treatment

**2014 Access to Medicines Index launched**

Haarlem – The 2014 Access to Medicine Index, launched on 17 November, presents an updated ranking of the top 20 pharmaceutical companies. Key findings suggest that companies do more to improve access although progress is uneven, and that pricing strategies are increasingly tailored. On the other hand, 18 of the 20 companies have been the subject of settlements or judgements regarding breaches in ethical marketing, bribery or corruption standards or competition laws in the last two years.

The Access to Medicines Foundation, based in the Netherlands, is an international not-for-profit organisation dedicated to addressing the challenges of access to medicine worldwide. The Index is published every two years and gives insights into what the pharmaceutical industry is doing to improve the situation. The Index is funded by the Bill & Melinda Gates Foundation, the Dutch Ministry of Foreign Affairs and the UK Department for International Development.


**New Lancet Commission on Essential Medicines Policies**

*The Lancet* has commissioned a group of 19 independent experts in a variety of disciplines to generate a report which is planned to be published by the end of 2015, 30 years after the Nairobi Conference on the Rational Use of Drugs. The Commission will formulate recommendations for global essential medicine policies for the next two decades.

Global access to essential medicines is a highly charged political issue. Radical civil society action was required to force the pharmaceutical sector to provide life-saving ARVs to people living with HIV/AIDS. Today, the discussions need to include second-line and third-line antiretrovirals, as well as medicines for cancer, hepatitis C, and non-communicable diseases. The Commission’s work will raise global awareness of the critical importance of essential medicines policies to achieve universal health coverage.


**WHO invites hepatitis medicines for prequalification**

Geneva – WHO has expanded its list of medicines invited for prequalification to include treatments for hepatitis B and C. The 12th Invitation for Expression of Interest (EOI) related to HIV and AIDS-related medicines includes sofosbuvir, simeprevir and ribavirin formulations. An additional dosage strength for flucytosine is also included.

► WHO Prequalification update, 19 September 2014.

The lists of medicines invited for prequalification (HIV/AIDS including hepatitis B and C, Malaria, Tuberculosis,
Reproductive Health, Influenza, Zinc, and Neglected Tropical Diseases) are available at http://apps.who.int/prequal - Information for applicants - Invitations for Expression of Interest (EOI).

**Antiviral Therapy special issue on access to HIV treatment**

London – A special issue of *Antiviral Therapy* on the subject of ARV access in resource-poor countries has been published in partnership with UNAIDS. It includes articles on all aspects of these life-saving medicines: discovery and development, production, market and pricing, procurement and supply, effective use in treatment regimens, and delivery to patients.

The special issue includes a review of the regulatory framework for access to safe, effective quality medicines. The article points to the disparities in regulatory capacity and describes how WHO-prequalification and related initiatives have increased access to good quality medicines worldwide and – perhaps more importantly – are now laying the groundwork for collaborative approaches aiming to ensure that pharmaceutical products meet the same, stringent quality standards in all parts of the world.

► [Antivir Ther. 2014;19 Supplement 3.](#) *Full supplement freely available on the International Medical Press web site.*


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**Intellectual property**

**Interagency symposium on access to medical technologies**

Geneva – The World Health Organization (WHO), World Intellectual Property Organization (WIPO) and World Trade Organization (WTO) have held their fourth trilateral symposium, titled “Innovation and access to medical technologies: challenges and opportunities for middle income countries”.

Middle-income countries today include many countries with a poor public health situation for large parts of their population. The symposium aimed to identify ways to strengthen the capacity of governments to develop and apply policies that ensure access to new products while fostering an environment conducive to innovation.

➤ [WTO News, 5 November 2014.](#)

**WHO report on patent status of hepatitis medicines**

Geneva – To help countries achieve equitable access to quality, effective, affordable and safe Hepatitis C treatments, WHO has published an analysis of the patent situation for seven new hepatitis treatments. The analysis, carried out by Thompson Reuters on behalf of WHO, provides crucial information about the patents themselves and the countries which they cover. This information is vital to inform government policies and actions when selecting and purchasing medicines for their populations.

➤ [WHO publishes analysis of patent situation of new hepatitis treatments [web page].](#) Published 4 November 2014.
NIH and FDA win top award for meningitis vaccine licensing deal

Washington – The National Institutes of Health (NIH) and the FDA have received the “2014 Deals of Distinction Award” for the year’s most outstanding intellectual property licensing deal for technology transfer of a new, low-cost serogroup A meningitis vaccine named MenAfriVac.

According to WHO, 80–85% of all meningitis infections in sub-Saharan Africa are from group A. The vaccine has a low production cost and does not require constant refrigeration. The technology was licensed from the NIH Office of Technology Transfer to PATH, a Seattle-based non-profit leader in global health innovation, and then sublicensed to the Serum Institute of India (SII) under the Meningitis Vaccine Project, a partnership of PATH and WHO.

The deal has enabled the manufacture of MenAfriVac at an affordable cost for 26 African countries where serogroup A meningitis is most common. To date, more than 150 million people in 12 African countries have been vaccinated, with no reported cases of serogroup A meningitis in vaccinated populations.

► Licensing Executives Society (USA and Canada) Inc. Press Release, 9 September 2014.

Medicines for children

Improving medicines for children in Canada

Ottawa – An expert panel report released by the Council of Canadian Academies addresses the importance of developing safe and effective medicines for children. The panel advises that studying medicines in children is always possible and is in their best interests. The report was requested by the Minister of Health, on behalf of Health Canada.

Children respond to medicines differently from adults, and many of the medicines that they take have not been proven safe and effective in children. The panel found that in the U.S. and the EU paediatric medicines research is encouraged, required, and monitored in ways that offer lessons for Canada, and that, while paediatric medicines research is a Canadian strength, it requires reinforcement and sustained capacity and infrastructure to realize its full potential. The report stresses the need for collaboration across sectors and countries, and for tailored solutions reflecting the unique Canadian context.

This comprehensive, evidence-based assessment of the state of research and regulations on children’s medicines will serve as an important resource for policy-makers, regulators, health care professionals and researchers in the years to come. It is available both in English and in French.


Medicines use

Study shows better drug and antibiotic use where there is policy implementation

A study of public sector medicines use and prescribing indicators indicates that between 2002 and 2008 implementation of rational medicines use policies in countries is associated with better medicines use in the public sector. For example, there was less antibiotic use for upper respiratory tract infection in those countries that reported implementation of policies than in those that did not.
Data came from surveys on medicine uses conducted in primary health care facilities by various researchers according to a methodology and indicators established by WHO in collaboration with INRUD, and from WHO databases for 2002–2008 on implementation of 36 policy variables.

Suboptimal medicine use is a global public health problem. The findings highlight the importance of WHO’s core normative functions, which have come under threat in recent years. The authors emphasize the importance of recognizing the critical role of the WHO and of ensuring that its core functions are sustained and enhanced.


WHO matters

Two WHO Expert Committee meetings held

Geneva – The World Health Organization (WHO) Expert Committees are the highest technical advisory bodies to the WHO Director-General and Member States. Two Expert Committee meetings on medicines were held concurrently in Geneva on 13-17 October 2014.

At its forty-ninth meeting, the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) adopted a number of specifications, general texts and International Chemical Reference Standards for The International Pharmacopoeia (see pages 431 ff. for an example of a global specification). The Committee further adopted 16 technical supplements and eight guidelines for manufacturers and regulators, including new guidance on good review practice prepared under the leadership of the Asian-Pacific Economic Cooperation’s Regulatory Harmonization Steering Committee.

At its sixty-fifth meeting the WHO Expert Committee on Biological Standardization (ECBS) discussed standards and guidance related to inactivated polio vaccine, changes in manufacturing, good manufacturing practices for biological products and regulatory risk assessment. It also reviewed studies to establish international standards, including the first WHO reference reagent for anti-malaria (Plasmodium falciparum) human serum to support the development of a malaria vaccine.

Cross-cutting topics addressed by both Committees included collaboration and capacity-building platforms, regulatory pathways for approval of needed products, and systems to prevent and manage medicines shortages.

The guidelines adopted by the Expert Committees are published as annexes to the WHO Technical Report Series. The texts adopted at this year’s meetings will be presented to the WHO Governing Bodies in 2015 for information and final comments, and will then constitute WHO technical guidance recommended for implementation by WHO Member States and other parties.

► ECSPP: Guidelines are available at www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines

► ECBS website: www.who.int/biologicals/expert_committee

WHO prequalification of medicines

2013 annual report

Geneva – The WHO Prequalification Team: medicines (PQTm) has published
its annual report for 2013. The year has seen a record number of products prequalified, including many ‘firsts’ of their kind. The prequalification teams for medicines, vaccines and diagnostics have been brought together within one WHO unit. A wide range of supporting activities, services and collaborative initiatives are ongoing to strengthen both prequalification and regulatory capacity in countries.

WHO currently has no regular budget to fund its prequalification activities. Financial support was received from UNITAID, which provided approximately 80% of the operational costs, from the Bill and Melinda Gates Foundation, and from the Global Fund, UNFPA and WHO’s Department of Neglected Tropical Diseases for procurement-related risk assessments by the Expert Review Panel (ERP). Although donor funding will continue, WHO is working towards a sustainable funding mechanism that will cover at least half of the operational costs for prequalification of medicines, diagnostics and vaccines.

In its 13 years of existence, PQTm has evolved into a global platform for regulators and manufacturers working together according to internationally recognized, harmonized quality standards. This enables them to cope with the challenges of today’s increasingly complex and globalized pharmaceutical markets. More support from the global community is needed to achieve broader impact in this crucial task.

Consultation documents

*The International Pharmacopoeia*

*Flucytosinum*
Flucytosine

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/14.599, December 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Flucytosine in The International Pharmacopoeia.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by *insert* and *delete* in the working document available at the above-mentioned web address.]

**Molecular formula.** $C_4H_4FN_3O$

**Relative molecular mass.** 129.1

**Graphic formula.**

![Graphic of Flucytosine](image)

**Chemical name.** 5-Fluorocytosine; 4-amino-5-fluoro-2(1H)-pyrimidinone; CAS Reg. No. 2022-85-7.

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

**Solubility.** Sparingly soluble in water; slightly soluble in ethanol (≈750 g/L) TS; practically insoluble in ether R.

**Category.** Antifungal.

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

**Additional information.** Flucytosine melts at about 295°C.
Requirements

**Definition.** Flucytosine contains not less than 99.0% and not more than 101.0% of \( \text{C}_4\text{H}_4\text{FN}_3\text{O} \), calculated with reference to the dried substance.

**Identity tests**

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

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

  B. The absorption spectrum of a 5.0 µg/mL solution in hydrochloric acid (0.1 mol/L) VS, when observed between 230 nm and 350 nm, exhibits a maximum at about 286 nm; the absorbance of a 1 cm layer at this wavelength is about 0.36.

  C. See the test described below under Related Substances, Test A. The principal spot obtained with solution (1) corresponds in position, appearance and intensity with that obtained with solution (2).

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

**Clarity and colour of solution.** Dissolve 0.5 g in carbon dioxide-free water R and dilute to 50 mL with the same solvent. This solution is clear and not more intensely coloured than standard colour solution Yw0 when compared as described under 1.11 Colour of liquids.

**Sulfated ash.** Determine the sulfated ash content as described under (2.3) using a platinum crucible; not more than 1 mg/g.

**Loss on drying.** Dry to constant weight at 105°C; it loses not more than 10 mg/g.

**Fluorides.** Prepare and store all solutions in plastic containers.

Prepare the following buffer solution. Dissolve 58 g of sodium chloride R in 500 mL of water R. Add 57 mL of glacial acetic R and 200 mL of a 100 g/L solution of cyclohexylenedinitrilotetra-acetic acid R in sodium hydroxide (~40 g/L) TS. Adjust the pH to 5.0–5.5 with sodium hydroxide (~200 g/L) TS and dilute to 1000 mL with water R.

Prepare the following solutions. For solution (1) dissolve 1.00 g of the test substance in water R and dilute to 100.0 mL with the same solvent. For solution (2) dissolve 4.42 g of sodium fluoride R, previously dried at 120°C for 2 hours in water R to obtain a solution containing 1.9 mg fluoride ion per mL. Dilute solution (2) further to obtain standard solutions with the following concentrations: solution (3) 19 µg/mL; solution (4) 1.9 µg/mL; and solution (5) 0.19 µg/mL.

Add to 20.0 mL each of solution (1), (3), (4) and (5) 10.0 mL of the buffer solution and stir the solution using a magnetic stirrer and a plastic-coated stirring bar. Use a fluoride-ion-selective electrode and a silver/silver chloride reference electrode system, connected to a potentiometer capable of indicating reproducibly a minimum of ±0.2 mV. Insert the previously rinsed and dried electrodes into the solutions, stir for 5 minutes and read the potential in mV. Plot the logarithms of the fluoride ion concentration in solution (3), (4) and (5) versus the measured potential.

Determine the concentration of fluoride ion in solution (1), reading off from the standard curve the value of µg of fluoride ion per mL correlating with the measured potential and divide by the sample mass taken to obtain the content in the sample; not more than 200 µg/g.
Related Substances.

Either test A or test B may be applied.

A. Impurity A (fluorouracil) and impurity B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 60 volumes of nitromethane R, 20 volumes of methanol R, 10 volumes of ethyl acetate R and 10 volumes of water R as the mobile phase. Apply separately to the plate 1 μL of each of the following two solutions. Use a mixture composed of 60 volumes of methanol R, 35 volumes of water R and 5 volumes of glacial acetic acid R as the solvent. For solution (1) use 10 mg of the test substance per mL. For solution (2) use 10 mg of flucytosine RS per mL. Apply also 20 μL of each of the following two solutions. Use the same solvent as described above. For solution (3) use 20 mg of the test substance per mL. For solution (4) use 30 μg of fluorouracil RS per mL. After application allow the spots to dry in a current of cool air. Develop over a path of 9 cm in an unsaturated chromatographic chamber. After removing the plate from the chromatographic chamber allow it to dry exhaustively in a current of air. Examine the chromatogram in ultraviolet light (254 nm). Flucytosine, impurity A (fluorouracil) and impurity B are eluted with the following Rf values: flucytosine about 0.26, impurity A (fluorouracil) about 0.54 and impurity B about 0.74.

In the chromatogram obtained with solution (3) any spot corresponding to impurity A (fluorouracil) or impurity B is not more intense than the principal spot in the chromatogram obtained with solution (4) (0.15%).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated particles of silica gel the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm).

As the mobile phase use a solution prepared as follows. Dissolve 13.6 g of potassium dihydrogen phosphate R in 950 mL of water R, adjust to pH 2.0 by adding phosphoric acid R and add 50 mL of methanol R.

Prepare the following solutions in a dissolution solvent prepared by dissolving 13.6 g of potassium dihydrogen phosphate R in 950 mL of water R and adding 50 mL of methanol R. For solution (1) use 0.3 mg of the test substance per mL. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 0.3 μg of flucytosine per mL. For solution (3) use 0.3 μg of fluorouracil RS per mL. For solution (4) mix 1.0 mL of solution (2) and 1.0 mL of solution (3).

Operate with a flow rate of 1.1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μL each of solution (1), (2), (3) and (4) and record the chromatograms for 15 times the retention time of flucytosine.

Use the chromatogram obtained with solution (3) to identify the peak due to impurity A (fluorouracil). Impurity B is eluted at a relative retention of about 12 with reference to flucytosine (retention time about 2.2 minutes).

The test is not valid unless the resolution between the peaks due to flucytosine and impurity A (fluorouracil) in the chromatogram obtained with solution (4) is not less than 5.0 and the symmetry factor for the peak due to flucytosine in the chromatogram obtained with solution (2) is not more than 2.0.
In the chromatogram obtained with solution (1):

- the area of any peak due to impurity A (fluorouracil) is not greater than 1.5 times the area of the corresponding peak obtained with solution (3) (0.15%);
- the area of any peak due to the impurity B, when multiplied by a correction factor of 0.6, is not greater than 1.5 times the area of the principal peak obtained with solution (2) (0.15%);
- the area of any other peak, other than the principal peak, is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%);
- the sum of the area of any peak corresponding to impurity A (fluorouracil), the corrected area of any peak corresponding to impurity B and the areas of all other peaks, other than the principal peak, is not greater than 3 times the area of the principal peak obtained with solution (2) (0.3%). Disregard any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.03%).

**Assay**

Dissolve about 0.1 g, accurately weighed, in a mixture of 40 mL of acetic anhydride R and 100 mL of glacial acetic acid R1, and titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 12.91 mg of C₄H₄FN₃O.

**Impurities**

A. 5-fluoropyrimidine-2,4(1H,3H)-dione (fluorouracil)

B. 2-ethoxy-5-fluoropyrimidin-4(3H)-one

**Reagent to be established**

Cyclohexylenedinitrilotetra-acetic acid R

trans-Cyclohexylene-1,2-dinitrilo-N,N,N',N'-tetra-acetic acid, C₁₄H₂₂N₂O₈H₂O.

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

*Melting point.* About 204°C.
**Flucytosine intravenous infusion**

**Description.** Flucytosine intravenous infusion is a clear, colourless or almost colourless solution.

**Category.** Antifungal.

**Storage.** Flucytosine intravenous infusion should be kept in a tightly-closed container, protected from light.

**Additional information.** Strengths in the current WHO Model List of Essential Medicines (EML): 2.5 g in 250 mL. Strengths in the current EML for Children: 2.5 g in 250 mL.

**Requirements**

Comply with the monograph for Parenteral preparations.

**Definition.** Flucytosine intravenous infusion is a sterile solution containing Flucytosine. It is supplied as a ready-to-use solution.

Flucytosine intravenous infusion contains not less than 90.0% and not more than 110.0% of the amount of Flucytosine \( (\text{C}_4\text{H}_4\text{FN}_3\text{O}) \) stated on the label.

**Identity tests**

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

  A. Evaporate 10 mL of the infusion to dryness on a water-bath and dry the residue at 105 °C for about 1 hour. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from flucytosine RS or with the reference spectrum of flucytosine.

  B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 60 volumes of nitromethane R, 20 volumes of methanol R, 10 volumes of ethyl acetate R and 10 volumes of water R as the mobile phase. Apply separately to the plate 1 μL of each of the following two solutions. Use a mixture composed of 60 volumes of methanol R, 35 volumes of water R and 5 volumes of glacial acetic acid R as the solvent. For solution (A) use an aliquot of the infusion to be tested. For solution (B) use 10 mg of flucytosine RS per mL. After application allow the spots to dry in a current of cool air. Develop over a path of 9 cm in an unsaturated chromatographic chamber. After removing the plate from the chromatographic chamber allow it to dry exhaustively in a current of air. Examine the chromatogram in ultraviolet light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).
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Consultation documents

C. The absorption spectrum (1.6) of the final solution prepared for Assay A, when observed between 230 nm and 350 nm, exhibits a maximum at about 286 nm and a minimum at about 245 nm.

**pH value (1.13).** pH of the infusion, 6.0–8.0.

**Pyrogens.** Carry out the test as described under 3.5 Test for pyrogens, per kg of the rabbit’s weight, 10 ml.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with base-deactivated particles of silica gel the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm).

As the mobile phase use a solution prepared as follows. Dissolve 13.6 g of potassium dihydrogen phosphate R in 950 mL of water R, adjust to pH 2.0 by adding phosphoric acid R and add 50 mL of methanol R.

Prepare the following solutions in a dissolution solvent prepared by dissolving 13.6 g of potassium dihydrogen phosphate R in 950 mL of water R and adding 50 mL of methanol R. For solution (1) dilute a quantity of the infusion to obtain a concentration of 0.3 mg of flucytosine per mL. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 0.3 μg of flucytosine per mL. For solution (3) use 0.3 μg of fluorouracil RS per mL. For solution (4) mix 1.0 mL of solution (2) add 1.0 mL solution (3).

Operate with a flow rate of 1.1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μL each of solution (1), (2), (3) and (4) and record the chromatograms for 15 times the retention time of flucytosine.

Use the chromatogram obtained with solution (3) to identify the peak due to impurity A (fluorouracil). Flucytosine is eluted at a retention time about 2.2 minutes.

The test is not valid unless the resolution between the peaks due to flucytosine and impurity A (fluorouracil) in the chromatogram obtained with solution (4) is not less than 5.0 and the symmetry factor for the peak due to flucytosine in the chromatogram obtained with solution (2) is not more than 2.0.

In the chromatogram obtained with solution (1):

- the area of any peak due to the impurity A (fluorouracil) is not greater than 5 times the area of the corresponding peak obtained with solution (3) (0.5%);

**Assay**

Dilute an accurately measured volume of the infusion with hydrochloric acid (0.1 mol/L) VS to give a solution containing about 0.1 mg per mL of Flucytosine. Dilute 5.0 mL of the resulting solution to 100.0 mL with the same solvent. Measure the absorbance of the resulting solution in a 1 cm layer at the maximum at about 286 nm. Calculate the content of Flucytosine (C₄H₄FN₃O) using the absorptivity value of 70.9 (A²⁰cm⁻¹ = 709).

**Impurities**

The impurity limited by the requirements of this monograph is listed in the monograph for Flucytosine.

***
ATC/DDD Classification

ATC/DDD Classification (Temporary)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2014. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 February 2015. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the January 2016 version of the ATC/DDD Index.

New ATC 5th level codes:

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<td>A16AB13</td>
</tr>
<tr>
<td>ataluren</td>
<td>M09AX03</td>
</tr>
<tr>
<td>atazanavir and cobicistat</td>
<td>J05AR15</td>
</tr>
<tr>
<td>belinostat</td>
<td>L01XX49</td>
</tr>
<tr>
<td>benzyl alcohol</td>
<td>P03AX06</td>
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<tr>
<td>blinatumomab</td>
<td>L01XC19</td>
</tr>
<tr>
<td>brivaracetam</td>
<td>N03AX23</td>
</tr>
<tr>
<td>bupropion and naltrexone</td>
<td>A08AA62</td>
</tr>
<tr>
<td>ceftolozane and enzyme inhibitor</td>
<td>J01DI54</td>
</tr>
<tr>
<td>dasabuvir</td>
<td>J05AX16</td>
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<tr>
<td>dasabuvir, ombitasvir, paritaprevir and ritonavir</td>
<td>J05AX46</td>
</tr>
<tr>
<td>drospirenone</td>
<td>G03AC10</td>
</tr>
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<td>efinaconazole</td>
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<tr>
<td>emtricitabine and tenofovir alafenamide</td>
<td>J05AR17</td>
</tr>
<tr>
<td>emtricitabine, tenofovir alafenamide, elvitegravir and cobicistat</td>
<td>J05AR18</td>
</tr>
<tr>
<td>insulin degludec and liaglutide</td>
<td>A10AE56</td>
</tr>
<tr>
<td>isavuconazole</td>
<td>J02AC05</td>
</tr>
<tr>
<td>lamivudine and raltegravir</td>
<td>J05AR16</td>
</tr>
<tr>
<td>lenvatinib</td>
<td>L01XE29</td>
</tr>
<tr>
<td>luliconazole</td>
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<tr>
<td>metformin and empagliflozin</td>
<td>A10BD20</td>
</tr>
<tr>
<td>nemonoxacin</td>
<td>J01MB08</td>
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<td>nintedanib</td>
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<td>nivolumab</td>
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<tr>
<td>obeticholic acid</td>
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</tr>
<tr>
<td>octenidine</td>
<td>R02AA21</td>
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<tr>
<td>olodaterol and tiotropium bromide</td>
<td>R03AL06</td>
</tr>
<tr>
<td>ombitasvir, paritaprevir and ritonavir</td>
<td>J05AX67</td>
</tr>
<tr>
<td>papillomavirus (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)</td>
<td>J07BM03</td>
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<tr>
<td>pembrolizumab</td>
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Continued/
### ATC/DDD Classification (Temporary)

**/Continued**

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
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<tbody>
<tr>
<td>pitolisant</td>
<td>N07XX11</td>
</tr>
<tr>
<td>rosuvastatin and valsartan</td>
<td>C10BX10</td>
</tr>
<tr>
<td>sebelipase alfa</td>
<td>A16AB14</td>
</tr>
<tr>
<td>sirolimus</td>
<td>S01XA23</td>
</tr>
<tr>
<td>smallpox, live attenuated</td>
<td>J07BX01</td>
</tr>
<tr>
<td>sofosbuvir and ledipasvir</td>
<td>J05AX65</td>
</tr>
<tr>
<td>sonidegib</td>
<td>L01XX48</td>
</tr>
<tr>
<td>tasimelteon</td>
<td>N05CH03</td>
</tr>
<tr>
<td>tedizolid</td>
<td>J01XX11</td>
</tr>
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</table>

**New DDDs:**

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD</th>
<th>unit</th>
<th>Adm. R.</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>abarelix</td>
<td>3.6</td>
<td>mg</td>
<td>P</td>
<td>L02BX01</td>
</tr>
<tr>
<td>albiglutide</td>
<td>5.7</td>
<td>mg</td>
<td>P</td>
<td>A10BX13</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>13.3</td>
<td>mg</td>
<td>P depot</td>
<td>N05AX12</td>
</tr>
<tr>
<td>azilsartan medoxomil</td>
<td>40</td>
<td>mg</td>
<td>O</td>
<td>C09CA09</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>0.2</td>
<td>g</td>
<td>O</td>
<td>A10BX11</td>
</tr>
<tr>
<td>cobicistat</td>
<td>0.15</td>
<td>g</td>
<td>O</td>
<td>V03AX03</td>
</tr>
<tr>
<td>daclatasvir</td>
<td>60</td>
<td>mg</td>
<td>O</td>
<td>J05AX14</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>15</td>
<td>mg</td>
<td>O</td>
<td>N06BA11</td>
</tr>
<tr>
<td>lomitapide</td>
<td>40</td>
<td>mg</td>
<td>O</td>
<td>C10AX12</td>
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<tr>
<td>loxapine</td>
<td>9.1</td>
<td>mg</td>
<td>Inhal powder&lt;sup&gt;2&lt;/sup&gt;</td>
<td>N05AH01</td>
</tr>
<tr>
<td>misoprostol</td>
<td>0.2</td>
<td>mg</td>
<td>V&lt;sup&gt;1&lt;/sup&gt;</td>
<td>G02AD06</td>
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<tr>
<td>olodaterol</td>
<td>5</td>
<td>mcg</td>
<td>Inhal sol</td>
<td>R03AC19</td>
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<tr>
<td>peginterferon beta-1a</td>
<td>8.9</td>
<td>mcg</td>
<td>P</td>
<td>L03AB13</td>
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<td>riociguat</td>
<td>4.5</td>
<td>mg</td>
<td>O</td>
<td>C02KX05</td>
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<tr>
<td>sultimab</td>
<td>37</td>
<td>mg</td>
<td>P</td>
<td>L04AC11</td>
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<tr>
<td>simeprevir</td>
<td>0.15</td>
<td>g</td>
<td>O</td>
<td>J05AE14</td>
</tr>
<tr>
<td>sucroferric oxyhydroxide</td>
<td>1.5</td>
<td>g</td>
<td>O</td>
<td>V03AE05</td>
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<tr>
<td>vedolizumab</td>
<td>5.4</td>
<td>mg</td>
<td>P</td>
<td>L04AA33</td>
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</tbody>
</table>

<sup>a</sup> Route of administration (Adm.R): O=oral; P=parenteral; V=vaginal; Inhal=inhalaation

1) vaginal insert, refers to the content of one vaginal insert

2) delivered dose
ATC/DDD Classification (Final)

The following ATC codes, DDDs and alterations were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in March 2014. These are considered as final and will be included in the January 2015 version of the ATC/DDD Index.

