WHO Drug Information

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Announcement

The 14th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the Health Sciences Authority, Singapore, in collaboration with the World Health Organization.

The ICDRA will take place in Singapore from 30 November to 3 December 2010.

Updated information is available at:
http://www.icdra2010.sg
http://www.who.int/medicines/icdra
International Nonproprietary Names

INN identifiers for biological products

The International Nonproprietary Names (INN) Programme was created by WHO in the 1950s with the intention of providing convenient common names for pharmaceutical substances. At the time of its origin, as well as during its later development, the INN Programme was inherently linked to progress in drug research and its success was reliant on the ability to deal appropriately with each new group of medicinal products that entered into therapeutic use. In the 1980s, the development of biotechnology products based on recombinant techniques led to highly novel therapeutic agents, thus creating a new need for adaptation of the INN system. The present article describes the ways that the INN Programme has responded to the challenges that arose in connection with this evolution.

Basic rules for the INN system set the limits within which all INN can be constructed. They include the need to properly define the substance or product that is named, to indicate in the name the pharmacological or therapeutic class to which the substance or product belongs by use of the INN stem system and, finally, to shape the name in a manner which facilitates its use by prescribers. (These issues are summarized on page 274.)

In its initial phase, the INN Programme was designed to cover only single chemical substances of well-defined structure although other groups of non-homogenous established products, including from natural sources, were also considered. When substances which had already been named by the INN Programme became available through new biotechnological processes, earlier decisions on naming non-homogenous products had an influence on defining and naming novel products. Practices recognized in naming and defining two specific product groups: low molecular weight heparins and insulins strongly influenced this approach. (A discussion of these practices is found on page 274 and 275.)

Specific approaches are needed when formulating definitions and, in particular, for creating suitable INN for biotechnological products. These approaches have been under active consideration by the INN Programme since the 1980s and were finally formulated in a 1994 INN guideline (1). Until now, 45 INN with Greek letter identifiers have been selected for glycosylated biological products.

Application of the guidelines in naming of individual groups of biological products containing carbohydrate residues in their structure is described on pages 275–277. Difficulties that relate to the use of Greek letter identifiers in naming of interferons are presented on page 279. The naming of monoclonal antibodies (mAbs), an important group of glycoproteins obtained by biotechnology, is not considered in this document as issues related to mAb names have been discussed separately at recent INN meetings and are also reviewed in two issues of WHO Drug Information (2). Related documents of

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interest are also available on the INN website including a document on INN for biological and biotechnology substances (3), documents relating to biologicals and mAbs (4) and an INN document on biosimilars (5).

Creating INN

In the selection of INN, two separate issues are considered which influence the final shape of the name: (i) the way in which the substance is identified, and (ii) the structure of the name.

In the case of individual chemical substances, the identification process is based on chemical names established by the International Union of Pure and Applied Chemistry (IUPAC). The chemical designation is further supported by a graphic formula.

In the case of products obtained by biotechnology, the identification process is more complicated because such products usually form a mixture (the word “complex” is sometimes used) of several (or more) individual substances of similar structure and activity. The use of these products occurs without separation into individual active components. Definition of such products occurs without separation into individual active components. Definition of such products is complicated and is made individually for each product group. Formulation of definitions has progressed in line with analytical methods that increasingly allow a highly precise description of the structure of individual components. Examples of such changes occurring for individual groups are presented later.

Creation of INN for single chemical substances involves selection of an appropriate stem indicating the expected activity (or the decision to select an INN outside the stem system) followed by additional elements (usually the prefix) to create a distinctive name. When an INN is selected for an active moiety, while a salt or an ester are employed in practice, an INNM system is used to create suitable two-word names.

However, creating INN for products obtained by biotechnology is a more complex process. While the selection of basic stems (-ase, -mab, -micin, -mycin, -poetin, etc.) can be carried out according to the normal INN system, the naming of individual components of each series requires specific decisions on the extent of supplementary information to be included in the name. Those issues may vary for individual groups, but the following remarks apply to all situations.

General rules for the construction of INN offer only a few options for introducing elements of additional information. In one-word names this can be done by insertion of specific infixes (or prefixes). Otherwise, inclusion of a second or even third word is necessary as in the case of INNM names. This approach is also used when describing complexes with metals or radioactive elements. The second-word approach is used frequently for biological products when the second word consists of a spelled out Greek letter.

Other identifiers widely used in scientific texts like numerals (Arabic or Roman), single letters (Latin alphabet), or single Greek letters in the original script, are precluded in INN. The reason for this rule is that such elements of names could lead to confusion and mistakes when used on a medical prescription, as numerals are used also to describe the dose (or concentration) or the number of dosage units. Single letters may also be confused, especially in handwriting.

The rules indicated above are also applied when selecting names for biological products with a glycoprotein structure. This can sometimes create additional difficulties, and is described later.
Selecting INN for natural and semisynthetic products

INN for LMW heparins
Low molecular weight (LMW) heparins are products obtained from natural heparin by chemical reaction leading to depolymerization and various changes in structure. Natural heparin is a sulfated polysaccharide (polyuronic acid), which is a mixture of components differing in chain length. LMW heparins also form mixtures of individual components that may differ in chain length and other structural features because they are produced from a natural heterogenous material by processes that do not warrant full homogeneity of the final product.

In 1983, when the first INN request for a LMW heparin was made, the INN Expert Group held prolonged discussions on whether this type of biological product should be included in INN system. It was concluded finally that selecting INN for such products would serve a useful purpose, and the stem -parin was selected for the group. The first name in the series was enoxaparin published in 1984. (The name was later modified to enoxaparin sodium.) The next group of requests for LMW heparins was given the INN nadroparin calcium, parnaparin sodium, reviparin sodium and tinzaparin sodium. Since then, a further eight INN containing the -parin stem have been selected.

As can be seen, individual members of the group are distinguished by using INN containing a common stem (-parin) and different prefixes. Individual products are defined in a rather complicated manner by description of manufacturing process, information on the structure of components and indication of molecular mass.

INN for insulins
Insulin serves as an example of the approach for naming a group of related peptides by using a parent name (insulin) followed (or preceded) by another word (or words) which is indicative of changes in the structure of the parent compound.

Insulin as such was never listed as an INN, being considered a well-established name. Between 1956 and 1958, INN were given to 6 insulin preparations: insulin zinc suspension (crystalline) and (amorphous), protamine zinc insulin injection, etc. The definition for each product described its preparation.

The first insulin obtained in 1982 by recombinant technology was given the INN insulin human, defined as “a protein having the normal structure of the natural antidiabetic principle produced by the human pancreas”. In this case the second word in the name served a dual purpose, to link the actual structure of the product with that of a natural product, following the pattern established in the case of beef insulin and pork insulin.

The two-word approach was maintained for six further INN for modified insulins produced by biotechnology: insulin argine, insulin lispro, etc. containing modifications in the amino-acid sequences, but in these cases the second word serves to indicate a structural change. The substances are defined by describing their chemical structure.

INN for erythropoietins
The first request for erythropoietin produced by biotechnology was made in 1988 by a US manufacturer. The request indicated that the substance was produced by “human clone \(\lambda\)HEPOFL13 protein moiety”. The manufacturer’s proposal to select erythropoietin as an INN was modified to eripoetin and this name was considered to be suitable provided that the product corresponded to the natural endogenous substance. It was also agreed that -poetin would be considered in the future as a stem for all erythropoietin type blood factors. Later in
1988 a second request for an INN for erythropoietin produced by biotechnology was received from another manufacturer.

However, during evaluation, the main problem that emerged concerning the recombinant form was that erythropoietin is a glycoprotein and that the activity of the substance depends strongly on the degree of glycosylation, as erythropoietin without the carbohydrate moiety is not active in vivo. Additionally, the recombinant forms differ in the type and degree of glycosylation and neither one is identical to the endogenous substance. Literature published on the subject confirmed that N-glycosylation is cell specific and site specific creating different glycoforms depending on the cell line used in the manufacturing process. It was also known that erythropoietin has three N-glycosylation sites at Asn^{24}, Asn^{38} and Asn^{53} and one O-glycosylation site at Ser^{126}. It was also known that carbohydrate moieties at N-terminals are quite complex (antennary structure).

On the basis of these arguments, the INN Group decided in 1989 to consider each request as representing a different product and to give an individual INN (6). Subsequently, the INN guideline adopted in 1994 (1) states that the Greek letter would serve to differentiate between compounds of the same amino acid sequence as human erythropoietin, which vary in the glycosylation pattern. INN for products with different amino acid sequence would be named using the -poetin stem and a random prefix (see darbepoetin alfa).

Between 1992 and 2007, six other INN were selected for erythropoietins produced by biotechnology: epoetin gamma, epoetin delta, epoetin epsilon, epoetin zeta (in Spanish dseta), epoetin theta (in Spanish zeta), epoetin kappa, and epoetin omega. In 2001, darbepoetin alfa was selected for an erythropoietin with a modified amino acid chain.

Definitions for all epoetins include information that the product is a 1-165-erythropoietin and contains a glycoform identifier expressed as α, β and γ, etc. In addition, definitions of epoetin alfa, epoetin beta, epoetin gamma, epoetin epsilon and epoetin omega also indicate the designation “human clone \( \lambda \)HEPOFL13 protein moiety” describing the gene coding of the amino acid sequence for human erythropoietin (HEPOFL being an abbreviation for Human Erythropoietin Fetal Liver source).

Definitions for three other epoetins include gene codes which are not in line with symbols used in regular gene nomenclature and are seemingly suggestions from manufacturers. The definition of epoetin delta contains the expression “human HMR4396” where the designation HMR4396 is the manufacturer’s code. A similar situation occurred in the case of epoetin kappa. In the case of epoetin zeta, the definition contains the expression “human clone B03XA01” where the designation B03XA01 is an ATC code for anti-anemic preparations. It may be appropriate to later delete these designations from the definitions.

**INN for enzymes**

INN for enzymes obtained from natural sources were usually selected to correspond to enzyme names established by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology. In those cases their structure was not further defined, but in the majority of cases the origin of the product was indicated. Recently, EC numbers have been added to the definitions.

The following examples show approaches that were used in this group of products. INN urokinase (published in 1966) was defined originally as “plasminogen activator isolated from human urine”, but the definition was changed in 1982 to “plas-
minogen activator isolated from human sources” to take account of the fact that the product started to be produced by human kidney cell culture in vitro. *Penicillinase* was defined as an enzyme obtained by fermentation from cultures of *Bacillus cereus*. *Kallidinogenase* was defined as an enzyme isolated from the pancreas or urine of mammals. *Stericase* was defined as alkaline *Bacillus sphaericus* proteinase.

In the 1990s, the situation progressed further when some specific enzymes that are glycoproteins started to be produced by biotechnology. The INN Group considered it necessary to indicate the glycoform by using the Greek letter system and a few examples are given here. INN *dornase alfa*, selected in 1993, was defined as “deoxyribonuclease (human clone 18-1 protein moiety)”. *Alglucosidase alfa* was defined as “human lysosomal prepro-α-glucosidase-(57-952)-peptide 199-arginine-223-histidine variant”. *Bucelipase alfa* was defined as “human bile-salt-activated lipase (cholesterol esterase, EC 3.1.1.13), glycoform alfa (recombinant hBSSL)”.

The use of Greek letters as identifiers was useful in the case of INN for α-galactosidase. *Agalsidase alfa* was selected for a product isolated from recombinant human cell line and INN agalsidase beta for a product obtained from a Chinese Hamster Ovary (CHO) cell line. The same approach was used for *conestat alfa* which was selected in 2007 for a specific C1 esterase inhibitor (serine protease inhibitor).

A rather different situation occurred in the group of plasminogen activators. Initial discussion on these products was held in April 1985 (7). The first request for a tissue plasminogen activator was made in 1985 for a recombinant product for which *alteplase* was finally selected in 1988. Another one, for urokinase-type recombinant plasminogen activator followed, for which *saruplase* was selected in 1987. During the period 1985–1987 discussions were centred on the suitability of treating these products as enzymes by using the -ase suffix, and the issue of glycosylation was not considered. Finally, two stems for plasminogen activators: -teplase (for tissue-type) and -uplase (for urokinase-type) were established in 1987 (8).

As this decision was made before the system of glycoform identifiers was introduced, subsequent INN containing -plase stems were selected without this identifier, as in the majority of cases the INN were given for products with modifications in the amino acid chain. In some definitions the notion that the product is a glycoprotein was included in the definition. *Silteplase* was defined as “N’-[N²-(N-glycyl-N-alanyl)-L-arginyl]plasminogen activator (human tissue-type protein moiety reduced), glycoform”. A similar remark was made in the definition for *nateplase* where “glycoform β” is mentioned.

However, the absence of a glycosylation identifier later created a specific difficulty in the group of urokinase-type plasminogen activators. *Nasaruplase* was defined as “prourokinase (enzyme-activating) (human clone pA3/pD2/pF1 protein moiety)”. This definition was later modified by adding “glycosylated”. At the same time *saruplase* — defined originally as “prourokinase (enzyme-activating) (human clone pUK4/pUK18 protein moiety reduced) — had to be changed by addition of “non-glycosylated”. In 2001, when another request was made for recombinant prourokinase produced by another cell line, *nasaruplase beta* was selected, defined as “prourokinase (enzyme-activating) human (clone pUK4/pUK18 protein moiety), glycosylated (murine cell line SP2/0)”. The use of a Greek letter identifier permitted a better separation of products differing in glycosylation patterns.
INN for other glycosylated biologicals
Production of biological products identical or analogous to natural proteins or glycoproteins by recombinant technology was also applied to other types of products. The naming system used for creating INN for these products is similar to that already discussed.

Blood coagulation factors and related products
In the group of blood coagulation factors (substances that are glycoproteins), the first INN requests for products obtained by biotechnology were made in 1993 for three products: blood coagulation factor VIIa, blood coagulation factor VIII and for blood coagulation factor VIII with a modified (truncated) amino acid structure.

The main issue centred on whether to retain the established descriptive names for products obtained by biotechnology or switch to the INN approach of one-word names composed of a suitable stem and a random prefix. The option that was finally accepted is reflected in the following policy statements:

• New names will only be given to products produced by recombinant biotechnology, but not to plasma derived products.

• Suitable stems will be created, glycosylation pattern may be reflected by addition of a Greek letter (spelled out).

• The distinction between natural and modified amino acid sequence will be indicated by using different prefixes.

This system was referred to as the “epoetin approach” (1).

INN eptacog alfa (activated) was selected in 1994 and defined as “(1-724)-(1637–1648)-blood coagulation factor VIII (human reduced) with 1649-2332- blood coagulation factor VIII (human reduced)”. Octocog alfa was defined as “blood coagulation factor VIII (human), glycoform α”. Other INN in the blood coagulation factor group include berococtocog alfa, eptacog alfa pegol (activated), nonacog alfa, and vatreptacog alfa (activated).

INN were also selected for two blood coagulation cascade inhibitors: drotrecocogin alfa (activated) and taneptacogin alfa, and for five further products related to blood coagulation processes: thrombin alfa, antithrombin alfa, troplasminogen alfa, thrombomodulin alfa, and so-thrombomodulin alfa.

Interleukins
The first INN in this group, teceleukin, was selected in 1985 for N-L-methionyl-interleukin-2 obtained by biotechnology. Subsequently, aldesleukin was selected in 1990 and celmoleukin in 1991 for interleukin-2 derivatives with modifications in the amino acid chain. Although natural interleukin-2 is a glycoprotein, the issue of glycosylation was not discussed at that time.

In 1994, the situation changed when a request was received for a derivative of interleukin-6. For this product, atexakin alfa was selected and defined as “1-(1-L-alanyl-l-proline)interleukin-6 (human clone HGF-15 protein moiety reduced), cyclic (54->50), (73->83)-bis(disulfide)”.

The formal decision to publish INN for glycosylated interleukins with a Greek letter in accordance with the general policy of naming glycosylated proteins was later confirmed in 1995 (10).

Following this decision, edodekin alfa was selected in 1998 for interleukin-12 and adargileukin alfa in 2003 for partially glycosylated modified interleukin-2.
**Tadekinig alfa** was selected in 2004 for interleukin-18 binding protein.

**Pituitary and placental glycoprotein hormones**

Preparations produced from human post-menopausal urine containing a mixture of follicle-stimulating pituitary hormone (FSH) and luteinizing hormone (LH) have been manufactured since the 1960s and pINN *menotrophin* and *follotrophin (human)* were selected in 1963 and 1965. These INN were later withdrawn, as their definitions were considered not suitable. However, the issue was revisited in 1987 when *urofollitropin* was selected for a product defined as “a preparation of menopausal gonadotrophin extracted from human urine but possessing negligible LH activity”.

In 1991, a request was received for human FSH produced by recombinant technology followed by a request for human LH also produced by biotechnology. After discussion, *follitropin alfa* and *lutropin alfa* were suggested as INN, with Greek letters indicating glycosylation. This proposal was however contested, because natural pituitary hormones contain two amino acid chains in their structure that were designated by biochemists as α and β subunits and these designations were widely used in the scientific literature. Although members of the INN Expert Group considered that the use of Greek letters in INN may lead to confusion, they conceded that such risk was minor (9).

The arguments against this selection may be of some relevance for scientists, but INN are intended primarily for use by health professionals such as physicians and pharmacists and not for scientists specialized in this area. As a result, *follitropin alfa* and *lutropin alfa* were selected as well as *follitropin beta*. *Corifollitropin alfa* was selected as a fusion protein composed of FSH and 118-145-chorionic gonadotropin (human β subunit). Recently, *varfollitropin alfa* was selected as FSH with amino acid modifications in both subunits.

Other INN selected in this group for glycoprotein hormones obtained by biotechnology are *thyrotropin alfa* (thyrotropin releasing hormone) and *chorio-gonadotropin alfa* (human chorionic gonadotropin).

**Other glycoproteins**

The Greek letter system was also employed for several other glycoproteins obtained by recombinant technology: *dibotermin alfa* and *eptotermin alfa* were selected for bone morphogenic proteins, *ismomultin alfa* was selected for cartilage glycoprotein 39, and *talactoferrin alfa* was selected for human lactoferrin.

**INN for interferons: difficulties with Greek letter identifiers**

When discussing the use of Greek letter identifiers to indicate possible differences in the glycosylation pattern of glycoproteins it is necessary to mention also the case of INN interferon nomenclature, since, in the naming system used for this group of products, the Greek letters have a different meaning. A short review of this peculiar situation is thus necessary.

The INN *interferon* was selected in 1962 and defined as “a protein formed by the interaction of animal cells with viruses capable of conferring on animal cells resistance to virus infection”. The definition corresponded to the level of scientific knowledge at that time. Later developments have shown that this designation also covered substances produced by different types of cells. Three types of interferons were established: leukocyte interferon, fibroblast interferon and immune interferon, each type corresponding to a group of substances.
In 1982, the first INN request for leukocyte interferon produced by recombinant technology was received, followed in 1983 by a request for a fibroblast interferon. During discussions concerning interferon nomenclature, several options were considered. One was to create a stem -feron, but this was rejected due to conflicts with established trademarks for interferon preparations. Another approach was to follow designations currently used in biochemical literature: INF-a (for leukocyte interferons), INF-b (for fibroblast interferons) and INF-l (for immune interferons). The latter approach was provisionally agreed in April 1982 (10) together with the decision to spell out the Greek letter. This approach to interferon nomenclature was finally approved in 1984 (11) when interferon alfa, interferon beta and interferon gamma were selected with appropriate definitions.

The general definition for interferon alfa introduced the possibility of indicating protein variants in the name by hyphenated addition of an Arabic number. In the case of interferon alfa-2 further possibility of distinguishing substances that differ in amino acid composition at specific positions of the amino acid chain could be made by the addition of a small case Latin letter. The system was published in INN list PL52. Using this system interferon alfacon-1 was selected in 1997, peginterferon alfa-2a and peginterferon alfa-2b in 2000 and albinterferon alfa-2b in 2008.

In interferon nomenclature, the Greek letter acquired a separate meaning, as it now identified the type of substance. The nomenclature also uses single letters and numbers, which is against normal INN practice. These differences are due to a decision by the INN Programme to follow the system established by the Interferon Nomenclature Committee [later renamed Nomenclature Committee of the International Society for Interferon and Cytokine Research (ISICR)]. In the 1980s, interferons were considered to be a highly important field of therapeutic progress, and the INN Programme considered that it was preferable to follow biochemical interferon nomenclature extensively used at that time, and thereby ignoring divergence with established rules for creating INN.

**Conclusion**

As shown, the INN Programme has skilfully responded to the demand for selection and naming of new groups of therapeutic products and, in particular, those manufactured by recombinant technology. The INN system has found ways for naming these products either by linkage to customary names for older biological products and/or creating appropriate names for newer members of each series.

The INN Programme has also been challenged with developing appropriate ways for defining products composed of mixtures of closely related components and to gradually upgrade the definitions in response to the enormous progress in elucidation of the structure of biological substances.

This daunting task has required the use of individual approaches while taking into account the specificity of each group. To the extent possible, a common style of coining INN nomenclature has evolved, especially for products with the glycoprotein structure, where the use of Greek letter identifiers is now firmly established and is confirmed by the use of these identifiers in 45 INN to date.

**References**

1. Report of the Twenty-fourth INN Consultation held in 1994. (See also reference 3: items 3.4 and 4.8.)


Safety and Efficacy Issues

Rituximab: multifocal leuko-encephalopathy

Canada — Healthcare professionals have been informed of important new safety information regarding the use of rituximab (Rituxan®) and progressive multifocal leuko-encephalopathy (PML).

Rituximab is authorized for the treatment of B-cell non-Hodgkin lymphoma (NHL), previously untreated B-cell chronic lymphocytic leukaemia (B-CLL), stage B or C, and rheumatoid arthritis in combination with methotrexate to reduce signs and symptoms in adult patients with moderate to severe rheumatoid arthritis who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies.