New ATC 5th level codes:

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<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
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<tbody>
<tr>
<td>asunaprevir</td>
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<tr>
<td>ceritinib</td>
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<tr>
<td>daclatasvir</td>
<td>J05AX14</td>
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<td>dasiprotimut-T</td>
<td>L03AX19</td>
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<td>decamethoxine</td>
<td>D08AJ10</td>
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<td>evolocumab</td>
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<td>fabomotizole</td>
<td>N05BX04</td>
</tr>
<tr>
<td>fimasartan</td>
<td>C09CA10</td>
</tr>
<tr>
<td>fluticasone furoate</td>
<td>R03BA09</td>
</tr>
<tr>
<td>ivermectin</td>
<td>D11AX22</td>
</tr>
<tr>
<td>linagliptin and empagliflozin</td>
<td>A10BD19</td>
</tr>
<tr>
<td>macimorelin</td>
<td>V04CD06</td>
</tr>
<tr>
<td>metformin and gemigliptin</td>
<td>A10BD18</td>
</tr>
<tr>
<td>mifepristone, combinations</td>
<td>G03XB51</td>
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<tr>
<td>siltuximab</td>
<td>L04AC11</td>
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<tr>
<td>sofosbuvir</td>
<td>J05AX15</td>
</tr>
<tr>
<td>susoctocog alfa</td>
<td>B02BD14</td>
</tr>
<tr>
<td>trifluridine, combinations</td>
<td>L01BC59</td>
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<tr>
<td>vorapaxar</td>
<td>B01AC26</td>
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Change of ATC level name:

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<tr>
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<th>ATC code</th>
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<tbody>
<tr>
<td>Sulfonamides, urea derivatives</td>
<td>Sulfonylureas</td>
<td>A10BB</td>
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New DDDs:

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD</th>
<th>unit</th>
<th>Adm. R. a</th>
<th>ATC code</th>
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</thead>
<tbody>
<tr>
<td>alemtuzumab</td>
<td>0.13</td>
<td>mg</td>
<td>P</td>
<td>L04AA34</td>
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<td>benzydamide</td>
<td>9</td>
<td>mg</td>
<td>O</td>
<td>A01AD02</td>
</tr>
<tr>
<td>dexlansoprazole</td>
<td>30</td>
<td>mg</td>
<td>O</td>
<td>A02BC06</td>
</tr>
<tr>
<td>fabomotizole</td>
<td>30</td>
<td>mg</td>
<td>O</td>
<td>N05BX04</td>
</tr>
<tr>
<td>granisetron</td>
<td>3.1</td>
<td>mg</td>
<td>TD</td>
<td>A04AA02</td>
</tr>
<tr>
<td>macitentan</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>C02XX04</td>
</tr>
<tr>
<td>sofosbuvir</td>
<td>0.4</td>
<td>g</td>
<td>O</td>
<td>J05AX15</td>
</tr>
<tr>
<td>vortioxetine</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>N06AX26</td>
</tr>
</tbody>
</table>

a Route of administration (Adm.R): O=oral; P=parenteral; TD=transdermal
International Nonproprietary Names for Pharmaceutical Substances (INN)

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

Lists of Proposed (1–109) and Recommended (1–70) International Nonproprietary Names can be found in Cumulative List No. 15, 2013 (available in CD-ROM only). The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

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

On trouvera d'autres listes de Dénominations communes internationales proposées (1–109) et recommandées (1–70) dans la Liste récapitulative No. 15, 2013 (disponible sur CD-ROM seulement). Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figurent pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–109) y Recomendadas (1–70) se encuentran reunidas en Cumulative List No. 15, 2013 (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.
### Proposed International Nonproprietary Names: List 112

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for List 112 Proposed INN not later than 15 May 2015.

**Publication date:** 16/01/2015

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**Dénominations communes internationales proposées: Liste 112**

Des observations ou des objections formelles à l’égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l’Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans *WHO Drug Information*, c’est à dire pour la **Liste 112 de DCI Proposées le 15 mai 2015 au plus tard**.

**Date de publication :** 16/01/2015

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**Denominaciones Comunes Internacionales Propuestas: Lista 112**

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en *WHO Drug Information*, es decir, para la **Lista 112 de DCI Propuestas el 15 Mayo de 2015 a más tardar**.

**Fecha de publicación:** 16/01/2015

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<table>
<thead>
<tr>
<th>Proposed INN</th>
<th>Chemical name or description: Action and use: Molecular formula</th>
<th>Chemical Abstracts Service (CAS) registry number: Graphic formula</th>
</tr>
</thead>
</table>
| **abemaciclib**
| abemaciclib | *N*-{5-[(4-ethylpiperazin-1-yl)methyl]pyridin-2-yl}-5-fluoro-4-[4-fluoro-2-methyl-1-(propan-2-yl)-1*H*-benzimidazol-6-yl]pyrimidin-2-amine | antineoplastic |
| abémaciclib | *N*-{5-[(4-éthylpipérazin-1-yl)méthyl]pyridin-2-yl}-5-fluoro-4-[4-fluoro-2-méthyl-1-(propan-2-yl)-1*H*-benzimidazol-6-yl]pyrimidin-2-amine | antinéoplasique |
| abemaciclib | *N*-{5-[(4-etilpiperazin-1-il)metil]piridin-2-il}-5-fluoro-4-[4-fluoro-2-metil-1-(propan-2-il)-1*H*-benzoimidazol-6-il]pirimidin-2-amina | antineoplásico |

![Chemical structure of abemaciclib](image)
amiselimodum

2-amino-2-{2-[4-(heptyloxy)-3-(trifluoromethyl)phenyl]ethyl}propane-1,3-diol

immunomodulator

C_{19}H_{30}F_{3}NO_{3}

942399-20-4

asinerceptum #

fusion protein for immune applications (FPIA) comprising the *Homo sapiens* FAS (Fas cell surface death receptor, TNFRSF6, tumor necrosis factor receptor (TNFR) superfamily member 6, FAS1, APO-1, CD95) extracellular domain, fused with *Homo sapiens* immunoglobulin G1 Fc fragment;

*Homo sapiens* FAS precursor fragment 26-172 (1-147) - gamma1 chain H-CH2-CH3 fragment [*Homo sapiens IGHG1*03 (hinge 5-15 (148-158), CH2 (159-268), CH3 (269-373), CHS (374-375))] (148-375); dimer (148-148':154-154':157-157')-trisdisulfide

immunomodulator

asinercept

protéine de fusion pour applications immunitaires (FPIA) comprenant le domaine extracellulaire d’*Homo sapiens* FAS (récepteur de mort membranaire Fas, TNFRSF6, membre 6 de la superfamille des récepteurs du facteur de nécrose tumoral (TNFR), FAS1, APO-1, CD95), fusionné au fragment Fc de l’immunoglobuline G1 d’*Homo sapiens*; *Homo sapiens* FAS fragment 26-172 du précurseur (1-147)-fragment H-CH2-CH3 de la chaîne gamma1 [*Homo sapiens IGHG1*03 (charnière 5-15 (148-158), CH2 (159-268), CH3 (269-373), CHS (374-375))] (148-375); dimère (148-148':154-154':157-157')-trisdisulfure

immunomodulateur
asinercept

proteína de fusión para aplicaciones inmunitarias (FPIA) que comprende el dominio extracelular de *Homo sapiens* FAS (receptor de muerte Fas de membrana, TNFRSF6, miembro 6 de la superfamilia de receptores del factor de necrosis tumoral (TNFR), FAS1, APO-1, CD95), fusionado con el fragmento Fc de la inmunoglobulina G1 de *Homo sapiens*; FAS de *Homo sapiens* fragmento 26-172 del precursor (1-147) -fragmento H-CH2-CH3 de la cadena gamma1 [*Homo sapiens* IGHG1*03* (bisagra 5-15 (148-158), CH2 (159-268), CH3 (269-373), CHS (374-375))] (148-375); dímero (148-148':154-154':157-157')-trisdisulfuro inmunomodulador

<table>
<thead>
<tr>
<th>Fusion chain / Chaine fusionnée / cadena fusionada</th>
</tr>
</thead>
<tbody>
<tr>
<td>QVTDINSKGL ELKTVTVTV QCMTLGLTGG QGEPCKFCCPF GERRDCTV 50</td>
</tr>
<tr>
<td>NQDDECYCPQ QGKSEYDDKA HFSEPPKCRCH LCELGHPCLE EINCTQPTQNT 100</td>
</tr>
<tr>
<td>KCSKPFPQFQ NETTRGKCFDP CTREKGSSH IECTLSTNCG KEEGKESCED 150</td>
</tr>
<tr>
<td>TRTCPFCFAP ELLGGPSVFL FPPFKEDTLM ISRTPETYTV VDVSDEHFE 200</td>
</tr>
<tr>
<td>VKFNYYVGQEVNAXKTPFR EQIIHSTTVY SVALSVLHGD QLNGKEVCKR 250</td>
</tr>
<tr>
<td>VSNHALPAPI KFISIAKQCG PREQGVTLP FSREMTNQK VSLLTLVSKG 300</td>
</tr>
<tr>
<td>YPSD2AVENWE SNQFENHMY TTPFVLDSGD SFFLYSVKTV DRRWQQQHVN 350</td>
</tr>
<tr>
<td>FCSEVYMEAL NNHYTQKSL5 LSQDK 375</td>
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</table>

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

<table>
<thead>
<tr>
<th>Intra-chain FAS</th>
<th>34-48 38-57 60-76 79-94</th>
</tr>
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<tbody>
<tr>
<td>82-102 104-118 121-132 124-140</td>
<td></td>
</tr>
<tr>
<td>34-48' 38-57' 60-76' 79-94'</td>
<td></td>
</tr>
<tr>
<td>82'-102' 104'-118' 121'-132' 124'-140'</td>
<td></td>
</tr>
<tr>
<td>IGHG1 (C23-C104) 189-249 295-353</td>
<td></td>
</tr>
<tr>
<td>189-249' 295'-353'</td>
<td></td>
</tr>
</tbody>
</table>

| Inter-chain IGHG1 (h5, h11, h14) 148-148' 154-154' 157-157' |
|---------------------|------------------------|
| N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación FAS: |
| 93, 111, 97, 117 | complex mono-, bi- and tetra-antennary oligosaccharides, partially sialylated, oligosaccharides complexes of structure ramifié (de 1 à 4 branches), partiellement sialylés, oligosacáridos complejos mono-bi, tri y tetra-antennados, parcialmente sialilados |
| 225, 225' | complex mono- and biantennary non-sialylated oligosaccharides, oligosaccharides complexes de structure ramifié (de 1 à 2 branches) non-sialylés, oligosacáridos complejo mono- y biantenado no-sialilado |

| Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales: |
| H CHS K2 C-terminal lysine clipping, coupure de la lysine C-terminale, supresión de lisina C-terminal: |
| 375, 375' |

atezolizumabum # atezolizumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* CD274 (programmed death ligand 1, PD-L1, PD-L1, B7 homolog 1, B7H1)], humanized monoclonal antibody; gamma1 heavy chain (1-448) [humanized VH (*Homo sapiens* IGHV3-23*04* (86.70%))-IGHD]-IGHJ4*01 [8.8.11] (1-118) -*Homo sapiens* IGHG1*03* (CH1 R120>K (215) (119-216), hinge (217-231), CH2 N84.4>A (298) (232-341), CH3 (342-446), CHS (447-448)) (119-448), (221-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-5*01* (87.90%))-IGKJ1*01* [6.3.9] (1'-107') -*Homo sapiens* IGKC*01* (108'-214')); dimer (227-227'-230-230')-bisdisulfide immunomodulator, antineoplastic
**Proposed INN: List 112**

**atézolizumab**

immunoglobuline G1-kappa, anti-[*Homo sapiens* CD274 (ligand 1 de mort programmée, PDL1, PD-L1, homologue 1 de B7, B7H1)], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-448) [VH humanisé (*Homo sapiens* IGHV3-23*04 (86.70%)-(IGHD)-IGHJ4*01)] [8.8.11] (1-118) -*Homo sapiens* IGH1*T03 (CH1 R120>K (215) (119-216), charnière (217-231), CH2 N84.4-A (298) (232-341), CH3 (342-446), CHS (447-448)) (119-448)], (221-214”)-disulfure avec la chaîne légère kappa (1’-214’)[V-KAPPA humanisé (*Homo sapiens* IGKV1-5*01 (87.90%)-IGKJ1*01) [6.3.9] (1’-107’)-*Homo sapiens* IGKC*01 (108’-214’)]; dimère (227-227”-230-230”)-bisdisulfure

**atezolizumab**

immunoglobulina G1-kappa, anti-[*Homo sapiens* CD274 (ligando 1 de muerte programada, PDL1, PD-L1, homólogo 1 de B7, B7H1)], anticuerpo monoclonal humanizado; cadena pesada gamma1 (1-448) [VH humanizado (*Homo sapiens* IGHV3-23*04 (86.70%)-(IGHD)-IGHJ4*01)] [8.8.11] (1-118) -*Homo sapiens* IGH1*T03 (CH1 R120>K (215) (119-216), bisagra (217-231), CH2 N84.4-A (298) (232-341), CH3 (342-446), CHS (447-448)) (119-448)], (221-214’)-disulfuro com la cadena ligera kappa (1’-214’)[V-KAPPA humanizado (*Homo sapiens* IGKV1-5*01 (87.90%)-IGKJ1*01) [6.3.9] (1’-107’)-*Homo sapiens* IGKC*01 (108’-214’)]; dímero (227-227”-230-230”)-bisdisulfuro

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

**avoralstatum**

avoralstat

3-{2-[(4-carbamimidoylphenyl)carbamoyl]-4-ethenyl-5-methoxyphenyl}-6-{(cyclopropylmethyl)carbamoyl}pyridine-2-carboxylic acid

*kallikrein inhibitor*
**Proposed INN: List 112**

**avoredstat**

Acide 3-{2-[(4-carbamidoylphenyl)carbamoyl]-4-éthényl-5-méthoxyphényl}-6-[(cyclopropylméthyl)carbamoyl]pyridine-2-carboxylique

Inhibiteur de la kallicréine

 ámbito 3-2-[[(4-carbamidolfenil)carbamoil]-4-etenil-5-metoxifenil}-6-[(ciclopropilmetil)carbamoil]piridina-2-carboxilico

Inhibidor de la kalikreína

\[ \text{C}_{28}\text{H}_{27}\text{N}_{5}\text{O}_{5} \quad 918407-35-9 \]

Axalimogenum filolisbacum #

**Axalimogene filolisbac**

A live attenuated recombinant strain of *Listeria monocytogenes (Lm)* bacterium bioengineered to secrete an antigen-adjuvant fusion (tLLO-E7) protein consisting of non-hemolytic listeriolysin O (truncated LLO, tLLO) fused to the human papilloma virus-16 (HPV-16) E7 protein, contained within the multi-copy plasmid pGG-55. The bacterial strain used, XFL-7, had been attenuated by excision of the essential transcription activator gene for virulence gene expression *prfA* (10403S Δ prfA) and complemented with a mutated, less active *prfA* to maintain in vivo retention. In plasmid pGG-55, the *Lm* hly promoter drives the expression of fusion protein tLLO-E7, an approximately 67-kDa protein. The tLLO fragment of the fusion gene codes for the first 440 amino acids of full-length listeriolysin and is genetically fused to the E7 gene using the restriction site *XhoI*. The plasmid pGG55 is retained in XFL-7 in vivo due to the expression of the mutated PrfA protein.

gene therapy product (antineoplastic)
axalimogène filolisbac

souche bactérienne vivante atténuée de Listeria monocytogenes (Lm) recombinante qui secrétant une protéine de fusion antigène-adjuvant (tLLO-E7) qui comprend une listériolysine O non-hémolytique (LLO tronquée, tLLO), fusionnée à la protéine E7 du papillomavirus humain de type 16 (HPV-16), contenue dans le plasmide à copies multiples pGC-55. La souche bactérienne utilisée, XFL-7, a été atténuée par excision du gène prfA essentiel à l’activation de la transcription des gènes de virulence (10403S ∆ prfA) et complété par un gène prfA muté, moins actif, afin de maintenir une rétention in vivo. Dans le plasmide pGC-55, le promoteur Lm hly contrôle l’expression de la protéine de fusion tLLO-E7, une protéine d’approximativement 67 kDa. Le fragment tLLO du gène de fusion code les premiers 440 acides aminés de la listériolysine et est génétiquement fusionné au gène E7 en utilisant le site de restriction XhoI. Le plasmide pGG55 est retenu dans XFL-7 in vivo par l’expression de la protéine PrfA mutée.

produit de thérapie génique (antinéoplasique)

axalimogène filolisbac

Cepa bacteriana viva atenuada de Listeria monocytogenes (Lm) recombinante secretando una proteína de fusión antigeno-adyuvante (tLLO-E7) que consiste en una listériolysina O no-hemolítica (LLO truncada, tLLO), fusionada con la proteína E7 del papillomavirus humano de tipo 16 (HPV-16) contenida en el plásmido multicopia pGC-55. La cepa bacteriana utilizada, XFL-7, se ha atenuado por escisión del gen prfA esencial a la activación de la transcripción de los genes de virulencia (10403S ∆ prfA) y completada por un gen prfA mutado, menos activo, con el fin de mantener la retención in vivo. En el plasmido pGC-55, el promotor Lm hly controla la expresión de la proteína de fusión tLLO-E7, una proteína de aproximadamente 67 kDa. El fragmento tLLO del gen de fusión codifica los primeros 440 aminoácidos de la listériolysina y se fusiona genéticamente con el gen E7 utilizando el sitio de restricción XhoI. El plásmido pGG55 es retenido en XFL-7 in vivo por la expresión de la proteína PrfA mutada.

producto para terapia génica (antineoplásico)

balixafortidum

balixafortide
chemokine CXCR4 receptor antagonist

balixafortide

antagoniste du récepteur CXCR4 de chimiokine
balixafortida


antagonista del receptor de quimiokina CXC tipo 4 (CXC4R)

\[
C_{85}H_{118}N_{24}O_{21}S_{2} \quad 1051366-32-5
\]

bovhyaluronidasum azoximerum #
bovhyaluronidase azoximer

hyaluronidase-2 bovine (hyaluronoglucosaminidase-2, Hyal-2, EC 3.2.1.35) Bos taurus precursor protein linked to poly[(1-(carboxymethyl)piperazin-1-i-um-1,4-diyl bromide]ethylene-co-[(piperazine-1,4-diy1 1-oxide)ethylene}] by an amido covalent bond enzyme

bovhyaluronidase azoximère

précurseur de la hyaluronidase-2 bovine (hyaluronoglucosaminidase-2, Hyal-2, EC 3.2.1.35) Bos taurus lié au poly[bromure de 1-(carboxyméthyl)pipérazin-1-i-um-1,4-diyléthylène-co-[1-oxyde de pipérazin-1,4-diyléthylène]} par une liaison covalente amide enzyme

bovhialuronidasaz oaximero

precursor de la hialuronidasa-2 bovina (hialuronoglucosaminidasa-2, Hyal-2, EC 3.2.1.35) Bos taurus unido al poli[bromuro de 1-(carboximetil)pipérazin-1-i-1,4-diylétileno-co-[1-oxido de pipérazin-1,4-diy1étileno]} por un enlace covalente amida enzima

1383710-57-3


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

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

Carrier & Hyal-2 (H2N-Enz) / Transporteur & Hyal-2 (H2N-Enz) / Transportador & Hyal-2 (H2N-Enz)
**brolucizumab**

**brolucizumab** immunoglobulin scFv, anti-[*Homo sapiens* VEGFA (vascular endothelial growth factor A, VEGF-A, VEGF)], humanized monoclonal antibody single chain; scFv (1-252) [methionyl (1) -humanized V-KAPPA (*Homo sapiens* IGKV1-5*01 (87.60%)-IGKJ2*01 E125>T (108), I126>V (109), K127>L (110) [6.3.12] (2-111) -21-mer (glycyl-tetragon(tetraglycyl-seryl)) linker (112-132) -humanized VH (*Homo sapiens* IGHV3-66*01 (80.40%)-(IGHD)-IGHJ1*01 [9.7.13] (133-252) angiogenesis inhibitor

**brolucizumab** immunoglobuline scFv, anti-[*Homo sapiens* VEGFA (facteur de croissance A de l’endothélium vasculaire, VEGF-A, VEGF)], anticorps monoclonal humanisé à chaîne unique; scFv (1-252) [méthionyl (1) -V-KAPPA humanisé (*Homo sapiens* IGKV1-5*01 (87.60%)- IGKJ2*01 E125>T (108), I126>V (109), K127>L (110) [6.3.12] (2-111) -21-mer (glycyl-tétragram(tétraglecyl-séryl)) linker (112-132) -VH humanisé (*Homo sapiens* IGHV3-66*01 (80.40%)-(IGHD)-IGHJ1*01 [9.7.13] (133-252) inhibiteur de l’angiogénèse

**brolucizumab** immunoglobulina scFv, anti-[VEGFA de *Homo sapiens* (factor de crecimiento A del endotelio vascular, VEGF-A, VEGF)], anticuerpo monoclonal humanizado monocatenario; scFv (1-252) [metionil (1) -V-KAPPA humanizado (*Homo sapiens* IGKV1-5*01 (87.60%)- IGKJ2*01 E125>T (108), I126>V (109), K127>L (110) [6.3.12] (2-111) -21-mer (glicil-tetrakis(tetraglicil-séryl)) conector (112-132) -VH humanizado (*Homo sapiens* IGHV3-66*01 (80.40%)-(IGHD)-IGHJ1*01 [9.7.13] (133-252) inhibitor de la angiogénesis

**centanafadinum**

**centanafadine** (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane monoaamine transport inhibitor

**centanafadine** (1R,5S)-1-(naphtalén-2-yl)-3-azabicyclo[3.1.0]hexane inhibiteur du transport des monoamines
centanafadina

\((1R,5S)-1-(\text{naftalen}-2-\text{-il})-3\text{-azabiclo}[3.1.0]\text{hexano}\)
inhibidor del transporte de monoaminas

\(\text{C}_{15}\text{H}_{15}\text{N}\)  924012-43-1

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crisaborol

crisaborole

4-[(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-5-yl)oxy]benzonitrile

non-steroidal anti-inflammatory

4-[(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-5-yl)oxy]benzonitrile

anti-inflammatoire non-steroidien

4-[(1-hidroxi-1,3-dihidro-2,1-benzoxaborol-5-il)oxi]benzonitrio

antinflamatorio no esteroide

\(\text{C}_{14}\text{H}_{10}\text{BNO}_3\)  906673-24-3

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dectrekumabum #

dectrekumab

immunoglobulin G1-kappa, anti-[\text{Homo sapiens L13} (interleukin 13, IL-13)], \text{Homo sapiens} monoclonal antibody;
gamma1 heavy chain (1-450) [\text{Homo sapiens} VH (IGHV3-33*01 (98.00%) -(IGHD)-IGHJ3*02) [8.8.13] (1-120) - IGHG1*03 (CH1 (121-218), hinge (219-233), CH2 (234-343), CH3 (344-448), CHS (449-450)) (121-450)), (223-216')-disulfide with kappa light chain (1'-216') [\text{Homo sapiens} V-KAPPA (IGKV3-11*01 (95.80%) -IGKJ2*01) [6.3.11] (1'-109') -IGKC*01 (110'-216')]; dimer (229-229":232-232")-bisdisulfide

immunomodulator

immunoglobuline G1-kappa, anti-[\text{Homo sapiens IL13} (interleukine 13, IL-13)], \text{Homo sapiens} anticorps monoclonal;
chaîne lourde gamma1 (1-450) [\text{Homo sapiens} VH (IGHV3-33*01 (98.00%) -(IGHD)-IGHJ3*02) [8.8.13] (1-120) - IGHG1*03 (CH1 (121-218), charnière (219-233), CH2 (234-343), CH3 (344-448), CHS (449-450)) (121-450)), (223-216')-disulfure avec la chaîne légère kappa (1'-216') [\text{Homo sapiens} V-KAPPA (IGKV3-11*01 (95.80%) -IGKJ2*01) [6.3.11] (1'-109') -IGKC*01 (110'-216')]; dimère (229-229":232-232")-bisdisulfure

immunomodulateur
dectrekumab

immunoglobulina G1-kappa, anti-[IL13 de Homo sapiens (interleukina 13, IL-13)], anticuerpo monoclonal de Homo sapiens;
cadena pesada gamma1 (1-450) [VH de Homo sapiens (IGHV3-33)*01 (98.00%) - (IGHD)-IGHJ3*02] [8.8.13] (1-120) -IGHG1*03 (CH1 (121-218), bisagra (219-233), CH2 (234-343), CH3 (344-448), CHS (449-450)) [(121-450)],
(223-216)-disulfuro con la cadena ligera kappa (1’-216’) [V-KAPPA de Homo sapiens (IGKV3-11)*01 (95.80%) - IGKJ2*01] [6.3.11] (1’-109’) -IGKC*01 (110’-216’)]; dímero (229-229’-232-232’)-bisdisulfuro
inmunomodulador

1528523-94-5

Heavy chain / Chaîne lourde / Cadena pesada
EVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PEGKLENVAI 50
IWYDDNYKY ADSVGRFVTI SRDNSKNTLY QGMISLRSAE TAVYTCARLW 100
FDDGFLFGLW QGQTVTVVSS ASTRFSFVFP LAPSVERSTG GTAALCCLUD 150
DVFPFRFYYYY MNGGALTGQD MTPAQLQES GLSFLSYTV VPSSSLGYQT 200
YICENVHIPS NTRVDIRKEK SCSDK7HTCP FCAPFELLLG PSVFLFLPPK 250
KDTLMISRTF ETVCYVLVDVS KEQVRKFINW YDQGVEHHVA KTPREZQYN 300
SMYRTDVLTVLNGWLDNG YCMEVYSNR IAPFTLETS RKKQGFLPPQ 350
VYTLPSFQAE MTRPVQSLTSC LVKGFPSID KAVVEESNGQP ENMTKFTPPFV 400
LDDGFSYFLY SKLTVDKSMQ QQNVFGSCSV WHEALNHHTY QRSLISSLPGC 450

Light chain / Chaîne légère / Cadena ligera
EIVLTLQSPAT LSLQSPGERAI LCSCRAGQTVL SYLVWYQQKPG QAPRLLIYD 50
ASMRAGTIFA RFSGGGSGTD PLTLIESLHP HADAVYCCQ RSDWFSYFTP 100
QGQTKLEIKR TVAAPSVFIF PPSDVLKQEG TASVCC9LNN FYDPFAAVQW 150
KVDNALQSGN SQGGYEQPDQ KSDTSL601 LTIKADTEK HRTACEYTH 200
QQLSAPTYKZ FNGECE 216

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 147-203 264-324 370-428
22’-96’ 147’-203’ 264’-324’ 370’-428’
Intra-L (C23-C104) 23’-88’ 136’-196’
23’’-88’’ 136’’-196’’
Inter-H-L (h 5-CL 126) 223-216’ 223’-216’
229-229’ 232-232’

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4: 300, 300’

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traducionales
H CHS K2 C-terminal lysine clipping:
450, 450’

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desfesoterodinum

desfesoterodine

2-[(1R)-3-[bis(propan-2-yl)amino]-1-phenylpropyl]-
4-(hydroxymethyl)phenol
muscarnic receptor antagonist


desfésotérodine

2-[(1R)-3-[bis(propan-2-yl)amino]-1-phénylpropyl]-
4-(hydroxyméthyl)phénol
antagoniste des récepteurs muscariniques


desfesoterodina

2-[(1R)-3-[bis(propan-2-il)amino]-1-fenilpropil]-
4-(hidroximetil)fenol
antagonista de los receptores muscarinicos
**deutetrabenazinum**

*deutetrabenazine*  
\( \text{rac-(3R,11bR)-9,10-di[}^{2}\text{H}_3)\text{methoxy]-3-(2-methylpropyl)-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one antipsychotic} \)

**deutétrabénazine**

*rac-(3R,11bR)-9,10-di[\( ^{2}\text{H}_3\)méthoxy]-3-(2-méthylpropyl)-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinoléin-2-one antipsychotique*

**deutetrabenazina**

*rac-(3R,11bR)-3-(2-metilprop)-9,10-di[\( ^{2}\text{H}_3\)metoxi]-1,3,4,6,7,11b-hexahidro-2H-pirido[2,1-a]isoquinolein-2-ona antipsicótico*

\( \text{C}_{19}\text{H}_{21}(^{2}\text{H}_6)\text{NO}_3 \)  

\( 1392826-25-3 \)

**durvalumabum #**

*durvalumab*  
Immunoglobulin G1-kappa, anti-[\( \text{Homo sapiens} \) CD274 (programmed death ligand 1, PDL1, PD-L1, B7 homolog 1, B7H1)], \( \text{Homo sapiens} \) monoclonal antibody; gamma1 heavy chain (1-451) [\( \text{Homo sapiens} \) VH (IGHV3-7*01 (99.00%)-IGHD)-IGHJ4*01] [8.8.14] (1-121) - IGHG1*03 (CH1 (122-219), hinge (220-234), CH2 (235-344) L1.3>F (238), L1.2>E (239), P116>S (335), CH3 (345-449), CHS (450-451)) (122-451), (224-215')-disulfide with kappa light chain (1'-215') [\( \text{Homo sapiens} \) V-KAPPA (IGKV3-20*01 (96.90%)-IGKJ1*01) [7.3.9] (1'-108') - IGKC*01 (109'-215')] dimer (230-230'':233-233'')-disulfide immunomodulator, antineoplastic
durvalumab

immunglobuline G1-kappa, anti-
[Homo sapiens] CD274 (ligand 1 de mort programmée, PDL1, PD-L1, homologue 1 de B7, B7H1)], Homo sapiens anticorps monoclonal; chaîne lourde gamma1 (1-451) [Homo sapiens] VH

(IGHV3-7*01 (99.00%) -IGHD-IGHJ4*01) [8.8.14] (1-121)
-IGHG1*03 (CH1 (122-219), charnière (220-234), CH2 (235-344) L1.3=F (238), L1.2=E (239), P116>S (335), CH3 (345-449), CHS (450-451)) (122-451)], (224-215)-disulfure avec la chaîne légère kappa (1'-'215') [Homo sapiens V-KAPPA (IGKV3-20*01 (96.90%) -IGKJ1*01) [7.3.9] (1'-108')-IGKC*01 (109-'215')]; dimère (230-230':233-233')-bisdisulfure

immunomodulateur, antinéoplasique

1428935-60-7

elafibranorum

elafibranor 2-(2,6-dimethyl-4-(3-[4-(methylsulfanyl)phenyl]-3-oxoprop-1-en-1-yl)phenoxy)-2-methylpropanoic acid peroxisome proliferator activating receptor (PPAR) agonist
élafibranor

Acide 2-(2,6-diméthyl-4-{3-[4-(méthylsulfanyl)phényl]-3-oxoprop-1-én-1-yl}phénoxy)-2-méthylpropanoïque
agoniste des récepteurs activés par les proliférateurs de peroxysomes

\[ C_{22}H_{24}O_4S \]

824932-88-9

eleclazinum

eleclazine

4-[(pyrimidin-2-yl)méthyl]-7-[4-(trifluorométhoxy)phényl]-3,4-dihydro-1,4-benzoxazine-5(2H)-one
vasodilatateur coronnaire et antiarythmique

\[ C_{21}H_{16}F_3N_3O_3 \]

1443211-72-0

elegentumabum #
elegentumab

Immunoglobulin G1-kappa, anti-[*Homo sapiens* ERBB3 (receptor tyrosine-protein kinase erbB-3, HER3)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-447) [*Homo sapiens* VH (IGHV3-23*01 (94.90%)-IGHD)-IGHJ4*01] [8.8.10] (1-117) - IGHG1*03 (CH1 (118-215), hinge (216-230), CH2 (231-340), CH3 (341-445), CHS (446-447)) (118-447), (220-214')-dissulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-12*01 (94.70%)-IGKJ1*01] [6.3.9] (1'-107')-IGKC*01 (108'-214')] dimer (226-226':229-229')-bisdisulfide
immunomodulator, antineoplastic
elgemtumab  
immunoglobuline G1-kappa, anti-[Homo sapiens ERBB3 (récepteur à activité tyrosine kinase erbB-3, HER3)], Homo sapiens anticorps monoclonal;  
chaîne lourde gamma1 (1-447) [Homo sapiens VH (IGHV3-23*01 (94.90%) -IGHD)-IGHJ4*01] [8.8.10] (1-117) -IGHG1*03 (CH1 (118-215), charnière (216-230), CH2 (231-340), CH3 (341-445), CHS (446-447)) (118-447), (220-214')-disulfure avec la chaîne légère kappa (1'-214') [Homo sapiens V-KAPPA (IGKV1-12*01 (94.70%) -IGKJ1*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (226-226''-229-229'')-bisdisulfure immunomodulateur, antinéoplasique

1512559-37-3

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<th>Heavy chain / Chaîne lourde / Cadena pesada</th>
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<td>EVQLLESGGG LVKPGQELRLS SCAASGFTPS SYAMESIVQA PKGGLENYQA 50</td>
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<td>INISGKSYTY ADSVRGAFIT SYRESNHLYV LQHNSLRAED TVVCTARGW 100</td>
</tr>
<tr>
<td>DEGFDWGGQG TTVSYASFA7 RGPVYPFLAP SEKSTSGOTA ALGCLVKDYF 150</td>
</tr>
<tr>
<td>PEPVTVSNWS GALTSGVNTF PAVLQESGGLY SLSSVVTYPS SALLGQTIC 200</td>
</tr>
<tr>
<td>NWHNHERMK YDKRVVEKPS ICATHTCPCPC APELLGGPSV FLFPPKPDFT 250</td>
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<tr>
<td>LMSKRYETV7 CTVVVSDKHED VRVFNMYDQ VGEVHMAKRT PREEQNYDTY 300</td>
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<tr>
<td>LPPKEXERMTK MQVISCLGIH KYSPPSNWEM WSVNHQFENNS YKFTTVYLLS 400</td>
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<tr>
<td>DGGSFLYSLK TVOKSRWQQG NVFSCSVHME ALHNTYQKLS LSLSQPCK 447</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Light chain / Chaîne légère / Cadena ligera</th>
</tr>
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<tbody>
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<td>DIQMTQSPSLS LASGVRDVT ITCRASQGIS NWLNYQKVQP GKAPKLKLYG 50</td>
</tr>
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<td>AISSLGVPFP RSFGDNGGTD FTLYISSQQP EDPATTYFQY YSFFPTVYQ 100</td>
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<td>GTYKVRKTV6 KASFGIFPPF DQELQCSSQA SVYCLNMFY SPRESSPYRKY 150</td>
</tr>
<tr>
<td>DNAQLGNSQ5 ESVRTQDSKD STYSLSTLT LEKADYEEKKK VYACEVTYRC 200</td>
</tr>
<tr>
<td>LSASPTVYK5N 8GEC 214</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrah-M (C23-C184) 22-96 144-200 261-321 367-425</td>
</tr>
<tr>
<td>22'-86' 144'-200' 261'-321' 367'-425'</td>
</tr>
<tr>
<td>Intrah-L (C23-C184) 23'-88' 134'-194'</td>
</tr>
<tr>
<td>Interh-L (h 5-CL 126) 220-214 220'-214'</td>
</tr>
<tr>
<td>Interh-H-H (h 11, h 14) 226-226' 226'-229'</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación</th>
</tr>
</thead>
<tbody>
<tr>
<td>H CH2 N84-8</td>
</tr>
<tr>
<td>H CHS K2 C-terminal lysine clipping: 447, 447'</td>
</tr>
</tbody>
</table>

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traducionales

emeraldum

emerald

N\textsuperscript{1},N\textsuperscript{3}-bis(2-sulfanyethyl)benzene-1,3-dicarboxamide  
chelating agent

éméramide

N\textsuperscript{1},N\textsuperscript{3}-bis(2-sulfanyléthyl)benzène-1,3-dicarboxamide  
chélateur
emeramida  
$N^1,N^3$-bis(2-sulfaniletil)benceno-1,3-dicarboxamida quelante  
C_{12}H_{16}N_{2}O_{2}S_{2}  
351994-94-0


epetraborol
epetraborole  
(3S)-3-(aminomethyl)-7-(3-hydroxypropoxy)-2,1-benzoxaborol-1(3H)-ol antibacterial

épétraborole  
(3S)-3-(aminométhyl)-7-(3-hydroxypropoxy)-2,1-benzoxaborol-1(3H)-ol antibactérien

epetraborol  
(3S)-3-(aminométil)-7-(3-hidroxipropoxi)-2,1-benzoxaborol-1(3H)-ol antibacteriano  
C_{11}H_{15}BNO_{4}  
1093643-37-8


eprosiclovirum
eprosiclovir  
2-amino-9-{{[(1S,2R)-1,2-bis(hydroxymethyl)cyclopropyl][methyl]}-1,9-dihydro-6H-purin-6-one antiviral (veterinary drug)

eprosiclovir  
2-amino-9-{{[(1S,2R)-1,2-bis(hydroxyméthyl)cyclopropyl][méthyl]}-1,9-dihydro-6H-purin-6-one antiviral (usage vétérinaire)

eprosiclovir  
2-amino-9-{{[(1S,2R)-1,2-bis(hidroximetil)ciclopropil][metil]}-1,9-dihidro-6H-purin-6-ona antiviral (uso veterinario)  
C_{11}H_{15}N_{5}O_{3}  
145512-85-2
**Proposed INN: List 112**

**Eptacogum beta (activatum)**

Eptacog beta (activated), recombinant DNA derived blood-coagulation factor VII (activated), extracted from transgenic rabbits' milk: blood-coagulation factor VII (EC 3.4.21.21, proconvertin, serum prothrombin conversion accelerator), human factor VII light chain (135-262)-disulfide with human factor VII heavy chain

**Eptacog beta (activado)**

Factor VII de la coagulación sanguínea (activado) a partir de ADN recombinante, extraído de leche de conejas transgénicas: factor VII de la coagulación sanguínea (EC 3.4.21.21, proconvertina, acelerador de conversión de la protrombina sérica), (135-262) disulfuro entre la cadena ligera y la cadena lourde del factor VII humano, glicoforma beta

**Eptacog beta (activé)**

Facteur VII de la coagulation sanguine (activé) à partir d’ADN recombinant, extrait du lait de lapins transgéniques: facteur VII de la coagulation sanguine (EC 3.4.21.21, proconvertine, accélérateur de conversion de la prothrombine sérique), (135-262) disulfure entre la chaîne légère et la chaîne lourde du facteur VII humain, glycoforme bêta

**Erlosibanum**

Erlosiban

\[
[(2S,4Z)-2-(hydroxymethyl)-4-(methoxyimino)pyrrolidin-1-yl][2'-methyl[1,1'-biphenyl]-4-yl]methanone
\]

**Erlosiban**

\[
[(2S,4Z)-2-(hydroxyméthyl)-4-(méthoxyimino)pyrrolidin-1-yl][2'-méthyl[1,1'-biphenyl]-4-yl]méthanone
\]
ertosibán

[[2S,4Z]-2-(hidroximetil)-4-(metoxiimino)pirrolidin-1-il][2'-metil][1,1'-bifenil]-4-il]metanona
antagonista de la oxitocina

C_{20}H_{22}N_{2}O_{3}  

1477482-19-1

evinacumab

immunoglobulin G4-kappa, anti-[Homo sapiens ANGPTL3 (angiopoietin-like 3)], human monoclonal antibody;
gamma4 heavy chain (1-453) [Homo sapiens VH (IGHV3-43*02 (92.90%) - (IGHD)-IGHJ3*02) [8.8.19] (1-126) -
IGHG4*01 (CH1 (127-224), S10=P (234) (225-236),
CH2 (237-346), CH3 (347-451), CHS (452-453) (127-453)),
(140-214')-disulfide with kappa light chain (1'-214') [Homo sapiens (V-KAPPA (IGKV1-5*03 (98.90%) - IGKJ2*01) [6.3.9] (1'-107') - IGKC*01 (108'-214')]; dimer (232-
232':235-235')-bisdisulfide
hypolipidaemic

evinacumab

immunoglobuline G4-kappa, anti-[Homo sapiens ANGPTL3 (angiopoïétine-like 3)], anticorps monoclonal humain;
chaîne lourde gamma4 (1-453) [Homo sapiens VH (IGHV3-43*02 (92.90%) - (IGHD)-IGHJ3*02) [8.8.19] (1-
126) -IGHG4*01 (CH1 (127-224), S10=P (234) (225-236),
CH2 (237-346), CH3 (347-451), CHS (452-
453) (127-453)), (140-214')-disulfure avec la chaîne légère kappa (1'-214') [Homo sapiens (V-KAPPA (IGKV1-5*03 (98.90%) - IGKJ2*01) [6.3.9] (1'-107') - IGKC*01 (108-
214')]; dimère (232-232':235-235')-bisdisulfure
hypolipémiant

evinacumab

immunoglobulina G4-kappa, anti-[ANGPTL3 (angiopoyetina-like 3) de Homo sapiens], anticuerpo monoclonal humano;
cadena pesada gamma4 (1-453) [VH de Homo sapiens (IGHV3-43*02 (92.90%) - (IGHD)-IGHJ3*02) [8.8.19] (1-
126) -IGHG4*01 (CH1 (127-224), S10=P (234) (225-236),
CH2 (237-346), CH3 (347-451), CHS (452-
453) (127-453)), (140-214')-disulfuro con la cadena ligera kappa (1'-214') [Homo sapiens (V-KAPPA (IGKV1-5*03 (98.90%) - IGKJ2*01) [6.3.9] (1'-107') - IGKC*01 (108-
214')]; dímero (232-232':235-235')-bisdisulfuro
hipolipemiante
Heavy chain / Chaîne lourde / Cadena pesada

EVQLVESGGG V1QPGSSLRKL SCAAGPGFTFD DYMNHVRQG PVCQSLGWSA 50
ISGGQGVTTVE ASYVRGGRFTI SRHDEKSNLP LQMQNLRAED TFFYCAKDL 100
EPTIVFQVPVDP AFDEIKVQTMTYVSSATKQGSPQVPLAPKVRKSESTAA 150
LGLLVVDVFYF EVPTVGSNSSG ALTSGVYRTFP AYVLQGQLVLG SLSSYTVPSQ 200
SLTGYTITCQ VVGQPSYNTVPVVRVEKPHQ FCPCPFCQPSF LGQPSVFLQF 250
APKPRKNIHSTQSKYECVVFVSQODNQDF VKNQVEQYVTVNATKFVE 300
QHSTRYRVS LVTYVHQLQLNQDEYKTVS HKFLPSEGIE TSQKQGQP 350
EPQYTLPFS QGRTENVQVS LVCLVQSGYP SDAKMEKSH QGPNVRKTYT 400
FIVLSSDGDF FYSLRVTSDK QSRQEQXVFS CSYMQHAEHN HYTGKSLSL 450
LDK 453

Light chain / Chaîne légère / Cadena ligera

DIQMTQSPST LSASVGDRVT ITCRASQSIR SWLAWYQQKP GKAPKLLIYK 50
ASSLEEGVPS RFSGSGSGTE FTLTISSLQP DDFASTYCGQ QNYSYSTFGQ 100
GTRLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNAQEQNSQ ESSLEQGSKG SLYLSSLTTL TSKADYRHIK VYACEVTEGQ 200
LSFVTIKSN RGE 214

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

Intra-H (C23-C104) 22-96 153-209 267-327 373-431
22’-96’ 153’-209’ 267’-327’ 373’-431’
Intra-L (C23-C104) 23-88’ 134-194’
23’-88’ 134’-194’
Inter-H-L (CH1 10-CL 126) 140-214’ 140’-214’
Inter-H-H (h8, h11) 232-232’ 235-235’

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

H CH2 N84.4: 303, 303’

flutafuranol (18F) flutafuranol (18F)

2-(2-[18F]fluoro-6-(methylamino) pyridin-3-yl)-1-benzofuran-5-ol
radiodiagnostic agent

flutafuranol (18F)

2-(2-[18F]fluoro-6-(méthylamino) pyridin-3-yl)-1-benzofuran-5-ol
produit de radiodiagnostic

flutafuranol (18F)

2-(2-[18F]fluoro-6-(metilamino) piridin-3-il)-1-benzofuran-5-ol
agente de radiodiagnóstico

C14H1118FN2O2 1211333-21-9

follitropinum delta #
follitropin delta

recombinant DNA derived heterodimer of human glycoprotein hormones alpha chain and follitropin subunit beta (FSH-beta) follicle-stimulating hormone, expressed in PER.C6 cells, glycoform delta
follicle stimulating hormone

follitropine delta

hétérodimère constitué de la chaîne alpha des hormones glycoprotéiques et de la sous-unité bêta de la follitropine (HFS-bêta) humaines, hormone folliculostimulante, exprimée dans les cellules PER.C6 à partir d’ADN recombinant, forme glycosylée delta
hormone folliculostimulante
folitropina delta

heterodímero constituido por la cadena alfa de las hormonas glicoproteicas y la subunidad beta de la folitropina (HFS-beta) humanas, hormona estimulante del folículo, expresada en células PER.C6 a partir de ADN recombinante, forma glicosilada delta

hormona estimulante del folículo

146479-72-3

alpha chain / chaîne alfa / cadena alfa
AFDQVDCIFEC TLEQEMPFSFQ PGSF11QCMG CCFSRAWTLP LR5KHTLUVQ 50
KNVTS ESTCC VAYS YRVTV MGFPXVHEI ACHISTCYYK 92

beta chain / chaîne bêta / cadena beta
NSCELTNITI AEKEECBFEC ISINTTWCCAY YCTRDLVYK DPARPRIQRT 50'
CTFLKLVET YRYPGCAHHA DSLITYFVAT QCHCGKCDSS STOCTYRGL2 100'
PSYCSFGEMK 111'

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
7-31 10-60 28-84 59-87
3-31 17-66 20-104 20-82 32-84 87-94

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-52 Asn-78 Asn-7' Asn-24'

gapotidacinum

gapotidacin

(2R)-2-[(4-(((3,4-dihydro-2H-pyran)[2,3-c]pyridin-6-yl)methyl)amino)piperidin-1-yl]methyl]-1,2-dihydro-3H,8H-2a,5,8a-triazaacenaphthylene-3,8-dione

antibacterial

gépotidacine

(2R)-2-[(4-(((3,4-dihydro-2H-pyran)[2,3-c]pyridin-6-yl)méthyl)amino)pipéridin-1-yl]méthyl]-1,2-dihydro-3H,8H-2a,5,8a-triazaacenaphthylène-3,8-dione

antibactérien

gapotidacina

(2R)-2-[(4-(((3,4-dihidro-2H-pirano)[2,3-c]piridin-6-il)méthy)amino)piperidin-1-il]méthy]-1,2-dihidro-3H,8H-2a,5,8a-triazaacenasfíleno-3,8-diona

antibacteriano

C_{24}H_{28}N_{6}O_{3} 1075236-89-3


gilteritinibum

gilteritinib

6-ethyl-3-(3-methoxy-4-{4-(4-méthylpipérazin-1-yl)pipéridin-1-yl}anilino)-5-{(oxan-4-yl)amino}pyrazine-2-carboxamide

tyrosin kinase inhibitor, antineoplastic

giltéritinib

6-éthyl-3-(3-méthoxy-4-{4-(4-méthylpipérazin-1-yl)pipéridin-1-yl}anilino)-5-{(oxan-4-yl)amino}pyrazine-2-carboxamide

inhibiteur de la tyrosine kinase, antinéoplasique
gilteritinib

6-etil-3-{4-[4-(4-metilpiperazin-1-il)piperidin-1-il]-
3-metoxianilino}-5-{(oxan-4-il)amino}pirazina-
2-carboxamida
inhibidor de la tirosina kinasa, antineoplásico