This is the first case of PML in a patient with rheumatoid arthritis who has not been previously treated with other potent biologic immunomodulating therapies. Previously, two fatal cases of confirmed PML were reported in patients with rheumatoid arthritis treated with rituximab.

Physicians should consider PML in any patient being treated with rituximab who presents with new onset neurologic manifestations (i.e., cognitive impairment, motor deficit, speech and vision impairment) and should be immediately referred for neurological consultation.

PML is a rare, progressive, demyelinating disease of the central nervous system that usually leads to death or severe disability. PML is caused by activation of the JC virus. JC virus resides in latent form in 40–80% of healthy adults. The factors leading to activation of the latent infection are not fully understood. PML has been reported in HIV-positive patients, immunosuppressed cancer patients, transplantation patients and patients with auto-immune diseases, including RA. There are no known interventions that can reliably prevent or adequately treat PML.


Darbepoetin alfa: risk of stroke

United States of America — A study has been published in the New England Journal of Medicine raising safety concerns about darbepoetin alfa and the risk of stroke. Additionally, among patients with a history of cancer, 60 of 188 patients taking darbepoetin alfa died compared to 37 of 160 on placebo.

Anaemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease. Although darbepoetin alfa can effectively increase haemoglobin levels, its effect on clinical outcomes in these patients has been inadequately tested.

The study involved 4038 patients with diabetes, chronic kidney disease, and anaemia. Primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease.
During the study, death or a cardiovascular event occurred in 632 patients assigned to darbepoetin alfa and 602 patients assigned to placebo. Death or end-stage renal disease occurred in 652 patients assigned to darbepoetin alfa and 618 patients assigned to placebo. Fatal or nonfatal stroke occurred in 101 patients assigned to darbepoetin alfa and 53 patients assigned to placebo. There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group.

Furthermore, the use of darbepoetin alfa in patients with diabetes, chronic kidney disease and moderate anaemia who were not undergoing dialysis did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke. For many persons involved in clinical decision making, this risk will outweigh the potential benefits.


**Vigabatrin and movement disorders**

**United Kingdom** — Vigabatrin (Sabril®) is an anti-epileptic indicated, in combination with other anti-epileptics, for the treatment of patients with resistant partial epilepsy (with or without secondary generalization) who have not responded to or who are intolerant of all other appropriate drug combinations. Vigabatrin is also indicated as monotherapy in the treatment of infantile spasms (West syndrome).

Researchers in Finland first raised concerns about a risk of movement disorders (including dystonia, dyskinesia, and hypertonia) and brain abnormalities on MRI (interpreted as cytotoxic oedema) associated with the use of vigabatrin, after they received reports of these adverse drug reactions from a Finnish healthcare professional.

A Europe-wide review completed in July 2009 involving experts in paediatric neurology from the UK assessed the evidence available on this issue, including preclinical data, clinical data, reported cases of adverse drug reactions, and relevant published literature.

Clinical trial data (1) for vigabatrin in infantile spasms provide evidence of brain MRI abnormalities at all doses, but in particular in young infants treated with high doses (≥125 mg/kg/day). These MRI abnormalities were transient, seemed to be dose dependent, and in most patients resolved even if treatment with vigabatrin continued.

The review concluded that it is not possible to correlate the MRI findings with the movement disorders based on the current data. Therefore, the two events of movement disorders and brain MRI abnormalities will be independently described in the updated product information for vigabatrin to reflect these new data. If new movement disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment in consultation with specialist advice.


**Alendronate: risk of low-energy femoral shaft fracture**

**New Zealand** — A number of published case reports have described atypical low energy stress fractures of the subtrochanteric and proximal femoral shaft in patients taking alendronate long-term (1–3). In some cases, the patient experi-
enced prodromal pain in the affected area weeks to months before a complete fracture occurred.

Prescribers should consider the risk of atypical stress fractures in alendronate-treated patients reporting pain of the subtrochanteric or proximal femoral shaft. It is important to note that the reported alendronate-associated fractures were frequently bilateral; therefore the contralateral femur should be examined if a fracture is suspected.

Factors which may increase the risk of fractures include: vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, and chronic alcohol abuse.

It is important to note that atypical stress fractures have also been reported in patients not taking bisphosphonates. In addition, it is possible that other bisphosphonates may be associated with an increased risk of atypical stress fractures. Medsafe advises that the interruption of bisphosphonate therapy in patients with atypical stress fractures should only be considered following an individual risk-benefit assessment.

References


**Ceftriaxone and calcium containing solutions**

**Canada** — Healthcare professionals have been informed of updated prescribing information for ceftriaxone when used with calcium-containing solutions via the intravenous (IV) route. This new safety information is based on the results of two recent in vitro studies that showed an increased risk of ceftriaxone-calcium precipitates in neonatal plasma.

The following are new recommendations:

- Ceftriaxone is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.
- In patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.
- Diluents containing calcium, such as Ringer solution or Hartmann solution, are not to be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.

Ceftriaxone is a long-acting broad spectrum cephalosporin antibiotic for paren-
teral use. Ceftriaxone is indicated for the
treatment of lower respiratory tract
infections, urinary tract infections, bac-
terial septicaemia, skin and skin structure
infections, bone and joint infections, intra-
abdominal infections, and meningitis
when caused by susceptible organisms.
Ceftriaxone is also indicated for uncompli-
cated gonorrhoea and for prophylaxis of
patients undergoing certain surgical
procedures.

Reference: Health Advisory dated 15 October
2009 at http://hc-sc.gc.ca/dhp-mps/medeff/
advisories-avis/prof/_2009/rituxan_5_hpc-cps-
eng.php

Etravirine: severe skin and
hypersensitivity reactions

Canada — Healthcare professionals
have been informed of important safety
information regarding severe skin reac-
tions in patients receiving combination
therapy including etravirine (Inten
cence®) tablets. Specifically, there have been
postmarketing reports of severe hyper-
sensitivity reactions sometimes accompa-
nied by hepatic failure, and a fatality due
to toxic epidermal necrolysis.

Severe, potentially life-threatening and
fatal skin reactions have been reported.
These include cases of Stevens-Johnson
syndrome, toxic epidermal necrolysis and
erythema multiforme. Hypersensitivity
reactions were characterized by rash,
constitutional findings, and sometimes
organ dysfunction, including hepatic
failure.

Discontinue etravirine immediately if
signs or symptoms of severe skin reac-
tions or hypersensitivity reactions develop
(including severe rash or rash accompa-
nied by fever, general malaise, fatigue,
muscle or joint aches, blisters, oral
lesions, conjunctivitis, facial oedema,
hepatitis, eosinophilia). Clinical status
including liver transaminases should be
monitored and appropriate therapy
initiated. Delay in stopping etravirine
treatment after the onset of severe rash
may result in a life-threatening reaction.

Cases within clinical and postmarketing
experience illustrate the importance of
vigilance and familiarity with the signs
and symptoms of severe skin rash and
hypersensitivity reactions. In Phase III
clinical trials, Grade 3 and 4 rashes were
reported in 1.3 % of subjects receiving
etravirine compared to 0.2 % of placebo
subjects. A total of 2 % of HIV-1-infected
patients receiving etravirine discontinued
from Phase III trials due to rash. Rash
occurred most commonly during the first
six weeks of therapy.

Reference: Communication dated 15 October
2009 from Janssen-Ortho Inc. at http://hc-
sc.gc.ca/dhp-mps/medeff/advisories-avis/
prof/_2009/rituxan_5_hpc-cps-eng.php

Oseltamivir phosphate:
dosing risk

Canada — The manufacturer of oselta-
mivir (Tamiflu®) has informed healthcare
professionals of important dosing and
administration information regarding
powder for oral suspension.

Oseltamivir is a viral neuraminidase
inhibitor authorized for use in the treat-
ment and prevention of uncomplicated
acute illness due to influenza infection in
adults and children above one year of
age who have been symptomatic for no
more than two days or have come in
close contact with an infected individual.
Health Canada has also issued an Interim
Order in July 2009 expanding use of
Tamiflu® as a treatment or prophylaxis for
children less than one year of age for
infection caused by the pandemic H1N1
2009 virus.

When dispensing commercially manufac-
tured oseltamivir powder for oral suspen-
sion (12 mg/mL), pharmacists should
ensure that the units of measure on the
prescription instructions match the dosing
device provided (e.g., a device graduated in mg for a prescription in mg).


Safety signal: hyponatraemia

New Zealand — The Centre for Adverse Reactions Monitoring (CARM) has examined recent reports of hyponatraemia in its database.

Hyponatraemia, defined as plasma sodium < 135 mmol/L, is caused by a range of medicines and clinical conditions. Medicine-related hyponatraemia occurs most often in the elderly early in the course of treatment. The mechanism is most often a syndrome of inappropriate antidiuretic hormone secretion or renal loss.

Medicines most often implicated in recent reports to CARM are selective serotonin or noradrenaline reuptake inhibitors (SSRIs/SNRIs) and thiazide diuretics. Other medicines reported more than once in 2007 and 2008 were anticancer agents, proton pump inhibitors, sodium valproate and ACE inhibitor/diuretic combinations. Carbamazepine has also been frequently implicated in the database.

Serious hyponatraemia (plasma sodium < 120 mmol/L) can lead to confusion, convulsions and serious neurological damage. Examination of serious symptomatic reports to CARM revealed that in most cases more than one hyponatraemic medicine was implicated. The reports that CARM has received support current advice that plasma sodium should be measured shortly after starting potentially hyponatraemic medicines, especially SSRIs or diuretics. Measurements should be repeated both before and after adding another hyponatraemic medicine. If there is mild persistent hyponatraemia the addition of further medicines or the development of clinical conditions that can decrease plasma sodium may lead to a more profound and symptomatic reaction.


Clopidogrel and omeprazole: reduced effectiveness

United States of America — The Food and Drug Administration (FDA) is alerting healthcare professionals to new safety information concerning an interaction between clopidogrel (Plavix®), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC®), a proton pump inhibitor (PPI). New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole.

Omeprazole inhibits the drug metabolizing enzyme CYP2C19 which is responsible for the conversion of clopidogrel into its active metabolite. New studies compared the active metabolite and its effect on platelets in clopidogrel plus omeprazole versus clopidogrel alone. The effect of clopidogrel on platelets was reduced by as much as 47% in people receiving clopidogrel and omeprazole together.

Other drugs that are potent inhibitors of the CYP2C19 enzyme would be expected to have a similar effect and should be avoided in combination with clopidogrel. These include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine. Since the level of inhibition among other PPIs varies, it is unknown to what extent other PPIs may interfere with clopidogrel. However, esomeprazole, a PPI that is a component of omeprazole,
inhibits CYP2C19 and should also be avoided in combination with clopidogrel.

Separating the dose of clopidogrel and omeprazole in time will not reduce drug interaction. Other drugs to avoid in combination with clopidogrel because they may have a similar interaction include: esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.


Bisphosphonates: osteonecrosis of the jaw

United Kingdom — The risk of osteonecrosis of the jaw is greater for patients receiving intravenous bisphosphonates for cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget disease. All patients with cancer should have a dental check-up before bisphosphonate treatment. During treatment, patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling

Individual bisphosphonates with different indications can be used for:

• Prophylaxis and treatment of osteoporosis.
• Treatment of Paget disease.
• As a component of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma.

A Europe-wide review has been completed on the risk of osteonecrosis of the jaw (ONJ) in association with the use of bisphosphonates. The review included data from the published literature, data provided by Marketing Authorization Holders (experimental and preclinical studies, clinical trials, and postmarketing reports) and guidelines. The review also incorporated advice from a group of experts representing all areas of medicine where bisphosphonates are used, dentistry and bone surgery, and representatives of patient organizations.

The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) reached conclusions on four main areas: definition and diagnosis of ONJ related to bisphosphonates, possible underlying pathophysiological mechanism(s), risk stratification, and risk minimization.

A patient may be considered to have ONJ related to bisphosphonates if all of the following three characteristics are present:

• Exposed or necrotic bone in the maxillofacial region that has persisted for more than 8 weeks.
• No history of irradiation of the jaw.
• Current or previous treatment with a bisphosphonate.


Intravenous promethazine: serious tissue injuries

New Zealand — Promethazine injection is highly caustic to the intima of blood vessels and surrounding tissues (1). Reports from the United States describe serious tissue reactions including thrombosis, nerve damage, tissue necrosis and gangrene in patients who have received intravenous promethazine. In rare cases, surgical intervention such as skin graft, fasciectomy or amputation has been
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required (1, 2). In New Zealand, promethazine injection is approved for the treatment of vomiting, allergic reactions (including anaphylaxis) and to induce sedation.

After reviewing the published literature, assessing New Zealand case reports, and consulting with healthcare professionals, Medsafe has concluded that there remains a clinical need for intravenous promethazine in New Zealand. However, Medsafe recommends that intravenous promethazine should only be used if the benefits clearly outweigh the risks in each patient. This may include emergency situations (such as treatment of anaphylaxis) or situations where intramuscular or oral administration is contraindicated.

To maximize safe use, Medsafe has offered the following advice:

• Deep intramuscular injection is the preferred route of administration of promethazine injection.

• Promethazine must not be administered subcutaneously or intra-arterially.

• An alternative medicine should be considered if intravenous administration is required.

• Promethazine should be administered through large patent veins. Veins in the hand and wrist should be avoided if possible (1).

• If intravenous administration is required, the maximum recommended concentration is 25 mg/mL and the maximum recommended rate of administration is 25 mg/minute. Further dilution and administration over 10–15 minutes may reduce the risks even further (1).

• The injection should be stopped immediately if pain or a burning sensation occurs.

• Patients should be advised to seek medical assistance if pain, a burning sensation, swelling or blistering occurs at any time after the administration of intravenous promethazine.

The New Zealand data sheet for promethazine is currently being updated in line with this advice (4).

References

Cyproterone: risk of meningiomas

United Kingdom — Cyproterone acetate is a derivative of progesterone, and has progestagenic, antiandrogenic, and antigonadotrophic effects. High-dose preparations available in the UK include Cyprostat-50® and Cyprostat-100®, which are indicated for use in the treatment of prostate cancer. Cyproterone acetate is also available as Androcur-50®, which is indicated for the control of libido in men with severe hypersexuality or sexual deviation (or both). In some EU countries, Androcur-50® is used for the treatment of androgenization in women.

Lower-dose cyproterone acetate is available for use in women as co-cyprindiol (Dianette®) in combination with 35 micrograms ethinylestradiol for the treatment of severe acne that is refractory to prolonged antibiotic therapy, and for moderately severe hirsutism.
Meningiomas are the most common intracranial tumours, with an annual incidence of six per 100 000 in the general population. Multiple meningiomas account for approximately 1–10 % of all cases. Though histologically benign, they can have serious consequences. The potential role of sex hormones in the development of meningiomas has been postulated: approximately 70% of meningiomas express progesterone receptors and about 30% express oestrogen receptors (1). The occurrence of (multiple) meningiomas has been reported in association with longer-term use (years) of cyproterone acetate at doses of 25 mg/day or higher.

Up to September 2009, 36 cases of meningioma, of which 19 described multiple meningioma, have been reported worldwide in association with high-dose cyproterone acetate. Nine cases were discussed in a published case series, (2) and 27 cases are unpublished case reports. Duration of treatment with cyproterone acetate ranged from 4 to 27 years and in all but one case it was prescribed at doses higher than 25 mg per day. Thirty-one of the cases were from France (which compared with other countries has extensive use of high-dose cyproterone acetate). None of the reported cases had a fatal outcome.

Advice for healthcare professionals:

- Patients with existing meningioma or a history of meningioma must not be prescribed cyproterone acetate at doses of 25 mg per day or higher.

- This advice does not apply to medicines that contain low-dose cyproterone acetate such as co-cyprindiol (Dianette®).

References


Gadolinium-containing contrast agents

European Union — The European Medicines Agency (EMEA) has adopted a set of recommendations aimed at minimizing the risk of nephrogenic systemic fibrosis (NSF) with gadolinium-containing contrast agents in patients at risk of developing the condition.

Gadolinium-containing contrast agents are used in patients undergoing magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) scans. The Agency’s Committee for Medicinal Products for Human Use (CHMP) reviewed these agents because of the association between the use of gadolinium-containing contrast agents and NSF, a rare, serious and sometimes life-threatening condition that is characterized by formation of connective tissues in the skin, joints, muscles and internal organs, in patients with severe kidney problems.

Based on currently available data, and with risk minimization measures in place, the CHMP considers that the balance of benefits and risks of these agents is acceptable.

References

Cesium chloride: cardiac risks

Canada — Use of stable cesium compounds (non-radioactive form of cesium salts, primarily cesium chloride) may pose a risk of life-threatening heart problems. Cesium, primarily in the form of cesium chloride, is promoted on the Internet to prevent various forms of cancer and as a self-administered cancer treatment.

While use of radioactive cesium in radiation treatment for cancer is authorized in Canada, Health Canada has not authorized any health products containing stable cesium compounds for oral or intravenous use, including cesium chloride. However, numerous Internet sites promote the oral use of cesium chloride as an alternative to chemotherapy.

Health Canada is aware of three cases of serious cardiac arrhythmias (irregular heartbeat) in Canadian consumers who took oral cesium chloride. These patients also experienced decreased or loss of consciousness.

Reference: Medeffect Health Advisory, 10 September 2009 at http://hc-sc.gc.ca

Washout or taper when switching antidepressants

Australia — Antidepressants are indicated for the treatment of major depressive disorders and may be indicated also for anxiety disorders, obsessive compulsive disorder, premenstrual dysphoric disorder and/or chronic pain. They include:

- Selective serotonin reuptake inhibitors (SSRI)
- Tricyclic antidepressants
- Noradrenergic and 5HT1-serotonergic receptor agonists
- Serotonin and noradrenaline reuptake inhibitors (SNRI)
- Noradrenaline reuptake inhibitors
- St John’s Wort (Hypericum perforatum)

These drugs have various mechanisms of action but they share a number of similar properties which may predispose individuals to suffer from adverse effects due to interactions when switching antidepressants even if they are of the same class.

One of the more serious possible outcomes is the development of serotonin syndrome – a potentially life threatening condition caused by the accumulation of serotonin in the central nervous system (1–4). Serotonin syndrome is a potential adverse effect of all antidepressants and it can occur when treatment is not interrupted as well as during switching, particularly in the elderly (1,3,4).

The risk of serotonin syndrome increases if there is simultaneous exposure to more than one drug that can cause this syndrome. The Therapeutic Goods Administration (TGA) has received several reports describing this situation, some of which include life-threatening outcomes.

To avoid the possibility of an interaction, an appropriate washout period is required to substantially clear the first antidepressant from the body before the second is introduced. Unfortunately, no simple advice on the appropriate washout period can be given. In general, a drug is not completely cleared until a period equivalent to 4–5 half lives has elapsed after a
drug is ceased. The half life of antidepressants varies substantially from about two hours for citalopram and moclobemide and up to six days or more for fluoxetine, while the effect of irreversible MAOIs such as phenelzine can persist for several weeks after the drug has been ceased.

There are no set guidelines on switching amongst antidepressants and factors that should be considered will vary depending on the properties of the antidepressants and the patient's situation including the duration of time the patient has been on the first antidepressant, patient age, other medications and other health issues (5,6).

Useful information on antidepressant-free intervals when changing from one antidepressant to another is available in the Therapeutic Guidelines — Psychotropic Medicines and in the Australian Medicines Handbook (5,6).

Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 28, Number 5, October 2009.

References


Zanamivir inhalation powder must not be nebulized

Singapore — Healthcare professionals have been informed of the death of a patient with influenza who received zanamivir (Relenza®) inhalation powder which was solubilized and administered by mechanical ventilation. The death was attributed to obstruction of the ventilator which could have been due to lactose in the formulation causing stickiness when the powder is mixed with the nebulizing solution.

The manufacturer wishes to highlight to healthcare professionals that Relenza® Inhalation Powder is not intended for reconstitution in any liquid formulation and is not recommended for use in any nebulizer or mechanical ventilator. Zanamivir for nebulization has not been approved by any regulatory authority and the safety, effectiveness and stability of zanamivir use by nebulization have not been established.


Pandemrix®: risk of fever

European Union — The European Medicines Agency (EMEA) is warning that young children may experience fever after their second dose of the pandemic influenza vaccine Pandemrix®. Prescribers and parents should monitor the temperature of the vaccinated child and, if necessary, take measures to lower the fever (e.g., giving an antipyretic such as paracetamol). However, the Agency noted that the second dose increases the immune response against pandemic influenza.

The Agency has recommended that this information be included in the prescribing
information, and be taken into consideration when deciding whether to give a second dose to children.


Weekly pandemic pharmacovigilance updates

European Union — The European Medicines Agency (EMEA) has published the first in a series of weekly pandemic pharmacovigilance updates.

These weekly bulletins will provide information on adverse reactions reported after the use of centrally authorized pandemic influenza vaccines and antivirals in the European Union and complement the information the Agency has been publishing regularly on the development and approval of medicines for use during the pandemic.

This information will support European institutions and Member States in their communications, and provide an additional resource when recommending the use of vaccines and antiviral treatments.

The information on adverse reactions in the update comes from EudraVigilance, the central European database on adverse reactions, managed by the Agency.

Biomedicines and Vaccines

International biological standards: 2009 update

Innovation in biological medicines is occurring in more countries than ever before. In addition, the supply chain for biological medicines is increasingly complex and international in nature. Despite technological advances, controlling the quality, safety and efficacy of biologicals remains difficult and highly specialized. Therefore, strengthening biological standardization and its implementation, in particular in emerging economies, remains a fundamental function for WHO. The aim is to provide tools that will translate into appropriate oversight of new biologicals of potential public health benefit or oversight of biological components in the supply chain. Developing standards for quality, and associated reference materials through its Expert Committees and Expert Advisory Panels is a key priority for WHO.

The Expert Committee on Biological Standardization advises WHO on international biological standardization and key developments affecting the quality, safety and efficacy of vaccines, biological therapeutics, blood products and biological diagnostics. The Expert Committee met in Geneva from 19–23 October 2009 to enable WHO to fulfil one of its constitutional responsibilities to “Develop, establish and promote international standards for biological products.”