C_{29}H_{44}N_{8}O_{3}
1254053-43-4

ibiglustatum

(3S)-1-azabicyclo[2.2.2]octan-3-yl N-[2-(2-(4-fluorophenyl)-
1,3-thiazol-4-yl)propan-2-yl]carbamate
ceramide glucosyltransferase inhibitor

ibiglustat

N-(2-[2-(4-fluorofernil)-1,3-thiazol-4-yl]propan-
2-yl)carbamate de (3S)-1-azabicyclo[2.2.2]octan-3-yI
inhibiteur de la céramide glucosyltransférase

ibiglustat

N-(2-[2-(4-fluorofenil)-1,3-thiazol-4-il]propan-2-il)carbamato
de (3S)-1-azabicielo[2.2.2]octan-3-il
inhibidor de la ceramida glucosiltransferasa

C_{20}H_{24}F_{3}N_{3}O_{2}S
1401090-53-6

indimilastum

N-[cis-4-[1-{4'-[[[(3R,5S)-3,5-dimethylpiperazin-
1-yl]methyl][1,1'-biphenyl]-3-yl]-6-fluoro-2,4-dioxo-
1,4-dihydropyrido[2,3-d]pyrimidin-3(2H)-yl]cyclohexyl}-
2-methyl-1,3-thiazole-4-carboxamide
phosphodiesterase IV inhibitor

indimilast

N-[cis-4-[1-{4'-[[[(3R,5S)-3,5-diméthylpipérazin-
1-yl]méthyl][1,1'-biphényl]-3-yl]-6-fluoro-2,4-dioxo-
1,4-dihydropyridino[2,3-d]pyrimidin-3(2H)-yl]cyclohexyl}-
2-méthyl-1,3-thiazole-4-carboxamide
inhibiteur de la phosphodiésterase IV
indimilast  
\[N-(cis-4-[1-(4'-(3\text{R},\text{5S})-3,5\text{-dimetilpiperazin-1-il}]-\text{metil})[1,1'\text{-bifenil}]-3-il]-6\text{-fluoro}-2,4\text{-dioxo}-1,4\text{-dihidropirido}[2,3-\text{d}]\text{pirimidin}-3(2\text{H})-il][ciclohexil]-2\text{-metil}-1,3\text{-tiazol-4-carboxamida}\]

\[C_{37}H_{40}FN_{7}O_{3}S\]

1038825-85-2

indusatumab #

indusatumab

immunoglobuline G1-kappa, anti-[\textit{Homo sapiens} GUCY2C (guanylate cyclase 2C, guanylyl cyclase C, GCC, guanylate cyclase C, GC-C, récepteur d’entérotoxine résistante à la chaleur, hSTAR, guanylate cyclase intestinale)], \textit{Homo sapiens} anticorps monoclonal; chaîne lourde gamma 1 (1-449) [\textit{Homo sapiens} VH (IGHV4-34*01 (94.80%) -IGHD-IGHJ1*01) [8.7.13] (1-119)-IGHG1*01 (CH1 (120-217), chaine (218-232), CH2 (233-342), CH3 (343-447), CHS (448-449)) (120-449)], (222-214**)-disulfure avec la chaîne légère kappa (1'-214') [\textit{Homo sapiens} V-KAPPA (IGKV3-15*01 (95.80%) -IGKJ1*01 K123=N (103) [6.3.9] (1'-107')-IGKC*01 (108'-214')] ; dimère (228-228**231-231**)-bisdisulfure

\textit{immunomodulateur, antinéoplasique}
indusatumab

immunoglobulina G1-kappa, anti-[GUCY2C de Homo sapiens (guanylate cyclase 2C, guanylyl cyclase C, GCC, guanylate cyclase C, GC-C, receptor de enterotoxina resistente al calor, hSTAR, guanylate cyclase intestinal)], anticuerpo monoclonal de Homo sapiens; cadena pesada gamma1 (1-449) [VH de Homo sapiens (IGHV4-34*01 (94.80%) -(IGHD)-IGHJ1*01) (8.7.13) (1-119)-IGHG1*01 (CH1 (120-217), bisagra (218-232), CH2 (233-342), CH3 (343-447), CHS (448-449)) (120-449)], (222-214')-disulfido con la cadena ligera kappa (1'-214') [V-KAPPA de Homo sapiens (IGKV3-15*01 (95.80%) -IGKJ1*01 K123->N (103) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (228-228'::231-231')-bisdisulfido inmunomodulador, antineoplásico

Indusatumabum vedotinum #

Indusatumab vedotin

immunoglobulin G1-kappa, anti-[Homo sapiens GUCY2C (guanylate cyclase 2C, guanylyl cyclase C, GCC, guanylate cyclase C, GC-C, heat-stable enterotoxin receptor, hSTAR, intestinal guanylate cyclase)], Homo sapiens monoclonal antibody; gamma1 heavy chain (1-449) [Homo sapiens VH (IGHV4-34*01 (94.80%) -(IGHD)-IGHJ1*01) (8.7.13) (1-119)-IGHG1*01 (CH1 (120-217), hinge (218-232), CH2 (233-342), CH3 (343-447), CHS (448-449)) (120-449)], (222-214')-disulfide with kappa light chain (1'-214') [Homo sapiens V-KAPPA (IGKV3-15*01 (95.80%) -IGKJ1*01 K123->N (103) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimer (228-228'::231-231')-bisdisulfide; conjugated, on an average of 3 to 4 cysteiny, to monomethylauristatin E (MMAE), via a cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC) type linker For the vedotin part, please refer to the document "INN for pharmaceutical substances: Names for radicals, groups and others"; immunomodulator, antineoplastic
indusatumab védotine

immunoglobuline G1-kappa, anti-[Homo sapiens GUCY2C (guanylate cyclase 2C, guanylyl cyclase C, GCC, guanylate cyclase C, GC-C, récepteur d’entérotoxine résistante à la chaleur, hSTAR, guanyly cyclase intestinale)], Homo sapiens anticorps monoclonal; chaîne lourde gamma 1 (1-449) [Homo sapiens VH (IGHV4-34*01 (94.80%) - (IGHD)-IGHJ1*01) [8.7.13] (1-119)-IGHG1*01 (CH1 (120-217), charnière (218-232), CH2 (233-342), CH3 (343-447), CHS (448-449)) (120-449), (222-214’)-disulfure avec la chaîne légère kappa (1’-214’) [Homo sapiens V-KAPPA (IGKV3-15*01 (95.80%) -IGKJ1*01 K123>N (103) [6.3.9] (1’-107’)-IGKC*01 (108’-214’)]; dimère (228-228’-231’)-bisdisulfure; conjugué, sur 3 à 4 cystéinyl en moyenne, au monométhylauristatine E (MMAE), via un linker clivable de type maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC).

Pour la partie védotine, veuillez-vous référer au document “INN for pharmaceutical substances: Names for radicals, groups and others”.

La fraction vedotina, peuvent en trouver en le document “INN for pharmaceutical substances: Names for radicals, groups and others”.

imunoglobulina G1-kappa con anti[GUCY2C de Homo sapiens (guanyloctil ciclasa 2C, guanilil ciclasa C, GCC, guanilato ciclasa C, GC-C, receptor de enterotoxina resistente al calor, hSTAR, guanilato ciclasa intestinal)], Homo sapiens anticuerpo monoclonal; cadena pesada gamma 1 (1-449) [Homo sapiens VH (IGHV4-34*01 (94.80%) - (IGHD)-IGHJ1*01) [8.7.13] (1-119)-IGHG1*01 (CH1 (120-217), bisagra (218-232), CH2 (233-342), CH3 (343-447), CHS (448-449)) (120-449), (222-214’)-disulfuro con la cadena ligera kappa (1’-214’) [Homo sapiens V-KAPPA (IGKV3-15*01 (95.80%) -IGKJ1*01 K123>N (103) [6.3.9] (1’-107’)-IGKC*01 (108’-214’)]; dímero (228-228’-231’)-bisdisulfuro; conjugada, en una media de 3 a 4 cisteinil, con monometilauristatina E (MMAE), mediante un conector escindible de tipo maleimidocaproyl-valyl-citrulnil-p-aminobenciloxicarbonil (mc-val-cit-PABC)
**infigratinib**

N’-(2,6-dichloro-3,5-dimethoxyphenyl)-N-[6-[4-(4-ethylpiperazin-1-yl)anilino]pyrimidin-4-yl]-N-methylurea

*tyrosine kinase inhibitor, antineoplastic*

**isatuximabum #**

**isatuximab**

immunoglobulin G1-kappa, anti-[*Homo sapiens* CD38 (ADP-ribosyl cyclase 1, cyclic ADP-ribose hydrolase 1, cADPR hydrolase 1, T10)], chimeric monoclonal antibody; gamma1 heavy chain (1-450) [*Mus musculus* VH (IGHV1-7*’01 (80.60%) - (IGHD)-IGHJ4*’01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*’01 (CH1 (121-218), hinge (219-233), CH2 (234-343), CH3 (344-448), CHS (449-450)) (121-450)], (223-214*)-disulfide with kappa light chain (1’-214*) [*Mus musculus* V-KAPPA (IGKV6-17*’01 (89.50%) -IGKJ2*’01) [6.3.9] (1’-107’) -*Homo sapiens* IGKC*’01 (108’-214’)]; dimer (229-229”:232-232”)-bisdisulfide

*immunomodulator, antineoplastic*
isatuximab

imunoglobulina G1-kappa, anti-[CD38 de Homo sapiens (ADP-riboisil ciclasa 1, hidrolasa 1 de ADP-ribosa ciclica, cADPr hidrolasa 1, T10)], anticuerpo monoclonal químérico;
cadena pesada gamma1 (1-450) [Mus musculus VH (IGHV1-7*01 (80.60%) -IGHD*01) [8.8.13] (1-120) -Homo sapiens IGHG1*01 (CH1 (121-218), bisagra (219-233), CH2 (234-344), CH3 (344-448), CHS (449-450)) (121-450)], (223-214")-disulfuro con la cadena ligera kappa (1'-214') [Mus musculus V-KAPPA (IGKV6-17*01 (89.50%) -IGKJ2*01) [6.3.9] (1'-107') -Homo sapiens IGKC*01 (108'-214')]; dímero (229-229".232-232")-bisdisulfuro inmunomodulador, antineoplásico

lanopepdenum
lanopepdén

lanopepdène
lanopepédén
lascufloxacinum
lascufloxacin
7-{{3S,4S}-3-[(cyclopropylamino)methyl]-4-fluoropyrrolidin-1-yl}-6-fluoro-1-(2-fluoroethyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
quinolone antibacterial

lascufloxacin
acide 7-{{3S,4S}-3-[(cyclopropylamino)méthyl]-4-fluoropyrrolidin-1-yl}-6-fluoro-1-(2-fluoroéthyl)-8-méthoxy-4-oxo-1,4-dihydroquinoléine-3-carboxylique
quinolone, antibiotique

lascufloxacin
ácido 7-{{3S,4S}-3-[(ciclopropilamino)metil]-4-fluoropirrolidin-1-il}-6-fluoro-1-(2-fluoroetil)-8-metoxi-4-oxo-1,4-dihidroquinoleina-3-carboxílico
quinolona, antibiótico

lavamilastum
lavamilast
4-{{3,5-dichloropyridin-4-yl}amino}-7-methoxy-8-{{6-(morpholin-4-yl)hexyl}oxy}quinolin-2(1H)-one
phosphodiesterase IV inhibitor

lavamilast
4-{{3,5-dichloropyridin-4-yl}amino}-7-méthoxy-8-{{6-(morpholin-4-yl)hexyl}oxy}quinoléin-2(1H)-one
inhibiteur de la phosphodiésterase IV

lavamilast
4-{{3,5-dicloropiridin-4-il}amino}-7-metoxi-8-{{6-(morfolin-4-il)hexil}oxi}quinolein-2(1H)-ona
inhibidor de la fosfodiesterasa IV
lilotomab #
lilotomab

Immunoglobulin G1-kappa, anti-[Homo sapiens CD37 (TSPAN26, tetraspanin-26)], Mus musculus monoclonal antibody; gamma1 heavy chain (1-443) [Mus musculus VH (IGHV1S135*01 (96.90%) -IGHD-IGHJ4*01) [8.8.12] (1-119) -IGHG1*01 (CH1 E84>Q (177), P95>T (193), R96=W (194) (120-216), hinge (217-229), CH2 (230-336), CH3 N84.2>D (395), N84.4>D (397) (337-441), CHS (442-443)) (120-443)], (221-214')-disulfide with kappa light chain (1'-214') [Mus musculus V-KAPPA (IGKV6-25*01 (93.70%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimer (223-223':226-226':228-228')-trisdisulfide

Immunomodulator, antineoplastic

lilotomab

Immunoglobuline G1-kappa, anti-[Homo sapiens CD37 (TSPAN26, tétraspaliene-26)], Mus musculus anticorps monoclonal; chaîne lourde gamma1 (1-443) [Mus musculus VH (IGHV1S135*01 (96.90%) -IGHD-IGHJ4*01) [8.8.12] (1-119) -IGHG1*01 (CH1 E84>Q (177), P95>T (193), R96=W (194) (120-216), charnière (217-229), CH2 (230-336), CH3 N84.2>D (395), N84.4>D (397) (337-441), CHS (442-443)) (120-443)], (221-214')-disulfide avec la chaîne légère kappa (1'-214') [Mus musculus V-KAPPA (IGKV6-25*01 (93.70%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (223-223':226-226':228-228')-trisdisulfure

Immunomodulateur, antinéoplasique

lilotomab

Inmunoglobulina G1-kappa, anti-[CD37 de Homo sapiens (TSPAN26, tetraspanina-26)], anticuerpo monoclonal de Mus musculus; cadena pesada gamma1 (1-443) [VH de Mus musculus (IGHV1S135*01 (96.90%) -IGHD-IGHJ4*01) [8.8.12] (1-119) -IGHG1*01 (CH1 E84>Q (177), P95>T (193), R96=W (194) (120-216), bisagra (217-229), CH2 (230-336), CH3 N84.2>D (395), N84.4>D (397) (337-441), CHS (442-443)) (120-443)], (221-214')-disulfuro con la cadena ligera kappa (1'-214') [Mus musculus V-KAPPA (IGKV6-25*01 (93.70%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (223-223':226-226':228-228')-trisdisulfuro

Inmunomodulador, antineoplásico
lokivetmabum # lokivetmab

immunoglobulin G2-kappa, anti-[Canis lupus familiaris IL31 (interleukin 31)], caninized monoclonal antibody; gamma2 heavy chain (1-452) [caninized VH (Canis lupus familiaris IGHV-E2RCC8 (85.90%)-(IGHD)-IGHJ) [8.8.11] (1-118)-Canis lupus familiaris IGHD2*01 (CH1 (119-216), hinge (217-234), CH2 (235-344), CH3 (345-451), CHS (452)) (119-452)], (133-217’)-disulfide with kappa light chain (1’-217’) [caninized V-KAPPA (Canis lupus familiaris IGKV-F1PNY2 (56.00%) -IGKJ) [10.3.9] (1’-111’)-Canis lupus familiaris IGKC*01 (112’-217’)]; dimer (230-230’*:233-233’*)-bisdisulfide immunomodulator (veterinary use)

lokivetmab

immunoglobuline G2-kappa, anti-[Canis lupus familiaris IL31 (interleukine 31)], anticorps monoclonal caninisé; chaîne lourde gamma2 (1-452) [VH caninisé (Canis lupus familiaris IGHV-E2RCC8 (85.90%)-(IGHD)-IGHJ) [8.8.11] (1-118)-Canis lupus familiaris IGHD2*01 (CH1 (119-216), charnière (217-234), CH2 (235-344), CH3 (345-451), CHS (452)) (119-452)], (133-217’)-disulfure avec la chaîne légère kappa (1’-217’) [V-KAPPA caninisé (Canis lupus familiaris IGKV-F1PNY2 (56.00%) -IGKJ) [10.3.9] (1’-111’)-Canis lupus familiaris IGKC*01 (112’-217’)]; dimère (230-230’*:233-233’*)-disulfure immunomodulateur (usage vétérinaire)
lokivetmab  immunoglobulina G2-kappa, anti-[Canis lupus familiaris IL31 (interleukina 31)], anticuerpo monoclonal caninizado; cadena pesada gamma2 (1-452) [VH caninizado (Canis lupus familiaris IGHV-E2RCC8 (85.90%) -IGHD)-IGHJ] [8.8.11] (1-118) -Canis lupus familiaris IGHG2*01 (CH1 (119-216), bisagra (217-234), CH2 (235-344), CH3 (345-451), CHS (452)) (119-452), (133-217')-disulfuro con la caden ligera kappa (1'-217') [V-KAPPA caninizado (Canis lupus familiaris IGKV-F1PNY2 (56.00%) -IGKJ] [10.3.9] (1'-111') -Canis lupus familiaris IGKC*01 (112-217'); dímero (230-230';233-233')-disulfuro inmunomodulador (uso veterinario)

1533403-95-0

Heavy chain / Chaîne lourde / Cadena pesada
EVQLVESGGD LVKPGGSLRL SCAVSGTFFP YGMMENVRQA PGKILQNYAT  50
ISYGSTYTTY PENIQGRRTI SRQANKNTLY LQMNMLRAED TAMYTVCRSGY 100
QVDTMOWQG GAVILRVEASE TTSAPVYFPLA FPEGSEGTGQ VALAICVQGQX 150
FFEEPTQWNW SGGLTSGVHT FFSVLQSGSL YSLESMQTVF SSWPVSETPTT 200
CNVHAPAKRT KVHEFVPKRE NQGRPFPFDC FCPAEPAEML GSVPVFFPFR 250
QFDLIAART FEITCYYWDL DREPFEQVIS WPQERQFXQF 300
NGCRVRVVSL PFGHQWLQKS KGPTCKVSNK ALPQFPEIELQ 350
SVTVLPPSFRE ELSDKNTVLT CLIKPGFIFPD IDQEMNGHGQ QFPSEXYTTT 400
PPQODGEGSL FLYEKLYVSD SWQRGDGFTPI CATYMEQGHH HYQESLEKS 450
PG  452

Light chain / Chaîne légère / Cadena ligera
EIVMTQSPAS LSLSQEEKVT ITCKASQSVS FAGTGLMHWY QQKPGQPAEL  50
LITRASNLEA GVPSSFEGGG SGTDFSSTIS SLEFEDVAYV YQQQPIREFRM 100
TFQGQTLKEI KRNRQGRAYV LFQPSFHQQI TCASHQVQCL HSPYQREDVY 150
KMRVQGVDQG TGQGSRVTEQ DRSTYSSLSS TLTMISSTYEL SHELSCPICE 200
HKELPSTLIK SFQSEC  217

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96  145-201  265-325  371-431
22'-96'  145'-201'  265'-325'  371'-431''
Intra-L (C23-C104) 23'-92'  138'-197'  265'-325'  371'-431''
23''-92''  138''-197''
Inter-H-L (CH1 11-CL 126) 133-217'  133'-217''
Inter-H-H (h 14, h 17)  230-230'  233-233''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4: 301, 301''

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales
Lacking H chain C-terminal lysine (CHS K2>del)

lopixibati chloridad
lopixibat chloride
1-[(4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1H-1λ6-benzotiepin-5-yl]phenoxo]methyl]phenyl[methyl]-1,4-diazabicyclo[2.2.2]octan-1-ium chloride ileal bile acid transporter inhibitor

chlorure de lopixibat
chlorure de 1-[(4-[(4R,5R)-3,3-dibutyl-7-(diméthylamino)-4-hydroxy-1,1-dioxo-2,3,4,5-tétrahydro-1H-1λ6-benzotéïpin-5-yl]phénoxy]méthyl]phényl[méthyl]-1,4-diazabicyclo[2.2.2]octan-1-ium inhibiteur du transporteur iléal d’acides biliaires

cloruro de lopixibat
cloruro de 1-[(4-[(4R,5R)-3,3-dibutyl-7-(dimeetilamino)-4-hidroxí-1,1-dioxo-2,3,4,5-tetraidro-1H-1λ6-benzotiepin-5-il]fenoxi]metil]fenil]metil]-1,4-diazabiciclo[2.2.2]octan-1-io inhibidor del transportador iliaco de ácidos biliares
lutetium ($^{177}$Lu) lilotomab satetraxetanum #

Immunoglobulin G1-kappa, anti-[Homo sapiens CD37 (TSPAN26, tetraspanin-26)], Mus musculus monoclonal antibody, lutetium (Lu 177) radiolabelled satetraxetan (DOTA derivative) conjugate; gamma1 heavy chain (1-443) [Mus musculus VH (IGHV1S135*01 (96.90%) -IGHD-IGHJ4*01) [8.8.12] (1-119) -IGHG1*01 (CH1 E84-Q (177), P95>T (193), R96>W (194) (120-216), hinge (217-229), CH2 (230-336), CH3 N84.2>D (395), N84.4>D (397) (337-441), CHS (442-443)) (120-443)], (221-214')-disulfide with kappa light chain (1'-214') [Mus musculus V-KAPPA (IGKV6-25*01 (93.70%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimer (223-223'':226-226'':228-228'')-trisdisulfide, an average of 1 to 2 amino groups ($N^6$ of lysines) are substituted: $N$-[rac-4-{{[(2R)-1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-2-yl]methyl}phenyl}carbamothioyl] ($^{177}$Lu)lutetium(3+) chelate

immunomodulator, antineoplastic

lutécium ($^{177}$Lu) lilotomab satétraxétan

Immunoglobuline G1-kappa, anti-[Homo sapiens CD37 (TSPAN26, tétraspanine-26)], Mus musculus anticorps monoclonal; conjugué au satétraxétan (dérivé DOTA) radiomarqué au lutécium (Lu 177); chaîne lourde gamma1 (1-443) [Mus musculus VH (IGHV1S135*01 (96.90%) -IGHD-IGHJ4*01) [8.8.12] (1-119) -IGHG1*01 (CH1 E84-Q (177), P95>T (193), R96>W (194) (120-216), charnière (217-229), CH2 (230-336), CH3 N84.2>D (395), N84.4>D (397) (337-441), CHS (442-443)) (120-443)], (221-214')-disulfure avec la chaîne légère kappa (1'-214') [Mus musculus V-KAPPA (IGKV6-25*01 (93.70%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimère (223-223'':226-226'':228-228'')-trisdisulfure, une moyenne de 1 à 2 groupes amino ($N^6$ de lysines) sont substitués: $N$-[rac-4-{{[(2R)-1,4,7,10-tétrakis(carboxyméthyl)-1,4,7,10-tétraazacyclododecan-2-yl]méthyl}phényl}carbamothioïl] chélate de ($^{177}$Lu)lutécium(3+)

immunomodulateur, antinéoplasique
lutecio (\(^{177}\text{Lu}\)) lililotomab satetraxetán imunoglobulina G1-kappa, anti-[CD37 de \textit{Homo sapiens} (TSPAN26, tetraspanina-26)], anticuerpo monoclonal de \textit{Mus musculus}, conjugado al satetraxetán (derivado DOTA) radiomarcado con lutecio (Lu 177); cadena pesada gamma1 (1-443) [IGHV1S135*01 (96.90%) -IGHV4*01 (88.12) (1-119) -IGHG1*01 (CH1 E84>Q (177), P95>T (193), R96=W (194) (120-216), bisagra (217-229), CH2 (230-336), CH3 N84.2-D (395), N84.4-D (397) (337-441), CHS (442-443)) (120-443)], (221-214')-disulfuro con la cadena ligera kappa (1'-214') [\textit{Mus musculus} V-KAPPA (IGKV6-25*01 (93.70%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dímero (223-223'-226-226'-228-228')-trisdisulfuro; una medida de 1 a 2 grupos amino (N\(^{6}\) de lisinas) están sustituidos; N-(rac-4-[(2R)-1,4,7,10-tetrakis(carboximetil)-1,4,7,10-tetraazaciclododecan-2-il]metil)fenil)carbamotioil que lato de (\(^{177}\text{Lu}\))lutecio(3+) inmunomodulador, antineoplásico.

\begin{align*}
\text{Heavy chain / Chaîne lourde / Cadena pesada} & \quad E1QCGQ5OSPELWFGQSFVYK SCKAGSYSFT DNYTMWNVQK SQKSSLEWGY 50 \\
& \quad IDPFYDGVTY QRKFGKATL TVDKESSHAT ILHNLSTSED SAVYCARSEP 100 \\
& \quad VQKAGNYQSG QSQTVSYYSA KTPFSYVSYL AFGQSSAQTH TSUlingen 150 \\
& \quad YPPFEVFTRT NSSGSLSSGV TFFAVLYQSDL YTLSSSEVTY SSTMPESETV 200 \\
& \quad CNVRKAFESRT KVQDKIVFERG CCGFKCICTV FEVSSVIFIPF PRKEDVLTLT 250 \\
& \quad LTFRPVCCTVV DISEKDFPQVF PSSPFVQYEV NTAQTDREEP QHPSTESYS 300 \\
& \quad ELFPMHQOWL NGKFFKRKV SAAQPAPIEK TISGKTRGRK APQVTIPPP 350 \\
& \quad KEQMQAKGRFS LTCMIDTFEPF EDTWEQMN QPPAEYNFENT QPIMDYSGY 400 \\
& \quad FDDSNLNIFF SNREAQHTFT CPVLIGELHN MTKSLEWSS PDR 443 \\
\text{Light chain / Chaîne légère / Cadena ligera} & \quad D1VMPQQ1XNL LSTSGVRKVS ITYCGSQQVS TAVNMYQKPF QSSPKLLEWN 50 \\
& \quad ASTTRKCFPD RFTGSSGQTD YLTLISMQA EDLLAYCRCQ HYSSTPFQGS 100 \\
& \quad GTKLEIFKAD AAPFYSIIPF SSEQLTTSGA SVFCLHLFNT PKDHVNYREI 150 \\
& \quad DGQERQMKVL NSTEMQGQSD STYSSSSTLAT LTYKERERIN SYCTEAWRT 200 \\
& \quad STSPVKEFNP RNEC 214 \\
\end{align*}

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

\begin{align*}
\text{Intra-H (C23-C104)} & \quad 22-96 \quad 146-201 \quad 257-317 \quad 363-421 \\
\text{Intra-L (C23-C104)} & \quad 23-88 \quad 134-194 \\
\text{Inter-H-L (h 5-CL 126)} & \quad 221-214' \quad 226-226' \quad 228-228' \\
\text{Inter-H-H (h 7, h 10, h 12)} & \quad 223-223' \quad 226-226' \quad 228-228' \\
\end{align*}

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

H CH2 N84.4: 293, 293'

Modified residues / Résidus modifiés / Restos modificados

\begin{align*}
K & \quad \text{An average of 1 to 2 are N-substituted by R} \\
& \quad \text{Una medida de 1 a 2 están N-sustituidos por R} \\
\end{align*}

**mereletinib**

N-(2-[(2-(dimethylamino)ethyl][methyl]amino)-4-methoxy-5-[[4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl]amino]phenyl)prop-2-enamide

tyrosine kinase inhibitor, antineoplastic

**mérélétinib**

N-(2-[(2-(diméthylamino)éthyl][méthyl]amino)-4-méthoxy-5-[[4-(1-méthyl-1H-indol-3-yl)pyrimidin-2-yl]amino]phényl)prop-2énanamide

inhibiteur de la tyrosine kinase, antinéoplasique
mereletinib

\[N-(2-[[2-(dimethylamino)ethyl](methyl)amino]-4-methoxy-5-[[4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl]amino]phenyl)prop-2-ynamida\]

inhibidor de la tirosina kinasa, antineoplásico

\[C_{28}H_{33}N_{7}O_{2}\]

motolimodum

motolimod

\[2\text{-amino}-N,N\text{-dipropyl}-8\{-4\{(pyrrolidine-1-carbonyl)phenyl\}\}-3H\text{-1-benzazepine-4-carboxamide}\]

immunomodulator, antineoplastic

\[C_{28}H_{34}N_{4}O_{2}\]

necuparanibum

necuparanib

low molecular mass heparan sulfate mimetic compound that is obtained by nitrous sodium depolymerization of heparin from porcine intestinal mucosa, sodium periodate glycol split oxidation of uronic acids elements and sodium borohydride reduction of aldehydes produced during oxidation; the majority of the components have a split ed uronic acid structure at the non-reducing end and a 2,5-anhydromannitol structure at the reducing end of their chain; the average molecular weight range is 5000 to 8000 Da; the degree of sulfatation is about 2 per disaccharidic unit

antineoplastic
nécuparanib
dérivé de basse masse moléculaire à action mimétique du sulfate d’héparane, obtenu par dépolymérisation
d’héparine de muqueuse intestinale de porc, catalysée par
du nitrite de sodium, puis dégradation oxydative des
glycols des unités uroniques par le périodate de sodium et réduction,
par le borohydrure de sodium, des aldéhydes produits; la majorité des composants ont, une structure éclatée d’acide uronique à leur extrémité non-réductrice et une structure 2,5-anhydromannitol à leur extrémité réductrice, une masse molaire comprise entre 4500 et 7200 daltons et un degré de sulfatation d’environ de 2 par unité disaccharide
antineoplásique

neladenosoni dalanas
dalanate de néladénoson L-alanyl-L-alaninate de
2-{4-[2-([2-(4-chlorophényl)-1,3-thiazol-4-yl]méthyl)sulfanyl]-3,5-dicyano-6-(pyrrolidin-1-yl)pyridin-4-yl]phenoxy}éthyle
agoniste des récepteurs de l’adénosine

1415139-34-2

\[
\begin{align*}
\text{R}^1 & = \text{H, SO}_3\text{H} \\
\text{R}^2 & = \text{COCH}_3, \text{SO}_3\text{H}
\end{align*}
\]

necuparanib
derivado de baja masa molecular de acción mimética de la del sulfato de heparán, obtenido por despolimerización de heparina de mucosa intestinal de cerdo, catalizada por nitrato de sodio, seguida de degradación oxidativa, con peróxido de sodio, de los glicoles de las unidades urónicas y reducción, con borohiduro de sodio, de los aldehídos producidos; la mayoría de los componentes tienen, una estructura abierta de ácido urónico en su extremo no-reductor y una estructura 2,5-anhidromanitol en el reductor, el peso molecular medio está comprendido entre 4500 y 7200 daltons y el grado de sulfatación es aproximadamente de 2 por unidad de disacárido antineoplásico

necuparanib
derivado de baja masa molecular de acción mimética de la del sulfato de heparán, obtenido por despolimerización de heparina de mucosa intestinal de cerdo, catalizada por nitrato de sodio, seguida de degradación oxidativa, con peróxido de sodio, de los glicoles de las unidades urónicas y reducción, con borohiduro de sodio, de los aldehídos producidos; la mayoría de los componentes tienen, una estructura abierta de ácido urónico en su extremo no-reductor y una estructura 2,5-anhidromanitol en el reductor, el peso molecular medio está comprendido entre 4500 y 7200 daltons y el grado de sulfatación es aproximadamente de 2 por unidad de disacárido antineoplásico
dalanato de neladenosón  
L-alanil-L-alaninato de 2-{4-[[2-(4-clorofenil)-1,3-tiazol-4-il]metil]sulfanil}-3,5-diciano-6-(pirrolidin-1-il)piridin-4-il]fenoxi]etilo
agonista del receptor de la adenosina

\[ \text{C}_{23}\text{H}_{34}\text{ClN}_{7}\text{O}_{4}\text{S}_{2} \]  
1239309-58-0

neloniclinum  
nelonicline  
(3R,4s,5S)-4-[[5-phenyl-1,3,4-thiadiazol-2-yl]oxy]-1-azaadamantane
nicotinic acetylcholine receptor agonist

célonicline  
(3R,4s,5S)-4-[[5-phenyl-1,3,4-thiadiazol-2-yl]oxy]-1-azaadamantane
agoniste du récepteur nicotinique à l'acétylcholine

neloniclina  
(3R,4s,5S)-4-[[5-fenil-1,3,4-tiadiazol-2-il]oxi]-1-azaadamantano
agonista del receptor nicotínico de la acetilcolina

\[ \text{C}_{17}\text{H}_{19}\text{N}_{3}\text{OS} \]  
1026134-63-3

nemolizumabum  
nemolizumab  
immunoglobulin G2-kappa, anti-[\text{Homo sapiens} \text{IL31RA} (interleukin 31 receptor subunit alpha)], humanized monoclonal antibody;
gamma2 heavy chain (1-445) [humanized VH (\text{Homo sapiens} \text{IGHV1-2*02} (83.70%) -(IGHD)-\text{IGHJ5*01}) [8.8.14] (1-121) -\text{Homo sapiens} \text{IGHG2*01} (\text{CH1 C10>S (135), R12>K (137), E16>G (141), S17>G (142) (122-219), hinge C4>S (223) (220-231), CH2 H30>Q (268) (232-340), CH3 R11>Q (355), Q98>E (419) (341-445)) (122-445), (224-214')-disulfide with kappa light chain (1'-121') [humanized V-KAPPA (\text{Homo sapiens} \text{IGKV1-39*01} (82.10%) -\text{IGKJ4*01}) [6.3.9] (1'-107') -\text{Homo sapiens} \text{IGKC*01} (108'-214')]; dimer (227-227'-230-230')-bisdisulfide immunomodulator
némolizumab

immunoglobuline G2-kappa, anti-[*Homo sapiens* IL31RA (sous-unité alpha du récepteur de l'interleukine 31)], anticorps monoclonal humanisé;
chaîne lourde gamma2 (1-445) [VH humanisé (*Homo sapiens* IGHV1-2*02 (83.70%) -(IGHD)-IGHJ5*01) [8.8.14] (1-121) -*Homo sapiens* IGHG2*01 (CH1 C10>S (135), R12>K (137), E16>G (141), S17>G (142) (122-219), charnière C4>S (223) (220-231), CH2 H30>Q (268) (232-340), CH3 R11>Q (355), Q98>E (419) (341-445)) (122-445)], (224-214'-disulfure avec la chaîne légère kappa (1'-214')] [V-KAPPA humanisé (*Homo sapiens* IKGV1-39*01 (82.10%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')] ; dimère (227-227”-230-230”)-bisdisulfure

immunomodulateur

1476039-58-3

1476039-58-3

nemolizumab

imunoglobulina G2-kappa, anti-[IL31RA de *Homo sapiens* (subunidad alfa del receptor de la interleukina 31)], anticuerpo monoclonal humanizado;
cadena pesada gamma2 (1-445) [VH humanizado (*Homo sapiens* IGHV1-2*02 (83.70%) -(IGHD)-IGHJ5*01) [8.8.14] (1-121) -*Homo sapiens* IGHG2*01 (CH1 C10>S (135), R12>K (137), E16>G (141), S17>G (142) (122-219), bisagra C4>S (223) (220-231), CH2 H30>Q (268) (232-340), CH3 R11>Q (355), Q98>E (419) (341-445)) (122-445)], (224-214')-disulfuro con la cadena ligera kappa (1'-214')] [V-KAPPA humanizado (*Homo sapiens* IKGV1-39*01 (82.10%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')] ; dímero (227-227”-230-230”)-bisdisulfuro

imunomodulador

1476039-58-3
nusinersen

\[ \text{all-} P - \text{ambo-} 2' - O - (2\text{-methoxyethyl}) - 5\text{-methyl-} P - \text{thiouridylyl-} (3'\text{-}5') - 2' - O - (2\text{-methoxyethyl}) - 5\text{-methyl-} P - \text{thiocytidylyl-} (3'\text{-}5') - 2' - O - (2\text{-methoxyethyl}) - 5\text{-methyl-} P - \text{thiouridylyl-} (3'\text{-}5') - 2' - O - (2\text{-methoxyethyl}) - 5\text{-methyl-} P - \text{thiocytidylyl-} (3'\text{-}5') - 2' - O - (2\text{-methoxyethyl}) - 5\text{-methyl-} P - \text{thiouridylyl-} (3'\text{-}5') - 2' - O \] 

**Proposed INN: List 112**

Survival Motor Neuron (SMN2) protein production

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nusinersen

\[ \text{tout-} P - \text{ambo-} 2' - O - (2\text{-méthoxyéthyl}) - 5\text{-méthyl-} P - \text{thiouridylyl-} (3'\text{-}5') - 2' - O - (2\text{-méthoxyéthyl}) - 5\text{-méthyl-} P - \text{thiocytidylyl-} (3'\text{-}5') - 2' - O - (2\text{-méthoxyéthyl}) - 5\text{-méthyl-} P - \text{thiouridylyl-} (3'\text{-}5') - 2' - O - (2\text{-méthoxyéthyl}) - 5\text{-méthyl-} P - \text{thiocytidylyl-} (3'\text{-}5') - 2' - O \] 

production de la protéine de survie des motoneurones (SMN2)

---

nusinersén

\[ \text{todo-} P - \text{ambo-} 2' - O - (2\text{-metoxietil}) - 5\text{-metil-} P - \text{tiuridilil-} (3'\text{-}5') - 2' - O - (2\text{-metoxietil}) - 5\text{-metil-} P - \text{tiocitidilil-} (3'\text{-}5') - 2' - O - (2\text{-metoxietil}) - 5\text{-metil-} P - \text{tiuridilil-} (3'\text{-}5') - 2' - O - (2\text{-metoxietil}) - 5\text{-metil-} P - \text{tiocitidilil-} (3'\text{-}5') - 2' - O \] 

producción de la proteína de la supervivencia de las motoneuronas (SMN2)
**Proposed INN: List 112**

**onalespibum**

**onalespib**

[2,4-dihydroxy-5-(propan-2-yl)phenyl](5-[(4-methylpiperazin-1-yl)methyl]-1,3-dihydro-2H-isoindol-2-yl)methanone  
*antineoplastic*

**onalespib**

[2,4-dihydroxy-5-(propan-2-yl)phényl](5-[(4-méthylpipérazin-1-yl)méthyl]-1,3-dihydro-2H-isoindol-2-yl)méthanone  
*antinéoplasique*

**onalespib**

[2,4-dihidroxi-5-(propan-2-il)fenil](5-[(4-metilpiperazin-1-il)metil]-1,3-dihidro-2H-isoindol-2-il)metanona  
*antineoplásico*

**ozanimodum**

**ozanimod**

5-(3-{{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1H-inden-4-yl}-1,2,4-oxadiazol-5-yl}-2-[(propan-2-yl)oxy]benzonitrile  
*immunomodulator*

**ozanimod**

5-(3-{{(1S)-1-[(2-hydroxyéthyl)amino]-2,3-dihydro-1H-indén-4-y]-1,2,4-oxadiazol-5-y]-2-[(propan-2-y)oxy]benzonitrile  
*immunomodulateur*

**ozanimod**

5-(3-{{(1S)-1-[(2-hidroxietil)amino]-2,3-dihidro-1H-inden-4-il}-1,2,4-oxadiazol-5-il}-2-[(propan-2-il)oxi]benzonitrilo  
*inmunomodulador*

**C<sub>23</sub>H<sub>34</sub>N<sub>6</sub>O<sub>12</sub>P<sub>1</sub>S<sub>1</sub> 1258984-36-9**

[2’-O-(2-methoxyethyl)](3’-5’)(P-thio)(mU-mC-A-mC-mU-mU-mC-A-mU-A-mU-G-mC-mU-G-G)
pegpleranib

5′-O-[[6-{N²,N⁶-bis[α-carbonyl-ω-methoxypoly(oxyethane-1,2-diy1)]-DL-lysylamido}hexyloxy]hydroxyphosphoryl]-2′-deoxyctidylyl-(3′→5′)-2′-deoxyadenyllyl-(3′→5′)-2′-deoxyguanylyl-(3′→5′)-2′-deoxyguanylyl-(3′→5′)-2′-deoxyctidylyl-(3′→5′)-2′-deoxy-2′-fluorouridylyl-(3′→5′)-2′-deoxyadenylyl-(3′→5′)-2′-deoxy-2′-fluorocytidylyl-(3′→5′)-2′-O-methylguanylyl-(3′→17)-hydroxy[(17-hydroxy-3,6,9,12,15-pentaoxaheptadecyl)oxy]phosphoryl-(1→5′)-2′-deoxyctidylyl-(3′→5′)-2′-deoxyguanylyl-(3′→5′)-thymidylyl-(3′→5′)-2′-deoxyadenylyl-(3′→5′)-2′-O-methylguanylyl-(3′→5′)-2′-deoxyctidylyl-(3′→5′)-2′-deoxyadenylyl-(3′→5′)-2′-O-methylguanylyl-(3′→5′)-2′-deoxyctidylyl-(3′→5′)-2′-deoxy-2′-fluorouridylyl-(3′→5′)-2′-deoxy-2′-fluorocytidylyl-(3′→5′)-2′-methylenadenyllyl-(3′→17)-hydroxy[(17-hydroxy-3,6,9,12,15-pentaoxaheptadecyl)oxy]phosphoryl-(1→5′)-thymidylyl-(3′→5′)-2′-deoxyguanylyl-(3′→5′)-2′-deoxyadenylyl-(3′→5′)-thymidylyl-(3′→5′)-2′-deoxy-2′-fluorocytidylyl-(3′→5′)-2′-deoxy-2′-fluorouridylyl-(3′→5′)-2′-O-methylguanylyl-(3′→3′)-thymidine

angiogenesis inhibitor

pegpléranib

5′-O-[[6-{N²,N⁶-bis[α-carbonyl-ω-méthoxypoly(oxyéthane-1,2-diy1)]-DL-lysylamido}hexyloxy]hydroxyphosphoryl]-2′-déoxyctidylyl-(3′→5′)-2′-déoxyadénylyl-(3′→5′)-2′-déoxyguanylyl-(3′→5′)-2′-déoxyguanylyl-(3′→5′)-2′-déoxyctidylyl-(3′→5′)-2′-déoxy-2′-fluorouridylyl-(3′→5′)-2′-déoxyadenylyl-(3′→5′)-2′-déoxy-2′-fluorocytidylyl-(3′→5′)-2′-O-méthylguanylyl-(3′→17)-hydroxy[(17-hydroxy-3,6,9,12,15-pentaoxaheptadécyl)oxy]phosphoryl-(1→5′)-thymidylyl-(3′→5′)-2′-déoxyguanylyl-(3′→5′)-2′-déoxyadenylyl-(3′→5′)-2′-O-méthylguanylyl-(3′→5′)-2′-déoxyctidylyl-(3′→5′)-2′-déoxy-2′-fluorouridylyl-(3′→5′)-2′-déoxy-2′-fluorocytidylyl-(3′→5′)-2′-déoxy-2′-fluorouridylyl-(3′→5′)-2′-O-méthyladénylyl-(3′→17)-hydroxy[(17-hydroxy-3,6,9,12,15-pentaoxaheptadécyl)oxy]phosphoryl-(1→5′)-thymidylyl-(3′→5′)-2′-déoxyguanylyl-(3′→5′)-2′-déoxyadenylyl-(3′→5′)-2′-O-méthylguanylyl-(3′→5′)-2′-déoxyctidylyl-(3′→5′)-2′-déoxy-2′-fluorouridylyl-(3′→5′)-2′-déoxy-2′-fluorocytidylyl-(3′→5′)-2′-O-méthylguanylyl-(3′→3′)-thymidine

inhibiteur de l’angiogénèse
pegpleranib

5'-O-[[6-(N2,N6-bis[α-carboxi-ω-metoxipolioxetano-1,2-dili)]-DL-lisilamido)hexil]oxy][hidroxifosforil]-2'-desoxiadenilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-O-metilguanilil-(3'→17)-hidroxi[(17-hidroxi-3,6,9,12,15-pentaoxaheptadecil)oxy]fosforil-(1→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiguani-nilil-(3'→5')-2'-O-metilguanilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-O-metilguanilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-desoxi-2'-fluorouridilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-desoxi-2'-fluorocitidilil-(3'→5')-2'-O-metilguanilil-(3'→3')-timidina

inhibidor de la angiogénesis

1618657-13-8

(3'-5')-R-dC-dA-dG-dCdUfl-dA-dCfl-Gm3'-17Xp1-
5'dC-dG-dT-da-GmA-dC-dUfl-dCfl-Am3'-
17Xp1-5'dT-dG-da-A-dCfl-dCfl-dUfl-Gm3'-3'dT

d (as prefix) = 2'-deoxy
fl (as suffix) = 2'-fluoro
m (as suffix) = 2'-O-methyl

rac

\[
\text{C}_{20}\text{H}_{15}\text{ClF}_{3}\text{N}_{5}
\]

1029044-16-3
pinometostatum

pinometostat 9-{5-deoxy-5-[(cis-3-[2-(5-tert-butyl-1H-benzimidazol-2-yl)ethyl]cyclobutyl](propan-2-yl)amino]-β-D-ribofuranosyl}-9H-purin-6-amine

antineoplastic

pinométostat 9-{5-déoxy-5-[(cis-3-[2-(5-tert-butyl-1H-benzimidazol-2-yl)éthyl]cyclobutyl](propan-2-yl)amino]-β-D-ribofuranosyl}-9H-purin-6-amine

antinéoplasique

pinometostat 9-{5-desoxi-5-[(cis-3-[2-(5-terc-butil-1H-benzoimidazol-2-il)étil]ciclobutil](propan-2-il)amino]-β-D-ribofuranosil}-9H-purin-6-alamina

antineoplásico

C₃₀H₴₂N₈O₃  1380288-87-8

radalbuvirum

radalbuvir 5-(3,3-dimethylbut-1-yn-1-yl)-3-[(1R)-N-[(1s,4s)-4-hydroxy-4-([(3S)-oxolan-3-yl]oxy)méthyl)cyclohexil]-4-méthylcyclohex-3-ène-1-carboxamido]thiophène-2-carboxylique

antiviral

radalbuvir acide 5-(3,3-diméthylbut-1-in-1-il)-3-[(1R)-N-[(1s,4s)-4-hidroxi-4-([(3S)-oxolan-3-il]oxi)metil]ciclohexil]-4-metilciclohex-3-eno-1-carboxamido]tiofeno-2-carboxílico

antiviral

C₃₀H₴₁NO₆S  1314795-11-3
ralinepagum
ralinepag
\{\textit{trans-4-\{\{(4-chlorophenyl)(phenyl)carbamoyl\}oxy\}methyl}\}cyclohexylmethoxy\}acetic acid
prostaglandin receptor agonist

ralinépag
acide \{\textit{trans-4-\{\{(4-chlorophényl)(phényl)carbamoyl\}oxy\}méthyl}\}cyclohexylmethoxy\}acétique
agoniste des récepteurs de prostaglandines

ralinepag
ácido \{\textit{trans-4-\{\{(4-clorofenil)(fenil)carbamoil\}oxi\}metil\}ciclohexil\}metoxi\}acético
agonista del receptor de prostaglandina

\(\text{C}_{23}\text{H}_{26}\text{ClNO}_5\) 1187856-49-0

relebactamum
relebactam
\(\text{(1R,2S,5R)-2-\{\left[piperidin-4-yl\right]\}carbamoyl}\}-7\text{-oxo-}1,6\text{-diazabicyclo}\{3.2.1\}\text{-octan-6-yl hydrogen sulfate}
\beta\text{-lactamase inhibitor}

rélébactam
hydrogénosulfate de \(\text{(1R,2S,5R)-2-\{\left[pipéridin-4-yl\right]\}carbamoyl\}-7\text{-oxo-}1,6\text{-diazabicyclo}\{3.2.1\}\text{-octan-6-yl}
inhibiteur de la bêta-lactamase

relebactam
hidrógenosulfato de \(\text{(1R,2S,5R)-2-\{\left[piperidin-4-il\right]\}carbamoil\}-7\text{-oxo-}1,6\text{-diazabiciclo}\{3.2.1\}\text{-octan-6-ilo}
inhibidor de la beta lactamasa

\(\text{C}_{12}\text{H}_{20}\text{N}_4\text{O}_6\text{S}\) 1174018-99-5

ridinilazolum
ridinilazole
\(2,2^{\text{\textdegree}}\text{-di(pyridin-4-yl)-1H,1'H-5,5'-bi(benzimidazole)}\)
antibiotic

ridinilazole
\(2,2^{\text{\textdegree}}\text{-di(pyridin-4-yl)-1H,1'H-5,5'-bi(benzimidazole)}\)
antibiotique

ridinilazol
\(2,2^{\text{\textdegree}}\text{-di(piridin-4-il)-1H,1'H-5,5'-bi(benzoimidazol)}\)
antibiótico
roneparstatum

roneparstat

heparan sulfate mimetic compound that is obtained by $N$-des-sulfo and $N$-acetyl reactions on heparin from porcine intestinal mucosa, sodium periodate glycol split oxidation of uronic acids elements and sodium borohydride reduction of aldehydes produced during oxidation; the majority of the components have a glucuronic acid (coming from the heparin starting material) and glucosamine (formed via decomposition of the glucuronic acid) structure at the non-reducing end and iduronic acid 2-sulphate or glycol split structure at the reducing end of their chain; the average molecular weight range is 15000 to 25000 Da; the degree of glycol split is about 25% $[m/(n+m)]$ and the degree of sulfatation is about 1.2 per disaccharidic unit.

antineoplastic
Proposed INN: List 112

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sacrosidase
invertase 2 (beta-fructofuranosidase 2, saccharase, EC=3.2.1.26) from Saccharomyces cerevisiae (strain ATCC 204508 / S288c, Baker’s yeast) enzyme

sacrosidase
invertase 2 (beta-fructofuranosidase 2, saccharase, EC=3.2.1.26) de Saccharomyces cerevisiae (souche ATCC 204508 / S288c, levure de boulanger) enzyme

sacrosidasa
invertasa 2 (beta-fructofuranosidase 2, sacarasa, EC=3.2.1.26) de Saccharomyces cerevisiae (cepa ATCC 204508 / S288c, levadura de cerveza) enzima

sapanisertibum
sapanisertib
3-(2-amino-1,3-benzoxazol-5-yl)-1-(propan-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine antineoplastic

sapanisertib
3-(2-amino-1,3-benzoxazol-5-yl)-1-(propan-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine antinéoplasique

sapanisertib
3-(2-amino-1,3-benzoxazol-5-il)-1-(propan-2-il)-1H-pirazolo[3,4-d]pirimidin-4-amina antineoplásico
seletalisib

3-(8-chloro-3-{(1R)-1-[(pyrido[3,2-d]pyrimidin-4-yl)amino]-2,2,2-trifluoroethyl}quinolin-2-yl)pyridine N-oxide

immunomodulator, phosphatidylinositol 3-kinase inhibitor

N-oxyde de 3-(8-chloro-3-{(1R)-1-[(pyrido[3,2-d]pyrimidin-4-yl)amino]-2,2,2-trifluoroéthyl}quinoléin-2-yl)pyridine

immunomodulateur, inhibiteur de la kinase phosphatidylinositol 3

N-óxido de 3-(8-cloro-3-{(1R)-1-[(pirido[3,2-d]pirimidin-4-il)amino]-2,2,2-trifluoroetil}quinolein-2-il)pirindina

inmunomodulador, inhibidor de la fosfatidilinositol 3 kinasa

C_{23}H_{14}ClF_{3}N_{6}O 1362850-20-1

setmelanotidum

N^2'-acetyl-L-arginyl-L-cysteinyln-D-alanyl-L-histidyl-D-phenylalanil-L-argiynl-L-tryptophyl-L-cysteinamide, cyclic (2-8)-disulfide

melanocortin receptor agonist

(2-8)-disulfure cyclique du N^2'-acétyl-L-argiynyl-L-cystéinyln-D-alanyl-L-histidyl-D-phénylnalanil-L-argiynyl-L-tryptophyl-L-cystéinamide

agoniste du récepteur de la mélanocortine

(2-8)-disulfuro cíclico del N^2'-acetil-L-argiinil-L-cisteinil-D-alanil-L-histidil-D-fenilalanil-L-argiinil-L-triptofil-L-cisteinamida

agonista del receptor de melanocortina
solcitinib

C₄₉H₆₈N₁₈O₉S₂

920014-72-8

\[
\text{H₃C} \begin{array}{cccccc}
\text{Arg} & \text{Cys} & \text{D-Ala} & \text{His} & \text{D-Phe} & \text{Arg} & \text{Trp} & \text{Cys} & \text{NH}_2 \\
\end{array}
\]

\text{solcitinib}

N\{5-\{4-(3,3-dimethylazetidine-1-carbonyl)phenyl\}[1,2,4]triazolo[1,5-a]pyridin-2-yl\}cyclopropanecarboxamide
tyrosine kinase inhibitor

solcitinib

N\{5-\{4-(3,3-dimethylazetidine-1-carbonyl)phenyl\}[1,2,4]triazolo[1,5-a]pyridin-2-yl\}cyclopropanecarboxamide

inhibiteur de la tyrosine kinase

solcitinib

N\{5-\{4-(3,3-dimethylazetidine-1-carbonyl)phenyl\}[1,2,4]triazolo[1,5-a]pyridin-2-yl\}cyclopropanecarboxamide

inhibidor de la tirosina kinasa

somapacitanum #

C₂₂H₂₃N₅O₂

1206163-45-2

\[
\text{O} \begin{array}{cccc}
\text{NH} & \text{N} & \text{N} & \text{CH₃}
\end{array}
\]

\text{somapacitanum}


somapacitan


somapacitán

somavaratanum #
somavaratan

rDNA derived human somatropin (growth hormone of 191 residues) fusion protein with a hydrophilic amino acid sequence* (913 residues) at the N-terminus and another** (146 residues) at the C-terminus, produced in *Escherichia coli*.