During its meeting, the Expert Committee established new WHO guidelines on the regulatory evaluation of “similar biotherapeutic medicines”. These products have a successful record in treating many life-threatening and chronic diseases. However, patients — particularly in developing countries — have limited access to such medicines. The expiration of patents and/or data protection for the first major group of innovative biotherapeutics is ushering in an era of products “similar” to the originals, with the potential to significantly enhance accessibility. The guidance developed by WHO on appropriate regulation of this new class of products is in response to requests from many developing countries.

Revised WHO recommendations for the production and control of live attenuated influenza vaccine were established by the Expert Committee. The purpose of these recommendations is to provide vaccine manufacturers and national regulatory authorities with guidance that can be applied in developing specific processes for the production and control of human, live attenuated influenza vaccines. These recommendations are also intended to provide guidance on the nonclinical and clinical evaluation of influenza vaccines and apply to the production and control of influenza vaccines using embryonated hen’s eggs as substrates. The future possibility to produce human, live attenuated influenza vaccines using cell cultures as substrates is anticipated and, therefore, guidance is also provided for this eventuality. The recommendations with possible modifications apply to human, live attenuated influenza vaccines produced with seasonal vaccine strains for use during the interpandemic period as well as vaccines produced with strains for use during pandemics.

Infections caused by Streptococcus pneumoniae are responsible for substantial morbidity and mortality, particularly in the very young and elderly. Pneumococci are grouped into many serotypes (~ 91)
on the basis of their chemically and serologically distinct capsular polysaccharides. Certain serotypes are much more likely than others to be associated with clinically apparent infections, to cause severe invasive infections and to acquire resistance to one or more classes of antibacterial agents. The development of pneumococcal conjugate vaccines in which each of the selected bacterial capsular polysaccharides is coupled with a protein carrier molecule has been a major advance in the prevention of invasive pneumococcal disease (IPD).

Since 2006, WHO has recommended that all countries should incorporate pneumococcal conjugate vaccines in routine immunization schedules for children less than 2 years of age with prioritization of their introduction in countries with high child mortality rates and/or high rates of HIV infection. A 7-valent pneumococcal conjugate vaccine (7vPnC) that employs CRM197 as the carrier protein for all seven serotypes was the first to be developed. This vaccine was licensed in the USA in 2000 and subsequently has become available in approximately 90 countries worldwide. Pneumococcal conjugate vaccines that contain three or six serotypes in addition to those in the 7vPnC vaccine have recently become available in some countries. The 10-valent vaccine includes tetanus toxoid, diphtheria toxoid or a novel protein derived from nontypable Haemophilus influenzae (protein D) as the carrier proteins while the 13-valent vaccine uses only CRM197 as the carrier protein.

WHO recommendations for pneumococcal conjugate vaccine production and control were first established in 2003 (1). Since the 7vPnC vaccine was already approved in many countries, it was considered unethical to assess the protective efficacy of future pneumococcal conjugate vaccines in infants and toddlers in comparison to an unvaccinated control group. The recommendations discussed the design of immunogenicity studies to support licensure of new pneumococcal conjugate vaccines (including those containing conjugated capsular polysaccharides of serotypes additional to those in the 7vPnC vaccine) intended to prevent IPD and for administration to children aged less than 2 years. It was considered essential that the immunogenicity studies with a new pneumococcal conjugate vaccine should provide a link back to the vaccine efficacy against IPD that was demonstrated for the 7vPnC vaccine.

Therefore, it was recommended that immune responses to each serotype in the 7vPnC vaccine that is also included in a new pneumococcal conjugate vaccine should be directly compared in randomized clinical studies and that the primary comparison of immune responses should be based on serotype-specific IgG antibody concentrations measured by enzyme-linked immuno-sorbant assay (ELISA). In order to facilitate these comparisons a WHO reference ELISA assay was established that includes pre-adsorption of sera with pneumococcal C polysaccharide (C-PS) and serotype 22F polysaccharide.

Prompted by issues raised during the development of newer pneumococcal conjugate vaccines since the publication of the WHO 2003 recommendations (1), WHO held a consultation in 2008 to consider new scientific evidence and to discuss the need to provide revised guidance for manufacturers and licensing authorities. The Expert Committee on Biological Standardization has established a revised document that has been developed to take into account the most recent developments (2).

The Expert Committee also reviewed proposals to establish 24 new or replacement reference preparations as WHO

Among the proposals, a reference panel covering the most prevalent hepatitis B genotypes worldwide was adopted to facilitate improvement of the quality of hepatitis B diagnostic devices and the traceability of test results between countries. Other reference materials for the control of the potency of blood products and the diagnosis of genetic diseases were also adopted this year. These preparations are expected to be widely used by regulators, manufacturers and blood establishments worldwide and will support international regulations for blood products and the safety of blood products (2).

References


International Harmonization

ICH Implementation: Quality Working Groups

In Brussels 2003, a new quality vision was agreed by parties of the International Conference on Harmonization (ICH) (1). This emphasized a risk and science-based approach to pharmaceuticals in an adequately implemented quality system. As a consequence, the guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) were drafted.

These concepts and principles depart from the traditional approaches to quality guidance, mainly based on end-product testing. Since it is important that proper implementation is strengthened by clarifying, explaining and removing ambiguities and uncertainties, an ICH Implementation Working Group (IWG) on ICH Q8, Q9 and Q10 has been formed and met during the recent ICH meeting held in Yokohama in June 2009. The IWG is drawn from the six member parties of the ICH: industry and medicines regulatory authorities of the European Union, Japan and United States of America (up to three experts per party). Observers to the ICH are allowed one expert and Interested Parties one expert each. The IWGs focus on the following issues:

Technical issues and related documentation

- Common understanding of terminology.
- Interrelationship between Q8, Q9 and Q10.
- Applicability to both review and inspection.
- Final status after partial implementation is established (level of details in the dossier).

Additional implementation issues

- Influence on existing ICH guidelines.

Communication and training

- Questions and Answers, ICH briefing packs.
- External collaboration.
- Workshops.

The aim of the ICH Quality Implementation Working Group (Q-IWG) is to provide enhanced harmonized implementation training to industry and regulators in the three ICH regions. In addition, the group can offer opportunities to train colleagues in non-ICH regions. The newly designed standards workshop is planned to be conducted by those ICH experts who developed the ICH Q8, Q9 and Q10 guidelines and members of the ICH. These are intended to be the only workshops reviewed and referenced by the Q-IWG and will be conducted by the same faculty in all three ICH regions.

Training will cover the integrated use of ICH Q8, Q9 and Q10 guidelines and Q&A (question and answers) across the product life-cycle, from development to manufacturing and commercialization. Unlike other conferences and workshops on these topics, training will present a case study throughout the entire life-cycle from development to manufacturing and commercialization. Regulatory assessment and GMP inspection implementation aspects will be discussed. Furthermore,
learning opportunities will be provided for participants to practise in small groups the necessary skills for implementation of the guidelines.

Workshop deliverables will include materials to support understanding of integrated use of the concepts described in ICH Q8, Q9 and Q10 guidelines. These materials will be used by both regulators and industry to implement the three guidelines in their organizations. If the ICH Global Cooperation Group (GCG) is organizing workshops outside an ICH region the Q-IWG will provide structure and content of the workshops. If WHO is organizing workshops, the Q-IWG can provide support.

The IWG is also looking into the availability of illustrative examples and case studies relevant to harmonized and consistent implementation. The initial goal was to reference existing material and develop examples and position papers.

A survey of conferences, publications and presentations has been carried out over the past six months. As a result, a list of relevant topics and activities was identified together with an analysis of specific needs for additional work. The review demonstrated that there is a large amount of publications and workshops available covering ICH Q 8, Q9 and Q 10. The final consensus was that the Q-IWG should initiate, encourage and collaborate in the development of articles consistent with Q8, Q9, Q10 guidelines and the recently developed Questions and Answers.


ICH Pharmacopoeial Discussion Group


Discussion focused on Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions. The ICH Q4B guideline was finalized (Step 4) on 1 November 2007.
This document describes a process for the evaluation and recommendation by the Q4B Expert Working Group (EWG) of selected pharmacopoeial texts to facilitate their recognition by regulatory authorities for use as interchangeable texts in the ICH regions. Following favourable evaluations, ICH will issue topic-specific annexes with information about these texts and their implementation (the Q4B Outcomes). Implementation of the Q4B annexes is intended to avoid redundant testing by industry.

Harmonization has been achieved by the PDG on nine of the ten General Chapters identified by the ICH Q6A Guideline. From those, eight have been evaluated in addition to two newly harmonized texts by the ICH Q4B Working Group as follows:

- Residue on Ignition/Sulphated Ash General Chapter (ICH Q4B Annex 1)
- Test for Extractable Volume of Parenteral Preparations General Chapter (ICH Q4B Annex 2)
- Test for Particulate Contamination: Sub-Visible Particles General Chapter (ICH Q4B Annex 3, includes English JP text)
- Microbial Enumeration Tests General Chapter (ICH Q4B Annex 4A)
- Tests for Specified Micro-organisms General Chapter (ICH Q4B Annex 4B)
- Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter (ICH Q4B Annex 4C)
- Disintegration Test (ICH Q4B Annex 5, includes English JP text)
- Uniformity of Dosage Units General Chapter (ICH Q4B Annex 6)
- Dissolution Test General Chapter (ICH Q4B Annex 7)
- Sterility Test General Chapter (ICH Q4B Annex 8, includes English JP text)
- Tablet Friability General Chapter (ICH Q4B Annex 9)
- Polyacrylamide Gel Electrophoresis General Chapter (ICH Q4B Annex 10).

ICH Q4B Annexes 1–5 and 8 have been signed off as ICH step 4 documents. Annexes 6 and 7 are pending feedback from PDG. Annex 9 and 10 are at the Step 2 stage.

PDG is working on the following general chapters within the harmonization process and they will be submitted for ICH Q4B evaluation upon final PDG sign off as being harmonized:

- Bulk and Tapped Density of Powders
- Analytical Sieving
- Capillary Electrophoresis
- Bacterial Endotoxin Test
- Colour Test (new method being reviewed).

Moreover, 26 of the 34 General Chapters and 40 of the 63 excipient monographs have been harmonized by PDG. In the course of indicating the harmonization statement in the three ICH pharmacopoeias, PDG has reviewed seven excipient monograph texts and identified typical discrepancies. A path to resolution has also been agreed that will facilitate further harmonization projects.

The possible implementation of these harmonized texts within the revision process of The *International Pharmacopoeia* will be reviewed by the forthcoming Forty-fourth WHO Expert Committee on Specifications for Pharmaceutical Preparations.
Background: The International Pharmacopoeia

The International Pharmacopoeia comprises a collection of quality specifications for pharmaceutical substances (active ingredients and excipients) and dosage forms together with supporting general methods of analysis intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements. The International Pharmacopoeia, or any part of it, may have legal status whenever a national or regional authority expressly introduces it into appropriate legislation.

Activities related to The International Pharmacopoeia are an essential element in the overall quality control and assurance of pharmaceuticals contributing to the safety and efficacy of medicines. The selection of monographs for inclusion in The International Pharmacopoeia recognizes the needs of specific disease programmes and the essential medicines nominated under these programmes; it is based primarily on those substances included in the current WHO Model List of Essential Medicines.

Work on The International Pharmacopoeia is carried out in collaboration with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and with other specialists. The process involves consultation of and input from WHO Member States and drug regulatory authorities, WHO Collaborating Centres and national drug quality control laboratories in all six WHO regions, standard-setting organizations and parties, including regional and national pharmacopoeias and with manufacturers around the world. Clearly defined steps are followed in the development of new monographs.
Prequalification of Medicines Programme

Prequalification of quality control laboratories

Increased availability and supply of good quality essential medicines for countries is an important component of the United Nations Millennium Development Goals. Unfortunately, several international funders and suppliers of essential medicines have faced difficulty in monitoring the quality of supplies in countries because of a lack of fully operational medicines quality control laboratories.

Given this situation, international donors and suppliers often preferred to have local medicine samples sent for analysis in quality control laboratories situated in Europe or North America. Such practices do not support sustainable development goals and are counter productive in building national capacity.

In collaboration with UNAIDS, UNICEF, UNFPA, the Global Fund, UNITAID, with support from the World Bank, WHO has set up a process to prequalify quality control laboratories that meet recommended international norms and standards for the analysis of medicines prequalified or being considered for prequalification by WHO.

As a first step, WHO has invited quality control laboratories in Africa to take part in the process. Laboratories were chosen based on their commitment to provide testing of pharmaceutical products for HIV/AIDS, tuberculosis and malaria (1). In September 2007, the scope of the procedure was extended and currently invitations are open to quality control laboratories in any region worldwide. WHO manages the assessment process and identifies which quality control laboratories should be given priority based on need.

Participation in the prequalification process is described in Procedures for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (2). For the time being, applying for and participation in the prequalification procedure is free of charge. However, the procedure also enables WHO to charge for the assessment of laboratories on a cost-recovery basis if the prequalification process is no longer funded by donors.

WHO assesses quality control laboratories through evaluation of preliminary information submitted by a laboratory and on-site inspection to assess compliance with the WHO guidelines on Good Practices for National Pharmaceutical Control Laboratories (3) and Good Manufacturing Practices (4). These and other related guidelines are published on the Prequalification Programme’s web site (5). International Standard Organization (ISO) certification (ISO/IEC 17025) is also encouraged. If assessment demonstrates that a laboratory meets WHO recommended standards, it is included in the official List of WHO Prequalified Quality Control Laboratories that is considered acceptable for use by United Nations agencies or other interested parties (6).

Once a laboratory is included in the WHO List of Prequalified Quality Control Laboratories, ongoing monitoring of its activities is performed. This includes re-inspection at regular intervals, evaluation of results from participation in an appropriate proficiency testing scheme, and monitoring and investigation of any
complaints concerning results of analysis or other service provided by the listed laboratories. To facilitate monitoring, each prequalified laboratory is requested to submit a brief annual report on its activities. An outline of the expected content of an annual report is available on the WHO web site (7).

A laboratory will be removed from the list if it is found that it no longer complies with the specified standards.

Update on progress
As of October 2009, eleven laboratories have been prequalified by WHO. Five prequalified laboratories are located in the WHO Africa Region, three in the Western Pacific Region and one in each of the three regions: Eastern Mediterranean Region, Europe Region and South-East Asia Region. Apart from these eleven prequalified laboratories, there are twenty-four quality control laboratories participating in the procedure (See Table

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Number of prequalified laboratories</th>
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<tbody>
<tr>
<td>Algeria</td>
<td>Africa</td>
<td>1</td>
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<td>France</td>
<td>Europe</td>
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<td>India</td>
<td>South-East Asia</td>
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<td>Kenya</td>
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<td>Morocco</td>
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<td>Singapore</td>
<td>Western Pacific</td>
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<td>South Africa</td>
<td>Africa</td>
<td>2</td>
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<tr>
<td>Vietnam</td>
<td>Western Pacific</td>
<td>1</td>
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</tbody>
</table>

Table 1. Prequalification of quality control laboratories

![Graph showing prequalified and participating QCLs from 2004 to Sep-09]
The majority of participating laboratories (26 of 35) are national quality control laboratories.

As part of the capacity building component of the WHO Prequalification of Medicines Programme, national quality control laboratories participating in the prequalification procedure are provided, if needed, with technical assistance in the form of a pre-audit or 1–3 week visit of an expert to the laboratory. The Programme also organizes training for national quality control laboratories and laboratories providing testing services to the government in the respective country.

**Inspections**
An inspection team is composed of a WHO prequalification inspector and a co-inspector appointed by WHO from a member inspectorate of the Pharmaceutical Inspection Cooperation Scheme (PIC/S). An inspector (or inspectors) from the national medicines regulatory authority of the country in which the laboratory is located is invited to participate as an observer. Prequalified laboratories are re-inspected on a regular basis, usually every two to three years. Fourteen quality control laboratory inspections were carried out between March 2004 and September 2009.

Over the years, the main observations of non-compliance during inspections include the following:

1. System of reference substances was insufficient in that:

**Figure 1. Cumulative number of critical observations from 14 inspections**

<table>
<thead>
<tr>
<th>Criteria*</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>1. Organization and management</td>
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<td>2. Quality system</td>
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<td>3. Control of documents</td>
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<td>4. Records</td>
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<td>5. Data processing equipment</td>
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<td>6. Personnel</td>
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<td>9. Specifications archiv</td>
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<td>10. Reagents</td>
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<td>11. Reference materials</td>
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<td>12. Calibration, validation &amp; verification of equipment, instruments &amp; other devices</td>
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<td>13. Traceability</td>
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<td>14. Incoming samples</td>
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<td>15. Analytical worksheet</td>
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<td>16. Testing</td>
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<td>17. Evaluation of test results</td>
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<td>18. Retained samples</td>
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<td>19. Safety</td>
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* Refers to sections of WHO Good Practices for National Pharmaceutical Control Laboratories
Figure 2. Cumulative number of major observations from 14 inspections

- Authorized written standard operating procedures for handling reference substances were not available, i.e.,
  - packing of working reference substances
  - labelling of working reference substances
  - acceptance criteria for working substances
- Inappropriate labelling of working standards
- Use of reference substances was not documented

2. Stocks of reagents and retention samples were not maintained under appropriate storage conditions.

3. The training system was insufficient in that:
   - Authorized written standard operating procedures for training were unavailable.
   - Training was not appropriately documented and assessed.

4. Authorized written standard operating procedures for internal audits were not available.

* Refers to sections of WHO Good Practices for National Pharmaceutical Control Laboratories
5. Reagents were not managed properly in that:

- Labels of some reagents did not specify shelf-life.
- Certificates of analysis were not available for all reagents.
- Reagents were not properly labelled.

6. Responsibilities, competencies and functions were not clearly defined in current job descriptions.

7. Computer software developed by the users was not appropriately validated or verified. Procedures were not established and implemented for protecting the integrity of data.

8. Authorized written standard operating procedures for the calibration of critical equipment were not available, i.e., HPLC, GC, dissolution and disintegration instruments. Equipment calibration and maintenance schedules were not available. Equipment not regularly qualified; IQ, OQ and prequalification protocols/reports were not available.

9. Validation of microbiological laboratory autoclave was not conducted in accordance with current guidelines.

10. Pharmacopoeial test methods were not verified.

11. Out-of-specifications were not recorded and handled properly.

References


Pharmacovigilance Focus

A/H1N1 vaccination safety: PaniFlow® surveillance tool

PaniFlow® is a new software tool for reporting adverse events following immunization which is now being offered free to a number of countries in a joint Uppsala Monitoring Centre (UMC)/ World Health Organization (WHO) initiative.

In response to A/H1N1 pandemic influenza and plans for vaccination of large populations, safety issues are a prime concern. Most developed countries already have well-established systems for monitoring the safety of vaccination programmes and detecting problems.

PaniFlow® is a web-based data management software which allows vaccination programme staff to record all adverse events as they occur from any location with an Internet connection. This ensures continued reporting, even when infrastructure, like regular mail, is disrupted. Cumulative data is immediately available locally, nationally, and to the UMC where international patterns of events can be analysed and shared. Data can also be incorporated into the international WHO Global Individual Case Safety Report database (VigiBase®) managed by UMC. The software has search and analysis tools which permit issues and problems to be examined in all relevant parameters.

Individual countries can quickly detect potential safety problems in their own populations and take remedial action if causality is established. At UMC, the global picture can be rapidly reviewed and the international community alerted when problems are suspected or confirmed.

In an emergency situation, where the priority has been to secure supplies of vaccines and get them widely distributed, safety surveillance can sometimes take second place. As a result of multiple variables and uncertainties only comprehensive monitoring on a global scale can reveal the true, detailed picture of the impact of vaccination on individual patients and on public health. This is important also in a situation where safety concerns have been publicly expressed and/or the credibility of A/H1N1 vaccination challenged.

PaniFlow® is based on VigiFlow®, which is the programme used throughout the world by many members of the WHO Programme for International Drug Monitoring for managing and reporting adverse drug reactions. It is based on the software originally developed jointly by the Swiss national drug regulatory authority, Swissmedic, and UMC for use in Switzerland. Both programmes are uniquely designed to meet the needs of healthcare personnel and serve the interests of patient safety. While some training to use the programmes is needed, their user friendliness has been progressively improved and data entry itself is a simple task.

The first countries being offered free use of PaniFlow® by UMC are: Croatia, Lithuania, Morocco, Serbia, Sierra Leone, Togo and Turkey. All are countries with a track-record of reporting adverse events following immunization and are familiar with using VigiFlow®.

Regulatory Action and News

Influenza vaccines for 2010 southern hemisphere winter

World Health Organization — It is recommended that vaccines for use in the 2010 influenza season (southern hemisphere winter) contain the following:

• an A/California/7/2009 (H1N1)-like virus
• an A/Perth/16/2009 (H3N2)-like virus
• a B/Brisbane/60/2008-like virus.


Romidepsin: approved for cutaneous T-cell lymphoma

United States of America — The Food and Drug Administration (FDA) has approved romidepsin (Istodax®), an injectable, for treatment of patients with cutaneous T-cell lymphoma (CTCL).

Cutaneous T-cell lymphoma is a slow-growing cancer of T-lymphocytes. Most cases start with dry skin, red rash, and severe itching. The skin may develop tumours that can become ulcerated, causing infection. In some cases, CTCL spreads to the blood, lymph nodes, or internal organs. Patients with localized CTCL on the skin are treated with topical agents or phototherapy, but chemotherapy may be used if the cancer advances. Romidepsin interferes with processes required for cell replication.

Romidepsin evaluation was based on two clinical studies involving 167 patients. About 35% of patients in both of the trials experienced tumour responses which lasted a median of 15 months in one study and 11 months in the other study. Six per cent of those studied had complete responses, indicating no apparent evidence of the tumour on physical, laboratory, and X-ray examination.

Common side effects include nausea, fatigue, infections, vomiting, decreased appetite, decreased red blood cell count, decreased platelet count, and decreases in the components of white blood cells.