* starting with alanine plus 76 dodecapeptides: EPAGSPTSTEEG (AE3G2P2S2T2), three different sequences of AG3P2S4T2 and 72 of 4 different sequences of AE2G2P2S3T2

** starting with glycylglycine plus 12 dodecapeptides of 4 different sequences of AE2G2P2S3T2 growth hormone derivative

somavaratán

proteína de fusión entre la somatropina humana (factor de crecimiento 191 restos) y dos proteínas hidrófilas, una*, de 913 restos, en el extremo N-terminal, y otra**, de 146 restos, en el extremo C-terminal, obtenida por técnicas de ADN recombinante en cultivos d'*Escherichia coli*.

*constituida por alanina seguida de 76 dodécapéptidos, EPAGSPTSTEEG (AE3G2P2S2T2) tres secuencias diferentes de AG3P2S4T2 y 72 de 4 secuencias diferentes de AE2G2P2S3T2

**constituida por glicilglicina seguida de 12 dodécapéptidos de 4 diferentes secuencias de AE2G2P2S3T2 derivado de la hormona de crecimiento
spanlecortemlocelum

spanlecortemlocel

consists of human expanded CD34+ hematopoietic stem cells that have been isolated from umbilical cord blood and cultured in vitro in media supplemented with THPO (thrombopoietin), KITLG (KIT ligand, stem cell factor, SCF), IL6 (interleukin 6), FLT3LG (fms-related tyrosine kinase 3 (FLT3) ligand), and an antagonist of AHR (aryl hydrocarbon receptor); typically contains >10% of cells expressing CD34
cell therapy product (hematopoietic stem cell transplantation)

spanlé cortemlocel

cellules souches hématopoïétiques humaines exprimant CD34+ isolées du sang de cordon ombilical et mises en culture in vitro en milieu enrichi en THPO (trombopoiétine), KITLG (ligand de KIT, facteur de cellules souches, SCF), IL6 (interleukine 6), FLT3LG (ligand de tyrosine kinase 3 fms-like (FLT3)) et un antagoniste d’AHR (récepteur des hydrocarbures aromatiques); typiquement, contient >10% de cellules exprimant CD34.
produit de thérapie cellulaire (transplantation de cellules souches hématopoïétiques)

espanlecortemlocel

células madre hematopoyéticas humanas que expresan CD34+ aisladas de sangre de cordón umbilical y cultivadas in vitro en un medio enriquecido en THPO (trombopoyetina), KITLG (ligante de KIT, factor de células madre (SCF)), IL6 (interleukina 6), FLT3LG (ligando de tirosina kinasa 3 fms-like (FLT3)) y un antagonista de AHR (receptor de hidrocarburos arilicos); normalmente, contiene >10% de células que expresan CD34.
producto de terapia celular (transplante de células madre hematopoyéticas)
**spebrutinibum**

**spebrutinib**

\[N-[3-((5\text{-fluoro}-2\text{-}[4-(2\text{-methoxyethoxy})anilino]pyrimidin-4\text{-yl})amino)phenyl]prop-2-enamide\]

*tyrosine kinase inhibitor, antineoplastic*

**spébrutinib**

\[N-[3-((5\text{-fluoro}-2\text{-}[4-(2\text{-méthoxyéthoxy})anilino]pyrimidin-4\text{-yl})amino)phényl]prop-2-énamide\]

*inhibiteur de la tyrosine kinase, antinéoplasique*

**espebrutinib**

\[N-[3-((5\text{-fluoro}-2\text{-}[4-(2\text{-metoxietoxi})anilino]pirimidin-4-il)amino]fenil]prop-2-enamida\]

*inhibidor de la tirosina kinasa, antineoplásico*

\[C_{22}H_{22}FN_{5}O_{3}\]

1202757-89-8

![Chemical structure of spebrutinib](image)

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**susoctocogum alfa #**

**susoctocog alfa**

recombinant DNA derived B-domain deleted porcine blood-coagulation factor VIII analogue, produced in BHK21 cells: des-(753-1418)-blood-coagulation factor VIII (procoagulant component) *Sus scrofa*, glycosylated

*blood coagulation factor*

**susoctocog alfa**

analoge du facteur de coagulation VIII porcin dont le domaine B a été supprimé, produit dans des cellules BHK21, à partir d’ADN recombinant: dès-(753-1418)-facteur VIII de coagulation (composant procoagulant) de *Sus scrofa* (porc), glycosylé

*facteur de coagulation sanguine*

**susoctocog alfa**

análogo del factor de coagulación VIII porcino del cual se ha suprimido el dominio B, producido en células BHK21 a partir de ADN recombinante: des-(753-1418)-factor VIII de coagulación (componante procoagulante) de *Sus scrofa* (cerdo), glicosilado

*factor de coagulación sanguínea*
**Proposed INN: List 112**

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

- 154-180
- 249-330
- 528-554
- 630-711
- 948-974
- 1015-1019
- 1137-1285
- 1290-1442

Modified residues / Résidus modifiés / Restos modificados

- Y346-718-719-723-780-796
- O-sulfoTyr

Glycosylation sites (N, S, T) / Sites de glycosylation (N, S, T) / Posiciones de glicosilación (N, S, T)

- Ser-44
- Asn-214
- Asn-240
- Ser-353
- Asn-582
- Ser-741
- Ser-752
- Thr-770
- Asn-926
- Asn-1234

**tazemetostatum**

**tazemetostat**

- \(N\)-[[4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-5-[[ethyl(oxyan-4-yl)amino]-4-methyl-4’-[[morpholin-4-yl)methyl][1,1'-biphenyl]-3-carboxamide

**antineoplastic**

**tazémétostat**

- \(N\)-[[4,6-diméthyl-2-oxo-1,2-dihydropyridin-3-yl)méthyl]-5-[[éthyl(oxyan-4-yl)amino]-4-méthyl-4’-[[morpholin-4-yl)méthyl][1,1’-biphényl]-3-carboxamide

**antineoplasique**

**tazemetostat**

- \(N\)-[[4,6-dimetil-2-oxo-1,2-dihidropiridin-3-il)métil]-5-[[eti(oxyan-4-il)amino]-4-metil-4’-[[morfolin-4-il)métil][1,1’-bifeni]-3-carboxamida

**antineoplásico**

\[C_{34}H_{44}N_4O_4\]

\[1403254-99-8\]
temsavirum

1-(4-benzoilpiperazin-1-yl)-2-[4-methoxy-7-(3-methyl-1H,1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl]ethane-1,2-dione
antiviral

C_{24}H_{23}N_{7}O_{4}  
701213-36-7

Tesidolumabum #

tesidolumab

Immunoglobulin G1-lambda2, anti-[Homo sapiens C5 (complement C5)], Homo sapiens monoclonal antibody; gamma1 heavy chain (1-446) [Homo sapiens VH (IGHV1-69*01 (96.90%) -[IGHD]-IGHJ4*01) [8.8.9] (1-116) -IGHG1*03 (CH1 (117-214), hinge (215-229), CH2 (230-339) L1.3>A (233), L1.2>A (234), CH3 (340-444), CHS (445-446) (117-446)], (219-213')-disulfide with lambda2 light chain (1'-214') [Homo sapiens V-LAMBDA (IGLV3-9*01 (88.20%) -[IGLJ2*01) [6.3.11] (1'-108') -IGLC2*01 (109'-214')]; dimer (225-225'".228-228")-bisdisulfide immunomodulator
tesidolumab, inmunoglobulina G1-lambda2, anti-[C5 (complemento C5) de Homo sapiens], anticuerpo monoclonal de Homo sapiens; cadena pesada gamma1 (1-446) [Homo sapiens]

VH (IGHV1-69*01 (96.90%) -IGHD-IGHJ4*01) [8.8.9] (1-116)

CH1 (117-214), bisagra (215-229), CH2 (230-339) L1.3>A (233), L1.2>A (234), CH3 (340-444), CHS (445-446), (219-213')-disulfuro con la cadena ligera lambda2 (1'-214') [Homo sapiens] V-LAMBDA

IGLV3-9*01 (88.20%) -IGLJ2*01 [6.3.11] (1'-108') -IGLC2*01 (109'-214')]; dímero (225-225':228-228'')

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

Intra-H (C23-C104) 22'-87' 136'-195'

Inter-H-L (h 5-CL 126) 219'-213' 219'-213''

Inter-H-H (h 11, h 14) 225-225'' 228-228''

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

H CH2 N84.4: 296, 296''

toreforantum

toreforant

5-(4,6-dimethyl-1H-benzimidazol-2-yl)-4-methyl-N-[3-(1-methylpiperidin-4-yl)propyl]pyrimidin-2-amine

histamine H4 receptor antagonist

5-(4,6-diméthyl-1H-benzimidazol-2-il)-4-méthyl-N-[3-(1-méthylpipéridin-4-il)propil]pirimidin-2-amina

antagonista del receptor H4 de histamina

5-(4,6-dimetil-1H-benzoimidazol-2-il)-4-metil-N-[3-(1-metilpiperidin-4-il)propil]pirimidin-2-amina

antagonista del receptor H4 de histamina
trofinetidum
trofinetide
glycyl-2-methyl-L-prolyl-L-glutamic acid
neuroprotectant

trofinétide
acide glycyl-2-méthyl-L-prolyl-L-glutamique
neuroprotecteur

trofinetida
ácido glicil-2-metil-L-prolil-L-glutámico
neuroprotector

C₁₃H₂₁N₃O₆
853400-76-7

vandortuzumab vedotinum #
vandortuzumab vedotin
immunoglobulin G1-kappa, anti-[Homo sapiens STEAP1 (six-transmembrane epithelial antigen of the prostate 1, PRSS24, STEAP)], humanized monoclonal antibody; gamma1 heavy chain (1-454) [humanized VH (Homo sapiens IGHV3-48*03 (80.80%) -(IGHD)-IGHJ4*01) [9.7.17] (1-124) -Homo sapiens IGHL1*01 (CH1 R120>K (221) (125-222), hinge (223-237), CH2 (238-347), CH3 (348-452), CHS (453-454)) (125-454)], (227-220')-disulfide with kappa light chain (1'-220') [humanized V-KAPPA (Homo sapiens IGKV1-16*01 (81.20%) -IGKJ1*01) [12.3.9] (1'-113') -Homo sapiens IGKC*01 (114'-220')] (125-454), (227-220')-disulfide; conjugated, on an average of 3 to 4 cysteiny1, to monomethylauristatin E (MMAE), via a cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC) type linker

For the vedotin part, please refer to the document "INN for pharmaceutical substances: Names for radicals, groups and others".
immunomodulator, antineoplastic

vandortuzumab védotine
immunoglobuline G1-kappa, anti-[Homo sapiens STEAP1 (antigène épithélial 1 à six-transmembrane de la prostate, PRSS24, STEAP)], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-454) [VH humanisé (Homo sapiens IGHV3-48*03 (80.80%) -(IGHD)-IGHJ4*01) [9.7.17] (1-124) -Homo sapiens IGHL1*01 (CH1 R120>K (221) (125-222), chaîne (223-237), CH2 (238-347), CH3 (348-452), CHS (453-454)) (125-454)], (227-220')-disulfure avec la chaîne légère kappa (1' -220') [V-KAPPA humanisé (Homo sapiens IGKV1-16*01 (81.20%) -IGKJ1*01) [12.3.9] (1'-113') -Homo sapiens IGKC*01 (114'-220')] (125-454), (227-220')-disulfure; conjugué, sur 3 à 4 cystéïny1 en moyenne, au monométhylauristatine E (MMAE), via un linker clivable de type maléimidocaproyl-valyl-citrullinyl-p-aminobenzzyloxycarbonyl (mc-val-cit-PABC)

Pour la partie védotine, veuillez-vous référer au document "INN for pharmaceutical substances: Names for radicals, groups and others".
immunomodulateur, antinéoplasique
vandortuzumab vedotina

immunoglobulina G1-kappa, anti-[STEAP1 de Homo sapiens (antígeno epitelial 1 seis-transmembrana de la próstata, PRSS24, STEAP)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-454) [VH humanizada (Homo sapiens IGHV3-48*03 (80.80%)-IGHD)-IGHJ4*01) [9.7.17] (1-124) -Homo sapiens IGHG1*03 (CH1 R120->K (221) (125-222), bisagra (223-237),CH2 (238-347), CH3 (348-452), CHS (453-454)) (125-454), (227-220)-disulfuro con la cadena ligera kappa (1’-220’) [V-KAPPA humanizado (Homo sapiens IGKVI-16*01 (81.20%) -IGKJ1*01) [12.3.9] (1’-113’) -Homo sapiens IGKC*01 (114’-220’); dímero (233-233”-236-236”)-bisdisulfuro; conjugado, en 3 – 4 restos cisteinil por término medio, con monometaisauristatina E (MMAE), mediante una secuencia de conexión escindible de tipo maleimidocaproil-valil-citrulinil-p-aminobenciloxicarbonil (mc-val-cit-PABC)
La fracción vedotina pueden encontrarla en el documento “INN for pharmaceutical substances: Names for radicals, groups and others”.

verosudilum

verosudil

Rho-associated protein kinase inhibitor

vérosudil

rac-(2R)-2-(dimethylamino)-N-(1-oxo-1,2-dihydroisoquinolin-6-yl)-2-(thiophen-3-yl)acetamide

verosudil

rac-(2R)-2-(dimethylamino)-N-(1-oxo-1,2-dihydroisoquinolín-6-il)-2-(thiофénil-3-il)acetámida

inhibiteur de la protéine kinase associée à la protéine Rho

inhibidor de la proteína kinasa asociada al Rho
verubecestatum

verubecestat

\[
N-(3-\{(5R)-3\text{-amino}-2,5\text{-dimethyl}-1,1\text{-dioxo-}
1,2,5,6\text{-tetrahydro}-1\lambda^6,2,4\text{-thiadiazin-5-yl}\text{-4-fluorophenyl}\text{-}
5\text{-fluoropyridine-2-carboxamide}
\]

\textit{beta-secretase inhibitor}

vérubécestat

\[
N-(3-\{(5R)-3\text{-amino}-2,5\text{-diméthyl}-1,1\text{-dioxo-}
1,2,5,6\text{-tétrahydro}-1\lambda^6,2,4\text{-thiadiazin-5-yl}\text{-4-fluorophényl}\text{-}
5\text{-fluoropyridine-2-carboxamide}
\]

\textit{inhibiteur de la sécrétase bêta}

verubecestat

\[
N-(3-\{(5R)-3\text{-amino}-2,5\text{-dimétil}-1,1\text{-dioxo-}
1\lambda^6,2,4\text{-tiadiazin-5-ii}\text{-4-fluorofenil}\text{-5-fluoropiridina-}
2\text{-carboxamida}
\]

\textit{inhibidor de la secretasa beta}

vosoritidum

c 17h17f2n5o3s 1286770-55-5

vosoritide

a modified recombinant human C-type natriuretic peptide (CNP) consisting of 39 amino acids comprised of the 37 C-terminal amino acids of the human CNP sequence plus the addition of 2 amino acids (Pro-Gly) on the N-terminus, produced in Escherichia coli:

\textit{\text{L-prolylglycyl-} (human C-type natriuretic peptide-\text{(17-53)}-peptide (CNP-37)), cyclic-(23-39)-disulfide natriuretic peptide}

vosoritide

peptide natriurétique de type C humain modifié consistant en une séquence de 39 acides aminés comprenant les 37 acides aminés C-terminaux du peptide humain CNP plus deux acides aminés (Pro-Gly) N-terminaux, produit par Escherichia coli:

\textit{L-prolylglycyl-(peptide natriurétique de type C humain-(17-53)-peptide (CNP-37)), (23-39)-disulfure cyclique peptide natriurétique}
vosoritida  
peptido natriurético de tipo C humano modificado 
consistente en una secuencia de 39 aminoácidos que 
comprende los 37 aminoácidos C-terminales del peptido 
humano CNP más dos aminoácidos (Pro-Gly) 
N-terminales, producido por *Escherichia coli*:

\[ \text{L-proiliglicil-(peptido natriurético de tipo C humano-(17-53)-} \]
\[ \text{peptido (CNP-37)), (23-39)-disulfuro cíclico} \]

\[ \text{peptido natriurético} \]

\[ \text{C}_{170}\text{H}_{290}\text{N}_{58}\text{O}_{51}\text{S}_{3} \]

\[ 1480724-61-5 \]

Sequence / Série / Secuencia

PGQEHFNAKR YKGANKQGLS KGCFGLKLDR IGSMSGLG 39

Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
23-39

zuretinol acetate

(2E,4E,6Z,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-
1-en-1-yl)nona-2,4,6,8-tetraen-1-yl acetate

11-cis-retinol replacement

acétate de zurétinol

acétate de (2E,4E,6Z,8E)-3,7-diméthyl-9-(2,6,6-
triméthylcyclohex-1-én-1-yl)nona-2,4,6,8-tétraén-1-yle

remplacement du 11-cis-rétinol

acetato de zuretinol

acetato de (2E,4E,6Z,8E)-3,7-dimetil-9-(2,6,6-
trimetilciclohex-1-en-1-il)nona-2,4,6,8-tetraen-1-il

tratamiento de sustitución de 11-cis retinol

\[ \text{C}_{22}\text{H}_{32}\text{O}_{2} \]

29584-22-3

# Electronic structure available on Mednet: [http://mednet.who.int/](http://mednet.who.int/)
# Structure électronique disponible sur Mednet: [http://mednet.who.int/](http://mednet.who.int/)
# Estructura electrónica disponible en Mednet: [http://mednet.who.int/](http://mednet.who.int/)

Names for Radicals and Groups
Some substances for which a proposed international nonproprietary name has been established may be used in the form of salts or esters. The radicals or groups involved may be of complex composition and it is then inconvenient to refer to them in a systematic chemical nomenclature. Consequently, shorter nonproprietary names for some radicals and groups have been devised or selected, and they are suggested for use with the proposed international nonproprietary names.

Dénominations applicables aux radicaux et groupes
Certaines substances pour lesquelles une dénomination commune internationale proposée a été établie sont parfois utilisées sous forme de sels ou d’esters. Les radicaux ou groupes correspondants sont alors quelques fois si complexes qu’il est malcommode de les désigner conformément à la nomenclature chimique systématique. Des dénominations communes abrégées ont donc été formées ou choisies pour certains d’entre eux et il est suggéré de les employer avec les dénominations communes internationales proposées.