Romidepsin may cause changes in an electrocardiogram (ECG). Periodic blood tests should be carried out to monitor electrolytes, and periodic ECG monitoring should be considered in patients at risk for certain heart rhythm abnormalities. Romidepsin may harm the fetus and women should not become pregnant while taking the drug.


Orciprenaline sulphate: withdrawal

United Kingdom — Orciprenaline sulphate (Alupent®) is to be withdrawn over the next year because a review has concluded that the benefit-risk profile is unfavourable. Patients who require a liquid oral formulation of a β-agonist should be switched to a more-selective short-acting β2-agonist such as salbutamol or terbutaline.

Orciprenaline sulphate (Alupent®) is a non-specific β-agonist indicated for reversible airways obstruction and suggested for maintenance therapy. It is currently available for oral administration as a syrup.
An analysis of the available literature has demonstrated that orciprenaline sulphate is significantly less efficacious than salbutamol in terms of both the extent and duration of bronchodilation. Reports and clinical trial data show a significantly increased incidence of cardiac side effects, mainly palpitations and tachycardia because of its non-selectivity. Importantly, clinical trial data show that cardiac side effects occur before maximum bronchodilation is achieved because of its non-selectivity.

Accordingly, the Commission on Human Medicines (CHM) has advised that the balance of benefit and risks for orciprenaline sulphate is no longer favourable and concluded that:

- There should be a planned withdrawal of orciprenaline sulphate from the UK market.
- There are no patient groups for whom transfer to a more-selective $\beta_2$-agonist would be inappropriate.


Artemisinin antimalarials: not for use as monotherapy

Mozambique — The risks of therapeutic failure and cases of resistance to artemisinin-derived antimalarials are elevated when used as monotherapy. In order to comply with World Health Organization recommendations, the Ministry of Health has determined that circulation in the national market of all artemisinin derived antimalarial medicines for use as monotherapy in oral administration is no longer permitted.

Reference: Communication from Ministry of Health, Maputo, Mozambique. Presidential Decree no. 11/95. 4 November 2009

Vitespen: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMEA) has been formally notified by the manufacturer of its decision to withdraw an application for a centralized marketing authorization for the medicine vitespen (Oncophage®), 20 $\mu$g solution for infusion.

Vitespen was expected to be used as an adjuvant treatment for localized renal cell carcinoma patients but received a negative opinion from the Committee for Medicinal Products for Human Use (CHMP) on 19 November 2009.


Aripiprazole: withdrawal of application for extension of indication

European Union — The European Medicines Agency (EMEA) has been notified by the manufacturer of its decision to withdraw an application for an extension of indication for the centrally authorized medicine aripiprazole (Abilify®) tablets, orodispersible tablets and oral solution.

Aripiprazole was expected to be used in the treatment of major depressive episodes, as adjunctive therapy, in patients who have had an inadequate response to previous treatment with antidepressants.

The company stated in its official letter that the withdrawal was based on the CHMP’s consideration that the long-term data provided in support of the proposed indication were insufficient, as long-term randomized controlled data are needed before this indication can be licensed.
Substandard and counterfeit medicines: USAID–USP Agreement

United States of America — With substandard and counterfeit versions of medicines intended to treat life-threatening diseases such as malaria, HIV/AIDS and tuberculosis posing a growing threat throughout the developing world, the US Agency for International Development (USAID) and the US Pharmacopeial Convention (USP) have launched a new five-year programme. Promoting the Quality of Medicines (PQM) Programme will serve as a primary mechanism to help assure the quality, safety and efficacy of medicines that are essential to USAID’s priority health programmes. This will be achieved by:

• Working with countries to strengthen their medicines regulatory bodies.

• Increasing the supply of good-quality medicines.

• Combating the availability of counterfeit and substandard medicines through testing programmes and other means.

• Conducting global advocacy to raise awareness of the dangers of substandard and counterfeit drugs.


Vandetinib: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMEA) has been formally notified of the manufacturer’s decision to withdraw its application for a centralized marketing authorization for the medicine vandetinib (Zactima®), 100 mg film-coated tablets.

Zactima was expected to be used in combination with chemotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received prior anticancer therapy.

In its official letter, the company stated that the withdrawal of the application was based on preliminary comments which indicate that at this point in time the Committee would be unlikely to conclude on a favourable benefit-risk balance for the product in the treatment of NSCLC in combination with chemotherapy.


Consultation Document

The International Pharmacopoeia

Artesunatum
Artesunate

Draft proposal for the *International Pharmcopoeia* (September 2009). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +4122791 4730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

[Note from Secretariat: The proposed revision deals primarily with the HPLC tests for related substances and assay.]

![Chemical Structure]

C_{19}H_{28}O_{8}

Relative molecular mass. 384.4

**Chemical name.** (3,5a,6,9a,10S,12R,12aR)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyran[4,3-]/1,2-benzodioxepin-10-ol, hydrogen succinate; CAS Reg. No. 182824-33-5.

**Description.** A fine, white crystalline powder.
**Solubility.** Very slightly soluble in water; very soluble in dichloromethane R; freely soluble in ethanol (~750 g/l) TS and acetone R.

**Category.** Antimalarial.

**Storage.** Artesunate should be kept in a well-closed container and protected from light.

**REQUIREMENTS**

Artesunate contains not less than 96.0% and not more than the equivalent of 102.0% of artesunate \((C_{19}H_{28}O_8)\) using Assay method A, and not less than 99.0% and not more than the equivalent of 101.0% of artesunate \((C_{19}H_{28}O_8)\) using Assay method B, both calculated with reference to the anhydrous substance.

**Identity tests**

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

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

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 5 volumes of ethyl acetate R and 95 volumes of toluene R as the mobile phase. Apply separately to the plate 2µl of the following 2 solutions in toluene R. For solution (A) use 0.10 mg of Artesunate per ml. For solution (B) use 0.10 mg of artesunate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in air, spray with anisaldehyde/methanol TS, and heat the plate to 120 °C for 5 minutes. Examine the chromatogram in ultraviolet light (254 nm).

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

C. Dissolve 0.1 g of Artesunate in 40 ml of dehydrated ethanol R, shake, and filter. To half of the filtrate (keep the remaining filtrate for test D) add about 0.5 ml of hydroxylamine hydrochloride TS2 and 0.25 ml of sodium hydroxide (~80 g/l) TS. Heat the mixture in a water-bath to boiling, cool, add 2 drops of hydrochloric acid (~70 g/l) TS and 2 drops of ferric chloride (50 g/l) TS; a light red-violet colour is produced.

D. Evaporate the remaining filtrate from test C on a water-bath to a volume of about 5 ml. Place a few drops of the mixture on a white porcelain dish, add 1 drop of vanillin/sulfuric acid TS1; a reddish-brown colour is produced.

*[Note from the Secretariat: melting range test has been deleted.]*

**Specific optical rotation.** Use a 10 mg/ml solution in dichloromethane R and calculate with reference to the anhydrous substance;

\[
[a]_D^{20^\circ} = +4.5^\circ \text{ to } +6.5^\circ.
\]
Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 20 µg/g.

Sulfated ash. Not more than 1.0 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 2 g of Artesunate; the water content is not more than 5 mg/g.

pH value. pH of an aqueous suspension containing 10 mg/g, 3.5 - 4.5.

Related substances

[Note from the Secretariat :
  • the TLC method has been deleted
  • HPLC chromatographic system has been changed to allow separation of the β-artenimol peak
  • limits for related substances have been modified (3 related substances are now specified, and a separate limit for the unknowns is now given)]

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

Use solutions (1) and (3) as described under Assay method A. For solution (4) dilute 1 ml of solution (1) to 100 ml with acetonitrile R.

Operate with a flow rate of 1.0 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (3) and (4). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes): α-artenimol about 0.58, β-artenimol about 0.91 and impurity B (artemisinin) about 1.30. The assay is not valid unless the resolution factor between the peaks due to β-artenimol and artesunate is at least 1. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

In the chromatogram obtained with solution (1)

• the combined areas of any peaks corresponding to α-artenimol and β-artenimol (impurity A) are not greater than the area of the principal peak obtained with solution (4) (1.0%);

• the area of any peak corresponding to impurity B (artemisinin) is not greater than 0.5 times the area of the principal peak obtained with solution (4) (0.5%);
• the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.07, is not greater than 0.2 times the area of the principal peak obtained with solution (4) (0.2%);

• the area of any other peak, other than the principal peak, is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

• The sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than twice the area of the principal peak obtained with solution (4) (2.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Assay

Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3 µm) (Luna® has been found suitable). As the mobile phase, use a mixture of 44 volumes of acetonitrile R and 56 volumes of buffer pH 3.0.

Prepare the buffer pH 3.0 by dissolving 1.36 g of potassium dihydrogen phosphate R in 900 ml of water R, adjust the pH to 3.0 with phosphoric acid (~1440 g/l) TS and dilute to 1000 ml with water R.

Prepare the following solutions in acetonitrile R. For solution (1) dissolve 40 mg of the test substance, accurately weighed, and dilute to 10 ml. For solution (2) dissolve 40 mg of artesunate RS, accurately weighed, and dilute to 10 ml. For solution (3) dissolve about 1 mg of artemimol RS, about 1 mg of artemisinin RS and about 10 mg of artesunate RS in 10 ml.

Operate with a flow rate of 1.0 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (2) and (3). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes): α-artenimol about 0.58, β-artenimol about 0.91 and impurity B (artemisinin) about 1.30. The assay is not valid unless the resolution factor between the peaks due to β-artenimol and artesunate is at least 1. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate. Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the percentage content of artesunate (C_{19}H_{28}O_{9}) with reference to the anhydrous substance.
B. Dissolve about 0.25 g of Artesunate, accurately weighed, in 25 ml of neutralized ethanol TS and titrate with sodium hydroxide (0.05 mol/l) VS, using 2 drops of phenolphthalein/ethanol TS as indicator.

Each ml of sodium hydroxide (0.05 mol/l) VS is equivalent to 19.22 mg of \( C_{19}H_{28}O_8 \).

**Impurities**

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

A. Artenimol
B. Artemisinin
C. \((3R,5aS,6R,8aS,12R,12aR)-Octahydro-3,6,9-trimethyl-3,12-epoxy-12\( H \)-pyrano[4,3-\( j \)]-1,2-benzodioxepine; 9,10-Didehydro-10-deoxyartemisinin (Glycan).\)

[Note from Secretariat: Systematic name of impurity C to be confirmed.]

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**Artesunati compressi**
**Artesunate tablets**

Draft proposal for the *International Pharmocopoeia* (September 2009). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

[Note from Secretariat: The proposed revision deals mainly with the HPLC tests for related substances and assay.]

**Category.** Antimalarial.

**Storage.** Artesunate tablets should be kept in a well-closed container.

**Additional information.** Strength in the current WHO Model List of Essential Medicines: 50 mg. Strength in the current WHO Model List of Essential Medicines for children: 50 mg.


REQUIREMENTS

Comply with the monograph for “Tablets”.

Artesunate tablets contain not less than 90.0% and not more than 110.0% of the amount of artesunate (C_{19}H_{28}O_{8}) stated on the label.

Identity tests

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

A. To a quantity of the powdered tablets containing 0.050 g of Artesunate add 25 ml of acetone R, shake and filter. Evaporate the filtrate at low temperature and dry overnight over desiccant silica gel R. Carry out the examination with the residue as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from artesunate RS or with the reference spectrum of artesunate.

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 5 volumes of ethyl acetate R and 95 volumes of toluene R as the mobile phase. Apply separately to the plate 2 μl of the following 2 solutions in toluene R. For solution (A) shake a quantity of the powdered tablets containing about 0.5 mg of Artesunate with 5 ml, filter and use the clear filtrate. For solution (B) use 0.10 mg of artesunate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in air, spray with anisaldehyde/methanol TS, and heat the plate to 120 °C for 5 minutes. Examine the chromatogram in ultraviolet light (254 nm).

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

C. To a quantity of the powdered tablets containing 0.1 g of Artesunate add 40 ml of dehydrated ethanol R, shake for a few minutes, and filter. To half of the filtrate (keep the remaining filtrate for test D) add about 0.5 ml of hydroxylamine hydrochloride TS2 and 0.25 ml of sodium hydroxide (~80 g/l) TS. Heat the mixture in a water-bath to boiling, cool, add 2 drops of hydrochloric acid (~70 g/l) TS and 2 drops of ferric chloride (50 g/l) TS; a light red-violet colour is produced.

D. Evaporate the remaining filtrate from test C on a water-bath to a volume of about 5 ml. Place a few drops of the mixture on a white porcelain dish, add 1 drop of vanillin/sulfuric acid TS1, a reddish-brown colour is produced.

Related substances

[Note from the Secretariat:]

- the TLC method has been deleted
- HPLC chromatographic system has been changed to allow separation of the β-artenimol peak
- limits for related substances have been modified (3 related substances are now specified, and a separate limit for the unknowns is now given).]
Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay method A.

Use solutions (1) and (3) as described below under Assay method A. For solution (4) dilute 1 ml of solution (1) to 100 ml with acetonitrile R. For solution (5) shake or sonicate a mixture of suitable amounts of each of the excipients stated on the label for 15 minutes with 10 ml acetonitrile, filter through a 0.45-µm filter and use the filtrate. Operate with a flow rate of 1.0 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (3), (4) and (5). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes): α-artenimol about 0.58, β-artenimol about 0.91 and impurity B (artemisinin) about 1.30. The assay is not valid unless the resolution factor between the peaks due to β-artenimol and artesunate is at least 1. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

In the chromatogram obtained with solution (1)

- the combined areas of any peaks corresponding to α-artenimol and β-artenimol (impurity A) are not greater than 3 times the area of the principal peak obtained with solution (4) (3.0%);

- the area of any peak corresponding to impurity B (artemisinin) is not greater than 0.5 times the area of the principal peak obtained with solution (4) (0.5%);

- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.07, is not greater than 0.3 times the area of the principal peak obtained with solution (4) (0.3%);

- the area of any other peak, other than the principal peak, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (4) (0.3%);

- the sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than 4 times the area of the principal peak obtained with solution (4) (4.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (4) (0.1%), and any peak eluting before acetonitrile, and, if information concerning the excipients used in manufacturing of the tablets is available, disregard any peak with the same retention time as that of any of the peaks in the chromatogram obtained with solution (5).

**Assay**

Either method A or method B may be applied.
A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3 µm) (Luna® is suitable). As the mobile phase, use a mixture of 44 volumes of acetonitrile R and 56 volumes of buffer pH 3.0.

Prepare the buffer pH 3.0 by dissolving 1.36 g of potassium dihydrogen phosphate R in 900 ml of water R, adjust the pH to 3.0 with phosphoric acid (~1440 g/l) TS and dilute to 1000 ml with water R.

Prepare the following solutions in acetonitrile R. For solution (1) weigh and powder 20 tablets. Shake or sonicate a quantity of the powder containing about 40 mg of Artesunate, accurately weighed, for 15 minutes with 10 ml of acetonitrile R. Filter the resulting solution through a 0.45-µm filter, discarding the first few ml of the filtrate. For solution (2) dissolve 40 mg of artesunate RS, accurately weighed, and dilute to 10 ml. For solution (3) dissolve about 1 mg of artemimol RS, about 1 mg of artemisinin RS and about 10 mg of artesunate RS in 10 ml.

Operate with a flow rate of 1.0 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20 µl each of solutions (1), (2) and (3). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes): α-artenimol about 0.58, β-artenimol about 0.91 and impurity B (artemisinin) about 1.30. The assay is not valid unless the resolution factor between the peaks due to β-artenimol and artesunate is at least 1. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of artesunate (C_{19}H_{28}O_{8}).

B. Weigh and powder 20 tablets. To a quantity of the powder containing about 0.5 g of Artesunate, accurately weighed, add 50 ml of neutralized ethanol TS, shake thoroughly, filter, and discard about 10 ml of the initial filtrate. Titrate 25 ml of the filtrate with sodium hydroxide (0.05 mol/l) VS, using 2 drops of phenolphthalein/ethanol TS as indicator.

Each ml of sodium hydroxide (0.05 mol/l) VS is equivalent to 19.22 mg of C_{19}H_{28}O_{8}.

**Dissolution.** Analyse the dissolution samples without delay.

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of dissolution buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute. At 45 minutes withdraw a sample of 10 ml of the medium through an inline filter. Allow the filtered sample to cool to room temperature [solution (1)].
Determine the concentration in solution (1) by carrying out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm) (Luna® has been found suitable). As the mobile phase, use a mixture of equal volumes of acetonitrile R and buffer pH 3.0 (prepare the buffer as described under Assay method A).

For solution (2) dissolve 25 mg of artesunate RS, accurately weighed, in acetonitrile R and dilute to 20 ml with the same solvent. Dilute 2 ml of the resulting solution to 50 ml with acetonitrile R.

Operate with a flow rate of 1.5 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 210 nm.

Inject alternately 100 μl each of solutions (1) and (2).

For each of the six tablets tested, calculate the total amount of artesunate (C₁₉H₂₈O₈) in the medium from the results obtained. The amount in solution for each tablet is not less than 80% of the amount stated on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% and the amount obtained for no tablet is less than 60%.

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Artesunate.
Illegal weight-loss medicines and dietary supplements

Netherlands — A survey on the health risk of drug substances detected in illegal weight-loss medicines and dietary supplements has recently been published by the National Institute for Public Health and the Environment (RIVM).

Between 2002 and 2007, analyses showed increasing numbers of counterfeit medicines and dietary supplements adulterated with drug substances. Use of these products may lead to psychosis, cardiovascular problems and even death. This is shown by a trend analysis on 256 suspect samples gathered by four national laboratories in the Netherlands, including the RIVM.

Adulterated dietary supplements pose the highest health risks. Because the substances used in the product are not mentioned on the label, consumers are not aware of the risks and assume they are taking a natural product. In the event of an adverse reaction, an adulterated dietary supplement is difficult to identify and correct medical treatment may be delayed.

Health risks are also high for counterfeit medicines because the composition and quality of ingredients are unknown. Internationally, use of illegal weight-loss medicines and dietary supplements has led to many cases of serious health conditions and occasionally even to death.


Southern Med Review

The Southern Med Review (SMR) is a growing independent, open access; peer reviewed journal which is currently published from Auckland, New Zealand. The journal is focusing on pharmaceutical policy and the aim of the journal is to disseminate commentary and empirical research findings, with a view to improve the rational use of and access to essential medicines.

All issues of the journal are freely accessible from the web site and the Editor welcomes submissions for its upcoming issues. Instruction for authors can be downloaded from http://www.fmhs.auckland.ac.nz/sop/smr/_docs/instructiontoauthors.pdf

Reference: University of Auckland at http://www.fmhs.auckland.ac.nz/sop/smr
International Nonproprietary Names for Pharmaceutical Substances (INN)

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

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

Dénominations communes internationales des Substances pharmaceutiques (DCI)

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

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

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

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

Las listas de Denominaciones Comunes Internacionales Propuestas (1–101) y Recomendadas (1–62) se encuentran reunidas en Cumulative List No. 13, 2009 (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.
Proposed International Nonproprietary Names: List 102

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 102 of Proposed INN not later than 31 May 2010.

Publication date: 31 January 2010

Dénominations communes internationales proposées: Liste 102

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 102 de DCI Proposées le 31 mai 2010 au plus tard.

Date de publication: 31 janvier 2010

Denominaciones Comunes Internacionales Propuestas: Lista 102

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 102 de DCI Propuestas el 31 de mayo de 2010 a más tardar.