Denominaciones para Radicales y Grupos
Ciertas sustancias para las cuales hay establecidas una denominación común internacional pueden usarse en forma de sales o de ésteres. Los radicales o grupos correspondientes pueden llegar a tener una composición tan compleja que resulte incómodo referirse a ellos mediante la nomenclatura química sistemática. Las siguientes denominaciones comunes abreviadas han sido ideadas o elegidas para algunos de estos radicales y grupos y se sugiere que se empleen con las denominaciones comunes internacionales propuestas.

dalanas
dalanate  L-alanyl-L-alaninate (ester)
dalanate  L-alanyl-L-alaninate (ester)
dalanato  L-alanil-L-alaninato (ester)

\[ \text{C}_8\text{H}_{11}\text{N}_2\text{O}_3 \]

satetraxetanum
satetraxetan  \( \text{rac}-(4-([(2R)-1,4,7,10-tetraakis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-2-yl]methyl)phenyl)carbamothioyl \)

satétraxétan  \( \text{rac}-(4-([(2R)-1,4,7,10-tétrakis(carboxyméthyl)-1,4,7,10-tétraazacyclododécan-2-yl]méthyl)phényl)carbamothioyle \)

satetrxetán  \( \text{rac}-(4-([(2R)-1,4,7,10-tetraakis(carboximetil)-1,4,7,10-tetraazaciclododecan-2-il]metil)fenil)carbamotiioilo \)

\[ \text{C}_{24}\text{H}_{34}\text{N}_5\text{O}_8\text{S} \]
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Proposed International Nonproprietary Names (Prop. INN): List 60
Dénominations communes internationales proposées (DCI Prop.): Liste 60
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 60
( WHO Drug Information, Vol. 2, No. 4, 1988 )

p. 13 natrii pentosani polysulfas replace the chemical name, the molecular formula and the structure by the following ones
pentosan polysulfate sodium remplace le nom chimique, la formule moléculaire et la structure par les suivants
pentosane polysulfate sodique sustitúyase el nombre químico, la fórmula molecular y la estructura por los siguientes
pentosano polisulfato de sodio

A mixture of the sodium salts of linear polymers of (1→4)-β-D-xylopyranan usually sulfated at the 2-and 3-positions and occasionally (approximately 1 in every 10 residues) substituted at the 2-position with a (4-O-methyl-2,3-di-O-sulfo-α-D-glucopyranosyluronic acid) group; the average molecular weight lies between 4000 and 6000 with a total molecular weight range of 1000 to 40000

un mélange de sels de sodium de polymères linéaires de (1→4)-β-D-xilopiranane habituellement sulfatés en positions 2 et 3 et parfois (approximativement 1 résidu sur 10) substitué en position 2 avec un groupe acide 4-O-méthyl-2,3-di-O-sulfo-α-D-glucopyranosyluronique; le poids moléculaire moyen est compris entre 4000 et 6000 avec un poids moléculaire total compris entre 1000 et 40000

una mezcla de sales sódicas de polímeros lineales de (1→4)-β-D-xilopiranano generalmente sulfatados en posiciones 2 y 3 y ocasionalmente (aproximadamente 1 resto cada 10) sustituido en posición 2 por un grupo ácido 4-O-metil-2,3-di-O-sulfo-α-D-glucopiranosiluronico; el peso molecular medio está comprendido entre 4000 y 6000 con un peso molecular total comprendido entre 1000 y 40000

\[
(C_5H_6Na_2O_{10}S_2)_n \quad (C_7H_8Na_2O_9S)_{0.1n} \quad (Na_2O_7S_2), \quad \text{average } n = \text{ca} \text{ 11 to 16}
\]

\[
\text{chain length } n = \text{ca. 11-16}
\]

or

\[
\text{ratio } = \text{ca. 1:9}
\]
Proposed INN: List 112

Proposed International Nonproprietary Names (Prop. INN): List 95
Dénominations communes internationales proposées (DCI Prop.): Liste 95
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 95

( WHO Drug Information, Vol. 20, No. 2, 2006 )

beroctocog alfa
replace the description by the following one
sustitúyase la descripción por la siguiente

human blood-coagulation factor VIII-(1-741)-peptide complex with human
blood-coagulation factor VIII-(1649-2332)-peptide

( WHO Drug Information, Vol. 21, No. 4, 2007 )

beroctocog alfa
replace the structure by the following one
sustitúyase la estructura por la siguiente

Heavy chain / Chaîne lourde / Cadena pesada

ATREYVLYGAE ELSDMYQEGD LEELPVDARF PPRVYKSSFF NTSVYVKTL 50
APVDTCHLFN IERFFPQFGQ LL/LPTIAGEE YDTTVTILEN MASHPVSHLA 100
VQVLYKWSAE QASYQDQPSQ KEREKGQYFF GQSRHTVYQV LEENGPMASEG 150
PCLLITYSIL HVLVIRNLGE GLIGALLCVR EGSALEEKTQ THKFIILLFA 200
VPFEDCKSNWS ETKSNLSQRH DAAASARWPFF MVHTVNYVRH SLPGILCCHR 250
KQVYRMVQCM QYTFRQVCSF LTQHTFLVRH HRQASLEISF ITETLACQTLR 300
MDGQFLPLFC HISSHQDQGD EAYVYVYDCFP EISPOQLMMNN EREDYDODD 350
TDEQSDQVFS DDQNSPQFQ IGVIAEKNHP TTWYHTPEAE EGMDAPLPVL 400
AEPGRSPEQY VLNHPSQFGQ RYREYKRPMA YTDFTPTPE ALOVHEGILG 450
PLLYCQVDYG LLLIFQKQQAS RPYHNYFQGQ TDYRVLPQHRR 1PQXNHKLD 500
FILLPGQSLF KMMVYTVVYGD PTKSDFPCLT RSYFYVYFGE ROLAGLQFCP 550
LITVKEVSD QRGQHIMEQK RNVILSFVDR ERNWSWILEN DQFLPHNAG 600
VQLEDFFQAI SHMHSINGQ FVDSSLQGLV EREAVYWTIL SGIAQFDLFS 650
VFFEGYTPRSH KTVFMDSLLT PPFEQELYTN SMENFQIAVF GCGNHFYAFF 700
GMTALLVS SCDKHDYFG DYESISAYL LSNNAAIEFR S 741

Light chain / Chaîne légère / Cadena ligera

EI 1650
TRTQLQDGQS RIIKLDGTSV EGDGDQGFSQ DEDENQFSRS QYVSKTHFYI 1700
AVERENYDG MGSSPRVYRE RAGGSQSVQF KKVVPQFPED GSFQPQPLRG 1750
ELNHELQGLL GYFIRAYEVD IMAKTRFQAG RSRSYFSSL YSREHDQRGA 1800
KFOREYKVFYKTRTQVRF HMAMPTKDOF OCKNAYQYGD VOLNKLHSG 1850
LGLPVLYCHF NTLNPVRSQR VTVQAPFLFF TIPFXTKSYW FTENNEKCR 1900
ACPYNQMEQF TFKTREYFIKR YINGTMYFPGL LGYAMIQQGR WRTILIPMSGN 1950
ENESHSIFGS HYTFVKXKXE YNMAYLXFL GPVEFVNLPSKAGNBVYCE 2000
LIGILNAMN STILFYVSNK CQTFPLMAGS KIRFOQQTAS GQVQWMAPKL 2050
ARLQHGSQIN A/RSTKYPSSW KIVQDLLAMP IKGILTQCSR QYRSYISQ 2100
FLGMSLCK KVHTROQST GTLNYPFDyg DSGHKEKIF NPPFAYVIR 2150
LTETHYSIK ROPLMSRODK LNSCMSPGON ESKAIQDSQI TASSYFTMFM 2200
ATWPSFEXKL HLRGSHMABF QVFFFFKEYL QYQPOKXRQV TTGTGQYKES 2250
LTQVQVXKIE LSSQHQOGQH WTVFYQDSVF KPYQQQQGQSF TPYVNLQDFP 2300
LITVLYRISF QSWWRQHLRK MEVLGCEAQD LQ 2332

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
153-179 248-329 528-554 630-711 1832-1858 1899-1903 2021-2169 2174-2326

Modified residues / Résidus modifiés / Restos modificados

Add/supprimer/suprimáse

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-41 Asn-239 Asn-1818 Asn-2118

delete/supprimer/suprimáse
Proposed International Nonproprietary Names (Prop. INN): List 109

Dénominations communes internationales proposées (DCI Prop.): Liste 109

Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 109

(Who Drug Information, Vol. 27, No. 2, 2013)

C3821H5813N1003O1139S35 + C3547H5400N956O1033S35

p. 169

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

dimethyl N,N'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenyleneaminodicyarbonyl)bis(2S)-pyrrolidine-2,1-diyl][[(2S)-3-methyl-1-oxobutane-1,2-diyl]]bis-carbamate
N,N'-([(2S,5S)-1-(4-tert-butylphényl)pyrrolidine-2,5-diyl]bis[4,1-phenyleneaminodicyarbonyl][(2S)-pyrrolidine-2,1-diyl]][[(2S)-3-méthyl-1-oxobutane-1,2-diyl]]bis-carbamate de diméthyle
N,N'-([(2S,5S)-1-(4-terc-butilfenil)pirrolidina-2,5-diil]bis[4,1-fenilenaoanodillicarbonil][(2S)-pirrolidina-2,1-diil][[(2S)-3-metil-1-oxobutano-1,2-diil]]bis-carbamato de dimetilo

p. 171 & 172

paclitaxel trevatidum
replace the chemical name by the following one
remplacer le nom chimique par le suivant
sustitúyase el nombre químico por el siguiente

short modified fragment of human amyloid beta A4 protein covalently linked to three molecules of paclitaxel through succinyl linkers:

fragment court et modifié de la protéine bêta A4 amyloïde humaine lié de façon covalente à trois molécules de paclitaxel par autant de succinyles :
N²¹,N⁶¹⁰,N⁶¹⁵-tris(4-[(1S,2R)-1-benzamido-3-[(4,10β-bis(acétyloxy)-2α-(benzoiloxi)-5β,20-époxi-1,7β-dihidroxi-9-oxotax-11-en-13α-yl]oxy]-3-oxo-1-phenylpropan-2-yl]oxy)-4-oxobutanoil) [(318-L-thréonine(P>T1),324-L-sérine(C>S7),325-L-arginine(G>R8),327-L-lysine(N>K10),332-L-lysine(D>K15)] précurseur de la protéine amyloïde bêta A4 humaine-(318-336)-peptide

fragmento corto y modificado de la proteína beta A4 amiloide humana unido covalentemente a tres moléculas de paclitaxel mediante succinilos :
N²¹,N⁶¹⁰,N⁶¹⁵-tris(4-[(1S,2R)-1-benzamido-3-[(4,10β-bis(acetiloxi)-2α-(benzoiloxi)-5β,20-époxi-1,7β-dihidroxi-9-oxotax-11-en-13α-il]oxy]-3-oxo-1-fenilpropan-2-il]oxy)-4-oxobutanoil) [(318-L-threonina(P>T1),324-L-serina(C>S7),325-L-arginina(G>R8),327-L-lysina(N>K10),332-L-lysina(D>K15)] precursor de la proteína amiloide beta A4 humana-(318-336)-péptido
Proposed International Nonproprietary Names (Prop. INN): List 112

Proposed International Nonproprietary Names (Prop. INN): List 110

Proposed International Nonproprietary Names (Prop. INN): List 111
Proposed INN: List 112

WHO Drug Information, Vol. 28, No. 4, 2014

546

p. 229 eflapegrastimum #
& 230 eflapegrastim
eflapégrastim
eflapégrastim

replace the description and the structure by the following ones
remplacer la description et la structure par les suivantes
sustitúyase la descripción y la estructura por las siguientes

human granulocyte colony-stimulating factor and human IgG4 Fc
dimer linked together with polyethylene glycol derivative, produced
in Escherichia coli:
Nα,1,N1.9-[ω-(oxypropane-1,3-diyl)-α-(propane-1,3-diyl)poly(oxyethylene)]
des-(1-L-alanine,37-39)-
[18-L-serine(C>S),69-L-serine(P>S)]human granulocyte colony-
stimulating factor (G-CSF, pluripoietin) (1-174)-peptide and
des-(1-8)-human immunoglobulin G4 Fc fragment (IGHG4*01
H-CH2-CH3) (9'-229')-peptide dimer (11'-11'')-disulfide

le facteur de stimulation de colonies de granulocytes humain et le
dimère du fragment Fc de l’IgG4 humaine, produits par Escherichia
coli, reliés par un radical substituant dérivé du polyéthylèneglycol:
Nα,1,N1.9-[ω-(oxypropane-1,3-diyl)-α-(propane-1,3-diyl)poly(oxyethylene)]
dés-(1-L-alanine,37-39)-
[18-L-serine(C>S),69-L-serine(P>S)]facteur de stimulation de
colonies de granulocytes humain (G-CSF, pluripoïétine) (1-174)-
peptide et (11'-11'')-disulfure du dimère de dés-(1-8)-fragment Fc de
l’immunoglobuline G4 humaine (IGHG4*01 H-CH2-CH3)
(9'-229')-peptide
dimère (11'-11'')-disulfide

producto de la unión, mediante un radical derivado del
poliethylenglicol, del factor estimulante de colonias de granulocitos
humano y el dímero del fragmento Fc de la IgG4 humana,
producidos por Escherichia coli.
Nα,1,N1.9-[ω-(oxipropano-1,3-diil)-α-(propano-1,3-diil)poli(oxyetileno)]
des-(1-L-alanina,37-39)-[18-L-serina(C>S),69-L-serina(P>S)]factor
estimulante de colonias de granulocitos humano (G-CSF, pluripoyetina)
(1-174)-peptido y (11'-11'')-disulfuro del dímero de des-(1-8)-fragmento Fc de
la inmunoglobulina G4 humana (IGHG4*01 H-CH2-CH3)
(9'-229')-peptido

dimero (11'-11'')-disulfuro

Human G-CSF derivative sequence / Séquence dérivée du G-CSF humain / Secuencia
derivada de G-CSF humano
TPLGAPSSLP QFLKLKSLEQ VRRQGDGAQ LQEKCLCTYK LCHPEELVLL 50
THSLIGLP MAP LSCHSDQALQ LASCLQLQLKS GFLYQGQLQ ALEGSPHELQ 100
PTLTLIQVD AV ATITIQWQQ EELQGPMAL QFTQGAMPAP AASAPRRAGQ 150
VLAVHLSGF LEVSYRLVHL LAQP 174

hIGHG4 Fc monomer / Monomère du Fc de hIGHG4 / Monómero de Fc de hIGHG4
FS CPAPFGLGIF SVLFPFFKPK DTLMISHTPE VTCVVVDVSQ 50*
EDPEPQPRTT VDGVFEVHNM TKPFRQFPFS NLYVRQVTVLV LAQDMLHRLG 100*
YKCRVYKNCCL PSIEKTKSK AKQPRPEPQ YTLFQPQERM TQKCVSITCL 150*
VKGFPYPSDIA VWSQVESQPE NNKTTTPFVL DSDGSFFLYS RLTVDKSRWQ 200*
EGPNFSCFVM HEALHPHTQ KLSLSSGLK 229*

hIGHG4 Fc monomer / Monomère du Fc de hIGHG4 / Monómero de Fc de hIGHG4
FS CPAPFGLGIF SVLFPFFKPK DTLMISHTPE VTCVVVDVSQ 50**
EDPEPQPRTT VDGVFEVHNM TKPFRQFPFS NLYVRQVTVLV LAQDMLHRLG 100**
YKCRVYKNCCL PSIEKTKSK AKQPRPEPQ YTLFQPQERM TQKCVSITCL 150**
VKGFPYPSDIA VWSQVESQPE NNKTTTPFVL DSDGSFFLYS RLTVDKSRWQ 200**
EGPNFSCFVM HEALHPHTQ KLSLSSGLK 229**

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
11'-11'' 36-42 43'-103' 43'-103'' 64-74 149-207 149'-207''

Modified residues / Résidues modifiés / Restos modificados

![Diagram](image-url)
suprimáse insertese funapide funapida

olipudase alfa insertese olipudasa alfa

peficitinib replace the chemical name by the following one

\[4-\{(1R,2s,3S,5s,7s)-5-hydroxyadamantan-2-yl\text{-}amino\}-1H\text{-}pyrrolo[2,3-b]pyridine\text{-}5\text{-}carboxamide\]

peficitinib remplacer le nom chimique par le suivant

\[4-\{(1R,2s,3S,5s,7s)-5-hydroxyadamantan-2-yl\text{-}amino\}-1H\text{-}pyrrolo[2,3-b]pyridine\text{-}5\text{-}carboxamide\]

peficitinib sustitúyase el nombre químico por el siguiente

\[4-\{(1R,2s,3S,5s,7s)-5-hidroxiadamantan-2-il\text{-}amino\}-1H\text{-}pirrolo[2,3-b]piridina\text{-}5\text{-}carboxamida\]

velpatasvir replace the chemical name by the following one

velpatasvir remplacer le nom chimique par le suivant

velpatasvir sustitúyase el nombre químico por el siguiente

\{\text{methyl }1\text{-}\{(2S,5S)-2\text{-}\{(2S,4S)-1\text{-}\{(2R)-2\text{-}\{(methoxycarbonyl)amino\}-2\text{-}phenylacetil\}-}\text{-}4\text{-}\{(methoxymethyl)pyrroloidin\text{-}2\text{-}yl\}-1H\text{-}imidazol-4-yl\}-1,11\text{-}dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-d]imidazol-2-yl\}-5\text{-}methylpyrroloidin-1-yl\}-3\text{-}methyl\text{-}1\text{-}oxobutan-2-yl\}\text{carbamate}\]

\{\text{methyl }1\text{-}\{(2S,5S)-2\text{-}\{(2S,4S)-1\text{-}\{(2R)-2\text{-}\{(méthoxycarbonyl)amino\}-2\text{-}phénylacétyl\}-}\text{-}4\text{-}\{(méthoxyméthyl)pyrroloidin\text{-}2\text{-}yl\}-1H\text{-}imidazol-4-yl\}-1,11\text{-}dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-d]imidazol-2-yl\}-5\text{-}méthylvyrroloidin-1-yl\}-3\text{-}méthyl\text{-}1\text{-}oxobutan-2-yl\}\text{carbamate de méthyle}\]

\{\text{methyl }1\text{-}\{(2S,5S)-2\text{-}\{(2S,4S)-1\text{-}\{(2R)-2\text{-}\{(metoxicarbonil)amino\}-2\text{-}fenilacetil\}-}\text{-}4\text{-}\{(metoximetil)pirrolidin\text{-}2-yl\}-1H\text{-}imidazol-4-il\}-1,11\text{-}dihidro[2]benzopirano[4',3':6,7]nafto[1,2-d]imidazol-2-il\}-5\text{-}metilpirrolidin-1-il\}-3\text{-}metil\text{-}1\text{-}oxobutan-2-il\}\text{carbamato de metilo}\]
ANNEX 1

PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

The following procedure shall be followed by the World Health Organization (hereinafter also referred to as “WHO”) in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with resolution WHA3.11 of the World Health Assembly, and in the substitution of such names.

Article 1 - Proposals for recommended international nonproprietary names and proposals for substitution of such names shall be submitted to WHO on the form provided therefore. The consideration of such proposals shall be subject to the payment of an administrative fee designed only to cover the corresponding costs of the Secretariat of WHO (“the Secretariat”). The amount of this fee shall be determined by the Secretariat and may, from time to time, be adjusted.

Article 2 - Such proposals shall be submitted by the Secretariat to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, such designated members hereinafter referred to as “the INN Expert Group”, for consideration in accordance with the “General principles for guidance in devising International Nonproprietary Names for Pharmaceutical Substances”, annexed to this procedure. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

Article 3 - Subsequent to the examination provided for in article 2, the Secretariat shall give notice that a proposed international nonproprietary name is being considered.

a) Such notice shall be given by publication in WHO Drug Information and by letter to Member States and to national and regional pharmacopoeia commissions or other bodies designated by Member States.

i) Notice shall also be sent to the person who submitted the proposal (“the original applicant”) and other persons known to be concerned with a name under consideration.

b) Such notice shall:

i) set forth the name under consideration;

ii) identify the person who submitted the proposal for naming the substance, if so requested by such person;

iii) identify the substance for which a name is being considered;

iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;

v) state the authority under which WHO is acting and refer to these rules of procedure.


2 See Annex 2.

3 Before 1987, lists of international nonproprietary names were published in the Chronicle of the World Health Organization.
c) In forwarding the notice, the Secretariat shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by WHO.

**Article 4** - Comments on the proposed name may be forwarded by any person to WHO within four months of the date of publication, under article 3, of the name in *WHO Drug Information*.

**Article 5** - A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in *WHO Drug Information*.

Such objection shall:

i) identify the person objecting;

ii) state his or her interest in the name;

iii) set forth the reasons for his or her objection to the name proposed.

**Article 6** - Where there is a formal objection under article 5, WHO may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by WHO of a substitute name or names, a name shall not be selected by WHO as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

**Article 7** - Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Secretariat shall give notice in accordance with subsection (a) of article 3 that the name has been selected by WHO as a recommended international nonproprietary name.

**Article 8** - In forwarding a recommended international nonproprietary name to Member States under article 7, the Secretariat shall:

a) request that it be recognized as the nonproprietary name for the substance; and

b) request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name and to prohibit registration of the name as a trademark or trade name.

**Article 9**

a) In the extraordinary circumstance that a previously recommended international nonproprietary name gives rise to errors in medication, prescription or distribution, or a demonstrable risk thereof, because of similarity with another name in pharmaceutical and/or prescription practices, and it appears that such errors or potential errors cannot readily be resolved through other interventions than a possible substitution of a previously recommended international nonproprietary name, or in the event that a previously recommended international nonproprietary name differs substantially from the nonproprietary name approved in a significant number of Member States, or in other such extraordinary circumstances that justify a substitution of a recommended international nonproprietary name, proposals to that effect may be filed by any interested person. Such proposals shall be submitted on the form provided therefore and shall:

i) identify the person making the proposal;

ii) state his or her interest in the proposed substitution; and

iii) set forth the reasons for the proposal; and

iv) describe, and provide documentary evidence regarding the other interventions undertaken in an effort to resolve the situation, and the reasons why these other interventions were inadequate.
Such proposals may include a proposal for a new substitute international nonproprietary name, devised in accordance with the General principles, which takes into account the pharmaceutical substance for which the new substitute international nonproprietary name is being proposed.

The Secretariat shall forward a copy of the proposal, for consideration in accordance with the procedure described in subsection (b) below, to the INN Expert Group and the original applicant or its successor (if different from the person bringing the proposal for substitution and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations).

In addition, the Secretariat shall request comments on the proposal from:

i) Member States and national and regional pharmacopoeia commissions or other bodies designated by Member States (by including a notice to that effect in the letter referred to in article 3(a), and

ii) any other persons known to be concerned by the proposed substitution.

The request for comments shall:

i) state the recommended international nonproprietary name that is being proposed for substitution (and the proposed substitute name, if provided);

ii) identify the person who submitted the proposal for substitution (if so requested by such person);

iii) identify the substance to which the proposed substitution relates and reasons put forward for substitution;

iv) set forth the time within which comments will be received and the person and place to whom they should be directed; and

v) state the authority under which WHO is acting and refer to these rules of procedure.

Comments on the proposed substitution may be forwarded by any person to WHO within four months of the date of the request for comments.

b) After the time period for comments referred to above has elapsed, the Secretariat shall forward any comments received to the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution. If, after consideration of the proposal for substitution and the comments received, the INN Expert Group, the person bringing the proposal for substitution and the original applicant or its successor all agree that there is a need to substitute the previously recommended international nonproprietary name, the Secretariat shall submit the proposal for substitution to the INN Expert Group for further processing.

Notwithstanding the foregoing, the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed for substitution.

In the event that a proposal for substitution shall be submitted to the INN Expert Group for further processing, the INN Expert Group will select a new international nonproprietary name in accordance with the General principles referred to in article 2 and the procedure set forth in articles 3 to 8 inclusive. The notices to be given by the Secretariat under article 3 and article 7, respectively, including to the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), shall in such event indicate that the new name is a substitute for a previously recommended international nonproprietary name and that Member States may wish to make transitional arrangements in order to accommodate existing products that use the previously recommended international nonproprietary name on their label in accordance with national legislation.
If, after consideration of the proposal for substitution and the comments received in accordance with the procedure described above, the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution do not agree that there are compelling reasons for substitution of a previously recommended international nonproprietary name, this name shall be retained (provided always that the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event that the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed to be substituted). In such an event, the Secretariat shall advise the person having proposed the substitution, as well as the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), Member States, national and regional pharmacopoeia commissions, other bodies designated by Member States, and any other persons known to be concerned by the proposed substitution that, despite a proposal for substitution, it has been decided to retain the previously recommended international nonproprietary name (with a description of the reason(s) why the proposal for substitution was not considered sufficiently compelling).

ANNEX 2

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. “oxacillin” and “oxacillin sodium”, “ibufenac” and “ibufenac sodium”.

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base. For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

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1 In its Twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, INN in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves the use of a characteristic “stem” indicative of a common property of the members of a group. The reason for, and the implications of, the change are fully discussed. The guiding principles were updated during the 13th Consultation on nonproprietary names for pharmaceutical substances (Geneva, 27-29 April 1983) (PHARM S/NOM 928 13 May 1983, revised 16 August 1983).
8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see General principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.\(^1\) Where a stem is shown without any hyphens it may be used anywhere in the name.

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
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</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-ac</td>
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<tr>
<td>-adolum</td>
<td>-adol}</td>
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<tr>
<td>-adol-</td>
<td>-adol}</td>
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<tr>
<td>-astum</td>
<td>-ast</td>
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<tr>
<td>-astinum</td>
<td>-astine</td>
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<tr>
<td>-aze pamum</td>
<td>-aze pam</td>
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<td>bol</td>
<td>bol</td>
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<td>-cain-</td>
<td>-cain-</td>
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<td>-cainum</td>
<td>-caine</td>
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<tr>
<td>-cef-</td>
<td>cef-</td>
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<tr>
<td>-cellinum</td>
<td>-cellin</td>
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<tr>
<td>-conazolum</td>
<td>-conazole</td>
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<td>cort</td>
<td>cort</td>
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<td>-coxibum</td>
<td>-coxib</td>
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<td>-entan</td>
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<td>gab</td>
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<td>gado-</td>
<td>gado-</td>
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<td>prost</td>
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<tr>
<td>-vaptanum</td>
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<td>vin-</td>
<td>vin-}</td>
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<tr>
<td>-vin-</td>
<td>-vin-}</td>
</tr>
</tbody>
</table>

\(^1\) A more extensive listing of stems is contained in the working document WHO/EMP/RHT/TSN/2013.1 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.
ANNEXE 1

PROCEDURE À SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDÉES POUR LES SUBSTANCES PHARMACEUTIQUES1

L’Organisation mondiale de la Santé (également désignée ci-après sous l’appellation « OMS ») observe la procédure exposée ci-dessous pour l’attribution de dénominations communes internationales recommandées pour les substances pharmaceutiques, conformément à la résolution WHA3.11 de l’Assemblée mondiale de la Santé, et pour le remplacement de telles dénominations.

Article 1 - Les propositions de dénominations communes internationales recommandées et les propositions de remplacement de telles dénominations sont soumises à l’OMS sur la formule prévue à cet effet. L’examen de telles propositions est soumis au paiement d’une taxe administrative destinée uniquement à couvrir les coûts correspondants assumés par le Secrétariat de l’OMS (« le Secrétariat »). Le montant de cette taxe est déterminé par le Secrétariat et peut être modifié de temps à autre.

Article 2 - Ces propositions sont soumises par le Secrétariat aux experts désignés à cette fin parmi les personnalités inscrites au Tableau d’experts de la Pharmacopée internationale et des Préparations pharmaceutiques, ci-après désignés sous l’appellation « le Groupe d’experts des DCI » ; elles sont examinées par les experts conformément aux « Directives générales pour la formation de dénominations communes internationales pour les substances pharmaceutiques » reproduites ci-après2.

La dénomination acceptée est la dénomination employée par la personne qui découvre ou qui, la première, fabrique et lance sur le marché une substance pharmaceutique, à moins que des raisons majeures n’obligent à s’écarter de cette règle.

Article 3 - Après l’examen prévu à l’article 2, le Secrétariat notifie qu’un projet de dénomination commune internationale est à l’étude.

a) Cette notification est faite par une insertion dans WHO Drug Information3 et par l’envoi d’une lettre aux Etats Membres et aux commissions nationales et régionales de pharmacopée ou autres organismes désignés par les Etats Membres.

   i) Notification est également faite à la personne qui a soumis la proposition (« le demandeur initial ») et à d’autres personnes portant à la dénomination mise à l’étude un intérêt notoire.

b) Cette notification contient les indications suivantes :

   i) dénomination mise à l’étude;

   ii) nom de l’auteur de la proposition tendant à attribuer une dénomination à la substance, si cette personne le demande ;

   iii) définition de la substance dont la dénomination est mise à l’étude ;

   iv) délai pendant lequel seront reçues les observations et les objections à l’égard de cette dénomination ; nom et adresse de la personne habilitée à recevoir ces observations et objections ;

   v) mention des pouvoirs en vertu desquels agit l’OMS et référence au présent règlement.


2 Voir annexe 2.

3 Avant 1987, les listes de dénominations communes internationales étaient publiées dans la Chronique de l’Organisation mondiale de la Santé.
c) En envoyant cette notification, le Secrétariat demande aux États Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l’étude par l’OMS.

**Article 4** - Des observations sur la dénomination proposée peuvent être adressées à l’OMS par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans *WHO Drug Information* (voir l’article 3).

**Article 5** - Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans *WHO Drug Information* (voir l’article 3).

Cette objection doit s’accompagner des indications suivantes :

i) nom de l’auteur de l’objection ;

ii) intérêt qu’il ou elle porte à la dénomination en cause ;

iii) raisons motivant l’objection contre la dénomination proposée.

**Article 6** - Lorsqu’une objection formelle est formulée en vertu de l’article 5, l’OMS peut soit soumettre la dénomination proposée à un nouvel examen, soit intervenir pour tenter d’obtenir le retrait de l’objection. Sans préjudice de l’examen par l’OMS d’une ou de plusieurs appellations de remplacement, l’OMS n’adopte pas d’appellation comme dénomination commune internationale recommandée tant qu’une objection formelle présentée conformément à l’article 5 n’est pas levée.

**Article 7** - Lorsqu’il n’est formulé aucune objection en vertu de l’article 5, ou que toutes les objections présentées ont été levées, le Secrétariat fait une notification conformément aux dispositions du paragraphe a) de l’article 3, en indiquant que la dénomination a été choisie par l’OMS en tant que dénomination commune internationale recommandée.

**Article 8** - En communiquant aux États Membres, conformément à l’article 7, une dénomination commune internationale recommandée, le Secrétariat :

a) demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée ; et

b) demande aux États Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur cette dénomination et interdire le dépôt de cette dénomination comme marque ou appellation commerciale.

**Article 9** -

a) Dans le cas exceptionnel où une dénomination commune internationale déjà recommandée donne lieu à des erreurs de médication, de prescription ou de distribution ou en comporte un risque démontrable, en raison d’une similitude avec une autre appellation dans la pratique pharmaceutique et/ou de prescription, et où il apparaît que ces erreurs ou ces risques d’erreur ne peuvent être facilement évités par d’autres interventions que le remplacement éventuel d’une dénomination commune internationale déjà recommandée, ou dans le cas où une dénomination commune internationale déjà recommandée diffère sensiblement de la dénomination commune approuvée dans un nombre important d’États Membres, ou dans d’autres circonstances exceptionnelles qui justifient le remplacement d’une dénomination commune internationale recommandée, toute personne intéressée peut formuler une proposition dans ce sens. Cette proposition est présentée sur la formule prévue à cet effet et doit s’accompagner des indications suivantes :

i) nom de l’auteur de la proposition ;

ii) intérêt qu’il ou elle porte au remplacement proposé ;

iii) raisons motivant la proposition ; et
iv) description, faits à l’appui, des autres interventions entreprises pour tenter de régler le problème et exposé des raisons pour lesquelles ces interventions ont échoué.

Les propositions peuvent comprendre une proposition de nouvelle dénomination commune internationale de remplacement, établie conformément aux Directives générales, compte tenu de la substance pharmaceutique pour laquelle la nouvelle dénomination commune internationale de remplacement est proposée.

Le Secrétariat transmet une copie de la proposition pour examen, conformément à la procédure exposée plus loin au paragraphe b), au Groupe d’experts des DCI et au demandeur initial ou à son successeur (s’il s’agit d’une personne différente de celle qui a formulé la proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles).

De plus, le Secrétariat demande aux entités et personnes ci-après de formuler des observations sur la proposition :

i) les États Membres et les commissions nationales et régionales de pharmacopée ou d’autres organismes désignés par les États Membres (en insérant une note à cet effet dans la lettre mentionnée à l’article 3.a), et

ii) toutes autres personnes portant au remplacement proposé un intérêt notoire.

La demande d’observations contient les indications suivantes :

i) dénomination commune internationale recommandée pour laquelle un remplacement est proposé (et la dénomination de remplacement proposée, si elle est fournie) ;

ii) nom de l’auteur de la proposition de remplacement (si cette personne le demande) ;

iii) définition de la substance faisant l’objet du remplacement proposé et raisons avancées pour le remplacement ;

iv) délai pendant lequel seront reçus les commentaires et nom et adresse de la personne habilitée à recevoir ces commentaires ; et

v) mention des pouvoirs en vertu desquels agit l’OMS et référence au présent règlement.

Des observations sur la proposition de remplacement peuvent être communiquées par toute personne à l’OMS dans les quatre mois qui suivent la date de la demande d’observations.

b) Une fois échu le délai prévu ci-dessus pour la communication d’observations, le Secrétariat transmet les observations reçues au Groupe d’experts des DCI, au demandeur initial ou à son successeur et à l’auteur de la proposition de remplacement. Si, après avoir examiné la proposition de remplacement et les observations reçues, le Groupe d’experts des DCI, l’auteur de la proposition de remplacement et le demandeur initial ou son successeur reconnaissent tous qu’il est nécessaire de remplacer la dénomination commune internationale déjà recommandée, le Secrétariat soumet la proposition de remplacement au Groupe d’experts des DCI pour qu’il y donne suite.

Nonobstant ce qui précède, le demandeur initial ou son successeur n’est pas habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu’il porte un intérêt durable à la dénomination commune internationale recommandée qu’il est proposé de remplacer.

Dans le cas où une proposition de remplacement est soumise au Groupe d’experts des DCI pour qu’il y donne suite, le Groupe choisit une nouvelle dénomination commune internationale conformément aux Directives générales mentionnées à l’article 2 et selon la procédure décrite dans les articles 3 à 8 inclus. La notification faite par le Secrétariat en vertu de l’article 3 et de l’article 7, respectivement, y compris au demandeur initial ou à son successeur (si ce n’est pas la même personne que celle qui a proposé le remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse
être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles),
doit dans un tel cas indiquer que la nouvelle dénomination remplace une dénomination commune
internationale déjà recommandée et que les Etats Membres peuvent souhaiter prendre des mesures
transitoires pour les produits existants qui utilisent la dénomination commune internationale déjà
recommandée sur leur étiquette conformément à la législation nationale.

Si, après examen de la proposition de remplacement et des observations communiquées
conformément à la procédure exposée plus haut, le Groupe d’experts des DCI, le demandeur initial ou son
successeur et l’auteur de la proposition de remplacement ne s’accordent pas sur le fait qu’il y a des
raisons impératives de remplacer une dénomination commune internationale déjà recommandée, cette
dernière est conservée (étant entendu toujours que le demandeur initial ou son successeur n’est pas
habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu’il
porte un intérêt durable à la dénomination commune internationale recommandée qu’il est proposé de
remplacer). Dans un tel cas, le Secrétariat informe l’auteur de la proposition de remplacement, ainsi que le
demandeur initial ou son successeur (s’il s’agit d’une personne différente de celle qui a formulé la
proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou
puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations
industrielles), les Etats Membres, les commissions nationales et régionales de pharmacopée, les autres
organismes désignés par les Etats Membres et toutes autres personnes portant un intérêt notoire au
remplacement proposé que, malgré une proposition de remplacement, il a été décidé de conserver la
dénomination commune internationale déjà recommandée (avec une brève description de la ou des
raisons pour lesquelles la proposition de remplacement n’a pas été jugée suffisamment impérative).

ANNEXE 2

DIRECTIVES GENERALES POUR LA FORMATION DE DENOMINATIONS
COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES
PHARMACEUTIQUES

1. Les dénominations communes internationales (DCI) devront se distinguer les unes des autres par leur
consonance et leur orthographe. Elles ne devront pas être d’une longueur excessive, ni prêter à confusion
avec des appellations déjà couramment employées.

2. La DCI de chaque substance devra, si possible, indiquer sa parenté pharmacologique. Les
dénominations susceptibles d’évoquer pour les malades des considérations anatomiques, physiologiques,
pathologiques ou thérapeutiques devront être évitées dans la mesure du possible.

Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants :

3. Lorsqu’on formera la DCI de la première substance d’un nouveau groupe pharmacologique, on tiendra
compte de la possibilité de former ultérieurement d’autres DCI appropriées pour les substances
apparentées du même groupe.

4. Pour former des DCI des acides, on utilisera de préférence un seul mot. Leurs sels devront être
désignés par un terme qui ne modifie pas le nom de l’acide d’origine : par exemple «oxacilline» et
«oxacilline sodique», «ibufénac» et «ibufénac sodique».

5. Les DCI pour les substances utilisées sous forme de sels devront en général s’appliquer à la base
active (ou à l’acide actif). Les dénominations pour différents sels ou esters d’une même substance active
ne différeront que par le nom de l’acide inactif (ou de la base inactive).

Dans son vingtième rapport (OMS, Série de Rapports techniques, N° 581, 1975), le Comité OMS d’experts des Dénominations communes pour les
Substances pharmaceutiques a examiné les directives générales pour la formation des dénominations communes internationales et la procédure à suivre
en vue de leur choix, compte tenu de l’évolution du secteur pharmaceutique au cours des dernières années. La modification la plus importante a été
l’extension aux substances de synthèse de la pratique normalement suivie pour désigner les substances liées ou dérivées de produits naturels. Cette
pratique consiste à employer des syllabes communes ou groupes de syllabes communes (segments-clés) qui sont caractéristiques et indiquent une
propriété commune aux membres du groupe des substances pour lequel ces segments-clés ont été retenus. Les raisons et les conséquences de cette
modification ont fait l’objet de discussions approfondies.

Les directives ont été mises à jour lors de la treizième consultation sur les dénominations communes pour les substances pharmaceutiques (Genève, 27-
En ce qui concerne les substances à base d’ammonium quaternaire, la dénomination s’appliquera de façon appropriée au cation et à l’anion en tant qu’éléments distincts d’une substance quaternaire. On évitera de choisir une désignation évoquant un sel aminé.

6. On évitera d’ajouter une lettre ou un chiffre isolé ; en outre, on renoncera de préférence au trait d’union.

7. Pour simplifier la traduction et la prononciation des DCI, la lettre « f » sera utilisée à la place de « ph », « t » à la place de « th », « e » à la place de « ae » ou « oe », et « i » à la place de « y » ; l’usage des lettres « h » et « k » sera aussi évité.

8. On retiendra de préférence, pour autant qu’elles respectent les principes énoncés ici, les dénominations proposées par les personnes qui ont découvert ou qui, les premières, ont fabriqué et lancé sur le marché les préparations pharmaceutiques considérées, ou les dénominations déjà officiellement adoptées par un pays.

9. La parenté entre substances d’un même groupe (voir Directive générale 2) sera si possible indiquée dans les DCI par l’emploi de segments-clés communs. La liste ci-après contient des exemples de segments-clés pour des groupes de substances, surtout pour des groupes récents. Il y a beaucoup d’autres segments-clés en utilisation active. La liste plus complète de segments-clés est contenue dans le document de travail WHO/EMP/RHT/TSN/2013.1 qui est régulièrement mis à jour.

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1 Une liste plus complète de segments-clés est contenue dans le document de travail WHO/EMP/RHT/TSN/2013.1 qui est régulièrement mis à jour et qui peut être demandé auprès du programme des DCI, OMS, Genève.
ANEXO 1

PROCEDIMIENTO DE SELECCIÓN DE DENOMINACIONES COMUNES INTERNACIONALES RECOMENDADAS PARA SUSTANCIAS FARMACÉUTICAS

La Organización Mundial de la Salud (OMS) seguirá el procedimiento que se expone a continuación tanto para seleccionar denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11, como para sustituir esas denominaciones.

**Artículo 1 -** Las propuestas de denominaciones comunes internacionales recomendadas y las propuestas de sustitución de esas denominaciones se presentarán a la OMS en los formularios que se proporcionen a estos efectos. El estudio de estas propuestas estará sujeto al pago de una tasa destinada a sufragar los costos de administración que ello suponga para la Secretaría de la OMS («la Secretaría»). La Secretaría establecerá la cuantía de esa tasa y podrá ajustarla periódicamente.

**Artículo 2 -** Estas propuestas serán sometidas por la Secretaría a los miembros del Cuadro de Expertos en Farmacopea Internacional y Preparaciones Farmacéuticas encargados de su estudio, en adelante designados como «el Grupo de Expertos en DCI», para que las examinen de conformidad con los «Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas», anexos a este procedimiento. A menos que haya poderosas razones en contra, la denominación aceptada será la empleada por la persona que haya descubierto o fabricado y comercializado por primera vez esa sustancia farmacéutica.

**Artículo 3 -** Tras el examen al que se refiere el artículo 2, la Secretaría notificará que está en estudio un proyecto de denominación internacional.

a) Esa notificación se hará mediante una publicación en *Información Farmacéutica OMS* y el envío de una carta a los Estados Miembros y a las comisiones nacionales y regionales de las farmacopeas u otros organismos designados por los Estados Miembros.

   i) La notificación será enviada también a la persona que haya presentado la propuesta («el solicitante inicial») y a otras personas que tengan un interés especial en una denominación objeto de estudio.

b) En esa notificación se incluirán los siguientes datos:

   i) la denominación sometida a estudio;

   ii) la identidad de la persona que ha presentado la propuesta de denominación de la sustancia, si lo pide esa persona;

   iii) la identidad de la sustancia cuya denominación está en estudio;

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2 Véase el anexo 2.

3 Hasta 1987 las listas de DCI se publicaban en la *Crónica de la Organización Mundial de la Salud.*
iv) el plazo fijado para recibir observaciones y objeciones, así como el nombre y la dirección de la persona a quien deban dirigirse; y

v) los poderes conferidos para el caso a la OMS y una referencia al presente procedimiento.

c) Al enviar esa notificación, la Secretaría solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de patente sobre la denominación propuesta, durante el periodo en que la OMS la tenga en estudio.

Artículo 4 - Toda persona puede formular a la OMS observaciones sobre la denominación propuesta dentro de los cuatro meses siguientes a su publicación en Información Farmacéutica OMS, conforme a lo dispuesto en el artículo 3.

Artículo 5 - Toda persona interesada puede presentar una objeción formal a una denominación propuesta dentro de los cuatro meses siguientes a su publicación en Información Farmacéutica OMS, conforme a lo dispuesto en el artículo 3.

Esa objeción deberá acompañarse de los siguientes datos:

i) la identidad de la persona que formula la objeción;

ii) las causas que motivan su interés por la denominación; y

iii) las causas que motivan su objeción a la denominación propuesta.

Artículo 6 - Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la OMS podrá reconsiderar el nombre propuesto o utilizar sus buenos oficios para intentar lograr que se retire la objeción. La OMS no seleccionará como denominación común internacional una denominación a la que se haya hecho una objeción formal, presentada según lo previsto en el artículo 5, que no haya sido retirada, todo ello sin perjuicio de que la Organización examine otra denominación o denominaciones sustitutivas.

Artículo 7 - Cuando no se haya formulado ninguna objeción en la forma prevista en el artículo 5, o cuando todas las objeciones presentadas hayan sido retiradas, la Secretaría notificará, conforme a lo dispuesto en el párrafo a) del artículo 3, que la denominación ha sido seleccionada por la OMS como denominación común internacional recomendada.

Artículo 8 - Al comunicar a los Estados Miembros una denominación común internacional, conforme a lo previsto en el artículo 7, la Secretaría:

a) solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate; y

b) solicitará a los Estados Miembros que adopten todas las medidas necesarias para impedir la adquisición de derechos de patente sobre la denominación, y prohíban que sea registrada como marca de fábrica o como nombre comercial.

Artículo 9

a) En el caso excepcional de que, debido a su semejanza con otra denominación utilizada en las prácticas farmacéuticas y/o de prescripción, una denominación común internacional recomendada anteriormente ocasione errores de medicación, prescripción o distribución, o suponga un riesgo manifiesto de que esto ocurra, y parezca que tales errores o potenciales errores no sean fácilmente subsanables con otras medidas que no sean la posible sustitución de esa denominación común internacional recomendada anteriormente; en el caso de que una denominación común internacional recomendada anteriormente difiera considerablemente de la denominación común aprobada en un número importante de Estados Miembros, o en otras circunstancias excepcionales que justifiquen el cambio de una denominación común internacional recomendada, cualquier persona interesada puede presentar propuestas en este sentido. Esas propuestas se presentarán en los formularios que se proporcionen a estos efectos e incluirán los siguientes datos:
i) la identidad de la persona que presenta la propuesta;

ii) las causas que motivan su interés en la sustitución propuesta;

iii) las causas que motivan la propuesta; y

iv) una descripción, acompañada de pruebas documentales, de las otras medidas que se hayan adoptado con el fin de resolver la situación y de los motivos por los cuales dichas medidas no han sido suficientes.

Entre esas propuestas podrá figurar una relativa a una nueva denominación común internacional sustitutiva, formulada con arreglo a los Principios generales y que tenga en cuenta la sustancia farmacéutica para la que se proponga la nueva denominación común internacional sustitutiva.

La Secretaría enviará al Grupo de Expertos en DCI y al solicitante inicial o a su sucesor (en el caso de que sea una persona diferente de la que ha presentado la propuesta de sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales) una copia de la propuesta, para que sea examinada de conformidad con el procedimiento descrito en el párrafo b) infra. Además, la Secretaría solicitará observaciones sobre la propuesta:

i) a los Estados Miembros y a las comisiones nacionales y regionales de las farmacopeas u otros organismos designados por los Estados Miembros (ello se hará incluyendo una notificación a tal efecto en la carta a la que se refiere el párrafo a) del artículo 3), y

ii) a cualquier persona que tenga un interés especial en la sustitución propuesta.

Al solicitar que se formulen estas observaciones se facilitarán los siguientes datos:

i) la denominación común internacional recomendada que se propone sustituir (y la denominación sustitutiva propuesta, si se ha facilitado);

ii) la identidad de la persona que ha presentado la propuesta de sustitución (si lo pide esa persona);

iii) la identidad de la sustancia a la que se refiere la sustitución propuesta y las razones para presentar la propuesta de sustitución;

iv) el plazo fijado para recibir observaciones, así como el nombre y la dirección de la persona a quien deban dirigirse; y

v) los poderes conferidos para el caso a la OMS y una referencia al presente procedimiento.

Toda persona puede formular a la OMS observaciones sobre la sustitución propuesta dentro de los cuatro meses siguientes a la fecha en que se realizó la solicitud de observaciones.

b) Una vez agotado el mencionado plazo para la formulación de observaciones, la Secretaría enviará todos los comentarios recibidos al Grupo de Expertos en DCI, al solicitante inicial o a su sucesor, y a la persona que haya presentado la propuesta de sustitución. Si después de examinar la propuesta de sustitución y las observaciones recibidas, el Grupo de Expertos en DCI, la persona que haya presentado la propuesta de sustitución y el solicitante inicial, o su sucesor, están de acuerdo en la necesidad de sustituir la denominación común internacional recomendada anteriormente, la Secretaría remitirá la propuesta de sustitución al Grupo de Expertos en DCI para que la tramite.

No obstante lo anterior, el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone.

En caso de que la propuesta de sustitución sea presentada al Grupo de Expertos en DCI para que la tramite, este grupo seleccionará una nueva denominación común internacional de conformidad con los
Proposed INN: List 112

Principios generales a los que se refiere el artículo 2 y al procedimiento establecido en los artículos 3 a 8 inclusive. En ese caso, en las notificaciones que la Secretaría ha de enviar con arreglo a los artículos 3 y 7, respectivamente, incluida la notificación al solicitante inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), se indicará que la nueva denominación sustituye a una denominación común internacional recomendada anteriormente y que los Estados Miembros podrán, si lo estiman oportuno, adoptar disposiciones transitorias aplicables a los productos existentes en cuya etiqueta se utilice, con arreglo a la legislación nacional, la denominación común internacional recomendada anteriormente que se haya sustituido.

En caso de que, después de haber estudiado la propuesta de sustitución y los comentarios recibidos de conformidad con el procedimiento descrito anteriormente, el Grupo de Expertos en DCI, el solicitante inicial o su sucesor y la persona que haya presentado la propuesta de sustitución no lleguen a un acuerdo sobre la existencia de razones poderosas para sustituir una denominación común internacional recomendada anteriormente, esta denominación se mantendrá (siempre en el entendimiento de que el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone). En ese caso, la Secretaría comunicará a la persona que haya propuesto la sustitución, así como al solicitante inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), a los Estados Miembros, a las comisiones nacionales y regionales de las farmacopeas o a otros organismos designados por los Estados Miembros a cualquier otra persona que tenga interés en la sustitución propuesta, que, pese a la presentación de una propuesta de sustitución, se ha decidido mantener la denominación común internacional recomendada anteriormente (con una descripción de la o las razones por las que se ha considerado que la propuesta de sustitución no estaba respaldada por razones suficientemente poderosas).

ANEXO 2

PRINCIPIOS GENERALES DE ORIENTACIÓN PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACÉUTICAS

1. Las denominaciones comunes internacionales (DCI) deberán diferenciarse tanto fonéticamente como ortográficamente. No deberán ser incómodamente largas, ni dar lugar a confusión con denominaciones de uso común.

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse las denominaciones que puedan tener connotaciones anatómicas, fisiológicas, patológicas o terapéuticas para el paciente.

Estos principios primarios se pondrán en práctica utilizando los siguientes principios secundarios:

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de poder formar DCI convenientes para las sustancias emparentadas que se agreguen al nuevo grupo.

4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre del ácido: p. ej. «oxacilina» y «oxacilina sódica»; «ibufenaco» y «ibufenaco sódico».

1 En su 20º informe (OMS, Serie de Informes Técnicos, N° 581, 1975), el Comité de Expertos de la OMS en Denominaciones Comunes para las Sustancias Farmacéuticas revisó los Principios generales para formar denominaciones comunes internacionales (DCI), y su procedimiento de selección, a la luz de las novedades registradas en los últimos años en materia de compuestos farmacéuticos. El cambio más importante había consistido en hacer extensivo a la denominación de sustancias químicas sintéticas el método utilizado hasta entonces para las sustancias originadas en productos naturales o derivadas de éstos. Dicho método conlleva la utilización de una «partícula» característica que indica una propiedad común a los miembros de un grupo. En el citado informe se examinan en detalle las razones y consecuencias de este cambio.

Los Principios generales de orientación se actualizaron durante la 13ª consulta sobre denominaciones comunes para sustancias farmacéuticas (Ginebra, 27 a 29 de abril de 1983) (PHARM S/NOM 928, 13 de mayo de 1983, revisado el 18 de agosto de 1983).
5. Las DCI para las sustancias que se usan en forma de sal deberán en general aplicarse a la base activa o al ácido activo. Las denominaciones para diferentes sales o esteres de la misma sustancia activa solamente deberán diferir en el nombre del ácido o de la base inactivos. En los compuestos de amonio cuaternario, el catión y el anión deberán denominarse adecuadamente por separado, como componentes independientes de una sustancia cuaternaria y no como sales de una amina.

6. Deberá evitarse el empleo de letras o números aislados; también es indeseable el empleo de guiones.

7. Para facilitar la traducción y la pronunciación, se emplearán de preferencia las letras «f» en lugar de «ph», «t» en lugar de «th», «e» en lugar de «ae» u «oe», e «i» en lugar de «y»; se deberá evitar el empleo de las letras «h» y «k».

8. Siempre que las denominaciones propuestas estén de acuerdo con estos principios, recibirán una consideración preferente las denominaciones propuestas por la persona que haya descubierto las sustancias, o que fabrique y comercialice por primera vez una sustancia farmacéutica, así como las denominaciones ya adoptadas oficialmente en cualquier país.

9. El parentesco entre sustancias del mismo grupo se pondrá de manifiesto en las DCI (véase el Principio 2) utilizando una partícula común. En la lista que figura a continuación se indican ejemplos de partículas para grupos de sustancias, en particular para grupos nuevos. Existen muchas otras partículas que se usan habitualmente. Cuando una partícula aparece sin guión alguno, puede utilizarse en cualquier lugar de la palabra.

<table>
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1 En el documento de trabajo WHO/EMP/RHT/TST/2013.1, que se actualiza periódicamente y puede solicitarse al Programa sobre Denominaciones Comunes Internacionales, OMS, Ginebra, figura una lista más amplia de partículas.
<table>
<thead>
<tr>
<th>Prefix</th>
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<th>Description</th>
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<td>poetum</td>
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<td>pril(at)</td>
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