Fecha de publicación: 31 de enero de 2010

<table>
<thead>
<tr>
<th>Proposed INN (Latin, English, French, Spanish)</th>
<th>Chemical name or description: Action and use: Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>acidum zibrofusidicum</td>
<td>zibrofusidic acid ((17\text{Z}))-16(\beta)-(acetyloxy)-24-bromo-3(\alpha),11(\alpha)-dihydroxy-29-norprotosta-17(20),24-dien-21-oic acid antibiotic</td>
</tr>
<tr>
<td>acide zibrofasidique</td>
<td>acide ((17\text{Z}))-16(\beta)-(acétyloxy)-24-bromo-3(\alpha),11(\alpha)-dihydroxy-29-norprotosta-17(20),24-dièn-21-oïque antibiotique</td>
</tr>
<tr>
<td>ácido zibrofusídico</td>
<td>ácido ((17\text{Z}))-16(\beta)-(acetiloxi)-24-bromo-3(\alpha),11(\alpha)-dihidroxii-29-norprotosta-17(20),24-dien-21-oico antibiotico</td>
</tr>
</tbody>
</table>

\(\text{C}_{31}\text{H}_{47}\text{BrO}_{6}\) 827603-95-2
afatinibum
afatinib
(2E)-N-[4-(3-chloro-4-fluoroanilino)-7-[[3S]-oxolan-3-yloxy]quinoxazolin-6-y]-4-(dimethylamino)but-2-enamide
antineoplastic

afatinib
(2E)-N-[4-(3-chloro-4-fluoroanilino)-7-[[3S]-oxolan-3-yloxy]quinoxazolin-6-y]-4-(dimeéthylamino)but-2-énamide
antineoplasique

afatinib
(2E)-N-[4-(3-cloro-4-fluoroanilino)-7-[[3S]-oxolan-3-yl]oxi]quinoxazolin-6-il]-4-(dimetilamino)but-2-enamida
antineoplásico

C_{24}H_{25}ClFN_{5}O_{3}
850140-72-6

atatagabalinum
atagabalin
[(3S,4S)-1-(aminomethyl)-3,4-dimethylcyclopent-1-yl]acetic acid
gabamimetic

atagabaline
acide [(3S,4S)-1-(aminométhyl)-3,4-diméthylcyclopent-1-yl]acético
gabamimétique

atagabalina
ácido [(3S,4S)-1-(aminometil)-3,4-dimetilciclopent-1-il]acético
gabamimético

C_{10}H_{19}NO_{2}
223445-75-8

barasertibum
barasertib
antineoplastic

barasertib
antineoplasique

barasertib
antineoplásico
benralizumab

benralizumab

benralizumab
Proposed INN: List 102

1044511-01-4

Heavy chain / Chaîne lourde / Cadena pesada
EVQLVQSGAE VKKPGASVKV SCKASGYTFT SYVIHWVRQR PGQGLAWMGY  50
INPYNDGTKY NERFKGKVTI TSDRSTSTVY MELSSLKED TAVYLCGREG 100
IRYYRVSVL TVLSQGWILG KEYYCKVSEN ALPAPIERTI SIQNSQPREP 150
QVYTLPPSOK ELTFFQSLI2 CLVGGFPSSD IAVGHSNGQ PENNYTFITP 200
YLDSSGFFFL VKLTVKSNR MQQNOWSQC VMHAEILSNY YQKSLHSPG 250
K

Light chain / Chaîne légère / Cadena ligera
DIQMTQSPSS LSASVGDRVT ITCGTSEDII NYLNWYQQKP GKAPKLLIYH  50
TSRLQSGVPS RFSGSGGTD TFLTISSLQP EDFATYYCQQ GYTLPYTFQQ 100
GYRELYRMTY AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 22-96 148-204 265-325 371-429
22''-96'' 148''-204'' 265''-325'' 371''-429''
Intra-L 25-88 134-194
25''-88'' 134''-194''
Inter-H-L 224-214 224'-214'
Inter-H-H 230-230' 233-233'

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
301, 301''

N-biotrustetanum
Acetic acid 2,2',2''-[10-(2-{[(3aS,4S,6aR)-2-octahexahydro-1H-thieno[3,4-d]imidazol-4-y]pentine}[amino]hexyl)[amino]-2-oxoethyl]-1,4,7,10-tetraazadodecane-1,4,7-triyl]triacetic acid
therapeutic carrier

Acide 2,2',2''-[10-(2-{[(3aS,4S,6aR)-2-octahexahydro-1H-thieno[3,4-d]imidazol-4-y]pentine}[amino]hexyl)[amino]-2-oxoéthyl]-1,4,7,10-tétraazadécane-1,4,7-triyl]triacétique
transporteur d'agent thérapeutique

Ácido 2,2',2''-[10-(2-{[(3aS,4S,6aR)-2-octahexahydro-1H-thieno[3,4-d]imidazol-4-y]pentine}[amino]hexyl)[amino]-2-oxoét-il]-1,4,7,10-tetraazadecano-1,4,7-trilo]triacético
transportador de un agente terapéutico

C_{32}H_{58}N_{8}O_{8}S

451478-45-8
canagliflozinum

(1S)-1,5-anhydro-1-C-(3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl)-D-glucitol
antidiabetic

C_{24}H_{25}FO_5S

842133-18-0

canagliflozin

(1S)-1,5-anhydro-1-C-(3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl)-D-glucitol
antidiabétique

canagliflozine

(1S)-1,5-anhydro-1-C-(3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl)-D-glucitol
antidiabétic

canagliflozina

(1S)-1,5-anhidro-1-C-(3-[[5-(4-fluorofenil)tiofen-2-il]metil]-4-metilfenil)-D-glucitol
antidiabético

carotegrastum

carotegrast

(2S)-2-(2,6-dichlorobenzamido)-3-[4-[[6-(dimethylamino)-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl]phenyl]propanoic acid
ant-inflammatory

C_{27}H_{24}Cl_2N_4O_5

401904-75-4

carotégrast

acide (2S)-2-(2,6-dichlorobenzamido)-3-[4-[[6-(diméthylamino)-1-méthyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl]phényl]propanoïque
anti-inflammatoire

carotegrast

ácido (2S)-2-(2,6-diclorobenzamido)-3-[4-[[6-(dimetilamino)-1-metil-2,4-dioxo-1,4-dihidroquinazolin-3(2H)-il]fenil]propanoico
antinflamatorio

C_{27}H_{24}Cl_2N_4O_5

401904-75-4
condoliasum #
condoliasum endolase, chondroitin ABC (C-ABC), glycosaminoglycan lyase chondroitin ABC endolase 1 (chondroitinase ABC) *Proteus vulgaris* enzyme
condoliasum endolase, chondroitin ABC (C-ABC), glycosaminoglycane lyase chondroitin ABC endolase 1 (chondroitinase ABC) *Proteus vulgaris* enzyme
condoliasum endolasa, chondroitina ABC (C-ABC). glicosaminoglicano liasa condroitina ABC endoliasa 1 (condroitinasa ABC) *Proteus vulgaris* enzima

C$_{5039}$H$_{7770}$N$_{1360}$O$_{1525}$S$_{22}$ 9024-13-9

## dalotuzumabum #

**dalotuzumab immunoglobulin G1-kappa, anti-[*Homo sapiens* IGF1R (insulin-like growth factor 1 receptor, IGF1-R, IGF-1R, CD221], humanized monoclonal antibody; gamma1 heavy chain (1-447) [humanized VH (*Homo sapiens* IGHV4-61*08 (79.80%) - (IGHD)-IGHJ4*01) [9.7.10] (1-117) - *Homo sapiens* IGHG1*03 (118-447)], (220-219')-disulfide with kappa light chain (1*'-219') [humanized V-KAPPA (*Homo sapiens* IGVK2-29'02 (78.00%) -IGKJ1*01) [11.3.9] (1*'-112') - *Homo sapiens* IGGC*01 (113-219')]; (226-226*:229-229")-bisdisulfide dimer antineoplastic**

dalotuzumab immunoglobuline G1-kappa, anti-[*Homo sapiens* IGF1R (récepteur du facteur de croissance 1 analogue à l'insuline (IGF1-R, IGF-1R, CD221)], humanisé anticorps monoclonal; chaîne lourde gamma1 (1-447) [VH humanisé (*Homo sapiens* IGHV4-61*08 (79.80%) - (IGHD)-IGHJ4*01) [9.7.10] (1-117) - *Homo sapiens* IGHG1*03 (118-447)], (220-219')-disulfure avec la chaîne légère kappa (1*'-219') [V-KAPPA humanisé (*Homo sapiens* IGVK2-29'02 (78.00%) - IGKJ1*01) [11.3.9] (1*'-112') - *Homo sapiens* IGGC*01 (113-219')] ; (226-226*:229-229")-bisdisulfure immunoglobuline G1-kappa, anti-[*Homo sapiens* IGF1R (insulin-like growth factor 1 receptor, IGF1-R, IGF-1R, CD221)], humanisé monoclonal antibody antiénoplásique
dalotuzumab

immunoglobulina G1-kappa, anti-[Homo sapiens IGF1-R (receptor del factor de crecimiento similar a la insulina 1/IGF1-R, IGF-1R, CD221)], anticuerpo monoclonal humanizado; cadenas gammagama (1-447) [VH humanizada (Homo sapiens IGHV4-6*08 (79.80%) -IGHD)-IGHJ4*01] [9.7.10] (1-117) -Homo sapiens IGHG1*03 (118-447)], (220-219")-disulfuro con la cadena ligera kappa (1'-219") [V-KAPPA humanizada (Homo sapiens IGGK2-29*02 (78.00%) -IGKJ1*01) [11.3.9] (1'-112')-Homo sapiens IGKC*01 (113'-219')]; dímero (226-226"-229-229")-bisdisulfuro antineoplásico

C6528H10086N1730O2018S40
1005389-60-5

Heavy chain / Chaîne lourde / Cadena pesada

QVQLQESGPV LDKPGTSSL VCTVSGNSIS GGHARWMIQP PPGGQLMGSG 50
WHNGHTNWKK KPEKLLKVTI STVDSSNHQS LELSLTVAAD TAWWCDKG 100
BVFPNDWQSG DLTVTVSAST QGSPVFLAP SDRVSQCGTA ALGCLKVVDYF 150
PEEFYTVSNMS GALEVEQYTF PANVQGSGLY SLPYTVTPS SLGQYVTCIC 200
NPHHKFNTK VDKKEVEKSC DKTHETCPCC APPELLGQPSV FLFPPRKPDT 250
LMLKSFNTY CVUVSDSHED PEKRVNYID GYVQHNNKTH PVEKHYVUTY 300
RVVSVTTLHV GQWNLHGRK YKVSNNKALF PJEKTISSAM QGGPFPVYTT 350
LFPPEEKNTK HQVILTLCKV GFYPSIYAEVE WESNGQPHFEN KYTTPVPVLS 400
DGFFLYSKLY TDCKSNMQQSC NFYESCSWKE ALHHNTQFGS LELIPGS 447

Light chain / Chaîne légère / Cadena ligera

DIVMTQSPSB LPYFPEGPAS ISCHGRHISV HSSNGWLSLQ MLKFPQSFGQ 50
LILHYKVRNL NVDYDRESGS GSCTDFTLKI SRVQAOQYYW MXFQGSHVP 100
MTFYQGTQTVQ JKEYVAAPSV FLFPPQSDG KSDTARVTLY LNFTYPREAK 150
VQKWYDLNQL SGHQQYSVTE QSQKSTYVEL SSTLTLSKAD YEHKPYACE 200
VTWGLSLPPV DKSFRRGEC 219

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

Intra-H 22.96 144-200 261-321 367-425 22"-96" 144"-200" 261"-321" 367"-425"
Intra-L 23"-93" 139"-199" 23""-93"" 139""-199""
Inter-H-L 226-219 226"-219"
Inter-H-H 226-226" 226-226"

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

Nanoprevirum

danoprevir

(2R,6S,12Z,13aS,14aR,16aS)-6-[[(tert-butoxycarbonyl)amino]-14a-[N-(cyclopropanesulfonyl)carbamoyl]-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,15,16,16a-hexadecahydrocyclopropa[pyrrolo[1,2-a][1,4]diazacyclopentadecin]-2-yl 4-fluoro-1,3-dihydro-2H-isindole-2-carboxylate antiviral

danoprévir

4-fluoro-1,3-dihydro-2H-isindole-2-carboxylate de (2R,6S,12Z,13aS,14aR,16aS)-6-[[(tert-butoxycarbonyl)amino]-14a-[N-(cyclopropanesulfonyl)carbamoyl]-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,15,16,16a-hexadecahydrocyclopropa[pyrrolo[1,2-a][1,4]diazacyclopentadécin]-2-yle antiviral

danoprevir

4-fluoro-1,3-dihydro-2H-isindol-2-carboxilato de (2R,6S,12Z,13aS,14aR,16aS)-6-[[(tert-butoxycarbonyl)amino]-14a-[N-(cyclopropanesulfonyl)carbamoyl]-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,15,16,16a-hexadecahydrocyclopropa[pyrrolo[1,2-a][1,4]diazaciclopentadecin]-2-ilo antiviral
derenofyllinum
derenofylline

*trans-4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexanol*
adenosine receptor antagonist

dérenofyline
dérénofyline

*trans-4-[(2-phényl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexanol*
antagoniste des récepteurs à l’adénosine

derenofilina
derenofilina

*trans-4-[(2-fenil-7H-pirrolo[2,3-d]pirimidin-4-il)amino]ciclohexanol*
antagonista del receptor de adenosina

\[C_{35}H_{46}FN_{5}O_{9}S\] 916881-67-9

\[\text{trans-4-[(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexanol}\]
adénosine récepteur antagoniste

dilmapimodum
dilmapimod

*8-(2,6-difluorophenyl)-2-[(1,3-dihydroxypropan-2-yl)amino]-4-(4-fluoro-2-méthylphényl)pyrido[2,3-d]pyrimidin-7(8H)-one*
immunomodulateur

dilmapimod
dilmapimod

*8-(2,6-difluorophenyl)-2-[(1,3-dihydroxypropan-2-yl)amino]-4-(4-fluoro-2-méthylphényl)pyrido[2,3-d]pyrimidin-7(8H)-one*
immunomodulateur

dilmapimod
dilmapimod

*8-(2,6-difluorofenil)-2-[(1,3-dihidroxipropan-2-il)amino]-4-(4-fluoro-2-metilfenil)pirido[2,3-d]pirimidin-7(8H)-ona*
immunomodulador
Proposed INN: List 102

C₂₁H₁₉F₃N₄O₃  444606-18-2

dinaciclib
  3-[(3-ethyl-5-[(2S)-2-(2-hydroxyethyl)piperidin-1-yl]pyrazolo[1,5-a]pyrimidin-7-yl)amino]methyl]pyridine 1-oxide
  **antineoplastic**

dinaciclib
  1-oxyde de 3-[(3-éthyl-5-[(2S)-2-(2-hydroxyéthyl)pipéridin-1-yl]pyrazolo[1,5-a]pyrimidin-7-yl)amino]méthyl]pyridine
  **antineoplasique**

dinaciclib
  1-óxido de 3-[(3-etil-5-[(2S)-2-(2-hidroxietil)piperidin-1-ll]pirazolo[1,5-a]pirimidin-7-ll)amino]metil]piridina
  **antineoplásico**

C₂₁H₂₈N₆O₂  779353-01-4

dipraglurant
  6-fluoro-2-[4-(pyridin-2-yl)but-3-yn-1-yl]midazo[1,2-a]pyridine
  **glutamate receptor modulator**

dipraglurant
  6-fluoro-2-[4-(pyridin-2-yl)but-3-yn-1-yl]midazo[1,2-a]pyridine
  **modulateur des récepteurs au glutamate**

dipraglurant
  6-fluoro-2-[4-(piridin-2-il)but-3-in-1-il]midazo[1,2-a]piridina
  **modulador del receptor de glutamato**

C₁₈H₁₉FN₃  872363-17-2
**duvoglustatum**

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

*Pompe’s disease therapy*

**emicerfontum**

*emicerfont*  
1-{1-[1-[(4-methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-
1H-pyrrolo[2,3-b]pyridin-4-yl]-1H-pyrazol-3-yl}imidazolidin-2-one

*antidepressant*

**florbetabenum**

*florbetaben*  
1-en-1-yl]-N-methylaniline

*diagnostic aid*
forétinib
N-[3-fluoro-4-{(6-méthoxy-7-[3-(morpholin-4-il)propoxy]quinoléin-4-il}oxy]phényl]-N'-(4-fluorophényl)cyclopropane-1,1-dicarboxamide antinéoplasique

C_{34}H_{34}F_{2}N_{4}O_{6} 849217-64-7

glembatumumab #
glembatumumab
immunoglobulin G2-kappa, anti-[Homo sapiens GPNMB (glycoprotein transmembrane NMB, hematopoietic growth factor inducible neurokinin-1 type, HGFIN) extracellular domain]. Homo sapiens monoclonal antibody, gamma2 heavy chain (1-445) [Homo sapiens VH (IGHV4-31*02 (94.90%) -IGHD)-IGHJ4*01 (10.7.11) (1-119) -IGHG2*01 (120-445)], (133-215')-disulfide with kappa light chain (1'-215') [Homo sapiens V-KAPPA (IGKV3-15*01 (96.80%) -IGKJ1*01 (8.3.10) (1'-108') -IGKC*01 (109'-215')); (221-221'-222-222'-225-225'-228-228')-tetrakisdisulfide dimer therapeutic carrier
glembatumumab

**immunoglobuline G2-kappa, anti-[**Homo sapiens** GPNMB (glycoprotéine transmembranaire NMB, facteur de croissance hématopoïétique inducible type neurokinine-1, HGFIN) domaine extracellulaire]. Homo sapiens anticorps monoclonal; chaîne lourde gamma2 (1-445) [Homo sapiens VH (IGHV4-31*02 (94.90%)-(IGHD)-IGHJ4*01) [10.7.11] (1-119) -IGHG2*01 (120-445)], (133-215')-disulfure avec la chaîne légère kappa (1-215') [Homo sapiens V-KAPPA (IGKV3-15*01 (96.80%)-IGKJ1*01) [6.3.10] (1-108') -IGKC*01 (109'-215')]; dimère ([221-221'':222-222'':225-225'':228-228''])-tétrakisdissulphure transporteur d’agent thérapeutique**

1020264-78-1

**Heavy chain / Chaîne lourde / Cadena pesada**

```
QVQGLERGPK LVVPEQTLSSL CTCVSQQGIS SFDYHYMWRH HPGKLEWQS  50
GYTYSQGTDT SNPLSKRVQ 1EVTSKMKQ SLTISYVAAT DTVYVYCAR 100
YNMMTVYDQG QQLYTSVEA SYGOSLPFLK PRQGSTHSA TALGZLWKE 150
YFPEPVTVSW HEGALTSQH YFPAVLQLSG LYSLSYVYTV PSNPSIVTQT 200
TOYDHKGQEN TRIDKTVKQ CVKCEQCPAP CPPGAGPVYL FPVPKDTIQA 250
ISBTRPVYCV VVDVSHDEDE VQPWWYDGD KVHAKTKR REQPSFTPV 300
VSILTVYWQD MLNGKGYKCV YSMLGFLPAP ERK1SKTRQK PRQPQYTLRF 350
PSNEMTPQW YVELTCLVQSF YPGCAENWEE SGGQRRNQXY TFFPMHLQGQ 400
SFLYKLTV DSKIWQQGHV FSCVSNHEAL NHHYQKDSL LIPGK      445```

**Light chain / Chaîne légère / Cadena ligera**

```
EIVMTQSPAT LSVSPGERAT LSCRASQSVD NNLVWYQQKP GQAPRLLIYG  50
ASTVVTQKIT LVSDGPERAT LECRAQSVQD NHLYWYQQKP GQAPRLLEYQ 50
ASTRAQGIPA RFSGUEKOTR PTLTHALEQ KGFAYTVQQ YHNNPPFQFG 100
QCTQIEKRT VAAEPVTFFP PSEDEKQSIT ASDVVCNLFN YVFRAQVKQKM 150
VNLQDSQEQ ESAYQKKQGK DTYQSLSFL TLRKAEYKNT HYTCAVTYKH 200
GLASSAYKSF NRGECL 215```

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

- **Intra-H** 22-97 146-202 259-319 365-423
- **Inter-H** 22'-97' 146'-202' 259'-319' 365'-423'

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

295, 295'

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**guaraprolsoum**

**guaraprole**

\((1\rightarrow6)\alpha-D-galactopyranosyl\-(1\rightarrow4)\beta-D-mannopyranose\)

2-hydroxypropyl ether

**pharmaceutical aid**

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**guaraprole**

éther 2-hydroxypropyle du \((1\rightarrow6)\alpha-D-galactopyranosyl\-(1\rightarrow4)\beta-D-mannopyranose\)

**adjuvant**
guaraprolosa  éter 2-hidroxipropílico de (1→6)-α-D-galactopirano-
(1→4)-β-D-mannopiranano
excipiente

\[ C_{18}H_{30}O_{15} \ (C_2H_4O) \_x \_n \]

39421-75-5

intedanib
intedanib

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

(intédanib)

(intédanib)

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

(intedanib)

intedanib

(3Z)-3-[[4-[N-metil-2-(4-metilpipera
ing-1-yl)acetamido]fenil]amino][fenil]metiliden]-2-oxo-2,3-dihidro-
1H-indol-6-carboxilato de metilo
antineoplásico

C_{31}H_{33}N_{5}O_{4}

656247-17-5

lasmiditanum
lasmidian

2,4,6-trifluoro-N-[6-[[1-methylpiperidine-4-y]carbonyl]pyridin-
2-y]benzamide
serotonin agonist

(lasmiditanum)

(lasmidian)

2,4,6-trifluoro-N-[6-[[1-méthylpipéridine-4-y]carbonyl]pyridin-
2-y]benzamide
agoniste de la sérotonine
lasmiditán
2,4,6-trifluoro-N-{6-[(1-metilpiperidina-4-il)carbonil]piridin-2-il}benzamida
agonista de serotonina
C₁₉H₁₈F₃N₃O₂
439239-90-4

latrepirdinum
latrepirdine
2,8-dimethyl-5-[2-(6-metilpiridina-3-il)etil]-2,3,4,5-tetrahidro-1H-pirido[4,3-b]indole
antihistaminic, nootropic

latrépirdine
2,8-diméthyl-5-[2-(6-méthylpyridin-3-yl)éthyl]-2,3,4,5-tétrahydro-1H-pyrido[4,3-b]indole
antihistaminique, nootrope

latrepirdina
2,8-dimetil-5-[2-(6-metilpiridin-3-il)etil]-2,3,4,5-tetrahidro-1H-pirido[4,3-b]indol
antihistamínico, nootropo
C₂₁H₂₅N₃
3613-73-8

linifanibum
linifanib
1-[4-(3-amino-1H-indazol-4-yl)phenyl]-3-(2-fluoro-5-methylfenil)urea
antineoplastic
linifanib
1-[4-(3-amino-1H-indazol-4-yl)phényl]-3-(2-fluoro-5-méthylphényl)urée
antineoplasique
linifanib
1-[4-(3-amino-1H-indazol-4-il)fenil]-3-(2-fluoro-5-metilfenil)urea
antineoplásico
C₂₁H₁₈FN₅O
796967-16-3
lunacalcipolum

lunacalcipol  
(1S,3R,5Z,7E,23E)-24-(2-methylpropane-2-sulfonyl)-9,10-secochola-5,7,10(19),16,23-pentaene-1,3-diol vitamin D analogue

lunacalcipol  
(1S,3R,5Z,7E,23E)-24-(2-méthylpropane-2-sulfonyl)-9,10-sécochola-5,7,10(19),16,23-pentaène-1,3-diol analogue de la vitamine D

lunacalcipol  
(1S,3R,5Z,7E,23E)-24-(2-metilpropano-2-sulfonil)-9,10-seccola-5,7,10(19),16,23-pentaeno-1,3-diol análogo de la vitamina D

C_{28}H_{42}O_{4}S  
250384-82-8

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mapracoratum

mapracorat  
(2R)-1,1,1-trifluoro-4-(5-fluoro-2,3-dihydro-1-benzofuran-7-yl)-4-methyl-2-\{[(2-methylquinolin-5-yl)amino]methyl\}pentan-2-ol anti-inflammatory

mapracorat  
(2R)-1,1,1-trifluoro-4-(5-fluoro-2,3-dihydro-1-benzofuran-7-yl)-4-méthyl-2-\{[(2-méthylquinoléin-5-yl)amino]méthyl\}pentan-2-ol anti-inflammatoire

mapracorat  
(2R)-1,1,1-trifluoro-4-(5-fluoro-2,3-dihidro-1-benzofuran-7-il)-4-metil-2-\{[(2-metilquinolin-5-il)amino]metil\}pentan-2-ol antiinflamatorio

C_{26}H_{26}F_{4}N_{2}O_{2}  
887375-26-0
marizomib

\[ (1'R,4'R,5'S)-4-(2\text{-chlooroethyl})-1-((S)-[1S]-\text{cyclohex-2-en-1-yl})[\text{hydroxy}]\text{methyl}-5\text{-methyl}-6\text{-oxa}-2\text{-azabicyclo[3.2.0]heptane-3,7-dione} \]

antineoplastic

marizomib

\[ (1'R,4'R,5'S)-4-(2\text{-chlooroethylyl})-1-((S)-[1S]-\text{cyclohex-2-en-1-yl})[\text{hydroxy}]\text{methyl}-5\text{-methyl}-6\text{-oxa}-2\text{-azabicyclo[3.2.0]heptane-3,7-dione} \]

antineoplasique

marizomib

\[ (1'R,4'R,5'S)-4-(2\text{-chloroethyl})-1-((S)-[1S]-\text{cyclohex-2-en-1-yl})[\text{hydroxy}]\text{methyl}-5\text{-methyl}-6\text{-oxa}-2\text{-azabicyclo[3.2.0]heptane-3,7-dione} \]

antineoplásico

\[ C_{15}H_{20}ClNO_{4} \]

437742-34-2

mavrilimumab

immunoglobulin G4-lambda, anti-[\text{Homo sapiens CSF2RA (granulocyte-macrophage colony-stimulating factor receptor subunit alpha, GM-CSF-R-alpha, CD116)]}, \text{Homo sapiens monoclonal antibody; gamma4 heavy chain} (1-447) [\text{Homo sapiens VH (IGHV1-24*01 (93.80%)-(IGHD)-IGHJ3*02 [8.8.13] (1-120)-IGHG4*01 (121-447)], (134-216')-disulfide with lambda light chain (1'-217') [\text{Homo sapiens VLAMBD}A (IGLV1-40*01 (87.90%) -IGLJ2*01 [9.3.11] (1'-111') -IGLC2*01 (112'-217'): (226-226':229-229')-bisdisulfide dimer immunomodulator}]

immunoglobuline G4-lambda, anti-[\text{Homo sapiens CSF2RA (sous-unité alpha du récepteur du facteur stimulant les colonies de granulocytes et de macrophages, GM-CSF-R-alpha, CD116)], \text{Homo sapiens anticorps monoclonal; chaîne lourde gamma4 (1-447) [\text{Homo sapiens VH (IGHV1-24*01 (93.80%)-(IGHD)-IGHJ3*02 [8.8.13] (1-120)-IGHG4*01 (121-447)], (134-216')-disulfure avec la chaîne légère lambda (1'-217') [\text{Homo sapiens VLAMBD}A (IGLV1-40*01 (87.90%) -IGLJ2*01 [9.3.11] (1'-111') -IGLC2*01 (112'-217'): dimère (226-226':229-229')-bisdisulfure immunomodulateur}]

immunoglobulina G4-lambda, anti-[CSF2RA (subunidad alfa del receptor del factor estimulante de colonias de granulocitos y macrofagos, GM-CSF-R-alfa, CD116) de \text{Homo sapiens}], anticuerpo monoclonal de \text{Homo sapiens; cadena pesada gamma4 (1-447) [\text{Homo sapiens VH (IGHV1-24*01 (93.80%)-(IGHD)-IGHJ3*02 [8.8.13] (1-120)-IGHG4*01 (121-447)], (134-216')-disulfuro con la cadena ligera lambda (1'-217') [\text{Homo sapiens VLAMBD}A (IGLV1-40*01 (87.90%) -IGLJ2*01 [9.3.11] (1'-111') -IGLC2*01 (112'-217'): dímero (226-226':229-229')-bisdisulfuro immunomodulador}]

mavrilimumab
moxetumomab pasudotox #
moxetumomab pasudotox

immunoglobulin Fv fragment fused to Pseudomonas toxin, anti-
[Homo sapiens CD22 (sialic acid-binding Ig-like lectin 2, Siglec-2, SIGLEC2, Leu-14, B-lymphocyte cell adhesion molecule, BL-CAM)],
Mus musculus monoclonal antibody disulfide stabilized Fv fragment with the variable heavy VH domain fused with the truncated form
PE38 of Pseudomonas aeruginosa exotoxin A (VH-PE38), disulfide linked with the variable kappa domain (V-KAPPA);
VH-PE38 (1-476) comprising the VH domain (1-123) [methionyl -Mus musculus VH [(IGHV5-12-1*01 -(IGHD)-IGHJ3*01) [8.8.16] (2-123)]
fused with a 7-mer linker (124-130) and with the Pseudomonas aeruginosa exotoxin A (ETA) PE38 fragment (131-476) [277-638 precursor fragment with del 389-405-N (131-476), containing domain II (131-243) with furin proteolytic cleavage site (152-164),
domain Ib (244-267), domain III (268-476)], (45-101')-disulfide with V-KAPPA (1'-108') [methionyl -Mus musculus V-KAPPA [(IGHKV10-96*01 -IGKJ1*01) [6.3.9] (2'-108')]
antineoplastic

moxétumomab pasudotox

fragment Fv d’immunoglobuline fusionné à la toxine de
Pseudomonas, anti-[Homo sapiens CD22 (Ig-like lectin 2 liant
l’acide sialique, Siglec-2, SIGLEC2, Leu-14, molécule d’adhésion
cellulaire du lymphocyte B, BL-CAM)], Mus musculus fragment Fv
d’anticorps monoclonal stabilisé par un pont disulfure avec le
domaine VH de la chaîne lourde fusionné à la forme tronquée PE38
de l’exotoxine A de Pseudomonas aeruginosa (VH-PE38), lié par un
pont disulfure au domaine variable kappa (V-KAPPA);
VH-PE38 (1-476) comprenant le domaine VH (1-123) [méthionyl -Mus musculus VH [(IGHV5-12-1*01 -(IGHD)-IGHJ3*01) [8.8.16] (2-123)]
fusionné à un 7-mer linker (124-130) et au fragment PE38 de
l’exotoxine A de Pseudomonas aeruginosa (ETA) (131-476)
[fragment précurseur 277-638 avec del 389-405-N (131-476),
domaine II (131-243) dont le site de clivage
proteolytique par la furine (152-164), domaine Ib (244-267), domaine
III (268-476)], (45-101’)-disulfure avec V-KAPPA (1’-108’)
[méthionyl- Mus musculus V-KAPPA [(IGHKV10-96*01 -IGKJ1*01) [6.3.9] (2’-108’)]
antinéoplasique
moxetumomab pasudotox

fragmento Fv de inmunoglobulina fusionado con toxina de *Pseudomonas*, anti-\textit{Homo sapiens} CD22 (lectina de tipo inmunoglobulina 2 que se une al ácido siálico, Siglec-2, SIGLEC2, Leu-14, molécula de adhesión celular del linfocito B, BL-CAM)]. *Mus musculus* fragmento Fv de anticuerpo monoclonal estabilizado por un puente disulfuro con el dominio VH de la cadena pesada fusionado a la forma truncada PE38 de la exotoxina A de *Pseudomonas aeruginosa* (VH-PE38), unida por un puente disulfuro al dominio variable kappa (V-KAPPA);

VH-PE38 (1-476) que comprende el dominio VH (1-123) [metionil - *Mus musculus* fragmento Fv de anticuerpo monoclonal estabilizado por un puente disulfuro con el dominio VH de la cadena pesada fusionado a la forma truncada PE38 (VH-PE38) (1-476) con del 389-405=N (131-476), comprende el dominio II (131-243) con el sitio de ruptura proteolítica por la furina (152-164), dominio Ib (244-267), dominio III (268-476), (45-101')- disulfuro con V-KAPPA (1-108) [metionil- *Mus musculus* V-KAPPA (IGHKV10-96*01 -IGKJ1*01) [6.3.9]] (2-108')

**antineoplásico**

102

1020748-57-5

narlaprevirum

narlaprevir

(1R,2S,5S)-N-[[3S]-1-(cyclopropylamino)-1,2-dioxoheptan-3-yl]-3-[[2S,3,3-dimethyl-2-[[1-[(2-methylprop-2-sulfonyl)methyl]cyclohexil]carbamoil]amino]butanoyl]-6,6-dimethyl-3-azabiciclo[3.1.0]hexane-2-carboxamida 

antiviral

narlaprévir

(1R,2S,5S)-N-[[3S]-1-(cyclopropylamino)-1,2-dioxoheptan-3-yl]-3-[[2S,3,3-dimethyl-2-[[1-[(2-méthylprop-2-sulfonil)méthyl]cyclohexil]carbamoil]amino]butanoyl]-6,6-diméthyl-3-azabiciclo[3.1.0]hexane-2-carboxamida 

antiviral

narlaprevir

(1R,2S,5S)-N-[[3S]-1-(ciclopropilamino)-1,2-dioxoheptan-3-yl]-3-[[2S,3,3-dimetil-2-[[1-[(2-metilprop-2-sulfonil)métil]ciclohexil]carbamoil]amino]butoxil]-6,6-dimetil-3-azabiciclo[3.1.0]hexane-2-carboxamida 

antiviral

narlaprevir

(1R,2S,5S)-N-[[3S]-1-(ciclopropilamino)-1,2-dioxoheptan-3-yl]-3-[[2S,3,3-dimetil-2-[[1-[(2-metilprop-2-sulfonil)metil]ciclohexil]carbamoil]amino]butoxil]-6,6-dimetil-3-azabiciclo[3.1.0]hexane-2-carboxamida 

antiviral
omadacyclinum

1. **Omadacycline**
   - **Chemical Structure**: C_{36}H_{61}N_{5}O_{7}S
   - **CAS Number**: 865466-24-6

   
   \[
   \text{omadacycline} \quad \text{(4S,4aS,5aR,12aS)-4,7-bis(dimethylamino)-9-[(2,2-dimethylpropyl)amino]methyl}-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide}

   \text{antibiotic}

omadacycline

1. **Omadacycline**
   - **Chemical Structure**: C_{29}H_{40}N_{4}O_{7}
   - **CAS Number**: 389139-89-3

   
   \[
   \text{omadaciclina} \quad \text{(4S,4aS,5aR,12aS)-4,7-bis(dimetilamino)-9-[(2,2-dimetilpropil)amino]methyl}-3,10,12,12a-tetrahidroxi-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahidrotetranco-2-carboxamida}

   \text{antibiótico}

omecamtiv mecarbilum

1. **Omeacamtiv mecarbil**
   - **Chemical Structure**: methyl 4-[(2-fluoro-3-[[N-(6-methylpyridin-3-yl)carbamoyl]amino]phenyl)methyl]piperazine-1-carboxylate

   
   \[
   \text{omecamtiv mecarbil} \quad \text{methyl 4-[(2-fluoro-3-[[N-(6-méthylpyridin-3-yl)carbamoyl]amino]phényl)méthyl]pipérazine-1-carboxylate}

   \text{de méthyle}

   \text{inotrope positif}

omécamtiv mécarbil

1. **Omecamelv mecarbil**
   - **Chemical Structure**: methyl 4-[(2-fluoro-3-[[N-(6-methylpyridin-3-yl)carbamoyl]amino]fenil)methyl]pipérazina-1-carboxiato de metilo

   
   \[
   \text{omecantiv mecarbilo} \quad \text{methyl 4-[(2-fluoro-3-[[N-(6-metilpiridin-3-il)carbamoi]amino]fenil)methyl]pipérazina-1-carboxilato de metilo}

   \text{inotrópico positivo}

---

338
plinabulinum

plinabulin

$\text{C}_{20}\text{H}_{24}\text{FN}_5\text{O}_3$

873697-71-3

$\begin{align*}
&\text{H}_3\text{C} \\
&\quad \text{N} \\
&\quad \text{H} \\
&\quad \text{N} \\
&\quad \text{O} \\
&\quad \text{F} \\
&\quad \text{N} \\
&\quad \text{H}_3\text{C} \\
&\quad \text{O} \\
&\quad \text{CH}_3
\end{align*}$

(3Z,6Z)-3-benzylidene-6-[[5-(tert-butyl)-1H-imidazol-4-yl]methylidene]piperazine-2,5-dione

antineoplastic

plinabuline

(3Z,6Z)-3-benzylidène-6-[[5-(tert-butyl)-1H-imidazol-4-yl]méthylidène]pipérazine-2,5-dione

antinéoplasique

plinabulina

(3Z,6Z)-3-bencilideno-6-[[5-(terc-butil)-1H-imidazol-4-il]metilideno]piperazina-2,5-diona

antineoplásico

C$_{19}$H$_{20}$N$_4$O$_2$

714272-27-2

pridopidinum

pridopidine

4-[3-(methanesulfonyl)phenyl]-1-propylpiperidine

antipsychotic

pridopidine

4-[3-(méthanesulfonyl)phényl]-1-propylpipéridine

antipsychotique

pridopidina

4-[3-(metanosulfonil)fenil]-1-propilpiperidina

antisicótico

C$_{19}$H$_{23}$NO$_2$S

346688-38-8

raseglurantum

raseglurant

2-[2-(3-fluorophenyl)ethyl]y]-4,6-dimethylpyridin-3-amine

glutamate receptor modulator

raséglurant

2-[2-(3-fluorophényl)éthyl]y]-4,6-diméthylpyridin-3-amine

modulateur des récepteurs au glutamate
raseglurant  
2-[2-(3-fluorofenil)etilil]-4,6-dimetilpiridin-3-amina  
*modulador del receptor de glutamato*

C<sub>15</sub>H<sub>13</sub>FN<sub>3</sub>  757950-09-7

remimazolamum  
remimazolam  
methyl 3-[(4S)-8-bromo-1-methyl-6-(pyridin-2-yl)-4H-imidazol[1,2-a][1,4]benzodiazepin-4-yl]propanoate  
anesthetic

C<sub>21</sub>H<sub>19</sub>BrN<sub>4</sub>O<sub>2</sub>  308242-62-8

resminostatum  
resminostat  
(2E)-3-[(4-[[dimethylamino)methyl][phenyl]sulfonyl]-1H-pyrrol-3-yl]-N-hydroxyprop-2-enamide  
antineoplastic

C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>S  864814-88-0
revamilast

phosphodiesterase IV inhibitor

révamilast

inhibiteur de la phosphodiésterase IV

revamilast

inhibidor de la fosfodiesterasa IV

C_{18}H_{9}Cl_{2}F_{2}N_{3}O_{4}  893555-90-3

rintatolimidum

poly(5')-inosinylyl-(3'→5') duplex with poly[dodecakis(3')-cytidylyl-(5'→3')-uridylyl-(5'→3')
immunomodulator

rintatolimod

poly(5')-inosinylyl-(3'→5') duplex avec poly[dodécakis(3')-cytidylyl-(5'→3')-uridylyl-(5'→3')
immunomodulateur

rintatolimod

poli(5')-inosinilil-(3'→5') dúplex con poli[dodecakis(3')-citidilil-(5'→3')-uridilil-(5'→3')
immunomodulador

[[C_{10}H_{11}N_{4}O_{7}P]_{13}]_{n}
[[C_{9}H_{12}N_{3}O_{7}P]_{12}[C_{9}H_{11}N_{2}O_{8}P]_{n}]
38640-92-5

secukinumabum #

immunoglobulin G1-kappa, anti-[Homo sapiens interleukin 17A (IL17A, IL-17A)], Homo sapiens monoclonal antibody, gamma1 heavy chain (1-457) [Homo sapiens VH (IGHV3-7*01 (92.90%) -IGHD)-IGHJ2*01] [8.8.20] (1-127) -IGHG1*03 (128-457), (230-215)-disulfide with kappa light chain (1'-215') [Homo sapiens VKAPPA (IGKV3-20*01 (100.00%) -IGKJ2*02) [7.3.9] (1'-108') -IGKC*01 (109'-215')] (269-236'-239-238')-bisdisulfide dimer
immunomodulator
### Proposed INN: List 102

**WHO Drug Information, Vol. 23, No. 4, 2009**

**Sécukinumab**

immunoglobuline G1-kappa, anti-[Homo sapiens interleukine 17A (IL17A, IL-17A)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-457) [*Homo sapiens* VH (IGHV3-7*01 (92.90%) -(IGHD)-IGHJ2*01) [8.8.20] (1-127) -IGHG1*03 (128-457)], (230-215')-disulfure avec la chaîne légère kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (100.00%) -IGKJ2*01) [7.3.9] (1'-108')-IGKC*01 (109-215')]; dimère (236-236'-239-239')-bisdisulfure immunomodulateur

**Secukinumab**

immunoglobulina G1-kappa, anti-[*Homo sapiens* IL17A (interleukina 17A, IL-17A)], anticuerpo monoclonal de *Homo sapiens*; cadena pesada gamma1 (1-457) [*Homo sapiens* VH (IGHV3-7*01 (92.90%) -(IGHD)-IGHJ2*01) [8.8.20] (1-127) -IGHG1*03 (128-457)], (230-215')-disulfuro con la cadena ligera kappa (1'-215') [*Homo sapiens* V-KAPPA (IGKV3-20*01 (100.00%) -IGKJ2*01) [7.3.9] (1'-108')-IGKC*01 (109-215')]; dimero bisdisulfuro-(236-236'-239-239')

**Inmunomodulador**

- 875356-43-7 (H chain), 875356-44-8 (L chain)

<table>
<thead>
<tr>
<th>Heavy chain / Chaîne lourde / Cadena pesada</th>
<th>Light chain / Chaîne légère / Cadena ligera</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVQLVHEGGG LVQPGGSLRL SCAASGFTFS NYW8OHVQQA PKGLESWVA 50</td>
<td>EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQPRLILY 50</td>
</tr>
<tr>
<td>HQGDSERYTV VGYYKSGFTI SRNARAEKLQL ESQMSLPYVD TAYVVCQVYD 100</td>
<td>GASRRATGIP DFISGSESGT TDTTLTSRLLE PEDFAVYYCQ QVGSKSCFG 100</td>
</tr>
<tr>
<td>YDLTQYTHIV VYFYQGGLGG LGTVSEASES KQSPVFPCLF SHEQFGQDTA 150</td>
<td>QGTRLEIKRT VAAVPVFIFP PIDSEQGSKG ADVVCILNNF YPRAEVQGQR 150</td>
</tr>
<tr>
<td>ALGCVLKDYF PEFPYTVSNL QALTSGVWTF PAVLQGSGLY SLSWTVTPS 200</td>
<td>QDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEEKH KVACVEVTQH 200</td>
</tr>
<tr>
<td>ZELGTQYTC WNNHHPFNTK VSKYVPFEC STMTCTCPFC APELQGPSPV 250</td>
<td>GLSVPYTVRP NQGECK 215</td>
</tr>
<tr>
<td>FLFPPPKKOT LMSRTPEVT CVVGVSVKED PEVKFNYVVD GVEVHIAKRT 300</td>
<td></td>
</tr>
<tr>
<td>PREQFNYTV KVSVLTVLR QWNLGGKRY CPVSRLKAPL PIFRTS1KAK 350</td>
<td></td>
</tr>
<tr>
<td>875356-43-7 (H chain), 875356-44-8 (L chain)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Intra-H</th>
<th>Intra-L</th>
<th>Inter-H-L</th>
<th>Inter-H-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>22-96</td>
<td>23-39</td>
<td>230-215</td>
<td>236-236'</td>
</tr>
<tr>
<td>154-210</td>
<td>135-195'</td>
<td>230'-215'</td>
<td>239-239'</td>
</tr>
</tbody>
</table>

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

30', 30'

**Sélexipagum**

**Sélexipag**

- 2-{4-[(5,6-diphenylpyrazin-2-yl)(propan-2-yl)amino]butoxy}-N-(methanesulfonyl)acetamide

*Prostanoid receptor agonist*

- 2-{4-[(5,6-diphénylpyrazin-2-yl)(propan-2-yl)amino]butoxy}-N-(méthanesulfonyl)acetamide

*Agoniste des récepteurs prostanoides*

- 2-{4-[(5,6-difenilpirazin-2-il)(propan-2-il)amino]butoxy}-N-(metanosulfonil)acetamida

*Agonista del receptor de prostanoide*
sotatercept #
sotatercept

fusion protein for immune applications (FPIA) comprising ACVR2A (activin receptor type 2A, activin receptor type IIa) fragment fused with immunoglobulin G1 Fc fragment, and binding activin, a member of the TGF beta family;

ACVR2A, 21-135 precursor fragment (1-115) -threonyl-triglycyl linker (116-119) -gamma1 chain H-CH2-CH3 fragment (120-344) [Homo sapiens IGHH1*03 hinge (120-127), CH2, A115>V (128-237), CH3 (238-344)]; (123-123':126-126')-bisdisulfide dimer

bone formation stimulant

sotatercept

protéine de fusion pour applications immunitaires (FPIA) comprenant un fragment d’ACVR2A (récepteur type 2A de l’activine, récepteur type IIa de l’activine) fusionné au fragment Fc de l’immunoglobuline G1, et liant l’activine, un membre de la famille du TGF bêta;

fragment précurseur 21-135 de ACVR2A (1-115) -linker thréonyl-triglycyl (116-119) -fragment H-CH2-CH3 de chaîne gamma1 (120-344) [Homo sapiens IGHG1*03 charnière (120-127), CH2, A115>V (128-237), CH3 (238-344)]; dimère (123-123'-126-126')-bisdisulfure stimulant de la formation osseuse

sotatercept

proteína de fusión para aplicaciones inmunitarias (FPIA) que comprende un fragmento de ACVR2A (receptor tipo 2A de la activina, receptor tipo IIa de la activina) fusionado al fragmento Fc de la immunoglobulina G1, y que capta la activina, un miembro de la familia del TGF beta;

fragmento precursor 21-135 de ACVR2A (1-115)-conector treonil-triglicil (116-119) -fragmento H-CH2-CH3 de cadena gamma1 (120-344) [Homo sapiens IGHG1*03 bisagra (120-127), CH2, A115>V (128-237), CH3 (238-344)]; dimero (123-123'-126-126')-bisdisulfuro estimulante de la formación del hueso
suvizumabum #

suvizumab  immunoglobulin G1-kappa, anti-[human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein gp120 third variable loop V3], humanized monoclonal antibody;
gamma1 heavy chain (1-448) [humanized VH (Homo sapiens IGHV1-46*01 (77.60%) -[IGHD]-IGHJ4*01 [8.8.11] -[1-118]-Homo sapiens IGHG1*01 (119-448)], (221-220')-disulfide with kappa light chain (1'-220') [humanized V-KAPPA (Homo sapiens IGKV4-1*01 (77.20%) -IGKJ1*01 [12.3.9] (1'-113') -Homo sapiens IGKC*01 (114'-220')]; (227-227':230-230')-disulfide dimer

immunomodulator, antiviral

Heavy chain / Chaîne lourde / Cadena pesada
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NSWIGWFRQA PQGQLEWIGD 50
IYPGGGYTNY NEIFKGKATM TADTSTNTAY MELSSLRSED TAVYYCSRGI 100
PGYAMDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI 200
CNHMKPSHT NVKKRVKPKS CDRTHTCPFC PAKELLOGPS VFLFPFWKDK 250
TLMISRTPEV TCVVVDVSHIE DPEVKFNWYV DGVEVHNAKT KPREEQYNST 300
YRVVSVLTVL HQWNGKEYK CQVSKNHALF APEIKTSKAA KQGQREFPQY 350
TLPQPSREDLT KNQYLSLTVAG KGFYPSDIAV BMESMQYFMN NYTTFFVYLD 400
SDGFFLYSK LTVDKSRWQO QNVFSCSVNH EALNHHYTKQ SLSLSFPG 448

Light chain / Chaîne légère / Cadena ligera
DIQMTQSPGS LEALGGVGRVT MCKSSQSGGLL NSGGKYNLYL RYVQQPQPPQ 50
KLLRWAFTG EGQGFPFSFSG SSQGTFPTT I5555PSGAA TYYCQNYRVR 100
PKWPSEQTVW EIYKITAAPAF VFIFFFFSDQ PKQSTAVSCV LLNFPYREA 150
NVQQRVDNL GQESQVJRST EQEIKDSTYS LSSTLYLSKA DRYKHKTYAC 200
BVHQQLSHP VTKSRNHEGC 250

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H 21'-96' 145'-201' 262'-322' 368'-426'
21'-96' 145'-201' 262'-322' 368'-426'
Intra-L 23'-94' 140'-200' 23'-94' 140'-200'
Inter-H-L 221'-220' 221'-220'
Inter-H-H 227-227' 230-230'

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

suvizumab  immunoglobuline G1-kappa, anti-[troisième boucle variable V3 de la glycoprotéine d'enveloppe gp120 du virus type 1 de l'immunodéficience humaine (VIH-1)], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-448) [VH humanisé (Homo sapiens IGHV1-46*01 (77.60%) -[IGHD]-IGHJ4*01 [8.8.11] -[1-118]- Homo sapiens IGHG1*01 (119-448)], (221-220')-disulfure avec la chaîne légère kappa (1'-220') [V-KAPPA humanisé (Homo sapiens IGKV4-1*01 (77.20%) -IGKJ1*01 [12.3.9] (1'-113') - Homo sapiens IGKC*01 (114'-220')]; dimère (227-227':230-230')-disulfure

immunomodulateur, antiviral

suvizumab  inmunoglobulina G1-kappa, anti-[tercer bucle variable V3 de la glicoproteína de la envoltura gp120 del virus tipo 1 de la inmunodeficiencia humana (VIH-1)], anticuerpo monoclonal humanizado;

cadena pesada gamma1 (1-448) [VH humanizado (Homo sapiens IGHV1-46*01 (77.60%) -[IGHD]-IGHJ4*01 [8.8.11] -[1-118]- Homo sapiens IGHG1*01 (119-448)], (221-220')-disulfuro con la cadena ligera kappa (1'-220') [V-KAPPA humanizada (Homo sapiens IGKV4-1*01 (77.20%) -IGKJ1*01 [12.3.9] (1'-113') - Homo sapiens IGKC*01 (114'-220')]; dimero bisdisulfuro (227-227':230-230')

immunomodulador, antiviral

914257-21-9
tafoxiparinum natricum

sodium salt of a low molecular mass heparin that is obtained by periodate oxidative depolymerization of heparin from porcine intestinal mucosa followed alkaline [β]-elimination and reduction of the products; the majority of the components have a 2-deoxy-6-O-sulfo-2-(sulfoamino)-α-O-glucopyranosyl structure at the non-reducing end and a (hydroxymethyl)allyl 2-deoxy-6-O-sulfo-2-(sulfoamino)-α-O-glucopyranoside structure at the reducing end of their chain; the average molecular mass is approximately 6000 Daltons and 80% of the components ranging between 2000 and 10000 Daltons; the degree of sulfatation is of 2 to 2.5 per disaccharidic unit

heparin derivative

tafoxiparine sodique

sel de sodium d’héparine de basse masse moléculaire obtenue par dépolymérisation oxydative, à l’aide de periodate, d’héparine de muqueuse intestinale de porc, suivie d’une [β]-élimination alcaline puis d’une réduction des produits. La majorité des composants présentent une structure 2-déoxy-6-O-sulfo-2-(sulfoamino)-α-O-glucopyranosyle à l’extrémité non réductrice et une structure 2-déoxy-6-O-sulfo-2-(sulfoamino)-α-O-glucopyranoside de (hydroxyméthyl)allyle à l’extrémité réductrice de leur chaîne; les masses moléculaires relatives des constituants ont une moyenne voisine de 6000 Daltons et celles de 80% des constituants sont comprises entre 2000 et 10000 ; le degré de sulfatation est compris entre 2 et 2.5 par unité disaccharide
dérivé de l’héparine

tafoxiparina sódica

sal sódica de la heparina de baja masa molecular obtenida de mucosa intestinal de cerdo por despolimerización oxidativa mediante un proceso controlado en el que se utiliza periodato, seguido de una [β]-eliminación alcalina y de una reducción de los productos. La mayoría de los componentes presentan la estructura 2-desoxi-6-O-sulfo-2-(sulfoamino)-α-O-glucopiranósilo en el extremo no reductor y la estructura 2-desoxi-6-O-sulfo-2-(sulfoamino)-α-O-glucopiranosido de (hidroximetilo)allyl en el extremo reductor de su cadena; la masa molecular relativa media es de aproximadamente 6000 daltons y la masa molecular relativa media de 80 % de los componentes está comprendida entre 2000 y 10000, el grado de sulfatación oscila entre 2 y 2,5 por unidad de disacárido
derivado de la heparina

936084-30-9

tenifatecanum

tenifatecan

(4S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3′,4′:6,7]indolizino[1,2-b]quinolin-9-yl (2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydro-2H-chromen-6-yl butanedioate

antineoplastic

ténifatécan

butanedioate de (4S)-4,11-diéthyl-4-hydroxy-3,14-dioxo-3,4,12,14-tétrahydro-1H-pyrano[3′,4′:6,7]indolizino[1,2-b]quinoléin-9-yle et de (2R)-2,5,7,8-tétraméthyl-2-[(4R,8R)-4,8,12-triméthyltridécyl]-3,4-dihydro-2H-chroméno-6-yle

antineoplasique
tenifatecán  butanodioato de (4S)-4,11-dietil-4-hidroxi-3,14-dioxo-3,4,12,14-
tetrahidro-1H-pirano[3',4':6,7]indolizin[1,2-b]quinolin-9-iloy y 
(2R)-2,5,7,8-tetrametil-2-{[(4R,8R)-4,8,12-trimetiltridecil]-3,4-dihidro-
2H-cromen-6-il}
atineoplásico

\[C_{32}H_{32}N_2O_9 \quad 850728-18-6\]

**tideglusibum**

tideglusib  4-benzyl-2-(naphtalen-1-il)-1,2,4-thiadiazolidine-3,5-dione
glycogen synthase kinase inhibitor

tidéglusib  4-benzyl-2-(naphtalén-1-il)-1,2,4-thiadiazolidine-3,5-dione
inhibiteur de la glycogène synthase kinase

**tideglusib**  4-bencil-2-(naftalen-1-il)-1,2,4-tiadiazolidina-3,5-diona
inhibidor de la glicógeno sintasa kinasa

\[C_{19}H_{14}N_2SO_2 \quad 865854-05-3\]

**tivozanibum**

tivozanib  1-{2-chloro-4-[(6,7-dimethoxyquinolin-4-il)oxy]phenyl}-3-(5-metil-
1,2-oxazol-3-il)urea
antineoplásico

tivozanib  1-{2-chloro-4-[(6,7-diméthoxyquinolín-4-il)oxí]fenil}-3-(5-métil-
1,2-oxazol-3-il)urée
antinéoplasique

tivozanib  1-{2-cloro-4-[(6,7-dimetoxiquinolín-4-il)oxí]fenil}-3-(5-metil-
1,2-oxazol-3-il)urea
antineoplástico
tonapofyllinum

3-{4-[2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1H-purin-8-yl]bicyclo[2.2.2]octan-1-yl}propanoic acid

adenosine receptor antagonist

C_{22}H_{19}ClN_{4}O_{5}  475108-18-0

C_{22}H_{32}N_{4}O_{4}  340021-17-2

C_{13}H_{8}N_{6}  577778-58-6

tonapofylline

4-

tonapophylline

4-

tonapofilina

4-

topiroxostatum

4-

4-

4-

xanthine oxidase and xanthine dehydrogenase inhibitor

inhibiteur de la xanthine oxidase et de la xanthine déhydrogenase

inhibidor de la xantinoxidasa y de la xantindeshidrogenasa

4-

4-

4-
tralokinumab #

**tralokinumab**

immunglobulin G4-lambda, anti-\{Homo sapiens\} IL13 (interleukin 13, IL-13). *Homo sapiens* monoclonal antibody; gamma4 heavy chain (1-449) [\(\text{Homo sapiens}\) VH (IGHV1-18*01 (92.90%) -IGHJ2*01) [8.8.15] (1-122) -IGHG4*01 (123-449)], (136-213')-disulfide with lambda light chain (1'-214') [\(\text{Homo sapiens}\) V-LAMBDA (IGLV3-21*03 (93.70%) -IGLJ2*01) [6.3.11] (1'-108') -IGLC2*01 (109'-214')]; (228-228'-231-231')-bisdisulfide dimer immunomodulator

**tralokinumab**

immunglobuline G4-lambda, anti-\{Homo sapiens\} IL13 (interleukine 13, IL-13). *Homo sapiens* anticorps monoclonal; chaine lourde gamma4 (1-449) [\(\text{Homo sapiens}\) VH (IGHV1-18*01 (92.90%) -IGHJ2*01) [8.8.15] (1-122) -IGHG4*01 (123-449)], (136-213')-disulfure avec la chaine légère lambda (1'-214') [\(\text{Homo sapiens}\) V-LAMBDA (IGLV3-21*03 (93.70%) -IGLJ2*01) [6.3.11] (1'-108') -IGLC2*01 (109'-214')]; dimère (228-228'-231-231')-bisdisulfure

**tralokinumab**

immunglobulina G4-lambda, anti-\[IL13 (interleukina 13, IL-13) de\] *Homo sapiens*, anticuerpo monoclonal de *Homo sapiens*; cadena pesada gamma4 (1-449) [\(\text{Homo sapiens}\) VH (IGHV1-18*01 (92.90%) -IGHJ2*01) [8.8.15] (1-122) -IGHG4*01 (123-449)], (136-213')-disulfuro con la cadena ligera lambda (1'-214') [\(\text{Homo sapiens}\) V-LAMBDA (IGLV3-21*03 (93.70%) -IGLJ2*01) [6.3.11] (1'-108') -IGLC2*01 (109'-214')]; dimero (228-228'-231-231')-bisdisulfuro

**immunomodulateur**

**immunomodulador**

1044515-88-9

Heavy chain / Chaîne lourde / Cadena pesada

**Heavy chain**

VQQLVQGSQEL VKPGQPSKTV SQKASQTYTF NYGSLWRVQA FQGGLEMRKM 50
ISNNQGDNQY GQERFGQRTY TNQTSQSTAY MEILRELASDD TATYCCARDS 100
SSAWARNFFD LMNWLTULTV SSASTGSPSV FPLAPCSRST SSIASSGCL 150
VRKKFPPFVT VSWHMCIALTS GYSFPFAQQL SSSLYLSELQP VYFQSSFQGT 200
RVTYCNVNEK PNYTRVMDYS ERYGQFCPS CEEAPFIZGDP SVFPPPSFPE 250
STDTMISRPET VTCVVDDVDS EDPEFQPPMY VQQEAYVHBIK TPEKQEEQNS 300
TNPVPYVLTV LNQGWAQGEK YRYKVSNGQF LSSEIEFTIK AKQGQdeeS 350
YTLPFQZKEM TNKQLSLZCL VRKGFPSDIA VEMRNGQFFE HNMSTTPQVL 400
DQDDSUPFLS KLYDKSMGQ EGDNPSCSDV KASLHMQY 449

Light chain / Chaîne légère / Cadena ligera

**Light chain**

SYVIZQPPSV SVAVKRGSTI TQGNHIGSK LYNWHRQKPG GQPQLVYIDD 50
GGDQSFIPER FGSAHSSONT QAWLISREAVG DADYYQWW YGDSDFPVFG 100
COTLTYQG PUKAPRNLTP FPSSSIEQAM KATLCLCLDLT YFGQATONM 150
KADDSSPVQK VETTTPSEQS NNKYYASSYL SL7FPEWSEQH GSYQCDTBE 200
GSPKTVATPC 214

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

**Intra-H**

22.96 "149-205" 263-323 369-427
22.96 "149-205" 263-323 369-427

**Intra-L**

22.87 "136-195" 22.97 "136-195"

**Inter-H-L**

136-213" 136-213"

**Inter-H-H**

228-228" 231-231"

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

298, 299
varlitinibum
varlitinib | N⁴-[3-chloro-4-[[1,3-thiazol-2-yl]methoxy]phenyl]-N⁶-[4R]-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]quinazoline-4,6-diamine
antineoplastic

veliparibum
veliparib | 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide
antineoplastic

verucerfontum
verucerfont | 3-(4-methoxy-2-methylphenyl)-2,5-dimethyl-N-[1S]-1-(3-methyl-1,2,4-oxadiazol-5-yl)propy]pyrazolo[1,5-a]pyrimidin-7-amine
antidepressant

vérucerfont | 3-(4-méthoxy-2-méthylphényl)-2,5-diméthyl-N-[1S]-1-(3-méthyl-1,2,4-oxadiazol-5-yl)propy]pyrazolo[1,5-a]pyrimidin-7-amine
antidépresseur
<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Molecular Formula</th>
<th>INN Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>verucerfont</td>
<td>C_{32}H_{38}N_{6}O_{2}</td>
<td>885220-61-1</td>
</tr>
</tbody>
</table>

**Verucerfont**: 2,5-dimetil-3-(2-metilfenil-4-metoxi)-N-[1(S)-1-(3-metil-1,2,4-oxadiazol-5-il)propil]pirazolo[1,5-al]pirimidin-7-amina antidepressivo

**Volasertib**

- **Volasertib**: N-[trans-4-[4-(cyclopropylmethyl)piperazin-1-il]cyclohexil]-4-[(7R)-7-ethyl-5-metil-6-oxo-8-(propan-2-il)-5,6,7,8-tetahidropteridin-2-il]amino]-3-metoxibenzamida antineoplásico

- **Volasertib**: N-[trans-4-[4-(cyclopropylméthyl)pipérazin-1-il]cyclohexil]-4-[(7R)-7-éthyl-5-méthyl-6-oxo-8-(propan-2-il)-5,6,7,8-tétrahydroptéridin-2-il]amino]-3-méthoxybenzamide antinéoplasique

| C_{34}H_{50}N_{8}O_{3} | 755038-65-4 |

**Vonicogum alfa**

- **Vonicog alfa [618-threonine,709-aspartic acid]von Willebrand factor Homo sapiens (1381A>T,1472H>D variant)**

  - **Vonicog alfa**: blood coagulation factor

- **Vonicog alfa [618-thréonine,709-acide aspartique]facteur de von Willebrand Homo sapiens (variant 1381A>T,1472H>D)**

  - **Vonicog alfa**: facteur de coagulation sanguine

- **Vonicog alfa [618-treonina,709-ácido aspártico]factor de von Willebrand Homo sapiens (variante 1381A>T,1472H>D)**

  - **Vonicog alfa**: factor de coagulación de la sangre
yttrium \(^{(90}Y\) clivatuzumabum tetraxetanum #

yttrium \(^{(90}Y\) clivatuzumab tetraxetan

immunoglobulin B1-kappa, anti-\((\text{Homo sapiens } \text{MUC1 (mucin 1, polymorphic epithelial mucin, PEM, CD227)})\), humanized monoclonal antibody, yttrium \(^{(90}Y\) radiolabelled tetraxetan conjugate; gamma\(^1\) human heavy chain (1-449) [humanized VH \((\text{Homo sapiens } \text{IGHV1-2*02 (79.60\%) - (IGHD)-IGHJ4*01 [8.8.12] (1-119) -Homovo sapiens } \text{IGH1*03 (120-449)}\), (222-215'-disulfide with kappa light chain \((1-119)\) [humanized V-\(\text{KAPPA (Homo sapiens } \text{IGHV1-13*02 (78.90\%) - (IGJK2*01 [7.3.9] (1-108) -Homovo sapiens } \text{IGKC*01 (109'-215')\); (228-228'-\(231\)-231')-bisulfide dimer; yttrium \(^{(90}Y\) radiolabelled tetraxetan (DOTA) conjugate antineoplastic

yttrium \(^{(90}Y\) clivatuzumabum tetraxetanum #

yttrium \(^{(90}Y\) clivatuzumabum tetraxetan

immunoglobulin B1-kappa, anti-\((\text{Homo sapiens } \text{MUC1 (mucin 1, polymorphic epithelial mucin, PEM, CD227)})\), humanized monoclonal antibody, yttrium \(^{(90}Y\) radiolabelled tetraxetan conjugate; gamma\(^1\) heavy chain (1-449) [humanized VH \((\text{Homo sapiens } \text{IGHV1-2*02 (79.60\%) - (IGHD)-IGHJ4*01 [8.8.12] (1-119) -Homovo sapiens } \text{IGH1*03 (120-449)}\), (222-215'-disulfide with kappa light chain \((1-119)\) [humanized V-\(\text{KAPPA (Homo sapiens } \text{IGHV1-13*02 (78.90%) - (IGJK2*01 [7.3.9] (1-108) -Homovo sapiens } \text{IGKC*01 (109'-215')\}; (228-228'-\(231\)-231')-bisulfide dimer; yttrium \(^{(90}Y\) radiolabelled tetraxetan (DOTA) conjugate antineoplastic
Proposed INN: List 102

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ytrio (90Y) clivatuzumab tetraxetán

inmunoglobulina G1-kappa, anti-[Homo sapiens MUC1 (mucina 1, mucina epitelial polimórfica, PEM, CD227)], anticuerpo monoclonal humanizado, conjugado al tetraxetano y radiomarcado con ytrio (90Y);
cadena pesada gamma 1 (1-449) [VH humanizada (Homo sapiens IGHV1-2*02 (79.80%)-(IGHD)-IGHJ4*01) [8.8.12] (1-119) -Homo sapiens IGHG1*03 (120-449)], (222-215’)-disulfuro con la cadena ligera kappa (1’-215’) [V-KAPPA humanizada (Homo sapiens IGKV1-13*02 (78.90%)-IGKJ2*01) [7.3.9] (1’-108’) -Homo sapiens IGKC*01 (109-215’)], dimero (228-228’..231-231’)-bisdisulfuro; conjugada al tetraxetano (DOTA) y radiomarcado con ytrio (90Y) antineoplásico

943976-23-6

Heavy chain / Chaîne lourde / Cadena pesada

QVQLQSGAE VKPGQAVYK SQHSLNWKQG PGQLEWIGY 50
INFYHCQTY NEKFKGKATL TRDTSINTAY MELELRKSGD TAVYYCARGF 100
GGYFDFAYHG QGTLVTTSSA STGKPSVFPL APEKPSGPGT AALGCLVKD 150
YFPRPVTSM NAGALTSGVN TFPVIQSGG LYSLESVTVT PSSSLQTZY 200
ICHVNKPSNH TKVDKVEFVP SCDKSTHCPF CPAPELLGGR SVLFPPRFKP 250
DTPMIRKTPF VTVVSTTVSN EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
THQVSVILYF LQHMWNLGE YKCKVSNKAL PAPIKTIKSK AKQIPEPQV 350
YTVPSDEESN YQGHSGITCL YKGFYPSDIA VEMEINGQFB NHYRTTFVPL 400
DSDEPFLYS KLVKQERWQ QCWVFQSCSM HEALNHYTVQ KSLDSLPOK 449

Light chain / Chaîne légère / Cadena ligera

DIQLTQSPSS LSAAVGQRTVT MTCSASSEVS S5YLVWYQQK PGAPKLWNY 50
STMNHSQCPV ARFGSGGSCT DPTLTISSQ PDSSASYCH QNRSRPYTFG 100
GTTKIEKHT VAAPSVTTPP PSDEQKSET ASVCLLIHNF YPRAKQVWV 150
VHNAQLGNS QSVEQDSKD DSTLSLSSTL TLSKADYKH KVVACEVYHQ 200
GSLFPYKTSF HQEKC 215

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

Intra-H 22-96 146-202 263-323 369-427
22’-96’ 146’-202’ 263’-323’ 369’-427’

Intra-L 23'-89' 135'-195'
23''-89'' 135''-195''

Inter-H-L 222-215’ 222’-215’

Inter-H-H 228-228’ 231-231’

Modified residues / Résidus modifiés / Residuos modificados

Substitution ratio of 2 to 5 lysyl (K)
out of the 90 of the antibody molecule
N6-(90Y-yttrium tetraxetan)-L-lysyl

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

299, 299’
zoleprodololum
zoleprodolol

(-)-1-[(2-[(3-methoxy-1,2,4-oxadiazol-5-yl)methoxy]phenoxy)-3-[(tert-butylamino)]propan-2-ol

terbutylamine antagonist

--
zoléprodolol
zoleprodolol

(-)-1-[(2-[(3-methoxy-1,2,4-oxadiazol-5-yl)methoxy]phenoxy)-3-[(tert-butylamino)]propan-2-ol

terbutylamine antagonist

--
zoleprodolol
zoleprodolol

(-)-1-[(2-[(3-metoxi-1,2,4-oxadiazol-5-il)metoxi]fenoxi)-3-[(terc-butilamino)]propan-2-ol

terbutylamine antagonist

C_{17}H_{25}N_{3}O_{5} 158599-53-2

and enantiomer
et énantiomère
y enantiómero
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Proposed International Non Proprietary Names (Prop. INN): List 99
Dénominations communes internationales proposées (DCI Prop.): Liste 99
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 99

p. 140 delete/supprimer/suprimáse insert/insérer/insértese
inolitazonum efatutazonum
inolitazone efatutazone
inolitazone éfatutazone
inolitazona efatutazona

Proposed International Non Proprietary Names (Prop. INN): List 101
Dénominations communes internationales proposées (DCI Prop.): Liste 101
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 101
(WHO Drug Information, Vol. 23, No. 2, 2009)

p. 171 tipapkinogenum sovacivecum #
tipapkinogene sovacivec
replace the description by the following
remplacer la description par la suivante
sustitúyase la descripción por la siguiente

an attenuated recombinant vaccinia viral vector (derived from the Modified Virus Ankara clone 33.1, MVATG33.1) containing an approximately 168 kilobasepair DNA genome encoding itself, human interleukin-2 (IL-2) and mutated-forms of the Human Papilloma Virus 16 (HPV-16) E6 and E7 antigens
vecteur viral de la vaccine recombinant atténué (dérivé du virus modifié Ankara clone 33.1, MVATG33.1) contenant un génome ADN d'approximativement 168 kilopaires de bases se codifiant lui-même, l'interleukine 2 humaine (IL-2) et des formes mutées du papillomavirus humain 16 (HPV-16) et les antigènes E6 et E7
vector viral vaccinia recombinante atenuado (derivado del Virus Modificado Ankara clon 33.1, MVATG33.1) contiene un DNA genómico de aproximadamente 168 kilopares de bases que codifican el propio virus, interleukina-2 (IL-2) humana y formas mutadas del Virus del papiloma humano 16 (HPV-16) y los antígenos E6 y E7

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

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.


2 See Annex 2.

2 Before 1987, lists of international nonproprietary names were published in the Chronicle of the World Health Organization.
Article 5 - A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in *WHO Drug Information*.

Such objection shall:

i) identify the person objecting;

ii) state his or her interest in the name;

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

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

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

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

a) request that it be recognized as the nonproprietary name for the substance; and

b) request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name and to prohibit registration of the name as a trademark or trade name.

Article 9

a) In the extraordinary circumstance that a previously recommended international nonproprietary name gives rise to errors in medication, prescription or distribution, or a demonstrable risk thereof, because of similarity with another name in pharmaceutical and/or prescription practices, and it appears that such errors or potential errors cannot readily be resolved through other interventions than a possible substitution of a previously recommended international nonproprietary name, or in the event that a previously recommended international nonproprietary name differs substantially from the nonproprietary name approved in a significant number of Member States, or in other such extraordinary circumstances that justify a substitution of a recommended international nonproprietary name, proposals to that effect may be filed by any interested person. Such proposals shall be submitted on the form provided therefore and shall:

i) identify the person making the proposal;

ii) state his or her interest in the proposed substitution; and

iii) set forth the reasons for the proposal; and

iv) describe, and provide documentary evidence regarding the other interventions undertaken in an effort to resolve the situation, and the reasons why these other interventions were inadequate.

Such proposals may include a proposal for a new substitute international nonproprietary name, devised in accordance with the General principles, which takes into account the pharmaceutical substance for which the new substitute international nonproprietary name is being proposed.

The Secretariat shall forward a copy of the proposal, for consideration in accordance with the procedure described in subsection (b) below, to the INN Expert Group and the original applicant or its successor (if different from the person bringing the proposal for substitution and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations).

In addition, the Secretariat shall request comments on the proposal from:

i) Member States and national and regional pharmacopoeia commissions or other bodies designated by Member States (by including a notice to that effect in the letter referred to in article 3(a), and
ii) any other persons known to be concerned by the proposed substitution.

The request for comments shall:

i) state the recommended international nonproprietary name that is being proposed for substitution (and the proposed substitute name, if provided);

ii) identify the person who submitted the proposal for substitution (if so requested by such person);

iii) identify the substance to which the proposed substitution relates and reasons put forward for substitution;

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

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

Comments on the proposed substitution may be forwarded by any person to WHO within four months of the date of the request for comments.

b) After the time period for comments referred to above has elapsed, the Secretariat shall forward any comments received to the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution. If, after consideration of the proposal for substitution and the comments received, the INN Expert Group, the person bringing the proposal for substitution and the original applicant or its successor all agree that there is a need to substitute the previously recommended international nonproprietary name, the Secretariat shall submit the proposal for substitution to the INN Expert Group for further processing.

Notwithstanding the foregoing, the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed for substitution.

In the event that a proposal for substitution shall be submitted to the INN Expert Group for further processing, the INN Expert Group will select a new international nonproprietary name in accordance with the General principles referred to in article 2 and the procedure set forth in articles 3 to 8 inclusive. The notices to be given by the Secretariat under article 3 and article 7, respectively, including to the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), shall in such event indicate that the new name is a substitute for a previously recommended international nonproprietary name and that Member States may wish to make transitional arrangements in order to accommodate existing products that use the previously recommended international nonproprietary name on their label in accordance with national legislation.

If, after consideration of the proposal for substitution and the comments received in accordance with the procedure described above, the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution do not agree that there are compelling reasons for substitution of a previously recommended international nonproprietary name, this name shall be retained (provided always that the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event that the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed to be substituted). In such an event, the Secretariat shall advise the person having proposed the substitution, as well as the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), Member States, national and regional pharmacopoeia commissions, other bodies designated by Member States, and any other persons known to be concerned by the proposed substitution that, despite a proposal for substitution, it has been decided to retain the previously recommended international nonproprietary name (with a description of the reason(s) why the proposal for substitution was not considered sufficiently compelling).
ANNEX 2

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. “oxacillin” and “oxacillin sodium”, “ibufenac” and “ibufenac sodium”.

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see General principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use. 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>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-ac</td>
</tr>
<tr>
<td>-adolum</td>
<td>-adol }</td>
</tr>
<tr>
<td>-adol-</td>
<td>-adol- }</td>
</tr>
<tr>
<td>-astum</td>
<td>-ast</td>
</tr>
<tr>
<td>-astinum</td>
<td>-astine }</td>
</tr>
<tr>
<td>-azepamum</td>
<td>-azepam }</td>
</tr>
<tr>
<td>bol</td>
<td>bol</td>
</tr>
<tr>
<td>-cain-</td>
<td>-cain- }</td>
</tr>
<tr>
<td>-cainum</td>
<td>-caine }</td>
</tr>
<tr>
<td></td>
<td>anti-inflammatory agents, ibufenac derivatives</td>
</tr>
<tr>
<td></td>
<td>analgesics</td>
</tr>
<tr>
<td></td>
<td>antiasthmatic, antiallergic substances not acting primarily as antihistaminics</td>
</tr>
<tr>
<td></td>
<td>antihistaminics</td>
</tr>
<tr>
<td></td>
<td>diazepam derivatives</td>
</tr>
<tr>
<td></td>
<td>steroids, anabolic</td>
</tr>
<tr>
<td></td>
<td>class I antiarrhythmics, procainamide and lidocaine derivatives</td>
</tr>
<tr>
<td></td>
<td>local anaesthetics</td>
</tr>
</tbody>
</table>

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/NO/928, 13 May 1983, revised 18 August 1983).

2. A more extensive listing of stems is contained in the working document WHO/PSM/QSM/2006.3 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.
ANNEXE 1

PROCEDURE A SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDEES 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 »). 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 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.

² Voir annexe 2.
Article 3 - Après l’examen prévu à l’article 2, le Secrétariat notifie qu’un projet de dénomination commune internationale est à l’étude.

a) Cette notification est faite par une insertion dans *WHO Drug Information*\(^1\) et par l’envoi d’une lettre aux États Membres et aux commissions nationales et régionales de pharmacopée ou autres organismes désignés par les États Membres.

   i) Notification est également faite à la personne qui a soumis la proposition (« le demandeur initial ») et à d’autres personnes portant à la dénomination mise à l’étude un intérêt notoire.

b) Cette notification contient les indications suivantes :

   i) dénomination mise à l’étude ;
   ii) nom de l’auteur de la proposition tendant à attribuer une dénomination à la substance, si cette personne le demande ;
   iii) définition de la substance dont la dénomination est mise à l’étude ;
   iv) délai pendant lequel seront reçues les observations et les objections à l’égard de cette dénomination ; nom et adresse de la personne habilitée à recevoir ces observations et objections ;
   v) mention des pouvoirs en vertu desquels agit l’OMS et référence au présent règlement.

c) En envoyant cette notification, le Secrétariat demande aux 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.

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\(^1\) Avant 1987, les listes de dénominations communes internationales étaient publiées dans la Chronique de l’Organisation mondiale de la Santé.
Article 9 -
a) Dans le cas exceptionnel où une dénomination commune internationale déjà recommandée donne lieu à des erreurs de médication, de prescription ou de distribution ou en comporte un risque démontrable, en raison d’une similitude avec une autre appellation dans la pratique pharmaceutique et/ou de prescription, et où il apparaît que ces erreurs ou ces risques d’erreur ne peuvent être facilement évitées par d’autres interventions que le remplacement éventuel d’une dénomination commune internationale déjà recommandée, ou dans le cas où une dénomination commune internationale déjà recommandée diffère sensiblement de la dénomination commune approuvée dans un nombre important d’Etats Membres, ou dans d’autres circonstances exceptionnelles qui justifient le remplacement d’une dénomination commune internationale recommandée, toute personne intéressée peut formuler une proposition dans ce sens. Cette proposition est présentée sur la formule prévue à cet effet et doit s’accompagner des indications suivantes :

i) nom de l’auteur de la proposition ;

ii) intérêt qu’il ou elle porte au remplacement proposé ;

iii) raisons motivant la proposition ; et

iv) description, faits à l’appui, des autres interventions entreprises pour tenter de régler le problème et exposé des raisons pour lesquelles ces interventions ont échoué.

Les propositions peuvent comprendre une proposition de nouvelle dénomination commune internationale de remplacement, établie conformément aux Directives générales, compte tenu de la substance pharmaceutique pour laquelle la nouvelle dénomination commune internationale de remplacement est proposée.

Le Secrétariat transmet une copie de la proposition pour examen, conformément à la procédure exposée plus loin au paragraphe b), au Groupe d’experts des DCI et au demandeur initial ou à son successeur (s’il s’agit d’une personne différente de celle qui a formulé la proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles).

De plus, le Secrétariat demande aux entités et personnes ci-après de formuler des observations sur la proposition :

i) les Etats Membres et les commissions nationales et régionales de pharmacopée ou d’autres organismes désignés par les Etats Membres (en insérant une note à cet effet dans la lettre mentionnée à l’article 3.a), et

ii) toutes autres personnes portant au remplacement proposé un intérêt notoire.

La demande d’observations contient les indications suivantes :

i) dénomination commune internationale recommandée pour laquelle un remplacement est proposé (et la dénomination de remplacement proposée, si elle est fournie) ;

ii) nom de l’auteur de la proposition de remplacement (si cette personne le demande) ;

iii) définition de la substance faisant l’objet du remplacement proposé et raisons avancées pour le remplacement ;

iv) délai pendant lequel seront reçus les commentaires et nom et adresse de la personne habilitée à recevoir ces commentaires ; et

v) mention des pouvoirs en vertu desquels agit l’OMS et référence au présent règlement.

Des observations sur la proposition de remplacement peuvent être communiquées par toute personne à l’OMS dans les quatre mois qui suivent la date de la demande d’observations.

b) Une fois échu le délai prévu ci-dessus pour la communication d’observations, le Secrétariat transmet les observations reçues au Groupe d’experts des DCI, au demandeur initial ou à son successeur et à l’auteur de la proposition de remplacement. Si, après avoir examiné la proposition de remplacement et les observations reçues, le Groupe d’experts des DCI, l’auteur de la proposition de remplacement et le demandeur initial ou son successeur reconnaissent tous qu’il est nécessaire de remplacer la dénomination commune internationale déjà recommandée, le Secrétariat soumet la proposition de remplacement au Groupe d’experts des DCI pour qu’il y donne suite.
Nonobstant ce qui précède, le demandeur initial ou son successeur n’est pas habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu’il porte un intérêt durable à la dénomination commune internationale recommandée qu’il est proposé de remplacer.

Dans le cas où une proposition de remplacement est soumise au Groupe d’experts des DCI pour qu’il y donne suite, le Groupe choisit une nouvelle dénomination commune internationale conformément aux Directives générales mentionnées à l’article 2 et selon la procédure décrite dans les articles 3 à 8 inclus. La notification faite par le Secrétariat en vertu de l’article 3 et de l’article 7, respectivement, y compris au demandeur initial ou à son successeur (si ce n’est pas la même personne que celle qui a proposé le remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles), doit dans un tel cas indiquer que la nouvelle dénomination remplace une dénomination commune internationale déjà recommandée et que les Etats Membres peuvent souhaiter prendre des mesures transitoires pour les produits existants qui utilisent la dénomination commune internationale déjà recommandée sur leur étiquette conformément à la législation nationale.

Si, après examen de la proposition de remplacement et des observations communiquées conformément à la procédure exposée plus haut, le Groupe d’experts des DCI, le demandeur initial ou son successeur et l’auteur de la proposition de remplacement ne s’accordent pas sur le fait qu’il y a des raisons impératives de remplacer une dénomination commune internationale déjà recommandée, cette dernière est conservée (étant entendu toujours que le demandeur initial ou son successeur n’est pas habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu’il porte un intérêt durable à la dénomination commune internationale recommandée qu’il est proposé de remplacer). Dans un tel cas, le Secrétariat informe l’auteur de la proposition de remplacement, ainsi que le demandeur initial ou son successeur (s’il s’agit d’une personne différente de celle qui a formulé la proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles), les Etats Membres, les commissions nationales et régionales de pharmacopée, les autres organismes désignés par les Etats Membres et toutes autres personnes portant un intérêt notoire au remplacement proposé que, malgré une proposition de remplacement, il a été décidé de conserver la dénomination commune internationale déjà recommandée (avec une brève description de la ou des raisons pour lesquelles la proposition de remplacement n’a pas été jugée suffisamment impérative).

ANNEXE 2

DIRECTIVES GENERALES POUR LA FORMATION DE DENOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES

1. Les dénominations communes internationales (DCI) devront se distinguer les unes des autres par leur consonance et leur orthographe. Elles ne devront pas être d’une longueur excessive, ni prêter à confusion avec des appellations déjà couramment employées.

2. La DCI de chaque substance devra, si possible, indiquer sa parenté pharmacologique. Les dénominations susceptibles d’évoquer pour les malades des considérations anatomiques, physiologiques, pathologiques ou thérapeutiques devront être évitées dans la mesure du possible.

Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants :

Lorsqu’on formera la DCI de la première substance d’un nouveau groupe pharmacologique, on tiendra compte de la possibilité de former ultérieurement d’autres DCI appropriées pour les substances apparentées du même groupe.

4. Pour former des DCI des acides, on utilisera de préférence un seul mot. Leurs sels devront être désignés par un terme qui ne modifie pas le nom de l’acide d’origine : par exemple « oxacilline » et « oxacilline sodique » , « ibufénac » et « ibufénac sodique ».

5. Les DCI pour les substances utilisées sous forme de sels devront en général s’appliquer à la base active (ou à l’acide actif). Les dénominations pour différents sels ou esters d’une même substance active ne différeront que par le nom de l’acide inactif (ou de la base inactive). En ce qui concerne les substances à base d’ammonium quaternaire, la dénomination s’appliquera de façon appropriée au cation et à l’ion 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.


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Une liste plus complète de segments-clés est contenue dans le document de travail WHO/PSM/QSM/2006.3 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;

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.


2 Véase el anexo 2.

3 Hasta 1987 las listas de DCI se publicaban en la Crónica de la Organización Mundial de la Salud.
c) Al enviar esa notificación, la Secretaría solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de patente sobre la denominación propuesta, durante el periodo en que la OMS la tenga en estudio.

**Artículo 4** - Toda persona puede formular a la OMS observaciones sobre la denominación propuesta dentro de los cuatro meses siguientes a su publicación en *Información Farmacéutica OMS*, conforme a lo dispuesto en el artículo 3.

**Artículo 5** - Toda persona interesada puede presentar una objeción formal a una denominación propuesta dentro de los cuatro meses siguientes a su publicación en *Información Farmacéutica OMS*, conforme a lo dispuesto en el artículo 3. Esa objeción deberá acompañarse de los siguientes datos:

1. la identidad de la persona que formula la objeción;
2. las causas que motivan su interés por la denominación; y
3. 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 ocasiona 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:

1. la identidad de la persona que presenta la propuesta;
2. las causas que motivan su interés en la sustitución propuesta;
3. las causas que motivan la propuesta; y
4. 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
La Secretaría solicitará observaciones sobre la propuesta:

i) a los Estados Miembros y a las comisiones nacionales y regionales de las farmacopeas u otros organismos designados por los Estados Miembros (ello se hará incluyendo una notificación a tal efecto en la carta a la que se refiere el párrafo a) del artículo 3), y

ii) a cualquier persona que tenga un interés especial en la sustitución propuesta.

Al solicitar que se formulen estas observaciones se facilitarán los siguientes datos:

i) la denominación común internacional recomendada que se propone sustituir (y la denominación sustitutiva propuesta, si se ha facilitado);

ii) la identidad de la persona que ha presentado la propuesta de sustitución (si lo pide esa persona);

iii) la identidad de la sustancia a la que se refiere la sustitución propuesta y las razones para presentar la propuesta de sustitución;

iv) el plazo fijado para recibir observaciones, así como el nombre y la dirección de la persona a quien deban dirigirse; y

v) los poderes conferidos para el caso a la OMS y una referencia al presente procedimiento.

Toda persona puede formular a la OMS observaciones sobre la sustitución propuesta dentro de los cuatro meses siguientes a la fecha en que se realizó la solicitud de observaciones.

b) Una vez agotado el mencionado plazo para la formulación de observaciones, la Secretaría enviará todos los comentarios recibidos al Grupo de Expertos en DCI, al solicitante inicial o a su sucesor, y a la persona que haya presentado la propuesta de sustitución. Si después de examinar la propuesta de sustitución y las observaciones recibidas, el Grupo de Expertos en DCI, la persona que haya presentado la propuesta de sustitución y el solicitante inicial, o su sucesor, están de acuerdo en la necesidad de sustituir la denominación común internacional recomendada anteriormente, la Secretaría remitirá la propuesta de sustitución al Grupo de Expertos en DCI para que la tramite.

No obstante lo anterior, el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone.

En caso de que la propuesta de sustitución sea presentada al Grupo de Expertos en DCI para que la tramite, este grupo seleccionará una nueva denominación común internacional de conformidad con los Principios generales a los que se refiere el artículo 2 y al procedimiento establecido en los artículos 3 a 8 inclusive. En ese caso, en las notificaciones que la Secretaría ha de enviar con arreglo a los artículos 3 y 7, respectivamente, incluida la notificación al solicitante inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), se indicará que la nueva denominación sustituye a una denominación común internacional recomendada anteriormente y que los Estados Miembros podrán, si lo estiman oportuno, adoptar disposiciones transitorias aplicables a los productos existentes en cuya etiqueta se utilice, con arreglo a la legislación nacional, la denominación común internacional recomendada anteriormente que se haya sustituido.

En caso de que, después de haber estudiado la propuesta de sustitución y los comentarios recibidos de conformidad con el procedimiento descrito anteriormente, el Grupo de Expertos en DCI, el solicitante inicial o su sucesor y la persona que haya presentado la propuesta de sustitución no lleguen a un acuerdo sobre la existencia de razones poderosas para sustituir una denominación común internacional recomendada anteriormente, esta denominación se mantendrá (siempre en el entendimiento de que el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone). En ese caso, la Secretaría comunicará a la persona que haya propuesto la sustitución, así como al solicitante inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), a los Estados Miembros, a las comisiones nacionales y regionales de las farmacopeas o a otros organismos designados por los Estados Miembros y a cualquier otra persona que tenga interés en la sustitución.
propuesta, que, pese a la presentación de una propuesta de sustitución, se ha decidido mantener la denominación común internacional recomendada anteriormente (con una descripción de la o las razones por las que se ha considerado que la propuesta de sustitución no estaba respaldada por razones suficientemente poderosas).

ANEXO 2

PRINCIPIOS GENERALES DE ORIENTACIÓN PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACÉUTICAS¹

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».

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.

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).

² En el documento de trabajo WHO/PSM/QSM/2006.3, que se actualiza periódicamente y puede solicitarse al Programa sobre Denominaciones Comunes Internacionales, OMS, Ginebra, figura una lista más amplia de partículas.